A

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entitled

"Studies in the Field of Acetylenic Compounds"

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PART 1.

ACETYLENIC OXIDATIVE COUPLING REACTIONS.

Introduction.

The formation of a bond between two carbon atoms, two oxygen atoms or a carbon and an oxygen atom by an oxidative coupling process involving a free, radical mechanism, is known to occur in the biosynthesis of many natural compounds and has also been successfully applied in a large number of laboratory syntheses.[1] A particular example of such bond formation is the coupling of two acetylenic residues to give a conjugated diyne system.

Since its discovery in 1869 the acetylenic oxidative coupling reaction has developed into a valuable synthetic tool. Its expansion over the past few years has been rapid and in various modifications it has figured prominently in the synthesis of a wide variety of compounds.

The reactions may be classified in the following way:

1. (a) Glaser Coupling

$$2RC\equiv CH + Cu^{+} \xrightarrow[\text{pH } 6]{NH_4Cl/O_2} R(C\equiv C)_2R$$

(b) **Coupling of Preformed Copper Acetylide**

$$2RC\equiv CH \xrightarrow{Cu^{+}} RC\equiv CCu \xrightarrow[NH_4Cl]{Cu^{+}/O_2} R(C\equiv C)_2R$$

2. Cupric Ion Coupling Reaction

$$2RC\equiv CH + 2Cu^{2+} \xrightarrow{\text{base}} R(C\equiv C)_2R + 2Cu^{+} + 2H^{+}$$

3. Chodkiewicz Coupling Reaction

$$2RC\equiv CH + BrC\equiv CR' \xrightarrow[\text{base}]{Cu^{+}} R(C\equiv C)_2R' + HBr$$

4. Oxidation of Grignard Acetylide

$$2RC\equiv MgBr \xrightarrow{\text{oxidant}} R(C\equiv C)_2R$$

5. Condensation of 1-bromoalkyne with Grignard Acetylide

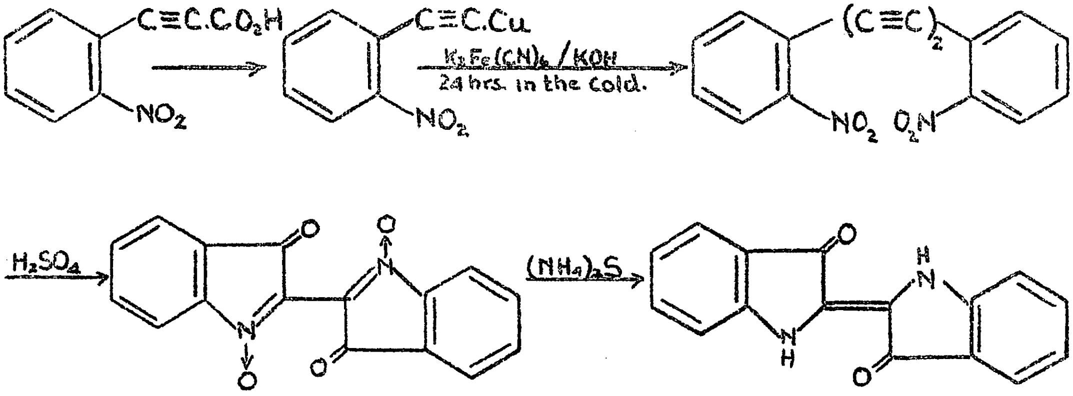
$$RC\equiv CMgBr + BrC\equiv CR' \xrightarrow{Cu^{2+}} R(C\equiv C)_2R' + MgBr_2$$

6. Miscellaneous Oxidative Coupling Reactions.

1. (a) Simple Glaser Coupling.

$$RC\equiv CH + Cu^{+} \xrightarrow[pH\ 5-6]{O_2} RC\equiv CC\equiv CR + H_2O$$

The accidental discovery by Glaser,[2] in 1869, that the copper derivative of phenylacetylene underwent smooth aerial oxidation with the formation of diphenyldiacetylene, has developed into a synthetic tool of considerable importance. Thus, in 1882, Baeyer[3] was able to provide unequivocable proof of the carbon skeleton of Indigo by a synthesis involving the oxidative coupling of o-nitrophenylacetylene.



Di-isatogen Indigo

The introduction of cuprous and ammonium chloride[4,5] into the reaction mixture proved to be a considerable improvement over Glaser's original conditions and a further advance in the technique of this form of coupling was made by a team, at the Imperial College, London, working under Sir Ian Heilbron[6,7] and later under Professor

E. R. H. Jones in London and Manchester,[8] which considerably extended the oxidative coupling of ethynyl carbinols using cuprous ammonium chloride.

$$CH_3CH(OH)C{\equiv}CH \xrightarrow[pH6.5\ O_2]{CuCl\ NH_4Cl} [CH_3CH(OH)C{\equiv}C]_2 \qquad 94\%\ \text{yield}$$

$$HOCH_2CH{=}CHC{\equiv}CH \longrightarrow [HOCH_2CH{=}CHC{\equiv}C]_2 \qquad 84\%\ \text{yield}$$

Extensive use has been made of the Glaser coupling in the synthesis of naturally occurring acetylenes. One of the first successful syntheses in this field was that by Sörensen[9] of <u>trans</u>-Lachnophyllum Ester, (obtained from the plant <u>Lachnophyllum gossypinum</u> Bge., a member of the Compositae family) by a mixed coupling of pent-1-yne and pent-3-en-1-yn-5-ol followed by oxidation and methylation.

$$CH_3(CH_2)_2C{\equiv}CH + HC{\equiv}CCH\overset{t}{=}CHCH_2OH \longrightarrow CH_3(CH_2)_2(C{\equiv}C)_2CH\overset{t}{=}CHCH_2OH$$

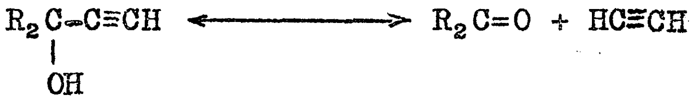
$$\longrightarrow CH_3(CH_2)_2(C{\equiv})_2CH\overset{t}{=}CHCOOMe$$

Shortly afterwards the same team synthesised Matricaria Ester[10] and related compounds.[11] Other natural products have been synthesised by this procedure.[12-20]

The reaction is generally performed in an aqueous alcohol solution containing cuprous chloride, ammonium chloride, a few drops of concentrated acid and the acetylenic material. Air or oxygen is bubbled through this mixture for periods of up to 8 hours, depending on the material being coupled and the temperature is maintained at room temperature or slightly above, e.g. ca. 50°.

Jones and his co-workers[8] advocated the use of oxygen instead of air and also 4-6 moles of cuprous salt, as these modifications tended to speed up the main reaction, thereby reducing any unwanted side reactions, e.g. ene-yne formation (see Cupric Ion Coupling).

Strongly basic conditions are generally not recommended; in the case of carbinols there may be a base catalysed reversal of the equilibrium.



$$\underset{\substack{|\\ OH}}{R_2C}-C\equiv CH \longleftrightarrow R_2C=O + HC\equiv CH$$

An examination of the function of the base in the Glaser coupling has been made by Cameron and Bennett.[21] Neutral conditions are normally quite satisfactory and the pH can usually be lowered as required to suit the particular compounds being coupled.[8]

One of the attractive features of the Glaser coupling is the mild reaction conditions involved. Although a temperature of 55° has been recommended by Bowden[6] the reactions can often satisfactorily take place at room temperature or below and can be worked up by extracting with solvent in the cold - these are important considerations when the products are highly unsaturated.

Probably the most varied aspect of the Glaser reaction has been the oxidants used to effect the coupling. Among the most successful have been air, oxygen, potassium ferricyanide and hydrogen peroxide[22] and the types of compounds coupled by the Glaser procedure include $1^{\underline{y}}$, $2^{\underline{y}}$ and $3^{\underline{y}}$ α-carbinols,[6,7,8] aromatic[23] and aliphatic[24] hydrocarbons, thienyl acetylenes,[25] α-diynes,[26] triynes,[27] and tetraynes,[28] esters,[19] acids,[19,29] ene-ynes,[30] allene-ynes,[31] ethers,[32] thio-ethers[33] and nitriles.[34]

As can be seen from the wide variety of compounds coupled, this procedure has been the most used and useful method to date, but it is more suited to water soluble compounds than, e.g. hydrocarbons, although the latter, with many other types of water insoluble compounds, have been successfully coupled, usually by introducing them in solvents such as alcohol or dioxan.

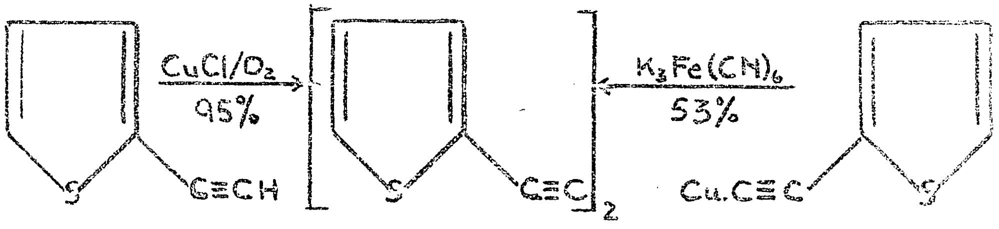
Although not ideally suited to the synthesis of unsymmetrical diynes or poly-ynes, the Glaser coupling has been the main route to many naturally occurring polyacetylenic and other unsaturated compounds, although it has now been largely superceded in this respect by the Chodkiewicz[35] procedure. The use of the Glaser in the synthesis of unsymmetrical compounds requires an excess of the more readily obtainable component, thus reducing the mixture to only two major substances, which require, of course, to be readily separable by chromatography.

1. (b) Oxidation of Preformed Copper Acetylide.

$$RC\equiv C.Cu \xrightarrow{\text{oxidant}} RC\equiv C.C\equiv CR$$

The oxidation of the pre-formed copper salt was first used by Baeyer in his classical synthesis of Indigo (see Glaser coupling). Although many subsequent workers,[5,25,39–42] used this form of coupling it is inferior to the improved Glaser coupling technique.[6]

Yields are comparatively low and the reaction is generally slow since the copper salt is much more



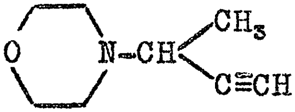
insoluble than the free ethynyl compound. Also the cuprous salt is non-crystalline and difficult to prepare in good yield, especially with hydrocarbons. On the other hand if a suitable complexing medium could be found the copper acetylides could be useful for mechanistic and reaction rate studies, since the only reaction involved should be the formation of product.

$$\mathrm{PhC{\equiv}C.Cu + Cu(OAc)_2 \xrightarrow[70\%]{} Ph(C{\equiv}C)_2Ph + Cu_2(OAc)_2}$$ [36]

Reagents which have been used in this form of coupling include alkaline potassium ferricyanide,[28] cupric salts[25] and oxygen.[37]

In the table below the following procedure is understood to be standard unless otherwise stated. The ethynyl compound alone or in solution is added to a solution of the CuCl (as its complex with NH_4Cl) in water at pH 6.5 and the mixture agitated at room temperature in the presence of an oxidant. The diyne is isolated by filtration and extraction with ether.

Typical Ethynyl Compound	Conditions	Yield %	Refs.
1. $CH_3CH{=}CH.C{\equiv}CH$	In MeOH, with oxygen, cis and trans compounds.	90	38
2. $CH_3CH_2SC{\equiv}CH$	Cu_2Cl_2 in concentrated NH_3OH and MeOH.	72	33

Typical Ethynyl Compound	Conditions	Yield %	Refs.
3. 	Homogeneous solution in 2N HCl at 50° for 9 hrs. in air	90	43
4. $CH_2=CH(CH_2)_4C\equiv CH$ $HO_2C(CH_2)_7C\equiv CH$	Cu_2Cl_2 with oxygen	30	13

2. Cupric Ion Oxidative Coupling.

$$2RC\equiv CH + 2CuX_2 \xrightarrow{\text{base}} (RC\equiv C)_2 + Cu_2X_2 + 2HX$$

For many years the use of cupric ion as an oxidising agent had been restricted to its action on a preformed acetylene intermediate such as the copper[44] or Grignard acetylide.[8,45] However, in 1956, prompted by the kinetic studies of Baxendale and Westcott,[46] Eglinton and Galbraith[47] introduced a reagent new[48] to the field of acetylenic coupling - cupric acetate in pyridine - with which they successfully coupled several monosubstituted acetylenic compounds. Since then extensive use has been made of this reagent in the coupling of mono- and di-ethynyl compounds by Eglinton,[36] Bohlmann,[49] Sondheimer[50] and their collaborators and also by several Japanese workers.[51]

The mild organic base used, *viz.* pyridine or similar bases such as morpholine, performs several important functions.

(1) It provides an excellent solvent medium in which both starting materials and products are generally stable.

(2) It removes the acetic acid formed during the course of the reaction, thus allowing the reaction to go to completion.

(3) It ensures a homogeneous organic reaction medium, a condition not previously obtainable, thus leading to increased yields.

Another advantage lies in the fact that the cuprous derivative is never present in sufficiently large concentration to precipitate from the reaction mixture. Solvation of the copper salts is also assisted by the addition of a quantity of methanol, although this has to be omitted where esters are being coupled, due to the danger of transesterification.

The temperature of the reaction mixture is generally between 60-70° and in order to ensure a high yield of a single product when several are possible, e.g. in cyclisations of α,ω-diynes, the acetylenic material is added over a period of 6-8 hours. Where no such complications are expected, however, the reaction will be substantially over in less than half this time, i.e. 1/2 - 1 hour.

This form of oxidative coupling is generally recommended for

(1) the more water insoluble compounds which would be difficult to handle with cuprous ion coupling

(2) for cyclisations where controlled dilution is required.

However, the reaction is slow for alkynyls and Bohlmann[52] has shown that, whilst alkyl ethynyls can be suitably coupled using the Glaser procedure, compounds with the more acidic hydrogen, e.g. $PhC{\equiv}CH$ and $RC{\equiv}CC{\equiv}CH$, are best coupled with the cupric ion/base reagent.

The homogeneous mildly basic media, coupled with high dilution, make this form of coupling especially suitable for cyclisation of α,ω-di-ethynyl compounds. The cyclisation of α,ω-diynes is best performed under high dilution conditions and in order to keep the temperature at a reasonable level sufficient ether may be added to act as the refluxing solvent. Even at comparatively high concentration Sondheimer[53] obtained almost entirely the corresponding cyclic dimers, trimers etc. from octa-1,7-diyne. Using high dilution technique we have found it possible to couple the same material to give a much higher yield of cyclic dimer and trimer than those obtained by Sondheimer. In general, however, the rate of reaction of α,ω-diacetylenic hydrocarbons has been shown to decrease with increasing number of methylenes between the ethynyl groups and this procedure is not ideally suited to alkynes of this type beyond $-(CH_2)_5-$ from the point of view of reaction time required.

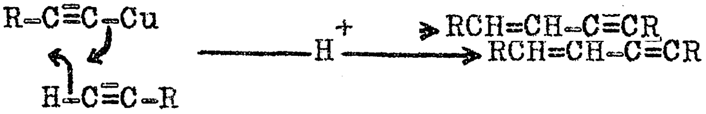
A rapid rate of reaction is obtained with α,ω-diacetylenic esters, especially if either fragment has a small number of methylenes, although if only one methylene is present the product tends to decompose under the basic reaction conditions.[54]

It has recently been found that under the coupling conditions the compound Bu^t C≡C.C≡C.CHCl.C≡C.CHCl.C≡CH both dehydrochlorinated and coupled to give satisfactory yields of the decayne.[55]

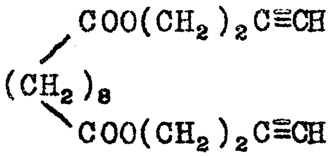
Coupling can take place even when there is only a catalytic amount of cupric ion, provided that it is regenerated by passage of oxygen.[54] This procedure, however, is not recommended since it is generally slow, although a modification using a catalytic quantity of cuprous ion in pyridine, with passage of air or oxygen, has been successfully used in the coupling of both aliphatic and aromatic hydrocarbons.[56]

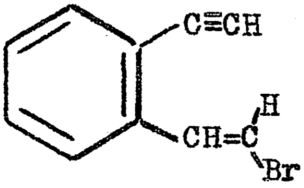
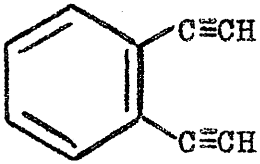
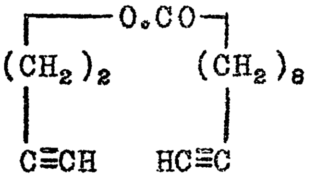
Since the reaction involves the reduction of $Cu^{++} \longrightarrow Cu^{+}$ it might be expected that ions such as cobaltic and ferric would be capable of bringing about the reaction as they are easily reduced to the corresponding cobaltous and ferrous states, but no success has so far been obtained in either aqueous or organic media.[57]

An important side reaction to this form of coupling is the formation of ene-yne material. Originally observed with acetylene, polymerisation occurred in the presence of a cuprous salt and strong acid to give initially $CH_2{=}CH.C{\equiv}CH$. Strauss[58] obtained $PhC{\equiv}C.CH{=}CHPh$ by aerial oxidation of copper phenylacetylide in hot glacial acetic acid. Weedon[59] has shown that under similar conditions a wide variety of cuprous acetylides react in this way, the yields of ene-yne material being in the region 30-80%, whilst Skattebol[60] has found that the rather reactive ethyl compound $MeO_2C.C{\equiv}CH$ forms the eye-yne in 30+% yield under normal Glaser conditions, the presence of oxygen being unnecessary. The reaction is presumed to take place by the addition of one molecule of the acetylene to an activated cuprous complex of another



The table lists a selection of the range of compounds coupled by this procedure.

	Ethynyl Compound	Conditions	Yield %	Refs.
1.	$CH_3(C\equiv C)_2H$ + $HC\equiv C.CH{=}CH.CH_2OH$	Cupric acetate, pyridine, methanol, water at 20° for 15 minutes.	60	49
2.	 $(CH_2)_8\begin{array}{l}COO(CH_2)_2C\equiv CH\\COO(CH_2)_2C\equiv CH\end{array}$	1.0 g. material in ether pyridine (1:6, 140 c.c.) added, under high dilution conditions over 2-3 hrs., to refluxing solution of cupric acetate (3.4 g.) in ether pyridine (1:6, 700 c.c.). Only monomer product isolated.	63	36

Ethynyl Compound	Conditions	Yield %	Refs.
3. 	Heated at water bath temperature for 30 minutes in cupric acetate/pyridine/methanol solution.	80	61
4. 	Under high dilution conditions similar to that used for example 4. A strained dimer was isolated.	43	62
5. 	2.5 g. in benzene (100 ml.) added over 8 hours to ether/benzene/pyridine (1:1:6, 800 ml.) containing 12 g. cupric acetate under high dilution conditions. Only monomer isolated.	88	54

3. **Chodkiewicz Coupling.**

(a) $$RC\equiv CH + BrC\equiv CR' \xrightarrow[\text{base}]{Cu^{+}} R(C\equiv C)_2R' + HBr$$

This reaction, perfected by the French workers Cadiot and Chodkiewicz,[35] provides a long desired solution to the problem of the synthesis of unsymmetrical diynes. It has been used extensively by Chodkiewicz and Cadiot to synthesise a wide range of acetylenic compounds.[35,64] They have also applied it in the synthesis of branched chain and hydroxy acids[35,64] and quinone carbinols[63] and the reaction has also been successfully employed in other laboratories,[65-67]

A catalytic amount of cuprous chloride dissolved in a suitable base (e.g. n-butylamine) is added to a solution of the ethynyl material in an organic solvent (e.g. alcohol or benzene). In order to maintain the concentration of the cuprous ion a reducing agent, hydroxylamine hydrochloride, is added in small amounts as required. To this vigorously stirred mixture a solution of the bromo-compound in the organic solvent is added dropwise. In many cases external cooling of the reaction mixture is advantageous.

The reaction may be stopped by addition of potassium cyanide or simply by destroying the base with ice-cold dilute sulphuric acid and ether extracting.

The Chodkiewicz coupling route would appear to be the most general for the preparation of conjugated polyacetylenes since almost any functional group is tolerated. Many of the naturally occurring acetylenes, which had been synthesised in low yield using the conventional Glaser mixed coupling, have recently been obtained in high yield by Cadiot and co-workers[68] using this reaction.

The fundamental reactions involved are

$$RC{\equiv}CH + Cu^{+} \longrightarrow RC{\equiv}CCu + H^{+} \quad \ldots\overset{fast}{\ldots\ldots}\ldots\ldots(1)$$

$$RC{\equiv}CCu + BrC{\equiv}CR' \longrightarrow R(C{\equiv}C)_2R' + CuBr \quad \ldots\ldots\ldots\ldots(2)$$

As reaction (2) regenerates Cu^{+} the cuprous ion has a purely catalytic function and need be present in only trace quantities, usually 1-2%. The overall reaction then becomes

$$RC{\equiv}CH + BrC{\equiv}CR' \longrightarrow R(C{\equiv}C)_2R' + HBr \quad \ldots\ldots\ldots(3)$$

The addition of a base facilitates the reaction by removing the liberated acid and assisting in the solution of the cuprous derivative, probably by formation of a complex.

Precautions have to be taken to minimise an unwanted side reaction (4) which leads to the self coupling of the bromoalkyne

$$R'C{\equiv}CBr + 3Cu^{+} \longrightarrow R'C{\equiv}CCu + Br^{-} + 2Cu^{2+} \quad \ldots\overset{Slow}{\ldots\ldots}\ldots(4)$$

$$\underline{R'C{\equiv}CCu + BrC{\equiv}CR' \longrightarrow R'(C{\equiv}C)_2R' + CuBr \quad \ldots\ldots\ldots\ldots(2a)}$$

$$2R'C{\equiv}CBr + 2Cu^{+} \longrightarrow R'(C{\equiv}C)_2R' + 2Br^{-} + 2Cu^{2+} \ldots\ldots(5)$$

The previously mentioned conditions, viz. catalytic quantity of cuprous salt, reducing agent, slow addition of a bromoalkyne with vigorous stirring, together with a careful choice of operating temperatures, tend to considerably reduce the possibility of this side reaction.

The apparent reactivity of the ethynyl component, generally the component bearing solubilising groups e.g. hydroxyl, is believed to be chiefly dependent on the properties of the cuprous derivative e.g. solubility in the reaction medium. The 1-bromoalkyne on the other hand has no such limitations, all of these compounds react very rapidly with the cuprous acetylide at room temperature.

If only small quantities of cuprous chloride are added to the reaction mixture, the large concentration of $RC\equiv CH$ will ensure that the concentration of cuprous ion is practically zero and hence the side reactions (4) will be repressed. It has not been investigated whether other metal ions are capable of inducing reaction (3) or (5) but the indications are that cuprous ion may well be unique in this respect.

The base is required to neutralise the liberated acid, to modify the oxidising power of the cuprous acetylide and to assist in its formation. The inorganic ammonium hydroxide has been widely used in the preparation of cuprous acetylides (Glaser coupling), but has the disadvantage of favouring reaction (4). Chodkiewicz and Cadiot found that reaction (3) gave high yields in presence of a primary alkylamine (1.8 mole per mol of ethynyl component). Where the feebly basic pyridine is used as the amine, inorganic bases may be employed to remove the overall acidity, but are ineffective alone in reaction (1). The chelating power of the amines must be the important factor; the chelating agent ethylene diamine is said to be ineffective - presumably because the cuprous salts are too tightly complexed.

Almost any solvent which will give homogeneous reaction conditions can be used but for very insoluble starting materials dimethyl formamide or N-methyl pyrrolidone are recommended. The 1-bromoalkyne may be added dissolved in the same solvent. The permissable temperature of the reaction mixture depends on the thermal stability of the expected products but generally it is not allowed to rise above 50° since higher temperatures favour reaction (4) and should thus be avoided.

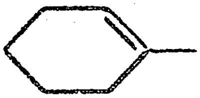
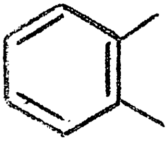
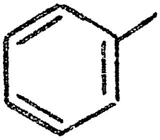
3. (b) The Self-Condensation of the 1-bromoalkyne.

$$2R'C\equiv CBr \xrightarrow{2Cu^{+}} (R'C\equiv C)_2 + 2Br^{-} + 2Cu^{2+}$$

This condensation, the unwanted side reaction of the mixed coupling, has been used extensively by Chodkiewicz as a means of estimating the purity of the 1-bromoalkyne, but rarely for synthetic purposes. Since the reaction is known to be instantaneous, however, it could be used in the synthesis of symmetrical diynes where the other procedures fail due to slow rate of reaction, precipitation of copper acetylide etc.

The following general procedure was adopted for all the syntheses listed below. The cuprous chloride-ethylamine (or <u>n</u>-butylamine) solution diluted with a suitable solvent was added to a mixture of hydroxylamine hydrochloride and the ethynyl compound dissolved in the same solvent. To this vigorously stirred solution the 1-bromoalkyne, also diluted with solvent, was added dropwise and the reaction mixture externally cooled when necessary. The reaction was stopped by addition of excess potassium cyanide and ether extracted.

$$R\text{-}C\equiv CH + BrC\equiv C\text{-}R' \xrightarrow[\text{base}]{Cu^{+}} R(C\equiv C)_2R' + HBr$$

	R	R'	Solvent	Temper-ature	Yield %	Refs.
1.	$HO_2C(CH_2)_8$–	$HO.CH_2$–	MeOH	19°	75	Cadiot and Chodkiewicz private communication.
2.	CH_3–	$Ph_2C(OH)$–	MeOH	20°	90	35
3.	Ph–	$(CH_3)_2N{-}CH_2$	H_2O	25°	86	35
4.	$CH_3C\ C$–	$HOCH_2CH\ CH$–	H_2O	20°	86	35
5.	$HO_2C(CH_2)_2$–		MeOH	–	90	64
6.			EtOH	20°	60	61 See also ref. 67

4. Oxidation of acetylenic Grignard derivatives.

$$RC\equiv CMgBr \xrightarrow{\text{Oxidant}} (RC\equiv C)_2$$

This route is not a good alternative to the oxidation of a preformed cuprous acetylide as substituent groups may be readily attacked by the Grignard reagent and it is not possible to use aqueous or alcoholic conditions. Conversely where the latter conditions cannot be used, this method would be suitable. This reaction has so far been tried only with hydrocarbons, yields 47–78%. Reagents used were iodine,[69] cupric[25,45,70] or cobaltic[45] salts. The presence of cuprous chloride has been shown to act as a catalyst.

$$C_4H_9C{\equiv}CMgBr \xrightarrow[25^\circ]{CuBr_2/ether} [C_4H_9C{\equiv}C]_2 \quad 60\%$$ [45]

5. Oxidative Coupling of Grignard with 1-bromoalkynes.

$$RC{\equiv}CMgBr + BrC{\equiv}CR' \xrightarrow{Co^{++}} R(C{\equiv}C)_2R' + MgBr_2$$

This reaction bears an obvious relation to the Chodkiewicz coupling in that both are metal catalysed condensations of 1-bromoalkynes with an acetylenic intermediate - in this case the Grignard derivative.

Weedon[71] has made an extensive study of this reaction, since the early work of Grignard[69] was shown to be unreliable.

Although the mechanism has not been elucidated it is likely to be essentially similar to that of the other coupling reactions since a catalyst, e.g. cobaltic chloride has been found to be essential.

The mixed product has been obtained in yields of ca. 35%, but the two possible competing reactions below, made it seem likely that this reaction will become of

$$RC{\equiv}CMgBr \longrightarrow (RC{\equiv}C)_2$$

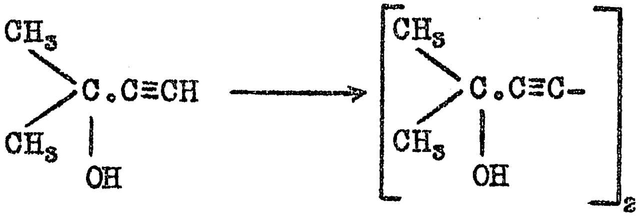
$$R'C{\equiv}CBr \longrightarrow (R'C{\equiv}C)_2$$

theoretical interest only.

6. Miscellaneous Coupling Reactions.

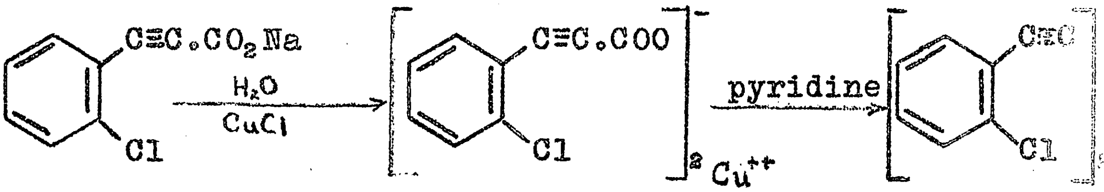
1. Electrolytic coupling.[72]

A small yield of dimer was obtained by electrolysis of dimethylethynyl carbinol using a nickel plated electrode. The reaction also works with a copper electrode or in the presence of copper salts or by using the cuprous acetylide.



20-30%

2. Disproportionation.[73]



3. Dimerisation by heat alone.[74]

$$(CH_3)_3C{\equiv}C.Cu \xrightarrow{150^\circ} (CH_3)_3(C{\equiv}C)_2(CH_3)_3$$

4. Potassium Permanganate Coupling.[75]

This form of oxidative coupling was first used by Schlubach and Wolf in 1950 to obtain diacetylene.

$$2HC{\equiv}CNa + 2KMnO_4 \longrightarrow HC{\equiv}C.C{\equiv}CH + 2KNaMnO_4$$

$$HC{\equiv}C.C{\equiv}CH + HC{\equiv}CNa \longrightarrow HC{\equiv}C.C{\equiv}CNa + HC{\equiv}CH$$

the maximum yield of 35% being obtained when only 90% of the theoretical amount of potassium permanganate was used. Up to the present time no detailed study has been made of this reaction, it will however, be given further consideration later.

Discussion.

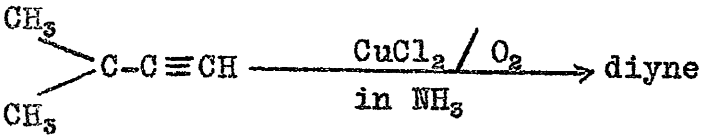
(i) Theoretical.

Despite the increased activity in the field of acetylenic oxidative coupling very little work has been done to determine the mechanism of the reaction. Those workers who have investigated this aspect have succeeded so far in postulating a possible mechanism but have failed to reach a definite conclusion from the limited experimental data available.

Among the earliest theories on the mechanism of the Glaser reaction was that of Salkind and his collaborators,[76] who postulated initial dissociation of the acetylene into radicals, which further combined to give the diyne. However, if one admits of radical dissociation, the role of the copper salts and oxygen in the process remains unexplained. A further point against this mechanism lies in the impossibility of effecting homolytic dissociation of the acetylene which requires 121 K cals/mole in an aqueous medium at room temperature.

Mkryan and Papazyan[77] and later Reppe,[37] proposed similar explanations of the oxidative coupling mechanism postulating a sequence of complexes.

Klebanski et al[78] examined the suggestion that the capacity of $RC{\equiv}CH$ to give diyne must be closely connected with structure, particularly the presence of easily polarised triple bond groups possessing a mobile hydrogen ($C{\equiv}C{-}H$). These workers found that the kinetics of the reaction were of the second order and



$$(CH_3)_2C{-}C{\equiv}CH \xrightarrow[\text{in } NH_3]{CuCl_2 / O_2} \text{diyne}$$

also that the reaction rate rapidly increased at pH 7-8, corresponding to the increase in the degree of ionisation of $RC{\equiv}CH$ and maximum degree of dissociation of the ammonia base at pH 8. A comparative study of the rates of oxidation of various acetylenes in aqueous pyridine using cuprous chloride and cupric chloride in ammonia solution in the presence of oxygen, indicated that the relative speeds were in the following order.

$$Ph{-} > PhCH(OH){-} > CH_3CH(OH){-} > Ph_2C(OH){-} > CH_3(CH_2)_3{-}$$

It was also noted that a straight line relationship exists between the degree of ionisation of the corresponding acids of $PhCOOH$, $CH_3(CH_2)_3COOH$ etc., and the capacity of the acetylenes to oxidise to the diyne i.e. the speed of formation of the diyne is directly proportional to the mobility of the hydrogen ion.

Klebanski and his co-workers have suggested that the mechanism of the Glaser coupling reaction can be expressed in the following oxidative scheme.

$$RC\equiv CH \longrightarrow RC\equiv C^- + H^+$$
$$RC\equiv C^- + Cu^{2+} \longrightarrow RC\equiv C\cdot + Cu^+$$
$$2RC\equiv C\cdot \longrightarrow [RC\equiv C]_2$$

Oxidation of the anion is regarded as the only reasonable explanation of the formation of radicals and this anion is obtained in the first (rate determining) step by an ionisation of the acetylene facilitated by the formation of a complex ion $(RC\equiv C\cdot CuCl\cdot NH_4Cl)_3^-$ as is evident from the drop in pH on admitting the ethynyl compound. Aerial oxidation of the cuprous ion in the cuprous chloride-ammonium chloride complex produces the cupric ion necessary for the second step and the resultant free radicals immediately combine to form the diyne.

$$2Cu^+ + \tfrac{1}{2}O_2 + H_2O \longrightarrow 2Cu^{2+} + 2OH^-$$
$$2Cu^{2+} + 2RC\equiv CH \longrightarrow 2Cu^+ + 2H^+ + (RC\equiv C)_2$$

It has been shown that reaction cannot take place with cuprous ion in the absence of oxygen but no base is necessary since OH^{-} is produced as a result of the $Cu^{+} \longrightarrow Cu^{2+}$ oxidation.

The same reaction sequence also holds for the oxidations involving cupric ion alone but in this case the addition of alkali is necessary to achieve reaction and ionisation is believed to proceed through the formation of unstable copper acetylides, since the 121 K cals/mole required for fission of the C-H bond is not favourable for the formation of simple ionic intermediates.

Recent work by Bohlmann,[52] on the variation of the rate of coupling with R of the reaction $2RC\equiv CH \longrightarrow (RC\equiv C)_2$ both in acid ($Cu^{+} + Cu^{2+}$) and base (Cu^{2+}) solution, has indicated that there may well be at least two pathways. As a result of his findings Bohlmann has recommended that compounds with the more acidic hydrogen e.g. $PhC\equiv CH$ are best coupled with the cupric ion/base reagent. The validity of this suggestion is borne out by the observed decrease in cyclisation rate of α,ω-diacetylenic hydrocarbons by means of cupric acetate and pyridine, with increase in chain length. There is, however, a further possible explanation of this phenomenon; the lack of reactivity may be due to an inherent lack in the catalyst i.e. the cupric ion in the Cu^{2+}/pyridine complex may be so strongly complexed as to require an activated ethynyl such as is present in aryl acetylenes or butynyl undecynoate to give satisfactory results. A more promising reagent in this respect has been described by Brackmann.[79] Whilst working with copper-amine alkoxide complexes, as catalysts for the oxidation of alcohols, he found that the most active complexes are derived from copper salts with non-complex forming ions (NO_3^-, ClO_4^-) and cyclic $2^{\underline{y}}$ amines (piperidine morpholine). The bulkiness of these amines prevents them from occupying more than two co-ordinate positions of Cu^{2+}. A study of the reaction mechanism has revealed a second effect contributing to the reactivity of complexes of the type Cu.(amine)$_2$.X.Y. The strong oxidising power of these complexes is attributed to a low free energy of activation of the rearrangement of the ligands accompanying the reaction provided the

$$\underset{\text{square planar}}{Cu^{2+}.(amine)_2.X.Y} \longrightarrow \underset{\text{linear}}{Cu^{+}.(amine)_2} + X + Y$$

ligands X and Y are weakly bonded to Cu^{2+}.

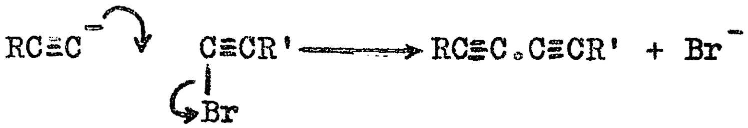
A preliminary experiment using cupric nitrate, morpholine and phenyl-acetylene has shown that this reagent is suitable for the coupling of acetylenes but until a detailed kinetic study has been made it is impossible to say whether or not the reagent will initiate a coupling reaction faster than the cupric ion/pyridine catalyst.

The above mechanistic considerations hold good for both the Glaser and Cupric Ion oxidative couplings but it is not yet clear whether or not they can be applied to the Chodkiewicz coupling reaction. It is not unlikely that anion formation occurs in reaction (1), via the formation of a complex similar to that already postulated for Cupric Ion coupling, the self coupling of this

$$RC\equiv CH + Cu^{+} \longrightarrow RC\equiv CCu + H^{+} \quad \ldots\ldots\ldots\ldots(1)$$

$$RC\equiv CCu + BrC\equiv CR' \longrightarrow RC\equiv C.C\equiv C.R' + CuBr \quad \ldots\ldots(2)$$

anion, through radical formation, being minimised by the low concentration of cuprous ion, thus reducing the possibility of the presence of cupric ion. The coupling reaction must therefore occur between this anion and the 1-bromoalkyne and although there is little doubt that complexes are involved it is feasible that the reaction could basically follow an S_N2 mechanism.



$$RC\equiv C^{-} \quad \underset{Br}{C}\equiv CR' \longrightarrow RC\equiv C.C\equiv CR' + Br^{-}$$

The fact that these halides, normally regarded as resonance stabilised, take part so readily in these reactions, whereas normal alkyl halides do

$$RC\equiv C \leftarrow Br \longleftrightarrow RC^{-}=C=Br^{+}$$

not, must be associated with the established power of the $-C\equiv C-$ linkage to complex metal ions $-\overset{M}{\overset{\uparrow}{C\equiv C}}$ e.g. where $M = Cu^{+}$, Ag^{+} Hg^{++}, such preliminary associations facilitating reaction (2).

The observed speed of coupling in the Chodkiewicz reaction with reference to a standard bromoalkyne was

$$\underline{p}\ NO_2-C_6H_5-C\equiv CH > PhC\equiv CH > Alk.C\equiv CH$$

and is evidently proportional to the acidity of the hydrogen ion.

Of all the metals capable of readily gaining or losing an electron only copper has so far been found suitable for the oxidative coupling of acetylenes.

Basically, the role of copper in these reactions appears to be that of an electron acceptor and it seemed likely that in such an electron transfer reaction ferric and cobaltic salts should be capable of acting in a similar capacity. A series of experiments was conducted with a wide variety of cupric salts and solvents[57,80] and with several ferric and cobaltic salts,[57] in order to determine the optimum conditions for the coupling reaction. Cupric salts were almost all successful in bringing about the coupling, except in cases where the cupric ion was too strongly complexed to allow of participation in the reaction e.g. cupric salicylate or the ethylene-diamine complex with cupric ion. Neither the ferric nor cobaltic salts were in any way successful. A further series of tests, involving ferrous chloride, ferrous sulphate and ferrous ammonium sulphate in water-methanol mixtures, did not give any precipitation on addition of phenylacetylene in methanol. A solution of ferrous chloride and phenylacetylene in pyridine was aereated with oxygen for two hours with complete recovery of starting material as the only result.

It has been pointed out by Chatt[81] that acceptor atoms may be divided into two classes; a class (a), which form the most stable complexes with the first ligand atom of each group viz with nitrogen, oxygen and fluorine and a class (b), which complex with the second or subsequent ligand atom. These class (b) acceptors are much less numerous than class (a) and are almost all derived from a number of neighbouring elements occupying an area of more or less triangular shape in the Periodic Table, the apex of this triangle being at copper; it is perhaps this unique position of copper which accounts for its significance in the oxidative coupling reaction. Chatt has further indicated that the most pronounced class (b) acceptors are Cu^+, Ag^+ and Hg^{2+}, all of which are known to form stable olefin complexes as well as acetylides. Evidently the co-ordination of carbon as a ligand atom occurs only to acceptors of a pronounced class (b) character, which in turn depends on the availability of electrons from the lower d-orbitals of the metal for dative π-bonding. The fact that the penultimate d-orbitals on a central carbon atom may form moderately strong σ bonds with free π orbitals on ligands[32] is a further indication that such bonds may be formed twix cuprous copper and the acetylenic carbon, whereas ferrous and ferric, cobaltous and cobaltic ions do not readily form such bonds. But this is unlikely to be the whole story and one must also consider the various redox potentials for these ions. It would be expected that in view of the above findings, the transformation $Cu^{+} \longrightarrow Cu^{+}$ would proceed more readily than the analogous transformation in the iron and cobalt series. This is borne out by the redox potentials for the following couples[33] - measured in aqueous media. However, these

Couple	$Cu^{+} = Cu^{2+} + e$;	$Fe^{2+} = Fe^{3+} + e$;	$Co^{2+} + Co^{3+} + e$
E°	-0.153	-0.771	-1.842

do not adequately describe the situation of the ions in the reaction medium, the copper normally being in the form of a complex. Data on the redox potentials of the three metals, when complexed with the same amine, is not available but the following potentials have been reported[33]

Complex	$Cu(A)_2^{+} \rightarrow Cu(A)_4^{2+}$;	$Co(A)_6^{2+} \longrightarrow Co(A)_6^{3+}$;	$Fe(B)_3 \rightarrow Fe(B)_3^{3+}$
E°	0.01	-0.1	1.06

(where A is ammonia and B the base orthophenanthroline) and these again illustrate that the oxidation $Cu^{+} \longrightarrow Cu^{2+}$ occurs readiest of all.

Although the mere collection of the above facts does not constitute proof, it does indicate that copper must indeed be unique in its ability to promote the oxidative coupling of acetylenes.

One form of oxidative coupling, which does not involve copper, is that discovered by Schlubach and Wolf[75] in 1950 and used by them to obtain diacetylene.

The reaction involves the oxidation of a sodium acetylide, in liquid ammonia, with potassium permanganate. As yet, no mechanism has been suggested for this coupling but the following postulate adequately describes the probable course of the reaction.

$$RC\equiv CNa \longrightarrow RC\equiv C^{-} + Na$$

$$RC\equiv C^{-} + MnO_4^{-} \longrightarrow RC\equiv C\cdot + MnO_4^{=}$$

$$2RC\equiv C\cdot \longrightarrow [RC\equiv C]_2$$

The ionisation of sodium acetylides is known to occur readily in liquid ammonia solution and the electron transfer $MnO_4^{-} + e \longrightarrow MnO_4$ is well authenticated.[84] A comparison of the above postulated mechanism with that for the copper catalysed couplings will serve to demonstrate the similarity between the two.

As can be seen from the above equations the reaction is likely to give very pure diyne, since the absence of $RC\equiv CH$ makes the formation of ene-yne impossible. The danger of oxidation of the product by the permanganate is avoided by using only 90% of the theoretical and working up the reaction mixture as soon as possible after addition of the ammonium chloride, normally added to destroy excess sodamide. Addition of the latter can result in the re-oxidation

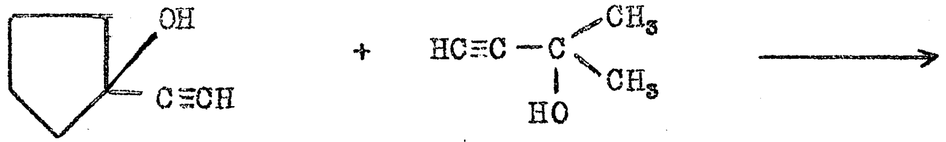
$$3MnO_4^{=} + 4H^{+} \longrightarrow 2MnO_4^{-} + MnO_2 + 2H_2O$$

of the manganous ion.[84]

The best results are obtained from compounds with the more acidic hydrogen i.e. the more highly ionised sodium salt.

Summary of Glaser Couplings.

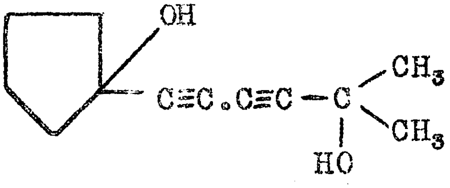
(i) Unsymmetrical.



Ethynylcyclopentanol

Dimethylethynyl carbinol

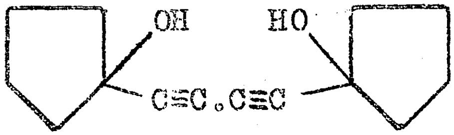
(i)



1-cyclopentanol-5-methyl hexa-1,3-diyn-5-ol

Nogaideli described this compound as the product from the above coupling but this results could not be confirmed.

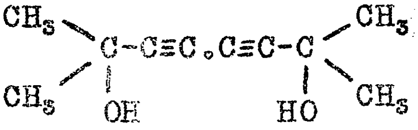
(ii)



Dicyclopentanoldiacetylene

The other possible products (i) and (ii) result from symmetrical couplings more likely under Glaser conditions.

(iii)



2,7-dimethyl-2,7-dihydroxy octa-3,5-diyne

(ii) Symmetrical

$MeO_2C(CH_2)_8C\equiv CH \longrightarrow [MeO_2C(CH_2)_8C\equiv C]_2$ 84%

Methyl undecynoate

Dimethyldocos-10,12-diyne dioate

Figure I.

(ii) Applications.

In the course of the present work the acetylenic compounds have been coupled largely by means of the Cupric Ion and Chodkiewicz coupling reactions. In one or two instances the Glaser coupling has been used and an investigation of the Permanganate Coupling was initiated.

1. Glaser Coupling.

One of the major drawbacks of the Glaser reaction is its unsuitability for the coupling of two unlike ethynyl compounds. Recently, however, Nogaideli[85] claimed to have achieved a high yield of the mixed product from a coupling of ethynylcyclopentanol and dimethylethynyl carbinol. On repeating this experiment, using the precise conditions specified by Nogaideli, the product proved to be a highly crystalline solid neither the analysis nor the melting point of which corresponded to any of the possible products (Figure 1). In view of the fact that the Glaser reaction has never been recommended for the coupling of unsymmetrical acetylenes it seems likely that the product obtained was a mixture, possibly even a eutectic mixture, the components of which were inseperable - alumina chromatography was tried with

Summary of Cupric Ion Coupling.

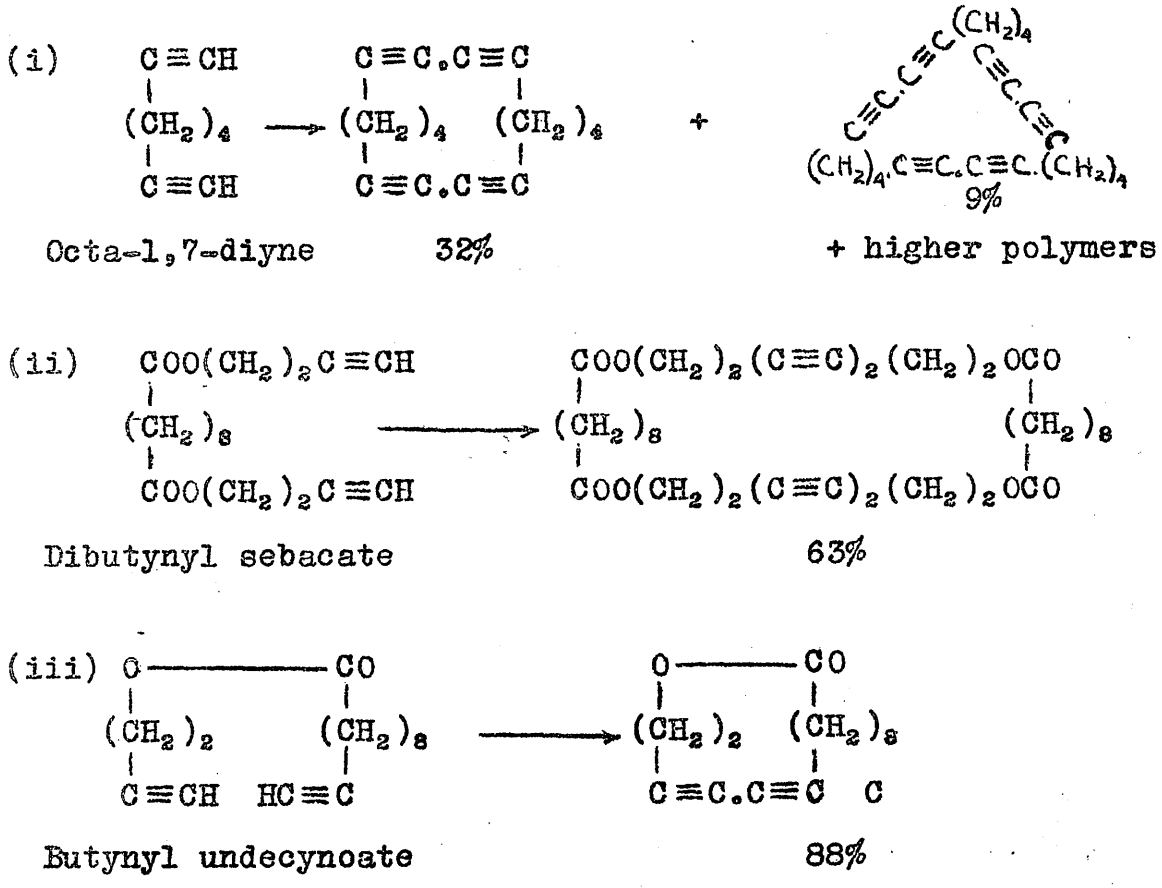


Figure 2.

no success. It is probable that Nogaideli also obtained a mixture, the component proportions of which were such as to give the melting point and analysis expected for the mixed product.

2. Cupric Ion Coupling.

An advantage of the Cupric Ion coupling reaction is its ready adaptability to high dilution conditions, thus making possible the intramolecular cyclisation of α,ω-diynes. The ester, di-butynyl sebacate, was successfully coupled to give a 63% yield of pure dimer, whilst octa-1,7-diyne, similarly cyclised, gave 32% dimer and 9% trimer (Figure 2), a considerable improvement on the yields previously obtained by Sondheimer[53] for the latter coupling.

With the successful cyclisation of the ester, dibutynyl sebacate, attention was turned to the possible synthesis of the cyclic lactone Pentadecanolide, commercially known as 'Exaltolide'. This compound is believed to occur naturally and is of commercial importance due to its musk like odour and fixative power for other scents.

The first practical synthesis of the lactone was

Synthesis of Exaltolide.

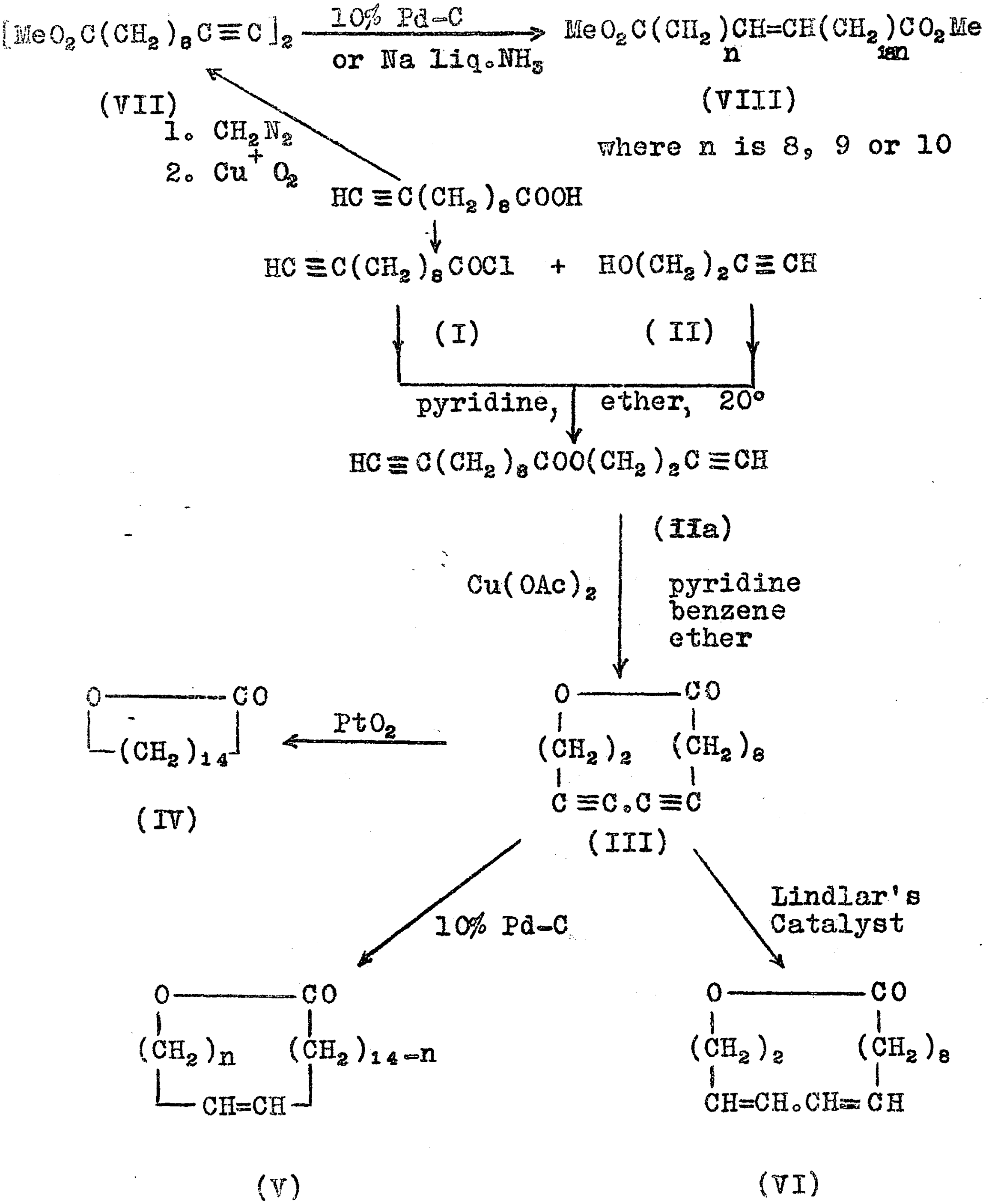


Figure 3.

achieved by Ruzicka and Stoll[86] by a Baeyer-Villiger oxidation of cyclopentadecanone. Thereafter, several successful syntheses of this and other lactones of the Exaltolide type were achieved,[87] especially by making use of the dilution principle developed by Ruggli and Ziegler.[88] The inherent disadvantages in the methods used were the long reaction times involved and the requirements of either 15-hydroxy or 15-bromopentadecanoic acid as starting material; these materials have been synthesised by various workers,[87,89] but the overall yields have generally been unsatisfactory.

The recent work on the formation of large rings by oxidative coupling of α,ω-diacetylenes indicated that the C_{15} lactone, (IV), (Figure 3) might be made by joining a C_{11} fragment, undeca-10-ynoic acid chloride, (I), and a C_4 fragment, but-1-yn-4-ol, (II), first by esterification, then by oxidative coupling to form the large diyne ring, (III), and subsequent reduction.

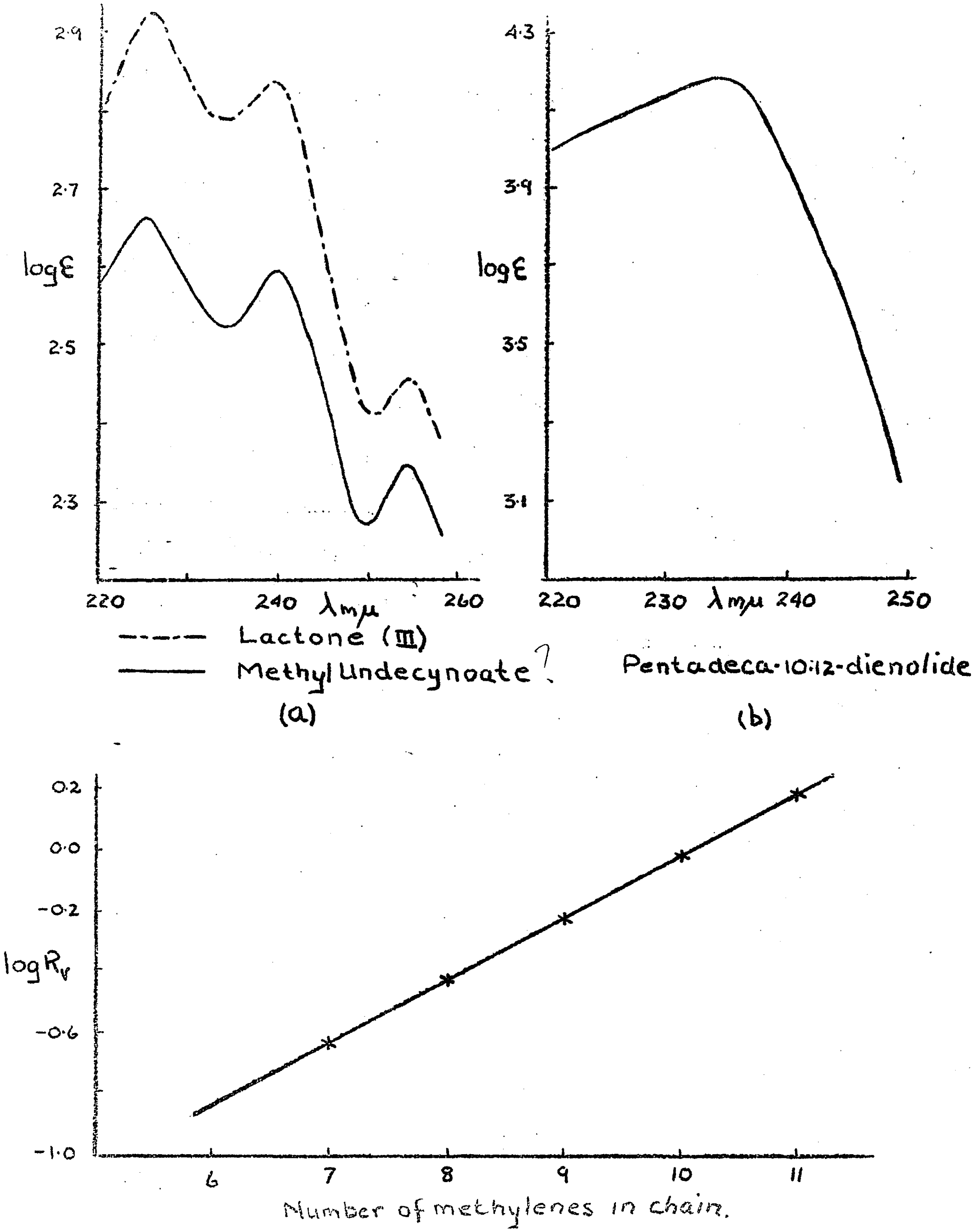
Since both the starting materials can readily be prepared, the synthetic scheme shown in Figure 3 was carried out.[90]

It was found that a 'Catalin' scale model of the lactone , (III), could be made in which the strain was no greater than that equivalent to one eclipsed H-H interaction, i.e. the conformation restricting diyne and lactone groups were sufficiently separated (by two methylene groups) to allow the ring to be formed.

The butynyl undecynoate was added over a period of 8 hours, under high dilution conditions,[91] to the refluxing solution of cupric acetate in pyridine to give a yield of 88% of the lactone, (III), This material had a very pleasant and particularly tenacious odour, especially in very low concentrations and showed an ultra violet spectrum typical of conjugated diynes (Figure 4a).

Complete hydrogenation of this lactone, (III), was achieved, with platinic oxide as catalyst, to give a pleasant smelling compound (IV), the physical properties of which were identical with those of an authentic sample of Exaltolide. The infra-red spectrum of the four major components in the synthesis (Figure 5) clearly illustrate the various stages.

One of the interesting features of the unsaturated lactone, (III), is the possibility of synthesising other perfumes by specific hydrogenations of the diyne system. For example, sodium in liquid ammonia should give a 1,4-reduction to give a centrally placed double bond, Lindlar reduction should give a conjugated diene whilst palladium on charcoal (Pd-C) might conceivably yield yet another olefinic compound.


2·9
2·7
logε
2·5
2·3
220
240
λmμ
260
Lactone (III)
Methyl Undecynoate ?
4·3
3·9
logε
3·5
3·1
220
230
λmμ
240
250
Pentadeca-10:12-dienolide
0·2
0·0
-0·2
log R_v
-0·6
-1·0
6
7
8
9
10
11
Number of methylenes in chain.

(a)

(b)

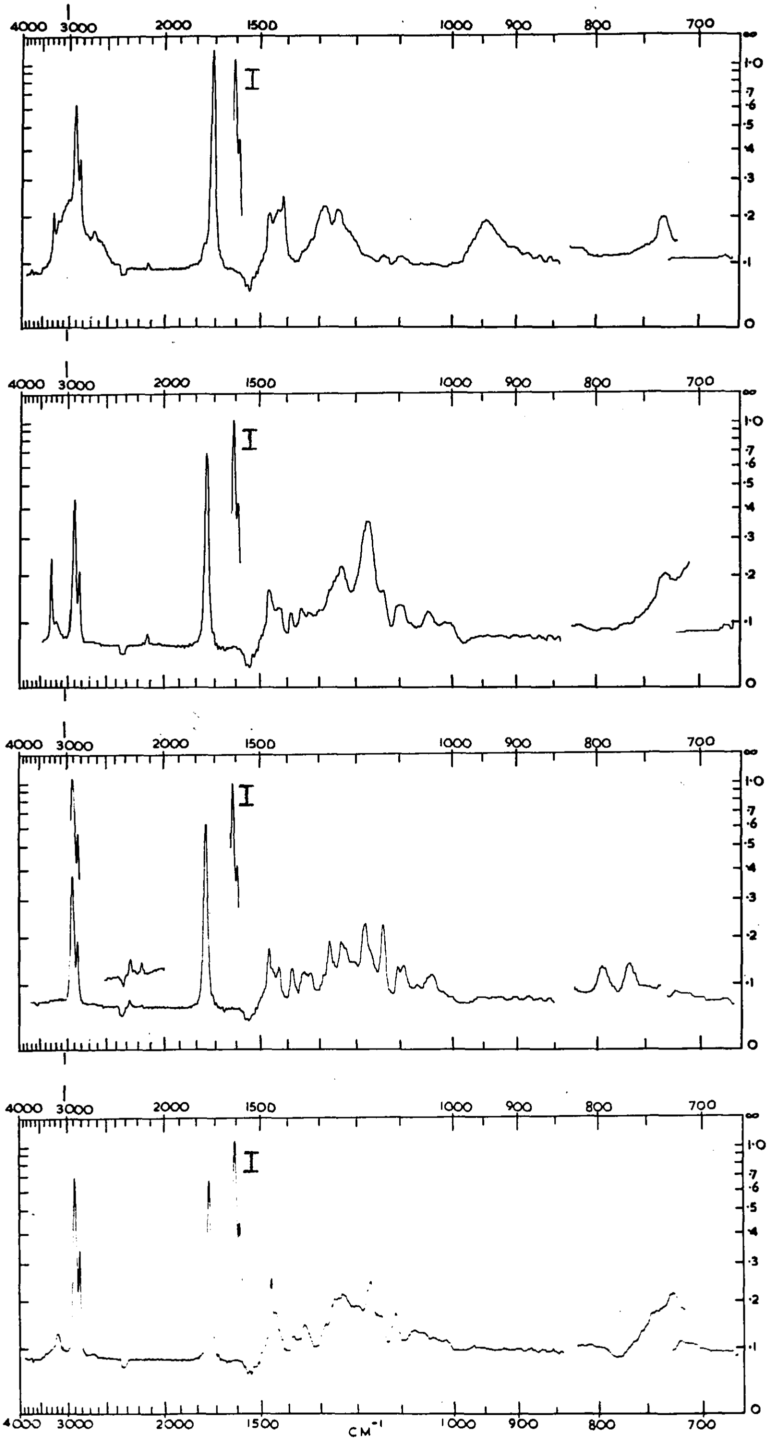
(c)

Figure 4.

The hydrogenation of a conjugated diyne system has already been investigated by Riley,[92] using Ra-Nickel at 100°C. Under these conditions Riley found that one or other of the triple bonds was first almost completely saturated before the remaining triple bond was attacked.

The compound used by Riley in his investigations was dimethyldocos-10,12-diyne dioate, (VII), and in order to obtain some idea of the products to be expected from a hydrogenation of the lactone, (III), with the various catalysts mentioned above, it was decided to initiate a parallel investigation using Riley's diyne-diester. Hydrogenation of dimethyldocos-10,12-diyne dioate, (VII), with 10% Pd-C gave a white crystalline solid (VIII), which showed the presence of trans as well as cis double bond in its infra-red spectrum. The procedure adopted to determine the position of the double bond involved its oxidative rupture to the carboxylic acids, followed by preparation of the methyl esters and examination of these by means of Gas-Liquid Chromatography, (G.L.C.). Obviously any oxidative procedure likely to cause further oxidations beyond that of the double bond would lead to erronious results; a method rigidly specific for the double bond was thus required. This requirement was met by the Rudloff oxidation technique,[93] (viz., material shaken over 10 hours

All spectra measured in carbon tetrachloride solution (25 mgs. c.c.; 0.1 m.m. cell). Region 840-700 cm.$^{-1}$ – Film.



Undecynoic acid.

Butynyl Undecynoate.

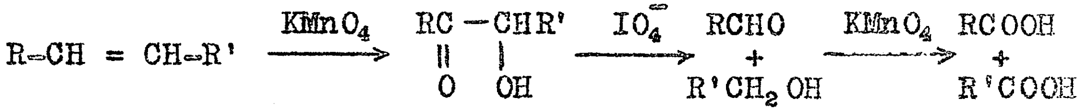
Lactone (III)

Exaltolide.

I – polystyrene reference peak.

Figure 5.

in aqueous <u>tert</u>-butanol with potassium permanganate - sodium metaperiodate solution at pH 7-8). The oxidation takes place in three stages. The first stage appears to be a complex sequence of reactions which involve permanganate ion in one electron exchanges leading, near neutrality, mainly to hydroxy ketones. The rapid periodate



$$R{-}CH = CH{-}R' \xrightarrow{KMnO_4} \underset{O}{\underset{\|}{RC}}-\underset{OH}{\underset{|}{CHR'}} \xrightarrow{IO_4^-} \begin{matrix} RCHO \\ + \\ R'CH_2OH \end{matrix} \xrightarrow{KMnO_4} \begin{matrix} RCOOH \\ + \\ R'COOH \end{matrix}$$

cleavage of the hydroxy ketone (and any diol which may have been formed) is the second stage whilst the last stage is the oxidation of the cleavage products by permanganate. The periodate serves also to regenerate the permanganate, which is present initially in catalytic quantity only.

The product obtained from the Rudloff oxidation of (VIII) was treated with excess ethereal diazomethane and the resultant esters examined by means of G.L.C. As a basis on which to interpret the results the G.L.C. curves of dimethyl suberate, azeleate and sebacate were also obtained. By calculation of the retention volumes, (R_V), of these last three standards and plotting log. R_V against the number of methylenes in the chain, a straight line graph was obtained. The results of all similar calculations for dimethyl dicarboxylic esters, with a higher or lower number of methylenes in the chain, should

Degradation of Dimethyldocos-10,12-diyne-dioate.

(i) $MeO_2C(CH_2)_8C\equiv C.C\equiv C(CH_2)_8CO_2Me$

$$\downarrow \text{10\% Pd-C}$$

$$\underbrace{MeO_2C(CH_2)_8CH{=}CH(CH_2)_{10}CO_2Me}_{70\%} + \underbrace{MeO_2C(CH_2)_9CH{=}CH(CH_2)_9CO_2Me}_{30\%}$$

$$\downarrow \begin{array}{l}\text{1. Rudloff Oxidation}\\ \text{2. } CH_2N_2/\text{ether}\end{array}$$

$$\begin{array}{ll} MeO_2C(CH_2)_8CO_2Me & 33\% \\ MeO_2C(CH_2)_{10}CO_2Me & 33\% \end{array} + MeO_2C(CH_2)_9CO_2Me \quad 33\%$$

(ii) $MeO_2C(CH_2)_8C\equiv C.C\equiv C.(CH_2)_8CO_2Me$

$$\downarrow \text{Na} \quad \text{liq.}NH_3$$

$$\underbrace{MeO_2C(CH_2)_8CH{=}CH(CH_2)_{10}CO_2Me}_{50\%} + \underbrace{MeO_2C(CH_2)_9CH{=}CH(CH_2)_9CO_2Me}_{50\%}$$

$$\downarrow \begin{array}{l}\text{1. Rudloff Oxidation}\\ \text{2. } CH_2N_2/\text{ether}\end{array}$$

$$\begin{array}{ll} MeO_2C(CH_2)_8CO_2Me & 25\% \\ MeO_2C(CH_2)_{10}CO_2Me & 25\% \end{array} + MeO_2C(CH_2)_9CO_2Me \quad 50\%$$

In each case the proportions of the dicarboxylic esters were obtained from the G.L.C. measurements and the percentages of the double bond isomers estimated from these.

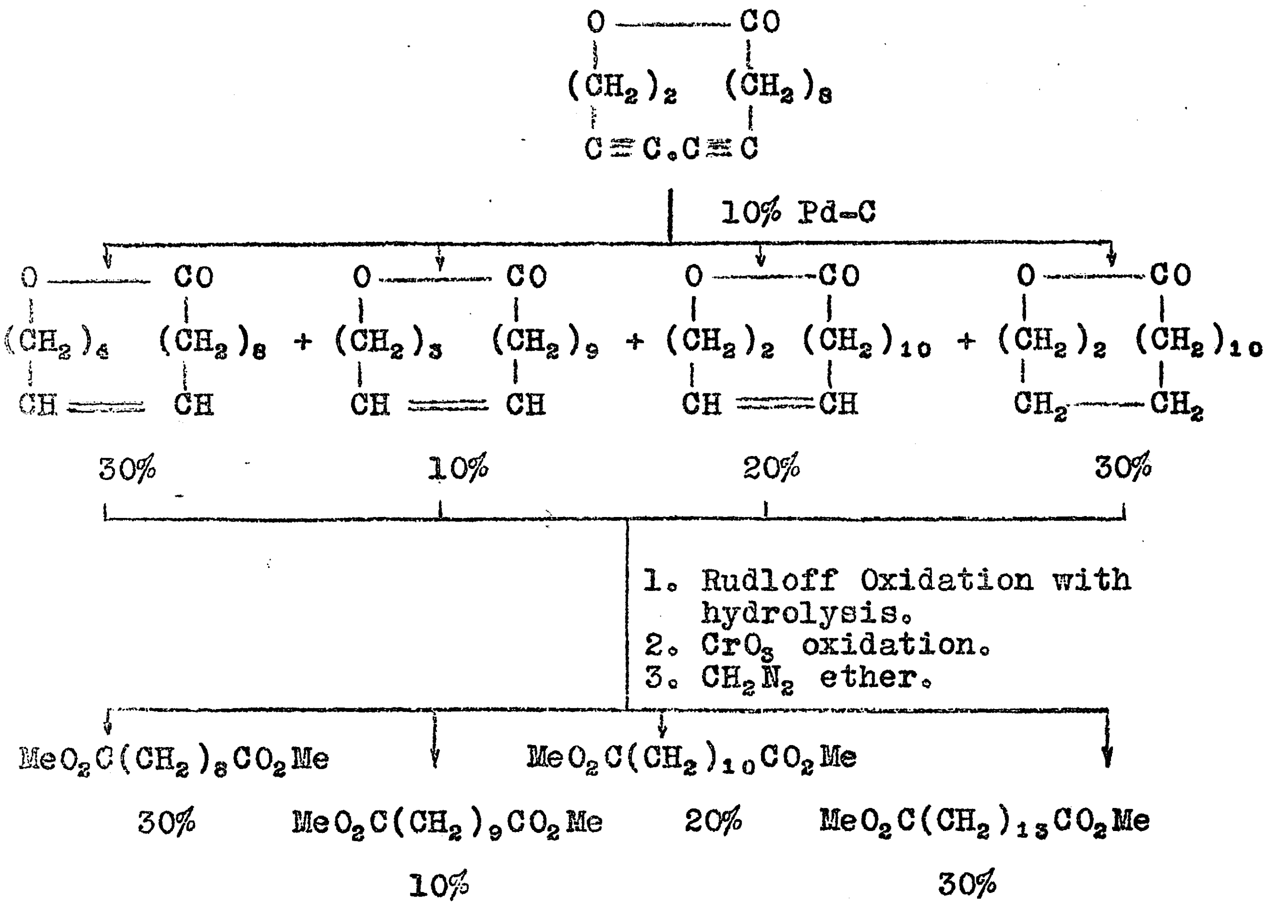
Figure 6.

all lie on the same straight line (Figure 4c). By this means it has been conclusively shown that 10% Pd-C is not a specific catalyst for hydrogenation of a symmetrical conjugated diyne. The response of the G.L.C. unit used in the measurements is said, by the makers, to be proportional to the quantity of material entering the detection chamber for compounds with a molecular weight greater than one hundred. It has thus been possible to extrapolate from the results the approximate proportions of double bond isomers initially present. The accuracy of the G.L.C. unit does not warrant precise figures hence those obtained have been largely rounded off (Figure 6).

By an exactly similar technique it was shown that the chemical reduction of the diyne, (VII), with sodium in liquid ammonia was also non-specific, the approximated amounts of the double bond isomers being the statistically expected proportions for a 50:50 1,4- and 1,2-reduction (Figure 6).

Hydrogenation of the lactone, (III), was not expected to give results identical with those obtained above since its unsymmetrical nature may well have some effect. Using a 10% Pd-C catalyst hydrogenation of the lactone, (III), was stopped when the theoretical amount of hydrogen had been absorbed. However, some inaccurate measurement must have been made since a microhydrogenation of the resultant oil showed that only 70% double bond material was present, the residue presumably being the saturated compound since a G.L.C. indicated that it contained no starting material. During the course of the Rudloff oxidation a hydrolysis stage opens the lactone ring to give a mixture of dicarboxylic and hydroxy acids, the latter being further oxidised by chromic acid oxidation in acetone solution.[103] The resultant mixed acids were methylated, using diazomethane and the esters examined by G.L.C. A sample of Exaltolide was also hydrolysed, oxidised by chromic acid, methylated and examined in the same manner to determine the retention time of the dimethyl-tridecamethylene dicarboxylate. The G.L.C. examination of the mixed esters gave a major peak at a position corresponding to the dimethyl ester of undecamethylene dicarboxylic acid, thus indicating an apparent large scale migration of the double bond. However, it soon became apparent that this unlikely result could have been due to a hydroxy acid having the same retention time as the above undecamethylene compound, since an infra-red spectrum of the mixture still showed the presence of hydroxyl material. The mixture

Degradation of Pentadeca-10,12-diynolide.



The 10% discrepancy is due to products formed by double bond migration not considered above.

Figure 7.

was consequently retreated with chromic acid, followed by methylation and this time the G.L.C. showed a vastly reduced $-(CH_2)_{11}-$ peak and a proportionately increased $-(CH_2)_{13}-$ peak. Hence, it would, indeed, appear that the hydroxy ester obtained by hydrolysis of the saturated lactone, (IV), has a retention time equal to that of the $-(CH_2)_{11}-$dicarboxylate. Although another infra-red spectrum still indicated a trace of hydroxyl material, sufficient data was available to extrapolate the probable final proportions of $-(CH_2)_{11}-$ and $-(CH_2)_{13}-$ dimethyl dicarboxylates and thus the percentages of the various double bond isomers in the original mixture (Figure 7).

All attempts to reduce the lactone, (III), with sodium in liquid ammonia met with failure, due to the opening of the lactone ring. Reduction of the lactone, (III), with Lindlar's catalyst gave an oil, a sample of which was microhydrogenated and shown to contain 1.9 double bond equivalents. The infra-red spectrum showed a cis double bond peak whilst the ultra-violet showed a main peak at 234 mμ. with ϵ 13,600 (Figure 4b). The absorption maxima for monocyclic dienes has been shown to increase in ring size beyond C_{10}[94] e.g. a C_{13} ring gives λ max. 232 mμ. It is also likely that as ring size increases the intensity values will approach those of the straight chain compounds, (ε 15,000+).

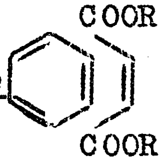
Several attempts were made to hydrate the conjugated diyne systems of both dimethyldocos-10,12-diyne dioate, (VII), and the lactone, (III); in both cases, however, inseperable mixtures were obtained, the infra-red spectrums of which showed acid (1700 $cm.^{-1}$) and ester (1740 $cm.^{-1}$) peaks but little indication of the expected products.

Up to the present time no attempt had been made to establish conclusively whether or not Exaltolide exists in the lactone form in nature. If it did exist as such its isolation by normal means would be difficult and extremely laborious. However, a far more elegant procedure presents itself in the form of G.L.C. Under carefully controlled conditions a sample of synthetic Exaltolide was chromatographed and its retention time measured. The roots of *Angelica archangelica officinalis* were crushed to a fine powder, extracted with light petroleum and the resultant gum fractionated by alumina chromatography followed by distillation. Each of the final fractions was examined by infra-red and G.L.C. under exactly the same conditions as those used for synthetic Exaltolide. One of the fractions (b.p. 100°/0.01 m.m.) showed a lactone peak in the infra-red and a large peak in the G.L.C. which exactly corresponded to that obtained with the synthetic Exaltolide. A commercial sample of

Table 1.

All spectra were recorded linearly in cm.$^{-1}$ as percentage transmission with a Unicam S.P. 100 double beam infra-red spectrometer equipped with an S.P. 130 sodium chloride prism, - 1500 lines per inch grating, double monochromator (vacuum).

A. Carbonyl absorption frequencies for esters of type



R.	ν	$\Delta\nu_{\frac{1}{2}}$	ε per C=O
1. $-CH_3$	1731	14	665
2. $-CH_2CH_3$	1725	15.5	634
3. $-CH_2C\equiv CH$	1735	15	640
4. $-(CH_2)_2C\equiv CH$	1730	14.5	735
5. $-(CH_2)_3C\equiv CH$	1727.5	14.5	656
6. $-(CH_2)_4C\equiv CH$	1726	14.5	632
7. Cyclic dimer of compound 6.	1726	16	Saturated solution

Angelica Oil, obtained by steam distillation of the roots, was also examined in this way and gave a peak in the G.L.C. coincident with that obtained for the synthetic lactone.

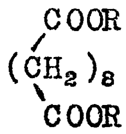
There seems, therefore, little doubt that the lactone does exist as such in nature.

One of the most interesting aspects of the class of compounds exemplified by lactone, (III), is the stereochemistry and effect of ring strain on absorption maxima. The carbonyl stretching frequency in small ring lactones is raised by ring strain but the reverse effect may hold in larger rings, due to conformational effects and steric interaction.

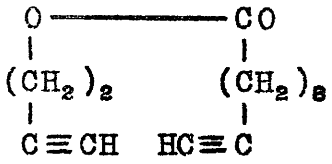
To determine such effects, if any, a study was made of the carbonyl absorption frequencies in the infra-red of available esters and lactones, the results of which are summarised in tables 1 and 2.

In all the series of esters 1-2, 3-6, 8-10 and 11-12, small but fairly uniform shifts occur, presumably due to the changing inductive effect of the alkyl groups.
In the series 3-6, the effect of the ethynyl group on the

Table 2.

B. Carbonyl absorption frequencies for esters of type 

$(CH_2)_8(COOR)_2$

	R	ν	$\Delta\nu_{\frac{1}{2}}$	ε per C=O
8.	$-CH_3$	1743	16	480
9.	$-CH_2CH_3$	1738	15.5	550
10.	$-(CH_2)_3CH_3$	1736	16.5	479
11.	$-CH_2C\equiv CH$	1749.5	20	504
12.	$-(CH_2)_2C\equiv CH$	1744	17	481
13.	Cyclic dimer of compound 12.	1741	16	659
14.	$(CH_2)_8$ (cyclic)	1737	15	530
C.	Miscellaneous Esters.			
15.	$[MeO_2C(CH_2)_8C\equiv C]_2$	1743	16	541
16.		1744	17	480
17.	Lactone (III)	1742	17.5	685
18.	Exaltolide	1736	15.5	609

carbonyl frequency is zero when the two groups are separated by four methylenes but an increase in frequency occurs as the two groups are brought closer together. This follows the well known pattern of the inductive effect as evaluated by acidity changes in substituted acids etc. The carbonyl stretching frequency of the saturated cyclic esters, 14 and 18 and the acyclic ester, 10, are almost identical and it would seem therefore that ring formation has no effect when the ring size is of this order. Whilst dimerisation of 6 to 7 gave no shift in the frequency, the cyclisation of the terminal diynes, 12 and 16, caused a slight decrease, probably due to the increased inductive effect of the conjugated diyne group through the two methylenes. The change in frequency on cyclisation of diyne 16 was not as great as that reported by Bergelson and his co-workers[96] and lends little support to his theory of transannular interaction between the carbonyl group and the diyne system.

3. Chodkiewicz Coupling.

This reaction, first described by Cadiot and Chodkiewicz,[35] provides an excellent route to the unsymmetrical diynes. The reaction conditions described by these workers, however, were invariably heterogeneous and since it was hoped to apply this procedure to the

Summary of Chodkiewicz Coupling.

1. Unsymmetrical

(a) $(CH_3)_2C(OH)C\equiv CH$ + $BrC\equiv CPh \rightarrow (CH_3)_2C(OH)(C\equiv C)_2Ph$

Dimethylethynyl carbinol — 1-Bromophenylacetylene — 1-Phenyl-5-methyl hexa-1,3-diyn-5-ol. 78%

(b) $(CH_3)_2C(OH)C\equiv CH$ + $IC\equiv CPh \longrightarrow (CH_3)_2C(OH)(C\equiv C)_2Ph$ 6%

1-Iodophenylacetylene

(c) $PhC\equiv CH$ + $IC\equiv CI \longrightarrow$ Inseparable mixture showing no evidence of expected product viz., diphenyltriacetylene.

Phenylacetylene — Di-iodoacetylene

2. Symmetrical

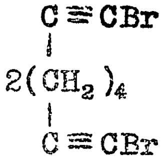
(a) $2PhC\equiv CBr \longrightarrow Ph(C\equiv C)_2Ph$ 94%

Diphenyldiacetylene

(b) $2CH_3(CH_2)_5C\equiv CBr \longrightarrow [CH_3(CH_2)_5C\equiv C]_2$ 58%

1-Bromo-oct-1-yne — Hexadeca-7,9-diyne

(c)



$$2\,(CH_2)_4\begin{cases}C\equiv CBr\\ C\equiv CBr\end{cases} \longrightarrow$$

Inseparable mixture showing no evidence of expected product viz., cyclohexadeca-1,3,9,11-tetrayne.

Figure 8.

synthesis of cyclic compounds an investigation was initiated to obtain the necessary homogeneous conditions. The reactions discussed below are summarised in Figure 8.

(i) Unsymmetrical.

It was with the above object in mind that attempts were made to couple 1-bromophenylacetylene and dimethyl-ethynyl carbinol, homogeneous conditions being obtained by use of n-butylamine as base and alcohol as solvent. Despite this, however, the maximum yield of mixed product was 78%, somewhat lower than that claimed by Chodkiewicz, (92%) but in the light of later results, further considered below, it seems likely that this may have been due to the use of excess base. However, at that time it was decided to try varying the solvent medium and it was found that although the yields were not greatly improved, alcohol benzene chloroform and tetrahydrofuran were equally satisfactory whilst acetonitrile, petrol and dioxan gave lower yields.

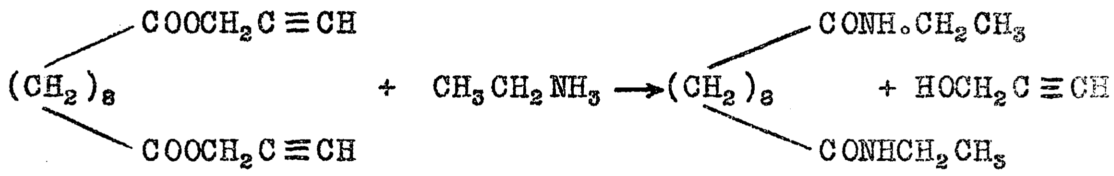
The 1-bromoalkynes required in the Chodkiewicz coupling can only be prepared pure with considerable difficulty and consequently the ease and speed with which 1-iodoalkynes can be prepared makes them an attractive alternative. Chodkiewicz, however, claimed these compounds were unsatisfactory, leading to extensive

side reactions and this claim was further substantiated during the course of the present work. 1-Iodophenylacetylene was prepared by the action of iodine on the sodium salt in liquid ammonia, the product being obtained in a pure form by low temperature crystallisation. Attempts to couple this compound with dimethylethynyl carbinol resulted in the recovery of starting material plus a trace of the mixed product, (Figure 8).
The attempted synthesis of diphenyltriacetylene by coupling phenylacetylene with di-iodoacetylene also failed, an ultra-violet spectrum of the product indicating no trace of the expected triyne system.

(ii) Symmetrical.

The self-coupling of 1-bromophenylacetylene was found to give a 94% of diphenyldiacetylene and an 84% yield of the diyne in a test run under high dilution conditions. These symmetrical couplings took place in the presence of a stoichiometric amount of cuprous chloride in an atmosphere of nitrogen. The addition of hydroxylamine hydrochloride and the use of only trace amounts of cuprous chloride, under the latter conditions of high dilution, resulted in a reduction of the 1-bromophenylacetylene to phenylacetylene. This reaction was probably brought about by the hydroxylamine but on replacing this with hydroquinone no coupling whatsoever was observed.

Attempts to cyclise α,ω-dibromodipropargyl sebacate under high dilution conditions, using n-butylamine as base, apparently resulted in aminolysis with no formation of cyclic material. The action of base on this ester was examined by allowing it to stand, separately, in triethylamine and ethylamine at room temperature for 12 hours. Examination of the material recovered from both of these solutions by infra-red indicated that whilst triethylamine had had no effect, whatsoever, the primary amine had clearly caused amide formation. The infra-red spectrum

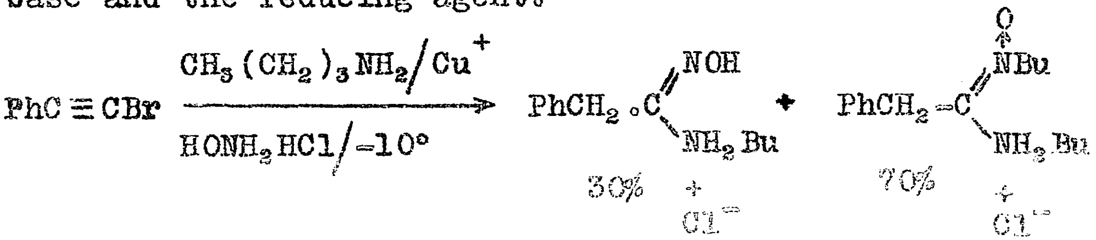


$$(CH_2)_8\begin{matrix} COOCH_2C\equiv CH \\ COOCH_2C\equiv CH \end{matrix} + CH_3CH_2NH_3 \longrightarrow (CH_2)_8\begin{matrix} CONH.CH_2CH_3 \\ CONHCH_2CH_3 \end{matrix} + HOCH_2C\equiv CH$$

showed peaks at 1640 and 1540 $cm.^{-1}$ as well as 3300 $cm.^{-1}$ ($-C\equiv CH$) but no evidence of an ester peak. It would appear that where such esters have only one methylene group between the triple bond and the ester group their stability to $1^{\underline{y}}$ and $2^{\underline{y}}$ amines is very much less than that of similar 'higher' esters.

The cyclisation of α,ω-diyne hydrocarbons by means of the Cupric Ion coupling reaction was known to be unsatisfactory; the very fast condensation of 1-bromoalkynes was expected to resolve this problem and hence the cyclisation of 1,8-dibromo-octa-1,7-diyne was attempted. The cyclic products expected from this reaction ha already been obtained by cyclisation of octa-1,7-diyne and the retention times on a G.L.C. column of the corresponding cyclic saturated hydrocarbons had been found. It was proposed, therefore, to hydrogenate a sample of the crude product obtained from the cyclisation of 1,8-dibromo-octa-1,7-diyne and examine this material by G.L.C., under exactly the same conditions as previously. The results showed no evidence of any of the expected cyclic products and it is unlikely that this method will be suitable for cyclisation reactions, a fact also discovered by Chodkiewicz.[95]

The reasons for the low yields of mixed product in the preliminary investigations were re-examined when an anomalous reaction was observed[96] in the self condensation of 1-bromophenylacetylene using n-butylamine as both base and solvent. In a few cases, under the normal Chodkiewicz conditions, the products obtained apparently resulted from a condensation involving the 1-bromophenylacetylene, the base and the reducing agent.



$$PhC\equiv CBr \xrightarrow[HONH_2HCl/-10^{\circ}]{CH_3(CH_2)_3NH_2/Cu^{+}} PhCH_2C(=NOH)\overset{+}{N}H_2Bu\ Cl^{-} + PhCH_2C(=\overset{O\uparrow}{N}Bu)\overset{+}{N}H_2Bu\ Cl^{-}$$

30% (a) 70% (b)

Summary of Permanganate Couplings.

	Compound	Solvent	Yield %	Remarks
(i)	$PhC\equiv CNa$	Liquid ammonia	67	Finely powdered potassium permanganate added in solid state to the sodium salt.
(ii)	$PhC\equiv CLi$	Liquid ammonia	20	- As above -
iii)	$CH_3(CH_2)_5C\equiv CNa$	Liquid ammonia	15	Solution of the permanganate in liquid ammonia slowly added to the sodium salt.
(iv)		Liquid ammonia	nil	- As above - Starting material largely recovered
(v)	$PhC\equiv CNa$	Diglyme	nil	Salt prepared by refluxing the acetylene in ether over sodium.[104] Ether removed and replaced by diglyme. Solution of permanganate in dimethylformamide then added dropwise at room temperature. Starting material recovered.
(vi)	$PhC\equiv CNa$	Ether	nil	Solid permanganate added to ether solution at room temperature.
vii)	$PhC\equiv CNa$	Dimethylformamide	10	As above for (v)

Figure 9.

The structure of (a) has been proved by synthesis but, as yet, that of (b) has only been partially verified. When the hydroxylamine hydrochloride was replaced by hydrazine hydrate only compound (b) was obtained. This may prove to be a competitive reaction in the Chodkiewicz coupling where excess base is used.

4. Permanganate Coupling.

The oxidation of sodium acetylide to diacetylene by means of potassium permanganate is the only successful instance of this form of coupling so far recorded.[75] However, we have found that a 67% yield of diphenyldiacetylene can be obtained by this procedure, using the sodium salt; the corresponding lithium salt gives a lower yield (20%) due, probably, to the higher degree of covalency in the lithium acetylides. Treatment of sodium phenylacetylene, in diglyme or dimethyl formamide, at room temperature, with a solution of potassium permanganate, in the same solvent, was not a success (Figure 9).

A similar lack of success was obtained in all attempts to self couple the sodium salt of 1-octyne or the sodium salt of propargyl alcohol, as its tetrahydropyranyl ether, in liquid ammonia, by means of permanganate, although a spectroscopic examination of the product obtained from 1-octyne indicated that some coupling had taken place.

A further attempt with the latter compound resulted in the isolation of a small yield of product. Several attempts to couple o-diethynyl benzene by this procedure also met with failure. This result, somewhat surprising in view of the comparative ease with which phenylacetylene couples, could have been due to the presence of excess sodamide to which the product may well be sensitive,

PART 1.

EXPERIMENTAL

General.

Unless otherwise stated, the following conditions apply to all physico-chemical measurements and procedures.

Melting points were measured on a Kofler hot stage and are corrected. Ultra-violet spectra were performed on solutions of spectroscopic alcohol, using a Unicam SP 500 spectrophotometer and an SP 100 spectrophotometer for more accurate work; infra-red measurements were recorded on a Perkin-Elmer Model 13 or 117.

Gas-liquid chromatographs (G.L.C.) were run on a Pye "Argon" chromatograph with a 4' column of 100-200 mesh Celite, using 5% Apiezon L as the stationary phase. The relative amounts of eluates were based on the measurement of peak areas by means of a planimeter, the mean of six determinations being taken; the quantitative results are therefore dependent on uniform detector response.

The alumina for chromatography was acid washed, neutralised and standardised according to Brockmann's method, Grade I was used. The light petroleum used had b.p. 60-80°.

The phrase 'the ether extract was worked up in the usual manner' implies that the extract was washed with dilute sulphuric acid, sodium bicarbonate, water, dried over magnesium sulphate, filtered and evaporated.

Attempted Glaser Coupling of Ethynylcyclopentanol and Dimethylethynyl Carbinol.

A mixture of ammonium chloride (59.8 g.), and cuprous bromide (29.8 g.) in 240 c.c. of water containing 2-3 drops of concentrated hydrochloric acid, was vigorously stirred till it became homogeneous. A stream of air was bubbled through this solution.

Dimethylethynyl carbinol (4.0 g.) and ethynylcyclopentanol (5.2 g.) were mixed and slowly added over a period of 30 minutes, to the above oxygenated solution. When the addition was complete, the mixture was heated to 50° for 45 minutes, then allowed to cool to room temperature; stirring was continued for a further five hours. The final reaction mixture was filtered free of suspended solid and the filtrate ether extracted. On working up the extract in the normal manner a white crystalline solid was obtained which recrystallised from ether-petrol mixtures as small needle crystals m.p. 94-97°, weight 7.2 g. Alumina chromatography afforded no further purification (Found: C, 76.1; H, 8.7% $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%.)

Since neither the melting point nor analysis of this solid corresponded to that of the expected product it must be assumed to be an inseperable eutectic mixture.

Dibut-3-yn-1-yl Sebacate.

Pyridine (10.5 g.) was added dropwise to a stirred solution of sebacoyl chloride (13.3 g. freshly prepared; b.p. 128-134°/ 0.3 m.m.) in dry ether (150 c.c.) containing but-3-yn-1-ol (8.0 g.). After removal of the precipitated pyridine hydrochloride, the neutral fraction was isolated as an ethereal solution and passed down a column of alumina (100 g.). The ester (11.0 g., 61%) crystallised from ether in plates, m.p. 65-65.5(.

(Found: C, 70.5; H, 8.4% $C_{18}H_{26}O_4$ requires C, 70.6; H, 8.5%) $\nu_{max.}$ (in Nujol) 3260 (≡CH), 2100 (-C≡C-) and 1740 cm.$^{-1}$ (ester).

Octa-3,5-diynylene sebacate.

A solution of dibut-3-yn-1-yl sebacate (1.0 g.) in ether-pyridine (1:6; 140 c.c.), was added during 2.5 hours to a refluxing solution of anhydrous cupric acetate (3.4 g.) in ether-pyridine (1:6; 700 c.c.), the drops of ester solution being continuously entrained by the refluxing solvent in a modified continuous extraction apparatus. After a further hour the resulting green solution was cooled and slowly added, with stirring, to 0.05$\overline{N}$-hydrochloric acid (5 l.) at 0° and the neutral fraction isolated with ether and its solution in benzene passed through alumina (Grade 3; 50 g.) the final elution being with ether-benzene. The solvent was removed and the residual solid recrystallised from light petroleum, giving <u>octa</u>-3,5-<u>diynylene</u> <u>sebacate</u> (630 mg., 63%) as tablets, m.p. 55-56°.

(Found: C, 71.2; H, 7.9% M, 334. $C_{18}H_{24}O_4$ requires
C, 71.1; H, 7.9% M, 304.)

$\nu_{max.}$ 2120 ($C\equiv C$) and 1720 cm.$^{-1}$ (ester)

$\lambda_{max.}$ 226, 238 and 254 mμ. (ε 686, 551 and 225 respectively).

<u>Cyclisation of Octa</u>-1,7-<u>diyne.</u>

A solution of octa-1,7-diyne (1.0 g.) in methanol (80 c.c.) was added during 4 hours to a refluxing solution of anhydrous cupric acetate (12.0 g.) in ether-methanol-pyridine (1:1:6; 800 c.c.), in a high dilution apparatus. A small sample of the reaction mixture showed no absorption at 3300 cm.$^{-1}$ ($\equiv$CH) after 1.5 hours but when addition was complete it was evident that some free ethynyl material was still present; this was removed by a further 4 hours reflux. The reaction mixture was reduced in bulk by distillation under reduced pressure and worked up in the usual manner to give a brown semi-crystalline mass (0.87 g.), which was chromatographed on alumina (Grade 5, 200 g.). The volume of each eluate was 30 c.c.

Fractions 1-10 were eluted with light petroleum (b.p. 40-60°) to give a white crystalline solid (0.28 g.) m.p. 161-162°, yield 32%.

(Found: C, 92.1; H, 7.9% $C_{16}H_{16}$ requires C, 92.4; H, 7.6%)

$\nu_{max.}$ 2210 cm.$^{-1}$ (C≡C).

$\lambda_{max.}$ 226, 240 and 254 mμ. (ε 580, 600 and 340 respectively).

A sample of this material was fully hydrogenated in ethyl acetate solution over Adams catalyst to give cyclohexadecane, m.p. 60-61°.

Fractions 11-17 were eluted with 60-80° petrol, giving white crystalline material, m.p. 170-172°, (0.08 g.), yield, 9.2%.

A sample of this material on hydrogenation as above, gave cyclotetracosane, m.p. 43-45°.

Residual fractions were not examined.

A gas-liquid chromatogram was run on the two fully saturated cyclic hydrocarbons obtained above using two available known cyclic hydrocarbons, cyclododecane and cyclotetradecane as standards. The column temperature was 204° and Argon flow rate 35 c.c./man.

	C_{12}	C_{14}	C_{16}	C_{14}
Retention Time (mins.)	1.35	2.7	5.55	88.5

The results showed that the two hydrocarbons obtained from the reaction were pure and contained the expected number of carbons, a straight line being obtained on drawing a graph of log R_V against the number of carbons in the ring.

Synthesis and Degradation of Dimethyldocos-10,12-diyne dioate (VIII).

1. Synthesis.

(i) 10,11-Dibromoundecanoic Acid.

10,11-Dibromoundecanoic acid waspprepared in 88% yield by the method of Black and Weedon.[17]

(ii) Undeca-10-ynoic Acid.[17]

Reaction between 10,11-dibromoundecanoic acid (146 g.) and a concentrated aqueous solution of potassium hydroxide (62%) yielded a dark viscous oil which was vacuum distilled to give undecynoic acid (49.3 g.) b.p. 138-140° 15 m.m. which crystallised from light petroleum (b.p. 40-60°) as white waxy flakes, m.p. 42°. The overall yield from undecylenic acid was 51% of the theoretical.

(iii) Methyl Undec-10-ynoate.[92]

Undecynoic acid (10.0 g.), in ether solution, was treated with an ethereal solution of diazomethane until a yellow colour persisted. The ester was obtained in 98%

yield $\nu_{\text{max.}}^{\text{liq.}}$ 3290 ($\equiv$CH) 2110 (C$\equiv$C) and 1735 cm.$^{-1}$ (ester).

(iv) The Oxidative Coupling of Methyl Undec-10-ynoate.[12]

The ester (9.6 g.) in ethanol (70 c.c.) was added dropwise with constant stirring to a solution of cuprous chloride (12.8 g.), ammonium chloride (22.4 g.) and concentrated hydrochloric acid (2 drops) in water (120 c.c.). The mixture was heated to 55-60° and air bubbled through for five hours. The cold mixture was then poured into water and ether extracted. The ether layer was filtered to remove copper salts, washedsseveral times with water, and dried and evaporated. The resultant solid was crystallised from ether at -50° to give pure dimethyl docos-10,12-diynoate, m.p. 41-42°, (8.0 g., 84%). (Found: C, 73.8; H, 9.8% $C_{24}H_{38}O_4$ requires C, 74.0; H, 9.8%) $\nu_{\text{max.}}^{\text{film}}$ 1735 cm.$^{-1}$ (ester).

$\lambda_{\text{max.}}$ 226, 239 and 254 mμ. (ε 464, 391 and 229 respectively).

2. Degradation.

(a) Hydrogenation of the Product using Palladium on Charcoal Catalyst.

The above diyne-diester (780 mg.) was hydrogenated, in ethyl acetate solution (30 c.c.), with 10% palladium on charcoal (100 mg.) at room temperature and pressure. The hydrogenation was stopped when three molar equivalents had been absorbed. Removal of the catalyst and evaporation of the solvent gave a white semi-crystalline solid (700 mgs., 88%).

$\nu_{\text{max.}}^{\text{film}}$ 966 (*trans* -CH=CH-) 720 cm.$^{-1}$ (*cis* -CH=CH-).

(i) Rudloff Oxidation of the Reduction Product.[95]

Sodium metaperiodate (2.24 g.) and potassium permanganate (0.066 g.) were dissolved in 150 c.c. of water.

The Pd-C reduction products (540 mgs.) were dissolved in *tert*-butanol (100 c.c.) and added to a solution of potassium carbonate (0.55 g.) in water (50 c.c.). The aqueous and alcoholic solutions were then mixed and shaken for ten hours at room temperature.

The reaction was stopped by the addition of enough sodium metabisulphite to reduce all free iodine to iodide and the *tert*-butanol removed over two hours by heating the flask at 60° on a rotary evaporator. The solution was then strongly acidified and ether extracted over ten hours. On drying the extract and evaporation of the solvent a white solid was obtained (500 mgs.), which showed $\nu_{\text{max.}}^{\text{film}}$ 1690 cm.$^{-1}$ (carboxyl).

(ii) Examination of the Oxidation Products by Gas-Liquid Chromatography.

The white solid obtained above was dissolved in ether and treated with excess diazomethane till the infra-red spectrum of the crude product showed only the typical ester peak at 1740 $cm.^{-1}$

In order to have a basis for comparison dimethyl suberate, azelate and sebacate were similarly prepared and examined, together with the unknown mixed esters, under the following conditions.

A few mgs. of the material to be examined were dissolved in decalin (0.1 c.c.) and 0.1 micro litres of this solution placed on the G.L.C. column by means of a micro pipette. (Column temperature 185°, Argon flow rate 30 c.c. min., chart speed 45 ins. hr.).

Both the standards and the oxidation products gave symmetrical peaks the retention times being measured from the air peak to a centre line drawn through each main peak. Using the formula given below it is possible to calculate the

$$R_v = \frac{r.d}{s} . \frac{p_1}{p_2} . \frac{T_1}{T_0}$$

where

R_v = Retention volume
r = Flow rate (1 hr.)
d = Distance of chart (ins.)
s = Chart speed (ins. hr.)
p_1 = Inlet pressure (lb $in.^2$)
p_2 = Outlet pressure (lb $in.^2$)
T_1 = Column temperature
T_0 = Room temperature

retention volume for each peak corresponding to a specific dicarboxylic diester. By plotting the curve of log retention volume against the number of methylenes in each diester a straight line was obtained for the standards and it was thus possible to identify the diesters obtained from the oxidation products and establish that the Pd-C reduction had not been specific. The following table details the results obtained from the G.L.C. of both the standards and the oxidation products.

(i) Standards.

Number of methylenes in the chain.	6	7	8
Retention Time (mins.)	2.0	3.1	4.8

(ii) Oxidation products from Pd-C reduction.

Number of methylenes in the chain.	7	8	9	10	11
Retention Time (mins.)	3.1	4.8	7.2	11.2	17.3
Proportion of each dicarboxylic diester in the mixture (%)	1.0	26	35	33	5.0

(b) Reduction of Dimethyldocos-10,12-diynoate (VII) with Sodium in Liquid Ammonia.

The diyne-diester (500 mgs.) in dry tetrahydrofuran (10 c.c.) was added with stirring to liquid ammonia (200 c.c.) at -35°. The initially clear solution quickly became white, due, apparently, to the precipitation and dispersion of fine solid particles of the ester. That the liquid ammonia did not react with the ester was proven by withdrawing a small sample of the mixture and recovering only unchanged ester. Sodium (200 mgs.) was added to the white suspension in small pieces over a period of ten minutes. A colour change from white to orange took place immediately after the final piece of sodium had been added; the immediate addition of solid ammonium chloride dispelled the orange colour. The ammonia was allowed to evaporate over a period of two hours and on working up the residue in the usual manner a yellowish solid was obtained (180 mgs.), the infra-red of which indicated the presence of amide groups possibly due to the formation of sodamide during the reduction.

$\nu^{\text{film}}_{\text{max.}}$ 3120 (CH=CH), 1735 (ester), 1720 (amide), 960 (trans CH=CH) 720 cm.$^{-1}$ (cis CH=CH).

(i) Rudloff Oxidation of the Sodium in Liquid Ammonia Reduction Products.[93]

Potassium carbonate (0.3 g.) in water (10 c.c.) was added to a solution of the reduction products in tert-butanol (70 c.c.). To this was added 100 c.c. of stock oxidant solution (14.0 g., sodium metaperiodate and 250 c.c. of 0.01M potassium permanganate make up to 1 litre). The mixture was shaken for 15 hours then treated as before, in this case, however, 5 c.c. of 10M potassium hydroxide solution was added after the sodium metabisulphite to hydrolyse the amide, to give a white solid, $\nu_{\text{max.}}^{\text{film}}$ 1690 cm.$^{-1}$ (carboxyl).

(ii) Examination of Oxidation Products by Gas Liquid Chromatography.

The acidic oxidation products were methylated with diazomethane and the resultant esters subjected to G.L.C. under the same conditions as previously.

The plot of log.(retention volume) against the number of methylenes in the chain, showed that reduction had given a 50:50 mixture of the two possible reduction products. The G.L.C. results are summarised in the following table.

Number of methylenes in the chain	8	9	10
Retention Time (mins.)	4.8	7.2	11.2
Proportion of each dicarboxylic diester in the mixture (%)	30	47	23

Synthesis of Exaltolide.[90]

(i) But-1-yn-4-yl Undecynoate (IIa).

Undecynoyl chloride (30 g., freshly prepared by action of thionyl chloride on the acid) was dissolved in anhydrous ether (200 c.c.) and but-1-yn-4-ol (10.5 g.) added.

Anhydrous pyridine (12 c.c.) was then added, dropwise with stirring and at such a rate that no rise in temperature occurred.

After removal of the precipitated pyridine hydrochloride, the neutral fraction was isolated as an ethereal solution and passed down a column of alumina (100 g.). *The ester* (30.8 g., 88%) crystallised from ether in plates m.p. 32.5-33°.

(Found: C, 76.6; H, 9.6% $C_{15}H_{22}O_2$ requires C, 76.8; H, 9.5%) $\nu_{max.}^{CCl_4}$ 3316 (≡CH), 2100 (C≡C), 1743 cm.$^{-1}$ (ester).

(ii) 15-*Hydroxypentadeca*-10,12-*diynoic acid lactone* (III).

A solution of butynyl undecynoate (2.5 g.) in ether-pyridine (1:8; 90 c.c.), was added during 8 hours to a refluxing solution of anhydrous cupric acetate (12.0 g.), in ether-benzene-pyridine (1:1:5; 800 c.c.), in a high dilution apparatus.

After a further 2 hours reflux the resultant green solution was cooled and slowly added with stirring to 0.05M sulphuric acid (5 c.c.) at 0°, the neutral fraction being isolated with ether and its solution in benzene passed through alumina (7 g.). Removal of the eluant gave *the lactone (III)* as a white crystalline solid (2.18 g., 88%), m.p. 53-54° which crystallised from light petroleum as long colourless platelets, m.p. 55-56°.

(Found: C, 77.7; H, 8.8% $C_{15}H_{24}O_2$ requires C, 77.5; H, 8.7%)

$\nu^{CCl_4}_{max.}$ 1742 cm.$^{-1}$ (ester)

$\lambda_{max.}$ 227.5, 238 and 254 mμ. (ε 815, 677 and 290 respectively).

The product from an earlier experiment had $\lambda_{max.}$ 228, 238 and 254 mμ. (ε 1070, 905 and 310 respectively) the high values of ε at 228 and 238 mμ. were presumably due to the presence of a small proportion (ca. 4%) of ene-yne material.

(iii) Pentadecanolide (Exaltolide). (IV).

The above diyne lactone (450 mgs.) was hydrogenated in ethyl acetate solution (50 c.c.) with Adams catalyst (PtO_2, 50 mg.) at room temperature and pressure. Uptake of hydrogen fell to zero after 180 c.c. (4 moles) had been absorbed. Filtration and evaporation yielded a yellow oil, the molecular distillation of which gave pentadecanolide as colourless plate crystals (330 mg., 71%), m.p. 32-33°.

(Found: C, 75.2; H, 11.7% $C_{15}H_{28}O_2$ requires C, 75.0; H, 11.8%.)

$\nu^{film}_{max.}$ 1730 cm.$^{-1}$ (ester).

The melting point of this solid was undepressed when mixed with an authentic sample of Exaltolide.

Ruzicka gives m.p. 31-32°,[86] Polak and Swartz 34°,[87] and Hunsdieker 37°.[87]

Hydrogenation of Lactone (III) and Degradation of Products.

(i) Hydrogenation of Pentadeca-10,12-diynolide (III) with Lindlar's Catalyst.

The lactone (232 mg.) was hydrogenated, in ethyl acetate solution (50 c.c.), with Lindlar's catalyst (26 mgs.) at room temperature and pressure. Uptake of hydrogen had considerably slowed after 40 minutes when the equivalent of 2 moles of hydrogen (47.5 c.c.) had been absorbed. Filtration and evaporation gave a yellow oil (200 mgs., 86%).

(Found: C, 76.2; H, 10.0% $C_{15}H_{24}O_2$ requires C, 76.3; H, 10.2%)

$\nu_{\max.}^{\text{film}}$ 1735 (ester), 720 cm.$^{-1}$ (*cis* CH=CH).

$\lambda_{\max.}$ 234 mμ (ε 13,600)

A small sample (16.3 mgs.) of this diene was fully hydrogenated in ethyl acetate solution (5 c.c.) with Adam's catalyst (PtO_2, 0.9 mgs.) at room temperature and pressure. A total uptake of 3.06 c.c. of hydrogen was recorded, equivalent to 1.9 double bonds.

(ii) Hydrogenation of Pentadeca-10,12-diynolide (III) using Palladium on Charcoal Catalyst.

The diyne-lactone (150 mgs.) was hydrogenated in ethyl acetate solution (25 c.c.) with 10% Pd-C (30 mgs.) at room temperature and pressure. When the compound had taken up the equivalent of 3 moles of hydrogen the rate of uptake fell almost to zero. Removal of the catalyst, by filtration and the solvent, by evaporation under vacuum gave a semi-crystalline white solid (138 mg., 92%). (Found: C, 75.9; H, 10.8% $C_{15}H_{26}O_2$ requires C, 75.6; H, 11.0%) $\nu_{\max.}^{\text{film}}$ 1745 (ester), 975 cm.$^{-1}$ (trans CH=CH).

This reduction product was examined by G.L.C., with a column temperature of 202° and Argon flow rate of 45 c.c./min., the following retention times were obtained.

	Reduced Product	Diyne Lactone	Exaltolide
Retention time (mins.)	6.2	12	6.2

Although it was clear from the G.L.C. results that the reduction product did not contain starting material, it was not possible to distinguish between the olefin, and any saturated material which may also have resulted from the reduction. Even at reduced temperature (185°) and flow rate (30 c.c./min.) only one peak was obtained from the reduction product.

A microhydrogenation, however, indicated that the product was largely, though not wholly, olefin; 17.66 mgs. over PtO_2 (1.0 mgs.) absorbed 1.25 c.c. of hydrogen equivalent to 70% double bond material.

(a) Rudloff Oxidation of the Palladium on Charcoal Reduction Product.[95]

To a solution of the above mono-ene compound (138 mgs.) in *tert*-butanol (100 c.c.), was added a solution of potassium carbonate (0.25 g.) in water (10 c.c.) followed by sodium metaperiodate (1.02 g.) and potassium permanganate (0.03 g.) dissolved in 100 c.c. of water. The mixture was shaken for 30 mins. at room temperature then sodium metabisulphite added to reduce all free iodine to iodide. Excess potassium hydroxide was then added and the lactone hydrolysed simultaneous with the removal of the *tert*-butanol by heating at 60° on a rotary evaporator for 3 hours. On working up as before, a mixture of dicarboxylic and hydroxy acids was obtained. In order to remove the hydroxyl group, this mixture was dissolved in acetone (100 c.c.) and treated with excess aqueous chromic acid solution (9.7 $\bar{N}$). The mixture was allowed to stand for 2 hours, the acetone removed under reduced pressure and the residue ether extracted over 8 hours to give a colourless gum (100 mg.).

(b) Examination of the Oxidation Products by G.L.C.

A small sample of Exaltolide was hydrolysed, the product oxidised as above with aqueous chromic acid and finally esterified with diazomethane. The retention time of the resultant diester $(CH_2)_{13}(COOMe)_2$ was measured under the same conditions as before. The colourless gum (100 mgs.) obtained above, was treated with excess diazomethane and the resultant oil subjected to G.L.C. The results of this examination indicated that not all the hydroxyl material had been oxidised and so the mixture was again treated with excess chromic acid, shaken for 8 hours and worked up as before. The results of the final G.L.C. examination are summarised in the table.

Number of methylenes in the chain	7	8	9	10	11	13
Retention Time (mins.)	3.1	4.8	7.2	11.2	17.3	43.5
Proportion of each dicarboxylic diester in the mixture	7	27	10	20	4	32

(iii) Reduction of Pentadeca-10,12-diynolide (III) with sodium in liquid ammonia.

The diyne-lactone (232 mgs.) in tetrahydrofuran (5 c.c.) was added to stirred liquid ammonia (150 c.c.), (a small sample of this solution yielded unchanged lactone), and sodium then added in small lumps over 30 minutes. The mixture slowly became pink then latterly went through purple to dark brown. Stirring was continued for 15 minutes after the addition of the sodium then excess dry ammonium chloride was added. The brown solution immediately became light yellow in colour.

On working up in the usual manner two fractions were obtained. The acidic material (132 mgs.) showed a peak in the infra-red at 1690 cm.$^{-1}$ indicating the presence of carboxylic acid. The neutral material (46.0 mgs.) with a small peak at 960 cm.$^{-1}$ in the infra-red showed traces of trans double bond. G.L.C. indicated only one major constituent but no further examination was attempted.

Attempted hydration of Pentadeca-10,12-diynolide.(III).

(i) With Mercuric Acetate in Acetic-Sulphuric Acid Mixture.[97]

The diyne lactone (202 mgs.) and mercuric acetate (150 mgs.) were refluxed for 5 hours in a solution of acetic and sulphuric acids (30 c.c., 1 drop). The final reaction mixture was diluted with water and ether extracted to give mainly acidic material.

$\nu_{\text{max.}}^{\text{film}}$ 1740 (ester), 1700 cm.$^{-1}$ (carboxyl).

(ii) With Mercuric Oxide and Boron Trifluoride-Ether Complex.[97]

The diyne lactone (130 mgs.) in methanol (10 c.c.) was added with shaking to a mercury complex prepared by mixing excess mercuric oxide, trichloroacetic acid (10 mgs.) and boron trifluoride-ether complex (1 c.c.) in methanol

(3 c.c.). The anticipated violent reaction did not ensue. The mixture was shaken for 2 hours, a small sample withdrawn and the infra-red spectrum of the product examined. The results indicated that no reaction had taken place. After a further 46 hours shaking the mixture was poured into dilute sulphuric acid and ether extracted. The final product was neutral but the infra-red spectrum indicated a rather complex mixture of starting material (1735 $cm.^{-1}$) and possible products (1700, 1600, 883 and 680 $cm.^{-1}$). A ferric chloride test gave a negative result.

Examination of the Root Extracts of Angelica Archangelic Officinalis.

A sample of the dried root was crushed to a fine powder and extracted in a Soxhlet apparatus with light petroleum over a period of 30 hours. Evaporation of the solvent gave a brown gum, shown by its infra-red spectrum to be an extremely complex mixture[99] which was chromatographed on alumina (10 g.) into three fractions. An infra-red examination showed that the second and largest of those fractions, eluted with benzene was most likely to contain the lactone Exaltolide. This fraction was therefore further purified by fractional distillation at a pressure of 0.01 m.m. and at various temperatures between 40-100°. In all, five fractions were collected.

The retention time of an authentic sample of Exaltolide was measured (R_T 18 mins.) and then each sample of distillate was examined under the same conditions (viz. column temperature 164°, Argon flow rate 30 c.c./min.) The sample obtained at 100°/0.01 m.m. showed a pronounced peak, with R_T 18 mins., which was further enhanced on mixing with an authentic sample of Exaltolide and it seems probable therefore that this material contains the lactone.

A commercial sample of Angelica Oil, obtained by steam distillation of the roots, was also fractionated and examined as above. Once again the sample, with b.p. 100°/0.01 m.m. gave a peak coincident with that of Exaltolide.

Chodkiewicz Couplings.

(i) 1-Phenyl-5-methyl-hexa-1,3-diyn-5-ol.

To a 100 c.c. 3-necked flask fitted with a stirrer and containing dimethylethynyl carbinol (0.893 g.) dissolved in ethanol (20 c.c.) was added an n-butylamine solution (5 c.c.) of cuprous chloride (0.02 g.) and hydroxylamine hydrochloride (1.2 g.).

1-Bromophenylacetylene (1.81 g.) in 10 c.c. of ethanol was slowly added to the above mixture over a period of 30 minutes, the temperature of the mixture being maintained at 18° during the addition by external cooling.

Ten minutes after the addition was complete the reaction mixture was poured into a large volume of water (200 c.c.) and ether extracted. This extract was worked up in the usual manner to give a crystalline solid (1.4 g., 78%) which recrystallised from petrol as colourless needles, m.p. 55-56°.

(Found: C,84.7; H,6.5% $C_{13}H_{12}O$ requires C,84.8; H,6.5%).

An attempt was also made to prepare this compound using 1-iodophenylacetylene; the reaction taking place in an atmosphere of nitrogen. An n-butylamine solution (4 c.c.) of curpous chloride (0.03 g.) in benzene (10 c.c.) was added to a stirred solution of dimethylethynyl carbinol (1.77 g.) and hydroxylamine hydrochloride (2.0 g.) in benzene (20 c.c.).

1-Iodophenylacetylene (4.56 g.) in 15 c.c. of benzene was added dropwise over 45 minutes, the reaction temperature was maintained at 0° by a CO_2- methanol bath. Working up the final reaction mixture as above gave 2.3 g. of a brown oil, the infra-red spectrum of which showed it to contain starting materials. The addition of petrol to this oil, however, precipitated a small quantity of crystalline material (0.2 g.) with m.p. 5 -54°, shown by mixed m.p. with an authentic sample to be the required product. The oil, however, was not further investigated.

(ii) Diphenyltriacetylene.

Phenylacetylene (5.1 g.) was dissolved in 10 c.c. of methanol and hydroxylamine hydrochloride (2.0 g.) added. The mixture was vigorously stirred and cooled to -10°. Cuprous chloride (0.05 g.) dissolved in 20 c.c. of *n*-butylamine was added to the above mixture and washed in with a further 20 c.c. of methanol.

Di-iodoacetylene (6.95 g.) in methanol (50 c.c.) was added dropwise over 35 minutes with vigorous stirring, the temperature of the reaction being maintained at -10° by external cooling. After the addition was complete the mixture was poured into a large volume of water (200 c.c.) and ether extracted. On working up this extract in the normal manner a dark red oil was obtained which was chromatographed on alumina (Grade 3, 100.0 g.). Elution with petrol gave 3.9 g. of phenylacetylene and further elution with benzene gave 0.3 g. of a dark red gum which had $\nu_{\text{max.}}^{\text{film}}$ 3360 ($\equiv$CH), 2190 and 2150 (C$\equiv$C).

No attempt was made to investigate this further.

(iii) Diphenyldiacetylene.

1-Bromophenylacetylene (3.66 g.), in benzene (10 c.c.), was added to a stirred solution of cuprous chloride (3.0 g.), in *n*-butylamine (30 c.c.) and benzene (20 c.c.), under an atmosphere of nitrogen. During the addition the temperature of the reaction mixture rose by 17°.

The reaction mixture was added to chilled, dilute hydrochloric acid and ether extracted. On working up in the usual manner 1.92 g. of crystalline material, m.p. 85-86°, was obtained. This constitutes a 94% yield of diphenyldiacetylene.

(iv) Hexadeca-7,9-diyne.

Curpous chloride (2.2 g.) was dissolved in 60 c.c. of ethylamine under nitrogen and 100 c.c. of methanol added. The resultant green solution was diluted with a further 500 c.c. of methanol and vigorously stirred. The 1-bromo-octyne (2.8 g.) was added over 5 minutes in methanol (70 c.c.).

The methanol was removed under suction on a steam bath and the residue poured into a large volume (1 litre) of acidified water and ether extracted. The extract yielded a mixture of starting material (0.7 g.) and some low melting crystals. These were recrystallised from petrol to give needle crystals, m.p. 75-76°, (0.7 g., 58% conversion).

(Found: C,88.1; H,11.7% $C_{16}H_{26}$ requires C,88.2; H,11.8%).

(v) Cyclo-hexadeca-1,3,9,11-tetrayne.

Cuprous chloride (0.65 g.) was dissolved in n-butylamine (30 c.c.) and the solution diluted with 500 c.c. of methanol. 1,8-Dibromo-octa-1,7-diyne (1.7 g.) in methanol (150 c.c.) was added to the above stirred mixture under a nitrogen atmosphere over a period of 8 hours. The solvent was removed under vacuum on a steam bath, cold dilute acid was added and the aqueous solution ether extracted to give 0.41 g. of a brown semi-crystalline gum which contained bromine. A sample of this material was hydrogenated over Adam's catalyst and the product examined by G.L.C. No evidence of cyclic material was obtained.

Oxidative Coupling by means of Potassium Permanganate.

(i) Diphenyldiacetylene.

Sodamide was prepared by dissolution of sodium (1.15 g.) in liquid ammonia (200 c.c.). Phenylacetylene (5.1 g.) in ether (50 c.c.) was added dropwise to the stirred sodamide suspension over a period of 30 minutes. The resultant mixture was stirred for a further 10 minutes before the finely crushed potassium permanganate (4.47 g.) was added in small (ca. 0.5 g.) portions. Each addition resulted in a violent reaction with vigorous frothing and deposition of a green solid on the walls of the flask.

When the addition of the permanganate was completed the liquid ammonia was allowed to evaporate and the residue thoroughly extracted with ether. This extract was worked up in the usual manner to give small brown needle crystals, which recrystallised from petrol as colourless needle crystals (3.4 g., 67%) m.p. and mixed m.p. 87-88°.

The oxidation of the lithium salt of phenylacetylene under the conditions described above resulted in a maximum yield of 20% of the diphenyldiacetylene.

(ii) Hexadeca-7,9-diyne.

Sodium (1.4 g.) was dissolved in liquid ammonia (500 c.c.) to give sodamide and 1-octyne (5.5 g.) added in ether (50 c.c.). The mixture was stirred for three hours and the solution of potassium permanganate (6.5 g.) in liquid ammonia added at such a rate that no purple colour developed. The final mixture was stirred over-night, the liquid ammonia being allowed to evaporate, water added to the residue and the mixture ether extracted several times. The extract was washed with water to neutrality, dried over magnesium sulphate and evaporated to give a colourless oil. On cooling this oil in a methanol-carbon dioxide bath a small quantity of crystalline material was deposited; this was isolated and recrystallised from a petrol-ether mixture to give small needle crystals, m.p. 76-77°, (0.8 g., 15%) and mixed m.p. with an authentic sample of hexadeca-1,7-diyne, 75-77°.

(iii) Attempted Coupling of o-Diethynylbenzene.

The disodium salt of the *o*-diethynylbenzene (0.78 g.) was prepared in the normal manner (0.36 g., sodium in 800 c.c. ammonia). After 3 hours stirring the potassium permanganate (1.76 g.) dissolved in liquid ammonia (500 c.c.) was added over a period of 4 hours. The final green solution was stirred for a further hour before the addition of solid ammonium chloride, to destroy excess sodamide, with the result that an immediate colour change to purple took place, with precipitation of manganese dioxide. The bulk of the liquid ammonia was evaporated on a water bath and the residue ether extracted. On working up the extract in the usual manner a brown gum was obtained which was only partly soluble in alcohol; an ultra-violet spectrum of the alcohol solution showing it to be largely starting material. An examination of the insoluble portion by infra-red spectrum indicated that it was probably polymeric and it consequently was not further investigated.

PART 2.

ELABORATIONS OF THE ETHYNYL GROUP.

SECTION 1.

MERCURY ACETYLIDES AND 1-HALOGENOALKYNES.

Synthesis of Mercury Acetylides and 1-Halogenoalkynes.

The diverse methods of oxidative coupling, described in the previous section, provide clear examples of the ease with which the ethynyl hydrogen may be replaced. Ready substitution by the electrophilic Grignard group,[98] the halogens,[100] mercury[102] or silver[105] is also possible, producing a series of acetylenic intermediates of considerable importance in organic synthesis. The silver acetylides have long been used as a means of estimating[106] and purifying ethynyl compounds, since they can readily be reconverted to the parent acetylene by treatment with potassium cyanide;[107] the more highly crystalline mercury acetylides, although finding a similar use, have also been employed in the characterisation of mono substituted acetylenes. The mercury acetylides find a further use in the synthesis of other intermediates; they react with lithium to give the corresponding lithium acetylide and with halogenating agents to give the 1-halogenoalkynes.[108] This latter property assumed some importance with the advent of the Chodkiewicz coupling procedure, which requires as a coupling component a 1-bromoalkyne and the methods of synthesising the mercury acetylides were therefore examined.

1. Mercury Acetylides.

Up to the present time only the method of Johnson and McEwen has been in general use for the synthesis of these compounds, viz., the interaction of the ethynyl material with a solution of mercuric chloride and potassium iodide in strong alkali.[102] The only other available routes require reaction between 1-iodoalkynes and a mercuric salt[109] and thus have no real practical value from a synthetic point of view.

The use of a strongly alkaline medium, whilst hardly suitable for alkali sensitive materials, seems unavoidable where the ethynyl compound itself is used directly in the reaction. The use of an acetylenic Grignard reagent, however, would eliminate the necessity for base and it has been found, in the present work, that such reagents reacted readily, in tetrahydrofuran solution, with mercuric chloride to give, in high yield, the corresponding mercury acetylide. This provided a ready, if somewhat indirect, means of preparing these compounds under completely neutral conditions.

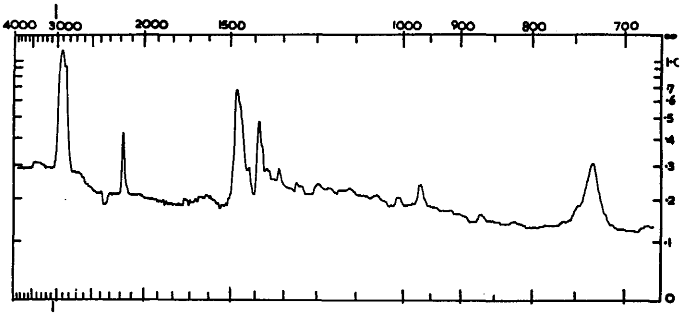
More direct was the reaction between freshly prepared yellow mercuric oxide and an ethynyl compound in the presence of anhydrous magnesium sulphate. A 62% yield of mercury diphenylacetylene was obtained on refluxing mercuric oxide, magnesium sulphate and phenylacetylene, in benzene solution, for 8 hours. A shorter reaction time resulted in the formation of an amorphous solid which could not be identified. Despite the long reaction time and heterogeneous conditions, the obvious potentialities of this procedure make it worthy of further investigation.

One disadvantage in the original procedure of Johnson and McEwen was the heterogeneous reaction environment. This was overcome by employing an organic base in which all the reactants were soluble. A solution of mercuric acetate in n-butylamine was found to react instantaneously with an ethynyl compound and the resultant mercury acetylide was isolated by evaporation of the amine and extraction of the residue with a suitable organic solvent. The use of n-butylamine both as solvent and base in the above reaction was found to be essential, since addition of any form of organic diluent resulted in the immediate precipitation of the mercuric acetate, thus destroying the homogeniety of the reaction mixture and slowing down, but not completely preventing, the process.

Owing to the difficulty in analysing these mercury acetylides, it was found necessary to rely on the

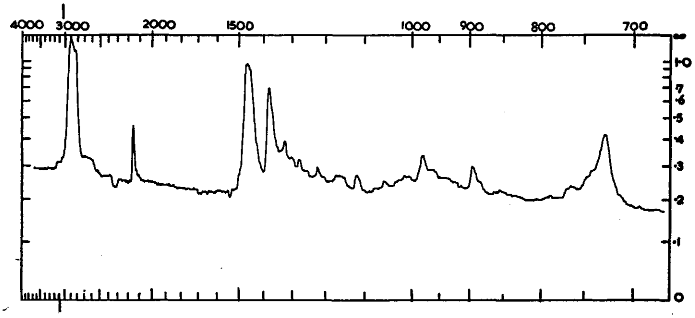
(a) Cyclic mercuric salt of tetradeca-1,13-diyne.

(Nujol)



(b) Di-octynyl mercury.

(Nujol)



(c) 1,8-Dibromo-octa-1,7-diyne.

(Film)

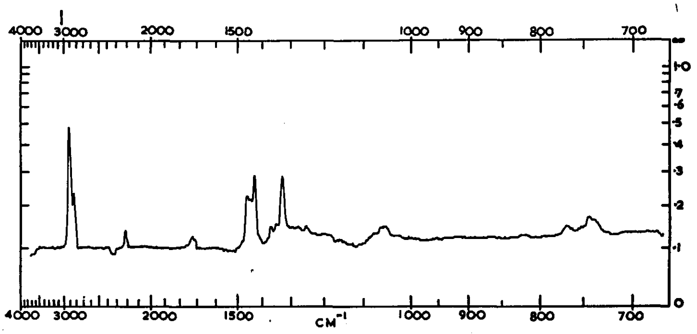


Figure 10.

disappearance of the ethynyl peak at 3300 cm.$^{-1}$ and the appearance of a pronounced peak at 2150 cm.$^{-1}$ (Figs. 10a and 10b) in the infra-red spectrum of the product as a means of identification; the peak at 2150 cm.$^{-1}$ was found to be characteristic of all the mercury acetylides prepared.

An attempt was made to synthesise a cyclic mercury acetylide by means of a high dilution modification of one of the above methods. Ideally, for such a synthesis to be a success, the ethynyl compound and an inorganic mercuric salt, in the required molar quantities and dissolved in a suitable solvent, should be simultaneously added to a non-volatile base, preferably soluble in the same solvent. Non-volatility is essential since the vapours of a volatile base would precipitate a reaction before the high dilution effect could come into play, thus producing a polymeric mercury acetylide. The solubility of potassium tert-butoxide in several organic solvents was examined but no solvent was found to give complete solution. Despite this, however, the addition of a tetrahydrofuran solution of mercuric chloride and tetradeca-1,13-diyne to a suspension of the butoxide in the same solvent precipitated an amorphous solid, the infra-red spectrum (Fig. 10a) and analysis of which

Table 3.

Synthetic Approaches to 1-Halogenoalkynes.

Compound	Author		Method	Refs.
$RC\equiv CBr$	Iositsch	1905	Bromination of Grignard.	111, 110
	Grignard	1915	Action of cyanogen bromide on Grignard.	112
	Strauss	1930	Action of sodium hypobromite on an ethynyl compound.	100
	Carothers	1933	Direct bromination of the mercury acetylide.	108
$RC\equiv CI$	Nef 1899	1899	Direct iodination of a silver or sodium acetylide.	113
	Lespieau	1908	Action of iodine and potassium iodide on a copper acetylide.	114
	Iositsch	1910	Iodination of Grignard.	111
	Vaughn	1933	Iodination of a sodium acetylide in liquid. ammonia.	115, 117
	Prévost	1935	Action of iodine-silver benzoate complex on an ethynyl compound.	116
$RC\equiv CCl$	Truchet	1931	Action of aryl sulphonyl chlorides on sodium acetylides.	118
	McCusker	1937	Direct chlorination of a sodium acetylide.	110
	Viehe	1958	Alkylation of chloroacetylene.	119

clearly showed it to be a cyclic mercury acetylide. Owing to the high degree of insolubility of this material it was not possible to evaluate the molecular weight and hence the actual size of the ring.

The mercury salts of α-hydroxyacetylenes could not be prepared by any of the above methods; the proximity of the free hydroxyl group to the triple bond apparently resulted in a type of hydration reaction taking place to give ketonic, non-crystalline oils. No such difficulty was experienced with β-hydroxyacetylenes or in the case of suitably protected α-hydroxyacetylenes. Thus, the mercury salt of the tetrahydropyranyl ether of propargyl alcohol was obtained in 86% yield using the mercuric acetate - n-butylamine procedure.

2. 1-Halogenoalkynes.

The necessity of using 1-bromoalkynes in the Chodkiewicz coupling procedure prompted an examination of the available methods of synthesising this family of compounds; these methods are summarised in table 3. In view of the tendency of many of these compounds to decompose on being heated,[108] a method of preparation was sought which would give the 1-bromoalkynes in a state such that further purification, e.g. by distillation, would not be necessary. Neither the bromination of the acetylene Grignards,[110] nor of the alkali metal acetylides,[110] the latter in a variety of solvents, fulfilled this requirement and hence these procedures, after a tentative investigation, were abandoned. The preparative method adopted by Chodkiewicz for the synthesis of 1-bromoalkynes was that due to Strauss and Kollek,[100] involving the interaction of the ethynyl compound with alkaline sodium hypobromite.

$$RC\equiv CH + NaOBr \longrightarrow RC\equiv CBr + NaOH$$

This procedure generally gave good yields of the requisite bromo compound but a rather prolonged reaction time was required, especially for alkylacetylenes. Other disadvantages in this method were the strongly basic medium and the necessity for further purification, since the product was invariably obtained contaminated with some starting material. Despite this, however, the procedure was used with some success during the course of the present work.

In 1933 Carothers and his co-workers[108] found that di-vinylethynyl mercury, on treatment with either bromine or iodine, gave the corresponding 1-bromo- or 1-iodovinyl-acetylene. In view of the ready availability of the mercury acetylides their bromination was investigated and since the reaction proved to be of general application this method was used wherever possible during the course of the present work. A solution of bromine in carbon tetrachloride was found to react instantaneously with a solution of a mercury acetylide in the same solvent, the resultant 1-bromoalkyne remaining in solution whilst mercuric bromide was precipitated. It was initially found that some residual mercuric bromide remained dissolved in the 1-bromoalkyne but this could be removed by diluting with chilled petrol and filtering. For a high degree of purity the last trace of mercuric bromide could be removed by passing the filtrate through a column of activated animal charcoal to which 10% by weight of 10% palladium on charcoal had been added. This procedure was suitable even with mercury acetylides which contained isolated double bonds, the bromine reacting preferentially with the metallic residue. Other brominating agents, such as pyridinium bromide perbromide[120] and the complex of bromine with dioxan,[121] have also been successfully employed but offer little advantage over the more direct bromination procedure.

In order to check the validity of Chodkiewicz's claim, that the 1-iodoalkynes were not suitable for use in his coupling procedure, both di-iodoacetylene and 1-iodophenylacetylene were prepared by the method of

Vaughn and Nieuwland.[115] These compounds, as well as being simple to prepare, have the advantage of being crystalline solids and hence, readily purified. They were, however, extremely malodorous and unstable and were decidely unsuitable for use in the Chodkiewicz coupling.

PART 2.

SECTION 1.

EXPERIMENTAL.

Synthesis of Mercury Acetylides.

(i) Mercuric Chloride-Potassium Iodide Method.[102]

Mercuric chloride (16.5 g.) and potassium iodide (40.5 g.) were heated with 40 c.c. of water till they were dissolved and 10% sodium hydroxide (35 c.c.) then added.

Phenylacetylene (5.1 g.) in ethanol (250 c.c.) was then added to the above solution with stirring over a period of 45 minutes. A white crystalline solid gradually separated out which crystallised from 96% ethanol as white plates, m.p. 124-125°, (10 g., 92%).

On substituting dilute ammonia solution for the sodium hydroxide a yield of 54% was achieved.

(ii) Mercuric Oxide Method.

Phenylacetylene (2.97 g.), freshly prepared yellow mercuric oxide (3.28 g.) and anhydrous magnesium sulphate (17.0 g.) were refluxed in benzene for 8 hours. The residual solid was removed by filtration and washed with potassium iodide solution to remove any trace of mercuric ion.

The bulk of the solvent, after drying over magnesium sulphate, was removed under suction and sufficient petrol added to cause a slight precipitation. This mixture was heated and allowed to cool slowly with the resultant precipitation of white crystalline plates, m.p. 123-124°, (3.8 g., 62%) mixed m.p. 124° with the sample prepared by the preceding method.

(iii) Mercuric Chloride - Grignard Method.

(b) Diphenylacetylenyl Mercury.

Mercuric chloride (6.0 g.), dissolved in tetrahydrofuran (25 c.c.), was added over a period of 5 minutes to a refluxing tetrahydrofuran (100 c.c.) solution of phenylacetylenemagnesium bromide (prepared from 5.1 g., of phenylacetylene).

Reflux was continued for a further hour and the resultant complex decomposed by the addition of aqueous ammonium chloride. The tetrahydrofuran solution was reduced in bulk and ether extracted. The extract was dried and evaporated to give a solid which crystallised from 96% ethanol as white plates, m.p. 123-124° (6.38 g., 84%) and mixed m.p. 123°.

(c) Dioctynyl Mercury

To a refluxing solution of octynylmagnesium bromide (from 2.2 g. of 1-octyne) in tetrahydrofuran was added a solution of mercuric chloride (2.75 g.) in the same solvent over 30 minutes. On working up as above and crystallising the resultant solid from petrol, small white flaky crystals were obtained, m.p. 82-83° (2.8 g., 69%).

(Found: C,45.8; H,6.4; Hg,45.3% $C_{18}H_{26}Hg$ requires
C,45.8; H,6.2; Hg,48.0%).

(iv) Mercuric Acetate Method.

(a) Dipehnylacetylenyl Mercury.

Mercuric acetate (1.86 g.) dissolved in 10 c.c. of n-butylamine was quickly added to a solution of phenylacetylene (1 g.) in n-butylamine (5 c.c.) When heat evolution from the mixture had ceased (1 minute) the solution was poured into water (150 c.c.) and ether extracted to give a white solid which crystallised from petrol in plates, m.p. and mixed m.p. 124-125° (1.95 g., 98%).

(b) Dioctynyl Mercury

1-Octyne (5.5 g.) in n-butylamine (10 c.c.) was added to a solution of mercuric acetate (8.0 g.) in 15 c.c. of n-butylamine. The mixture was allowed to stand at room temperature for 30 minutes before pouring into a large volume of water (150 c.c.) and ether extracting to give crystalline flakes, m.p. and mixed m.p. 82–83° (8.2 g., 78%).

(c) Mercuric Salt of 1-trans-β-Bromovinyl-2-ethynylbenzene

The acetylenic material (3.96 g.) was added to an n-butylamine solution (15 c.c.) of mercuric acetate (3.8 g.) and the mixture allowed to stand for two minutes before pouring on to ice-chilled dilute acid (50 c.c., 0.5N sulphuric acid). An insoluble, yellow, amorphous solid was immediately precipitated which was removed by filtration and washed several times with ethyl acetate (3 x 25 c.c.). The filtrate was extracted with ethyl acetate and the combined extracts washed with water till washings were neutral. The extracts were dried and evaporated to give a crystalline solid which crystallised from benzene as colourless plates, m.p. 187–188°, (4.5 g., 78%).

(d) Mercuric salt of the Tetrahydropyranyl ether of Propargyl Alcohol.

Mercuric acetate (3.2 g.) was dissolved in n-butylamine (15 c.c.) and the ether (2.8 g.) in 10 c.c. of amine added. The mixture was allowed to stand for one hour at room temperature then worked up as for 1-octyne.

The resultant white crystalline solid crystallised from benzene in needles, m.p. 104-105° (4.1 g., 86%).

Attempted syntheses of the cyclic mercury salt of Tetradeca-1,13-diyne.

Potassium (3 g.) was dissolved in the minimum quantity of *tert*-butanol and excess solvent removed under suction. The potassium *tert*-butoxide was suspended in tetrahydrofuran (250 c.c.) and the flask attached to a high dilution apparatus. Tetradeca-1,13-diyne (3.8 g.) and mercuric chloride (5.42 g.) were separately dissolved in 30 c.c. of tetrahydrofuran and the solutions mixed. The final solution was then added dropwise, over 10 hours, under high dilution conditions, to the refluxing suspension of potassium *tert*-butoxide in tetrahydrofuran.

The final reaction mixture was filtered and the filtrate evaporated to dryness to give only trace amounts of starting materials. The solid residue was washed several times with water, to remove potassium chloride, then methanol and dried. A grey white amorphous solid was obtained (5.77 g.) which softened to a brown glass at 160° and thence remained unmolten up to 360°.

A small sample of the material (0.41 g.) was refluxed for 6 hours with excess aqueous potassium cyanide solution to give tetradeca-1,13-diyne (200 mgs., m.p. and mixed m.p. 32-33°). This result served to confirm the analysis.

(Found: C,43.5; H,5.7; Hg,50.6% $(C_{12}H_{20}Hg)_n$ requires
C,43.3; H,5.1; Hg,51.5%).

Since the infra-red spectrum showed no free ethynyl (Fig.10a) it seemed likely that the acetylide was cyclic but with a ring of undetermined size.

Synthesis of 1-bromoalkynes.

(i) Sodium Hypobromite Method.

(a) 1-Bromophenylacetylene.

The hypobromite solution was prepared *in situ* by mixing 100 g. of finely crushed ice, 50 c.c. of $10\bar{N}$ sodium hydroxide and 11 c.c. of liquid bromine. Phenylacetylene (20.4 g.), dissolved in a little tetrahydrofuran (10 c.c.), was added to the above solution and the resultant mixture agitated by means of a 'Vibromischer' for 5 hours.
At the end of this time sufficient ammonium chloride solution was added to destroy the excess hypobromite and the mixture ether extracted and worked up in the usual manner. The resultant yellow oil n_D^{14} 1.6080 (32.4 g., 89%) had $\nu_{max.}^{film}$ 2200 cm.$^{-1}$ (C≡C) and showed no trace of ethynyl material.

(Found: C,52.7; H,2.7; Br,44.0% C_8H_5Br requires
C,53.0; H,2.8; Br,44.2%).

(b) 1,8-Dibromo-octa-1,7-diyne.

Octa-1,7-diyne was added in 25 c.c. of tetrahydrofuran to an ice cold aqueous solution of sodium hypobromite (prepared in situ from 50 g. ice, 25 c.c. of 10N sodium hydroxide and 5.5 c.c. of liquid bromine).

The mixture was agitated by a 'Vibromischer' for 24 hours and worked up as above to give a yellow oil which still contained free ethynyl material (peak at 3300 cm.$^{-1}$). This was removed by dissolving the yellow oil in alcohol and treating this solution with excess of an aqueous ammoniacal silver nitrate solution; the resultant precipitate was removed by filtration and the filtrate ether extracted several times. The combined extracts were washed with water, dried and evaporated to give an oil which solidified, on cooling to -5°, to give white needle crystals, m.p. 19-20° (6.6 g., 56%).

(Found: C,36.5; H,3.3; Br,60.4% $C_8H_8Br_2$ requires
C,36.4; H,3.1; Br,60.5%).

(ii) Bromination of the Mercury Acetylides.

(a) 1-Bromophenylacetylene.

A solution of bromine (0.55 g.) in carbon tetrachloride (10 c.c.) was slowly added to a stirred solution of the mercury acetylide (0.7 g.) in the same solvent (35 c.c.) at room temperature. When almost half the bromine solution had been added a white solid slowly started to precipitate and the red bromine colour persisted in the reaction solution.

After addition was complete (15 minutes) the mixture was stirred for a further 30 minutes and the solvent then removed under vacuum on a water bath (temperature 60°). The residue was extracted thrice with 20 c.c. of chilled petrol and the suspended solid removed by filtration.

The filtrate not only contained the required product but also some residual mercuric bromide and this was completely removed by passing down a short column of charcoal containing one part in ten of 10% palladium on charcoal.

The solvent was removed under suction to give a yellow oil n_D^{23} 1.6075 (0.55 g., 87%) $\nu_{max.}^{film}$ 2200 cm.$^{-1}$ ($C\equiv C$).

(b) 1-Bromo-oct-1-yne.

A solution of liquid bromine (3.2 g.) in carbon tetrachloride (25 c.c.) was added slowly and with stirring to a solution of 1-octyne (4 g.) in the same solvent (100 c.c.).

The procedure followed was exactly as above and the resultant product proved to be a yellowish oil (2.8 g., 75%) $\nu^{\text{film}}_{\text{max.}}$ 2190 cm.$^{-1}$ ($C \equiv C$).

(c) 1-trans-β-Bromovinyl-2-bromoethynylbenzene.

To a solution of the mercury salt (3.4 g.) in benzene (150 c.c.) was added a solution of bromine (1.81 g.) in benzene (20 c.c.) dropwise and with continuous stirring. Instant decolourisation occurred until 80% of the bromine solution had been added; beyond this stage a red colour persisted in the reaction mixture. After the addition was complete the mixture was stirred for a further 10 minutes, the solvent removed under suction on a water bath and the residue washed with petrol and filtered free of precipitated mercuric bromide, the final traces of which were removed as above. The resultant yellow oil (2.45 g., 79%) had b.p. $< 70°/10^{-4}$ m.m. and showed only one peak on a gas-liquid chromatogram (column temperature 171°; Argon flow rate 40 c.c./minute; retention time 14 minutes) $\nu^{\text{film}}_{\text{max.}}$ 2190 cm.$^{-1}$ ($C \equiv C$).

(c) 1,8-Dibromo-octa-1,7-diyne.

An attempt to prepare the cyclic mercury salt of this diyne, by the method of Elsner and Paul,[102] yielded an amorphous polymeric solid, 3.1 g. of which was dry-packed into a small condenser and bromine (1.3 c.c.), in carbon tetrachloride (30 c.c.), passed slowly down through the solid packing. A uniform temperature was ensured by passage of water through the condenser jacket. When all the bromine solution had been added the column was washed with a further 10 c.c. of carbon tetrachloride and the final solution evaporated to give, on crystallisation from benzene, crystalline solid, m.p. 70° which showed on analysis that six bromine atoms had been added to the octa-1,7-diyne molecule.

(Found: C,16.6; H,1.7; Br,81.7% $C_8H_8Br_6$ requires
C,16.4; H,1.7; Br,82.0%).

(iii) Bromination of Sodium and Lithium Acetylides.

(a) Lithium Acetylides.

Lithamide was prepared in the usual manner (from 0.35 g. of lithium) and phenylacetylene (5.0 g.) in dioxan (50 c.c.) added to the suspension in liquid ammonia (250 c.c.). This mixture was stirred at -35° for 30 minutes then allowed to heat up to room temperature the ammonia being driven off in a stream of nitrogen. The ammonia was replaced by dry dioxan (200 c.c.) and the solution refluxed under nitrogen for 45 minutes.

Liquid bromine (0.8 g.) dissolved in dioxan (50 c.c.) was added over one hour to the above solution at room temperature. The resultant mixture was filtered free of suspended solid and a sample of the filtrate worked up and examined by infra-red.

The product was shown to contain starting material (3300 cm.$^{-1}$) and carbonyl material (1710 cm.$^{-1}$) in small amounts. The difficulty in removing the latter impurity resulted in further work on this procedure being suspended.

Another method which gave a similar result involved the preparation of the acetylide by reaction between *n*-butyl lithium or phenyl lithium and phenylacetylene in ether and bromination of the product with bromine in carbon tetrachloride.

(b) Sodium Acetylides.[104]

Clean sodium (1.4 g.) was chopped into small pieces and covered with ether (90 c.c.) in a 3-necked flask fitted with a reflux condenser stirrer and dropping funnel. Phenylacetylene (5.5 g.) in ether (10 c.c.) was added dropwise and spontaneous evolution of hydrogen occurred within 2-3 minutes. The mixture was stirred for 3 hours with gentle reflux and the ether then removed under suction and replaced by diglyme (100 c.c.). To the resultant purple solution liquid bromine (2.8 c.c.) in diglyme (10 c.c.) was added dropwise at room temperature with external cooling.

When addition was complete the mixture was poured into a large volume of water and ether extracted several times. On working up this extract a brown oil was obtained, the infra-red spectrum of which showed that once again appreciable reaction had taken place but the final product also contained starting material and carbonyl material (3300 and 1700 cm.$^{-1}$ respectively).

Synthesis of 1-iodoalkynes.

(i) Di-iodoacetylene.[115]

Iodine (100 g.) was placed in a 2 litre beaker, externally cooled by liquid ammonia, and 750 c.c. of liquid ammonia rapidly added. A stream of pure dry acetylene was passed into the brown solution for 3 hours i.e. until brown colour disappeared and the ammonia then allowed to evaporate. When only 100 c.c. of ammonia remained water was slowly added with stirring and the resultant precipitate removed by filtration. This solid was dissolved in petrol (300 c.c.) and the solution treated with calcium chloride (35 g.). The petrol solution was decanted off and allowed to stand overnight at -40°. The precipitated di-iodoacetylene (33 g., 30%)

m.p. 78-79° was removed by filtration through a cold funnel.

(ii) 1-Iodophenylacetylene.

The sodium salt of phenylacetylene was prepared in the usual manner in liquid ammonia (from 2.3 g. sodium and 10.2 g. of phenylacetylene). Iodine (25.4 g.) was dissolved in dimethylformamide (100 c.c.) and slowly added to the stirred ammonia solution. When addition was complete the ammonia was allowed to evaporate and the residue worked up in the usual manner to give a dark brown oil (10.8 g., 84.5%). On allowing this oil to stand at -5° for several days large colourless needles were obtained which melted to a yellowish oil at room temperature.

(Found: C, 42.1; H, 2.2; I, 55.4% C_8H_5I requires
C, 42.2; H, 2.2; I, 55.7%).

SECTION 2.

CONVERSION OF ETHYNYL COMPOUNDS
INTO
CARBOXYLIC ACIDS.

Conversion of Ethynyl Compounds to Carboxylic Acids.

Although ethynyl compounds may readily be converted to homologous carboxylic acids by interaction of their metallic derivatives and carbon dioxide, little work is extant on their conversion into acids of the same carbon content. Such a transformation has been achieved in this work by means of

(i) Oxidation of acetylenic Grignard reagents,

(ii) Faworsky rearrangement of derived bromoketones.

(i) Oxidation of Acetylenic Grignard Reagents.

The oxidation of alkyl and aryl Grignards is a well authenticated reaction known to produce good yields of alcohols and phenols respectively. It was hoped that a similar oxidation of an acetylenic Grignard would result in a 'reverse hydration' to give, finally, the corresponding saturated acid. The mechanism of the reaction has been suggested as proceeding via the peroxide,[122] and thus

$$\mathrm{RMgX} + \mathrm{O_2} \longrightarrow \mathrm{ROOMgX} \xrightarrow{\mathrm{RMgX}} \mathrm{2ROMgX} \xrightarrow{\mathrm{H}^+} \mathrm{2ROH} + \mathrm{2MgXOH}$$

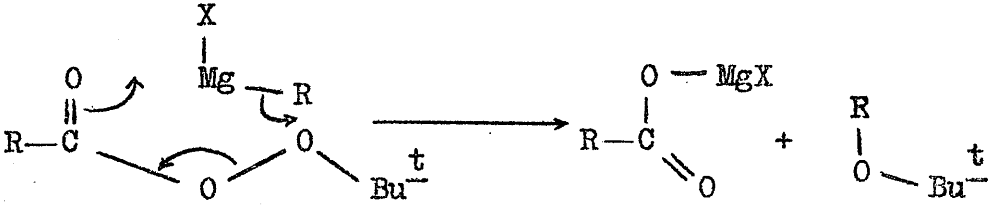
the acetylenic Grignard, assuming the same mechanism to apply, should produce, via the ketone, a substituted acetic acid.

$$\begin{tikzcd}
\mathrm{RC{\equiv}CMgX} + \mathrm{O_2} \arrow[r] & \mathrm{RC{\equiv}C.OMgX} \arrow[r] & {[\mathrm{RC{\equiv}COH}]} \arrow[r] & \mathrm{RCH{=}C{=}O} \arrow[d, "\mathrm{H_2O}"] \\
& & & \mathrm{RCH_2COOH}
\end{tikzcd}$$

The oxidation of acetylenic Grignards has not, as yet, been very fully investigated although the results so far obtained indicate that the reactivity of the alkynyl Grignard group is such that oxidation occurs only slowly and to a small extent.[123] This inertness was pointed out by Kroeger and Nieuwland,[124] who found that hexynylmagnesium bromide yielded only a trace of n-hexanoic acid after oxygen had been bubbled through its solution at -30° for 8 hours. Further work by Dobson,[125] on various acetylenic Grignard and lithium derivatives using oxygen and ozone, served to confirm the earlier findings. Dobson also found that the use of oxygen at room temperature with pressures up to 40 atmospheres for 24 hours increased the carboxylic acid yield to 21%. One unsatisfactory aspect of this procedure, however, was the tendency of the mixture to explode rather violently during the course of the reaction.

This stability of acetylenic Grignards towards oxygen was also observed by Walling and Buckler[126] in a study of acetylenic hydroperoxides. In one of these experiments they bubbled oxygen through pentynylmagnesium bromide solution for 12 hours and isolated 4.3% of n-pentanoic acid together with a small amount of hydrocarbon, which was found to be a dimer of pentyne of unknown structure. Octynylmagnesium bromide gave similar results. During the course of the present work phenylacetylenemagnesium bromide was agitated in an atmosphere of oxygen for 7 hours by means of a 'Vibromischer', which ensured an extremely intimate mixing of the two phases; the only compound isolatable proved to be diphenyldiacetylene, in very small yield. It is not unlikely therefore that the " dimers" obtained by Walling and Buckler were the corresponding diynes formed by an oxidative coupling of the acetylenic radicals.

In recent years new and more powerful oxidising agents, such as *tert*-butylhydroperoxide[127] and trimethyl borate, followed by hydrogen peroxide,[128] have helped to facilitate even further the oxidation of aryl and alkyl Grignards and good yields of the corresponding *tert*-butyl ethers have been obtained by the action of *tert*-butyl perbenzoate on these reagents.[127]



Since the application of these peroxy compounds to the oxidation of acetylenic Grignard reagents had not been investigated, their reaction with 1-octynylmagnesium bromide was examined under various temperature conditions from $-80°$ to room temperature. The results were not promising; in the case of both tert-butylhydroperoxide and the trimethyl borate reagent no trace of the expected carboxylic acid was obtained. Indeed in all of the reactions with these reagents, including tert-butyl perbenzoate, the starting material, 1-octyne was largely recovered.

Having abandoned his attempts at the direct oxidation of acetylenic Grignards with oxygen and ozone, Dobson sought a method of converting 1-alkynes into saturated carboxylic acids in as few steps as possible. He noted that acetylenic amines of the type $RC\equiv CNH_2$ had never been isolated, the inherently unstable structures apparently rearranging to the only isolatable product, the isomeric nitrile RCH_2CN. Thus, a process for converting 1-alkynes to amines of this type should lead automatically to the desired nitriles, which would be readily hydrolysed to the carboxylic acid. In 1938 Sheverdina and Kocheschkov[129] noted that O-methylhydroxylamine reacted with alkyl Grignard reagents to give the corresponding primary amines. This was further developed by Brown and Jones[130] and it was the experimental conditions of these latter workers which Dobson used in his investigations. The reaction requires two moles of Grignard reagent to one of O-methylhydroxylamine in the following manner.

$$2RMgBr + MeONH_2 \longrightarrow RH + RNHMgBr + MeOMgBr$$

$$RNHMgBr + MeOMgBr + 2H_2O \longrightarrow RNH_2 + MeOH + 2MgBrOH$$

In the case of the Grignard compounds of 1-alkynes the following reaction was anticipated.

$$2RC{\equiv}CMgBr + MeONH_2 \longrightarrow RC{\equiv}CH + MeOMgBr + RC{\equiv}CNHMgBr$$

$$RC{\equiv}CNHMgBr + H_2O \longrightarrow [RC{\equiv}CNH_2] \longrightarrow RCH_2CN$$

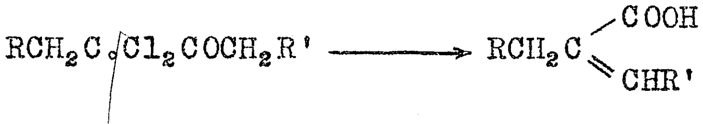
Dobson made a detailed study of this reaction, determined the optimum conditions and obtained 45-55% yields of the nitriles.

O-Methylhydroxylamine can be prepared fairly simply but the procedure is somewhat protracted[131] and its volatility makes it awkward to handle during the course of a reaction. Sheverdina and Kocheschkov had extended their work to include another reagent, O-benzyl hydroxylamine, which, although more readily synthesised and easier to handle, was never used by Dobson.

During the course of the present work the reaction of both O-methyl and O-benzylhydroxylamine on octynylmagnesium bromide was studied, employing the optimum reaction conditions defined by Dobson. With O-methyl hydroxylamine the yield of n-octanoic acid was comparable with that obtained by Dobson, whilst the use of O-benzyl hydroxylamine did not lead to substantially increased yields.

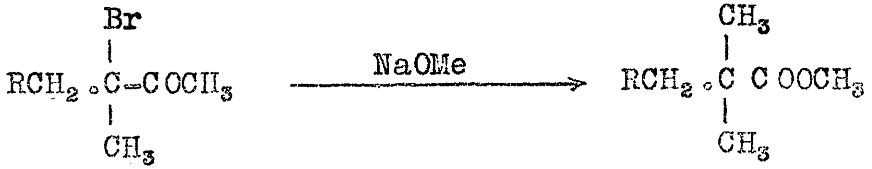
(ii) Fawrosky Rearrangement of Derived Bromoketones.

Although Linneman and de Zotta[134] were the first to note the action of alkali on an α,α-dichloroketone, the general nature of this reaction was demonstrated by Faworsky[135] who obtained a series of α,β-unsaturated acids in this manner.

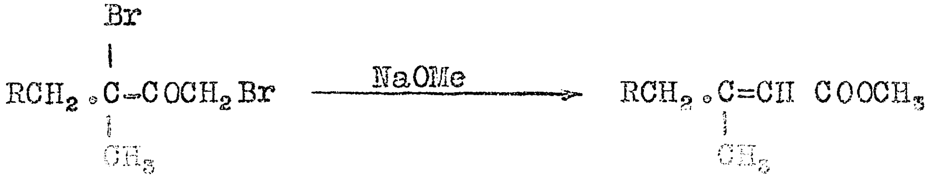


$$RCH_2CCl_2COCH_2R' \longrightarrow RCH_2C\begin{matrix}\diagup COOH\\ \diagdown\!\!\diagdown CHR'\end{matrix}$$

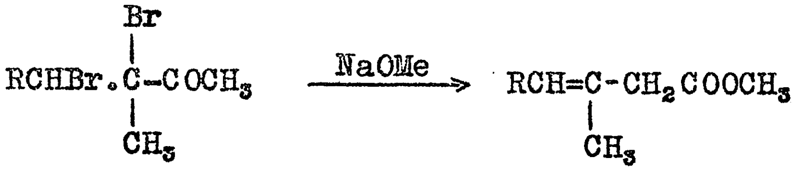
Subsequent workers have clearly shown that the reaction is applicable to a variety of α-halogenated ketones of widely varying complexity.[146-140] Treatment with sodium methoxide was found to convert α-bromoketones into saturated esters,[136,137,141] (Equation 1); the rearrangement of α,α-dibromoketones under similar conditions gave esters of α,β-unsaturated acids,[139,140,142] (Equation 2). Although

1.


$$RCH_2.\overset{\overset{Br}{|}}{\underset{\underset{CH_3}{|}}{C}}-COCH_3 \xrightarrow{NaOMe} RCH_2.\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}\ COOCH_3$$

2.


$$RCH_2.\overset{\overset{Br}{|}}{\underset{\underset{CH_3}{|}}{C}}-COCH_2Br \xrightarrow{NaOMe} RCH_2.\underset{\underset{CH_3}{|}}{C}=CH\ COOCH_3$$

3.


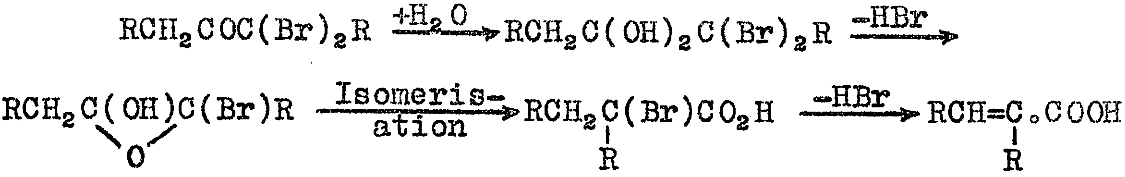
$$RCHBr.\overset{Br}{\underset{CH_3}{C}}-COCH_3 \xrightarrow{NaOMe} RCH{=}\underset{CH_3}{C}-CH_2COOCH_3$$

4.


$$RCH_2.\overset{Br}{\underset{CH_3}{C}}-COCHBr_2 \xrightarrow[EtOH]{KOH} RCH_2\underset{CH_3}{C}{=}CBrCOOH$$

the rearrangement of a steroidal α,β-dibromoketone gave an α,β-unsaturated acid, extension of this reaction to simpler aliphatic and alicyclic α,β-dibromoketones showed that β,γ-unsaturated acids resulted and, if these were unstable, underwent a rearrangement involving migration of the double bond,[143,144] (Equation 3). More recently Wagner and Moore[145] have prepared a steroidal α,α,α'-tribromoketone and obtained, on treatment with alcoholic potassium hydroxide, an α-bromo-α,β-unsaturated acid. They have extended and studied this rearrangement with simpler compounds and obtained in every case the corresponding α-bromo-α,β-unsaturated acid.

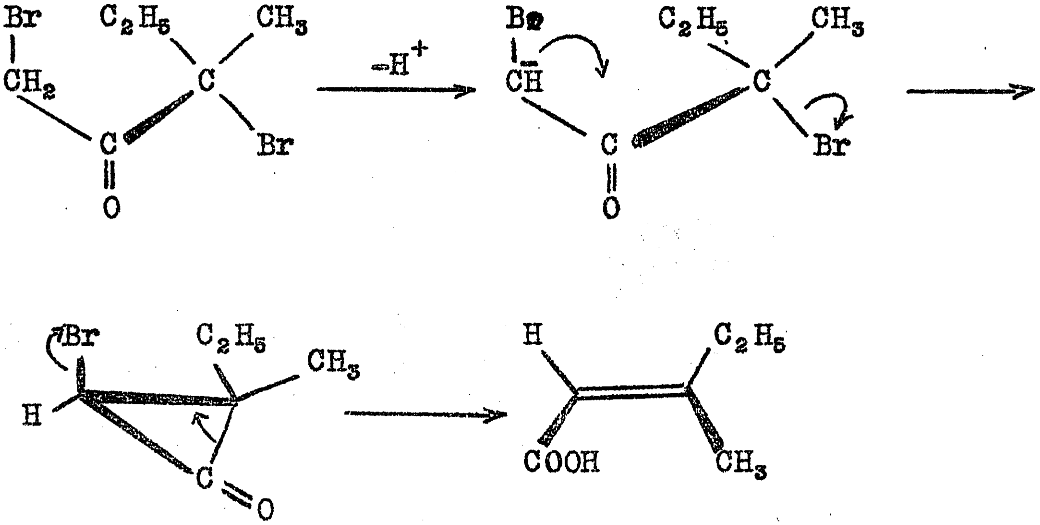
The original mechanism (I) for these reactions, proposed by Faworsky[142], was an extremely reasonable one for that period but the reaction has been examined more recently by several workers and a more modern interpretation of the mechanism suggested. Loftfield[146] proposed a mechanism (II) involving the intermediate formation of a cyclopropanone ring which enabled him to predict



$$RCH_2COC(Br)_2R \xrightarrow{+H_2O} RCH_2C(OH)_2C(Br)_2R \xrightarrow{-HBr}$$

$$RCH_2C(OH)C(Br)R \xrightarrow[\text{ation}]{\text{Isomeris-}} RCH_2\underset{R}{C}(Br)CO_2H \xrightarrow{-HBr} RCH{=}\underset{R}{C}\cdot COOH$$

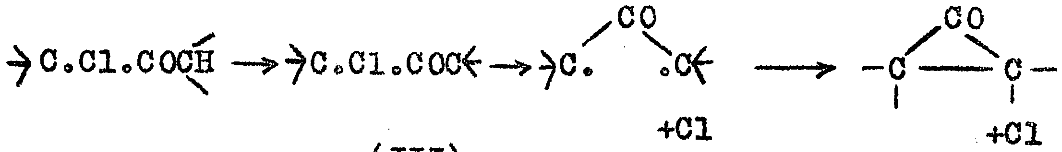
(I)



(II)

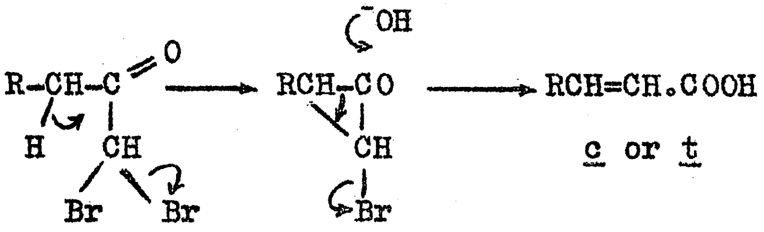
^{-}OH

correctly the products obtained from a large variety of polyhaloketones. Both Loftfield's mechanism and a contemporary suggestion by Aston and Newkirk,[147] that the intermediate took the form of a zwitterion, were considered by Burr and Dewar[148] to be individually inadequate. They proposed (III) the initial formation of a zwitterion, which, they postulated, then cyclised to the Loftfield cyclopropanone intermediate.



(III)

With α,α-dibromoketones a cyclopropanone intermediate is only capable of opening in one way but with the



possibility of both the <u>cis</u> and <u>trans</u> compound being produced.[149]

The ready addition of hypohalous acids to triple bonds has been amply demonstrated by several workers[142,150] and this, together with the subsequent Faworsky rearrangement of the resultant α,α-dihalogenoketones, presented an attractive method of obtaining α,β-unsaturated acids from acetylenic starting materials. It was therefore decided to examine this possibility, using 1-octyne as the model compound.

$$CH_3(CH_2)_5C\equiv CH \rightarrow CH_3(CH_2)_5COCHBr_2 \longrightarrow CH_3(CH_2)_4CH{=}CH.COOH$$

Using <u>N</u>-bromoacetamide as their source of hypobromous acid, the addition to a steroidal ethynyl group has been studied by Salamon and Reichstein[150] For the purposes of the present work, however, it was decided to use *N*-bromosuccinimide and examine the addition of hypobromous acid to both mono- and disubstituted acetylenes. The initial conditions employed for 1-octyne were similar to those described for the addition of hypobromous acid to double bond compounds, *viz.*, *N*-bromosucciminide shaken in a two phase, water-ether mixture with the acetylene. The product from this reaction, however, proved to be 1,2-dibromo-oct-1-ene and not the expected α,α-dibromoketone. A similar result has been obtained by the interaction of *N*-bromoacetamide and tert-α-hydroxyacetylenic alcohols[152] but acetylation of the hydroxyl group allowed normal hypobromous acid addition to take place. The reaction conditions prescribed by Salamon and Reichstein,[150] *viz.*, an aqueous acetic acid solution of sodium acetate, *N*-bromoacetamide and the ethynyl compound, allowed to stand for two hours with only occassional shaking, when applied to 1-octyne gave satisfactory yields of 1,1-dibromo-octan-2-one. The main difference between the two reaction media described above is essentially one of pH and it seems likely, therefore, that the anomalous bromine addition will occur under neutral, or perhaps even alkaline, conditions, whilst an acidic medium, will result in the normal addition of hypobromous acid. Some support for this hypothesis may be found in the work of Braude and Waight,[153] who discovered that the presence of amine or quaternary ammonium salts caused cyclohexene and allylbenzene to react with N-bromosuccinimide by addition of bromine across the double bond.

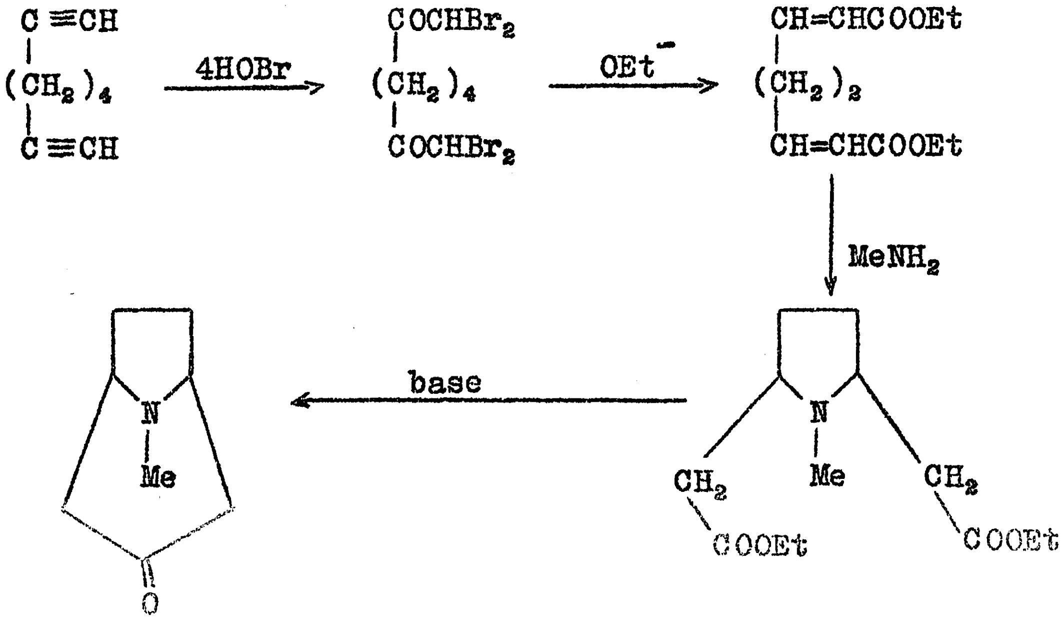
Having established the optimum conditions for the addition of hypobromous acid to a terminal triple bond our attention was directed towards the reaction between N-bromosuccinimide and a compound containing both mono- and di-substituted triple bonds. The readily available undeca-1,7-diyne was chosen as the model compound and, under the same conditions as those used for 1-octyne, gave an α,α-dibromoketone which was shown by its infra-red spectrum, still to contain a free ethynyl group. The reason for this preferential attack on the disubstituted triple bond is not known but the precipitation of the resultant α,α-dibromoketone from the aqueous reaction medium effectively prevented any further reaction with the terminal bond. Such additions of hypobromous acid to a disubstituted triple bond can occur in two ways,

$$2RC\equiv C.R' + 4HOBr \longrightarrow RCOCBr_2R' + RCBr_2COR' + 2H_2O$$

and in an attempt to determine if one or both of these

α,α-dibromoketones were obtained the product was converted to a simple ketone by hydrogenation followed by debromination. The properties of this debrominated material were compared with those of propylheptyl and butylhexyl ketones, the two possible products and found to be similar to both. A separation by G.L.C. was attempted but all three materials showed the same retention times. In fact, the only suitable means of distinguishing between propylheptyl and butylhexyl ketones lay in the melting point of their semicarbazone derivatives, (56° and 75° respectively). The semicarbazone derivative of the material from undeca-1,7-diyne proved to be a low melting solid, m.p. 36°, which chromatography on silica gel failed to purify further.[154] It is, therefore, impossible at the present time to arrive at a definite conclusion regarding the manner in which the hypobromous acid adds across the disubstituted triple bond. The 1,1-dibromo-octan-2-one, obtained by the addition of two moles of hypobromous acid across the triple bond of 1-octyne, on treatment with sodium methoxide at 5°, followed by three hours reflux of the reaction mixture, yielded 1-octenoic acid; as shown by its analysis and infra-red spectrum (1700, 1650 and 968 cm.$^{-1}$). In order to establish the stereochemistry of the double bond, the amide, 1-octenamide, was prepared; purification of this derivative gave a product, m.p. 133-135°, with preliminary softening at 172° (Lit. for *cis* amide, 66-67° and *trans* amide, 134-135°).[155] This fact, together with the appearance of a moderately intense *trans* double bond peak (968 $cm.^{-1}$) in both the acid and the amide, would appear to confirm that the product was mainly the *trans* isomer. Although there was no evidence of a *cis* double bond peak in the infra-red spectrum it is probable that the *cis* isomer was also formed.

The successful preparation of the above α,β-unsaturated acid prompted an investigation into the possible application of this reaction sequence in the synthesis of tropinone, starting from octa-1,7-diyne. The following scheme was examined.



The addition of hypobromous acid to the diyne gave a crystalline tetrabromo-diketone, which proved to be extremely sensitive to base. The attempted Faworsky rearrangement resulted in an intractable gum with a complex infra-red spectrum. It appeared likely that several possible side reactions, e.g. internal aldol condensation, may have taken place.

Since the addition of hypobromous acid across a triple bond gave an α,α-dibromoketone, it was hoped to complement this reaction by obtaining an α-bromoketone from the addition of one mole of ethyl hypobromite followed by hydrolysis.

The addition of a mole of ethyl hypobromite across a disubstituted double bond has already been successfully demonstrated[156] no one, however, had investigated the possibilities of this reaction with triple bond compounds. Once again 1-octyne was chosen as the model compound and on treating this with N-bromosuccinimide, in absolute ethanol at room temperature, the only isolatable product proved to be 1,2-dibromo-oct-1-ene. Reduction of the reaction temperature to -10°, however, gave a colourless oil which decomposed on distillation but which analysed correctly for a product resulting from the addition of two moles of ethyl hypobromite across the triple bond.

Since only the theoretical amount of N-bromosuccinimide was used, it would seem that the rate of addition of this molecule across double bonds may well be faster than the rate of addition across triple bonds. The addition of two moles defeated the purpose of the experiment, hence, a means of converting this product to the required enol-ether was immediately sought. This was satisfactorily accomplished by refluxing the product with activated zinc in absolute ethanol.[157] The structure of the α-bromoketone, obtained by hydrolysis of the enol-ether, was established by an independent synthesis of 1-bromo-octan-2-one and a comparison of their isothiouronium picrate derivatives; these proved to be identical.

PART 2.

SECTION 2.

EXPERIMENTAL.

Oxidation of Octynylmagnesium Bromide.

(i) tert-Butyl Hydroperoxide.

Ethyl bromide (10.9 g.) and magnesium (2.4 g.) were refluxed in 100 c.c. of tetrahydrofuran solution for one hour in a nitrogen atmosphere. 1-Octyne (11.0 g.) was added, in tetrahydrofuran (50 c.c.), over 30 minutes and the mixture allowed to reflux under nitrogen for 20 hours. The final reaction mixture, on cooling, precipitated a white crystalline solid.

tert-Butylhydroperoxide (9.0 g.) was dissolved in 100 c.c. of tetrahydrofuran and the solution cooled to 0°C. The octynylmagnesium bromide was slowly added, in small portions, as a slurry in tetrahydrofuran, to this cooled solution and the mixture stirred for one hour at 0° and one hour at room temperature. The complex was decomposed by addition of dilute sulphuric acid and the residue ether extracted. Working up in the usual manner yielded no acidic material but 18.0 g. of neutral material, the infra-red spectrum of which showed it to consist of a mixture of 1-octyne and the hydroperoxide. The latter was largely removed by washing with ferrous ammonium sulphate solution, (5 x 100 c.c.) and the residue, on careful distillation, yielded pure 1-octyne (9.7 g.), b.p. 124-126°, n_D^{20} 1.4155 (Lit., b.p. 126°, n_D^{20} 1.4159).

(ii) tert-Butyl Perbenzoate.

The octynylmagnesium bromide, prepared as above (from 11.0 g. 1-octyne, 10.9 g. ethyl bromide and 2.4 g. magnesium) was added, in small portions as a slurry in tetrahydrofuran, to the cooled (0°) solution of the perbenzoate (19.0 g.) in the same solvent. On working up in the usual manner both acidic and neutral fractions were obtained.

The acidic fraction yielded white plate crystals (1.5 g.), m.p. 125°, undepressed on mixing with an authentic sample of benzoic acid. The neutral fraction (26.3 g.) appeared, from its infra-red spectrum, to be a mixture of starting materials and was exhaustively washed with ferrous ammonium sulphate solution to remove the perbenzoate. Careful distillation of the residue gave pure 1-octyne (9.0 g.), b.p. 125-126°, n_D^{20} 1.4156.

(iii) Trimethyl Borate and Hydrogen Peroxide.

The octynylmagnesium bromide was prepared using exactly the same quantities and procedure as before but in this case with ether as the solvent. The resultant slurry was added to a stirred ethereal solution of trimethyl borate (11.45 g.) cooled to -80°, over a period of 30 minutes and the reaction mixture then allowed slowly to attain room temperature. Still under an atmosphere of nitrogen and with continuous stirring, 100 c.c. of 10% hydrochloric acid was slowly run into the above solution and after a further 15 minutes the acidic phase was separated off. The ether layer was washed twice with water and an aqueous hydrogen peroxide solution (30 c.c. of 10% H_2O_2) slowly added. After the addition the mixture was stirred for 30 minutes, the layers then separated and the ether layer freed from peroxide by washing with ferrous ammonium sulphate (6 x 100 c.c.). The ether layer was then worked up in the usual manner to give a neutral fraction only, distillation of which yielded unchanged octyne (9.5 g.) b.p. 126°, n_D^{20} 1.4155.

(iv) Oxidation of Phenylacetylenemagnesium Bromide with Oxygen.

The phenylacetylenemagnesium bromide was prepared in the usual manner (5.1 g. phenylacetylene, 5.4 g. ethyl bromide and 1.2 g. magnesium in 150 c.c. tetrahydrofuran), in a 250 c.c. three-necked flask which was then fitted with a 'Vibromischer' agitator and attached to a hydrogenation type apparatus. The whole apparatus was first flushed with dry oxygen, then sealed off from the atmosphere under a slight positive pressure of oxygen. The acetylenic Grignard was violently agitated in this oxygen atmosphere, at room temperature for 7 hours, resulting in an apparent uptake of 165 c.c. of oxygen. Decomposition of the complex with dilute acid and working up the residue in the usual manner gave unchanged phenylacetylene (3.7 g.) and some diphenyldiacetylene (0.8 g.) m.p. 84-86° and mixed m.p. with an authentic sample of diphenyldiacetylene 83-85°.

Preparation of O-Methylhydroxylamine.

O-Methylhydroxylamine was prepared, as its hydrochloride, by the method of Rollefson and Aldershaw[131] and of Andrewes, King and Walker.[132] The free amine, generated by treatment of the hydrochloride with strong base, had b.p. 50-51°.

Preparation of O-Benzylhydroxylamine.

O-Benzylhydroxylamine was prepared using the procedure of Fuller and King.[133] The clear oil had b.p. 110°/22 m.m. (Lit. b.p. 118-119°/30 m.m.). (Found: C, 68.0; H, 7.2; N, 11.3% C_7H_9NO requires C, 68.2; H, 7.3; N, 11.4%).

Action of O-Methylhydroxylamine on Octynylmagnesium Bromide.

The Grignard of 1-octyne was prepared in the usual manner (7.0 g. octyne, 7.0 g. ethyl bromide and 1.54 g. magnesium in 100 c.c. ether) and the solution cooled to -40° before addition of an ethereal solution of excess O-methylhydroxylamine. The first few drops of the amine resulted in the immediate formation of a white solid. After the addition the mixture was maintained at -40° for one hour, then slowly allowed to attain room temperature. The complex was decomposed with dilute hydrochloric acid, ether extracted and the extract worked up in the usual manner to give a brown oil which distilled to a colourless liquid (3.4 g., 42%) b.p. 88°/10 m.m.
(Found: C, 76.7; H, 12.0; N, 11.0% $C_8H_{15}N$ requires
C, 76.8; H, 12.0; N, 11.2%).
The nitrile was ~~-~~hydrolysed by refluxing with 4.0 g. of potassium hydroxide in aqueous ethanol for 12 hours to give crude octanoic acid (2.9 g., 74%) b.p. 135-136°/21 m.m. n_D^{20} 1.4282. (Lit., b.p. 124°/10 m.m., n_D^{20} 1.4285).

The overall yield from 1-octyne was 31%.

Action of O-Benzylhydroxylamine on Octynylmagnesium Bromide.

The 1-octyne Grignard (from 11.0 g. octyne, 10.

ethyl bromide, 2.4 g. magnesium) was prepared by refluxing the above mixture in tetrahydrofuran overnight under nitrogen. The mixture was cooled to −40° and O-benzylhydroxylamine (6.45 g.), in 25 c.c. of tetrahydrofuran, added over 30 minutes with vigorous stirring. The temperature was maintained at −40° for one hour then allowed slowly to attain room temperature. The resultant complex was decomposed with dilute acid, the solution extracted with ether several times and the extract worked up in the usual manner to give a yellow oil. Distillation of this oil yielded 3.7 g. of 1-octyne, b.p. 70°/25 m.m., 4.13 g. of a material, b.p. 96°/15 m.m. - the infra-red spectrum of which showed it to contain a nitrile plus an alcohol - and a residue of high boiling oil which was not examined. The nitrile and alcohol mixture was refluxed with 4.0 g. of potassium hydroxide in aqueous ethanol for 15 hours, the mixture then poured into dilute acid and ether extracted. The extract was washed several times with water, to remove the last trace of alcohol, dried over magnesium sulphate and evaporated to give octanoic acid (2.3 g.) b.p. 134-136°/ 20 m.m., n_D^{18} 1.4300.

(Found: C, 66.5; H, 11.0% $C_8H_{16}O_2$ requires C, 66.6; H, 11.1%)

The overall yield from 1-octyne was 30% based on the O-benzylhydroxylamine used.

Reaction of N-Bromosuccinimide with 1-Octyne.

(i) 1,2-Dibromo-oct-1-ene.

1-Octyne (5.0 g.) and N-bromosuccinimide (22.5 g., 70% excess) were added to a water-ether (1:1; 60 c.c.) mixture and the whole agitated for 20 hours. The ether layer was then separated from the aqueous layer, washed with sodium metabisulphite, bicarbonate and water, dried over magnesium sulphate and evaporated. The resultant yellow oil showed peaks in its infra-red spectrum at 3070, 1600 and 1480 cm.$^{-1}$ as well as a weak carbonyl peak.

Distillation of the liquid (52°/0.5 m.m.) gave an almost colourless oil (10.7 g.) plus a little high boiling residue, which was not examined. This oil had the same infra-red spectrum as before but with no trace of carbonyl peaks and somewhat enhanced double bond peaks.
(Found: C,35.7; H,5.2; Br,58.8% $C_8H_{14}Br_2$ requires
C,35.6; H,5.2; Br,59.2%).
Reflux of a small sample of this compound with zinc in absolute ethanol yielded 1-octyne. The structure of this compound, therefore, can only be $CH_3(CH_2)_5CBr{=}CHBr$ (yield 88% n_D^{25} 1.5020).

(ii) 1,1-Dibromo-octan-2-one.

Sodium acetate trihydrate (40.0 g.) was dissolved and N-bromosuccinimide (48.0 g., 100% excess) partially dissolved, in an acetic acid-water mixture (3:2, 500 c.c.) to which was added 1-octyne (8.8 g.) in 10 c.c. of acetic acid. After allowing this mixuure to stand for two hours, with only occassional shaking, the precipitated oil was separated from the aqueous phase by decantation. The combined oil and ether extracts of the aqueous phase were washed with metabisulphite, bicarbonate and water, dried over magnesium sulphate and evaporated, to give a dark, yellow oil which distilled at 80-82°/0.4 m.m. to a clear yellowish oil n_D^{21} 1.4950 (15.6 g., 68%).
(Found: C,33.5; H,5.1; Br,55.9% $C_8H_{14}Br_2O$ requires C,33.6; H,4.9; Br,56.0%).

Using Brady's reagent the 2,4-dinitrophenylhydrazone derivative was prepared, crystallised from absolute ethanol, dried in a vacuum pistol for three days at 70° and analysed, m.p. 179-180°.
(Found: C,47.7; H,4.3; N,22.4% Required for the structure $CH_3(CH_2)_5CRCHR$ where R is the 2,4-dinitrophenylhydrazine radical C,47.8; H,4.4; N,22.3%).

Faworsky Rearrangement of 1,1-Dibromo-octan-2-one.

Sodium (5.0 g.) was dissolved in 150 c.c. of absolute ethanol and the solution temperature reduced to 5° by external cooling. The dibromoketone (14.0 g.) was dissolved in 50 c.c. of ethanol and added to the stirred sodium ethoxide solution over a period of one hour, the temperature of the reaction mixture being maintained at 5° throughout. The final mixture was refluxed on a steam bath for three hours, then diluted with water, acidified and ether extracted. The extract was washed several times with water, dried over magnesium sulphate and evaporated, to give a colourless oil (3.5 g., 50.4%) b.p. 94°/0.4 m.m., n_D^{18} 1.4590. (Reported for *trans*-1-octanoic acid, b.p. 143° 15 m.m., n_D^{17} 1.4610). $\nu_{\max.}^{\text{film}}$ 1700 (carboxyl), 1650 (CH=CH) and 968 cm.$^{-1}$ (*trans* CH=CH).

(Found: C,67.5; H,9.7% $C_8H_{14}O_2$ requires C,67.6; H,9.9%).

The acid chloride of 2.0 g. of this acid was prepared by treatment with oxalyl chloride in tetrahydrofuran. On bubbling gaseous ammonia through this solution for a few minutes, a white solid was precipitated, which crystallised from water in large flakes, m.p. 133-135° (crude material 1.5 g., 70%). (Reported for *trans*-1-octanamide m.p. 134-135°).

(Found: C,67.8; H,10.4; N,10.0% $C_8H_{15}NO$ requires C,68.0; H,10.6; N,9.9%).

Reaction of N-Bromosuccinimide with Octa-1,7-diyne.

Octa-1,7-diyne (3.5 g.) in glacial acetic acid (50 c.c.) was added to a mixture of N-bromosuccinimide (47.0 g., 100% excess) and sodium acetate trihydrate (40.0 g.) in acetic acid (400 c.c.) and water (200 c.c.) The mixture was vigorously stirred for 2.5 hours to prevent precipitation of any mono-ethynyl compound. On allowing to settle a white crystalline solid was precipitated which was readily removed by filtration and crystallised from aqueous acetic acid. The filtrate, on further dilution, precipitated more crystalline material which was recovered as above. A continuous ether extraction of the filtrate, followed by removal of the ether and dilution of the residual acetic acid solution with water, yielded a final batch of crystals. Any attempt to neutralise the acetic acid solution by the addition of bicarbonate apparently resulted in decomposition of the product. The collected crystalline material crystallised from aqueous acetic acid or ethanol as hard white plates (9.1 g., 60%) m.p. 77-78°.
(Found: C, 21.1; H, 2.0; Br, 69.5% $C_8H_{10}Br_4O_2$ requires C, 21.0; H, 2.2; Br, 69.7%).

Attempted Faworsky Rearrangement of α,α,ω,ω-Tetrabromo-octa-2,7-dione.

Sodium (0.5 g.) was dissolved in ethanol (50 c.c.) and the solution cooled to 0°. The diketone, dissolved in 50 c.c. of ethanol, was added dropwise at such a rate that the temperature of the reaction mixture did not rise above 3°. When 10 c.c. of the diketone solution had been added, the mixture darkened in colour and a brown precipitate separated. After the addition was complete the mixture was refluxed on a steam bath for three hours and, on working up in the usual manner, yielded a black intractable gum, which chromatography failed to purify. Since it was obvious that the extensive decomposition of the starting material had occurred, the gum was not further examined.

Reaction of N-Bromosuccinimide with Undeca-1,7-diyne.

Undeca-1,7-diyne (7.8 g.) was dissolved in 10 c.c. of glacial acetic acid and added to a solution of N-bromosuccinimide (17.8 g. - stoichiometric quantity for reaction with one triple bond) and sodium acetate trihydrate (15.7 g.) in an acetic acid-water mixture (1:1, 400 c.c.). The mixture was allowed to stand for two hours, with occassional shaking, before working up, as for 1-octyne, to give a golden oil b.p. 96-98/0.4 m.m.

(14.1 g., 87%). $\nu_{max.}^{film}$ 3300 (C≡CH) and 1745 cm.$^{-1}$ (COCBr$_2$)
(Found: C,40.8; H,5.2% $C_{11}H_{16}Br_2O$ requires
C,40.7; H,5.0%).

Hydrogenation of a sample of this oil (5.0 g.), in ethyl acetate solution, over 10% palladium on calcium carbonate, gave an unstable, yellow oil b.p. 83-84°/0.02 m.m. On refluxing this oil with amalgamated zinc powder and glacial acetic acid, for 10 hours, a clear liquid with a strong fruity odour was obtained, which still contained bromine. Careful fractional distillation, however, yielded a ketonic material free of halogen (1.4 g., 54%) b.p. 118°/20 m.m., n_D^{20} 1.4259. Examination of this material by G.L.C. (column temperature 113° and Argon flow rate 42 c.c./min.) showed it to be identical with either propylheptyl or butylhexyl ketones, both these known ketones and the product having the same retention time, R_T 12 mins., no identification was possible by G.L.C., even when a carbowax column was used.

The ketonic material (0.8 g.) was added, in methanol, to a solution of semicarbazide hydrochloride (2.25 g.) in water (5 c.c.) and pyridine (3.0 g.) added dropwise to the mixture. The resultant solution was heated on a steam bath for a few minutes, allowed to cool and the precipitated oil extracted.

This oil was dissolved in chloroform saturated with water (2 c.c.) and the solution poured onto a 2 cm. diameter column of silica gel (30.0 g.) to which 60% water had been added, by weight. Elution with aqueous, saturated chloroform (7 x 25 c.c. fractions) yielded a residue only in the first two fractions. This semi-crystalline material, after drying in a vacuum pistol at room temperature for 48 hours, had m.p. 30-36°.

The semicarbazones of authentic samples of propylheptyl and butylhexyl ketones were prepared as above and a separation of a mixture of these two derivatives attempted by chromatography with no success.

Reaction of N-Bromosuccinimide with 1-Octyne in Ethanol.

Finely powdered, recrystallised N-bromosuccinimide (25.0 g., 0.2 moles excess) was added to a solution of 1-octyne (12.5 g.) in absolute ethanol (150 c.c.), at -10°, over a period of 10 hours. The mixture was continuously stirred for a further 10 hours at -10°, then allowed to attain room temperature over 4 hours. The mixture was again cooled, to ensure that all the succinimide and unchanged N-bromosuccinimide would come out of solution and filtered; the solid residue had m.p. 124° (succinimide m.p. 126°).

The alcoholic filtrate was diluted in a large volume of water, the precipitated oil separated off and the aqueous residue ether extracted. The oil was added to this ether extract which was then washed with a bicarbonate solution and water, dried over magnesium sulphate and evaporated. The colourless oil showed only a trace of ethynyl, no carbonyl and no double bond peaks in the infra-red. There was no peak at 780 cm.$^{-1}$, apparently characteristic of the compound $CH_3(CH_2)_5CBr{=}CHBr$ obtained in previous attempts. Distillation at any pressure down to 0.01 m.m. resulted in decomposition of the bulk and a small distillate of double bond material, the analysis of which did not correspond to any of the possible products. The crude material was therefore placed under suction (12 m.m.), at room temperature, till no trace of 1-octyne showed in its infra-red spectrum, the octyne thus removed being collected in a cold trap, (5.7 g.) and the residual colourless oil analysed.
(Found: C, 40.3; H, 6.5; Br, 44.4; OEt, 24.7% $C_{12}H_{24}Br_2O_2$ requires C, 40.1; H, 6.6; Br, 44.4; OEt, 25.0%).
$\nu_{max.}^{film}$ 1050 cm.$^{-1}$ (ether).
The yield of this compound (n_D^{25} 1.4689) was 20.0 g. (79% based on the N-bromosuccinimide used).

A sample of this material was refluxed for one hour on a steam bath in ethanolic, dilute sulphuric acid and yielded a carbonyl compound which gave a 2,4-dinitrophenylhydrazone derivative, m.p. 179-180°, undepressed on mixing with a sample of the derivative obtained from 1,1-dibromo-octan-2-one thus proving that the structure of the original material must have been $CH_3(CH_2)_5C(OEt)_2CHBr_2$.

<u>Treatment of 1,1-dibromo-2,2-diethoxyoctane with activated zinc.</u>

1,1-Dibromo-2,2-diethoxyoctane (1.88 g.), in 50 c.c. of absolute ethanol, was refluxed, on a steam bath, with activated zinc (0.8 g.), for 5 hours. The mixture was filtered, washed with ammonium chloride solution and ether extracted to give a clear oil (0.88 g., 72%), b.p. 58°/0.8 m.m.

(Found: C,50.8; H,8.1; Br,34.2% $C_{10}H_{19}BrO$ requires
C,51.0; H,8.2; Br,34.2%)

$\nu_{\text{max.}}^{\text{film}}$ 3100 (CH=CH), 1620 and 855 (CH=C$<$) and 1110 cm.$^{-1}$ (ether).

Hydrolysis of this material as above yielded 1-bromo-octan-2-one, characterised by its isothiouronium picrate derivative, m.p. 185-187°.

(Found: C, 42.3; H, 4.5; N, 16.0% $C_{14}H_{21}N_5O_8S$ requires
C, 42.0; H, 4.8; N, 16.2%).

1-Bromo-octan-2-one was also prepared, by treating the acid chloride of heptanoic acid with diazomethane and the resultant compound with a 40% v/v solution of hydrobromic acid in glacial acetic acid. The isothiouronium picrate derivative of this ketone had m.p. 186-187°, undepressed on mixing with that obtained previously.

PART 3.

SYNTHETIC APPROACHES TO CYCLODODECA-1,5,9-TRIYNE.

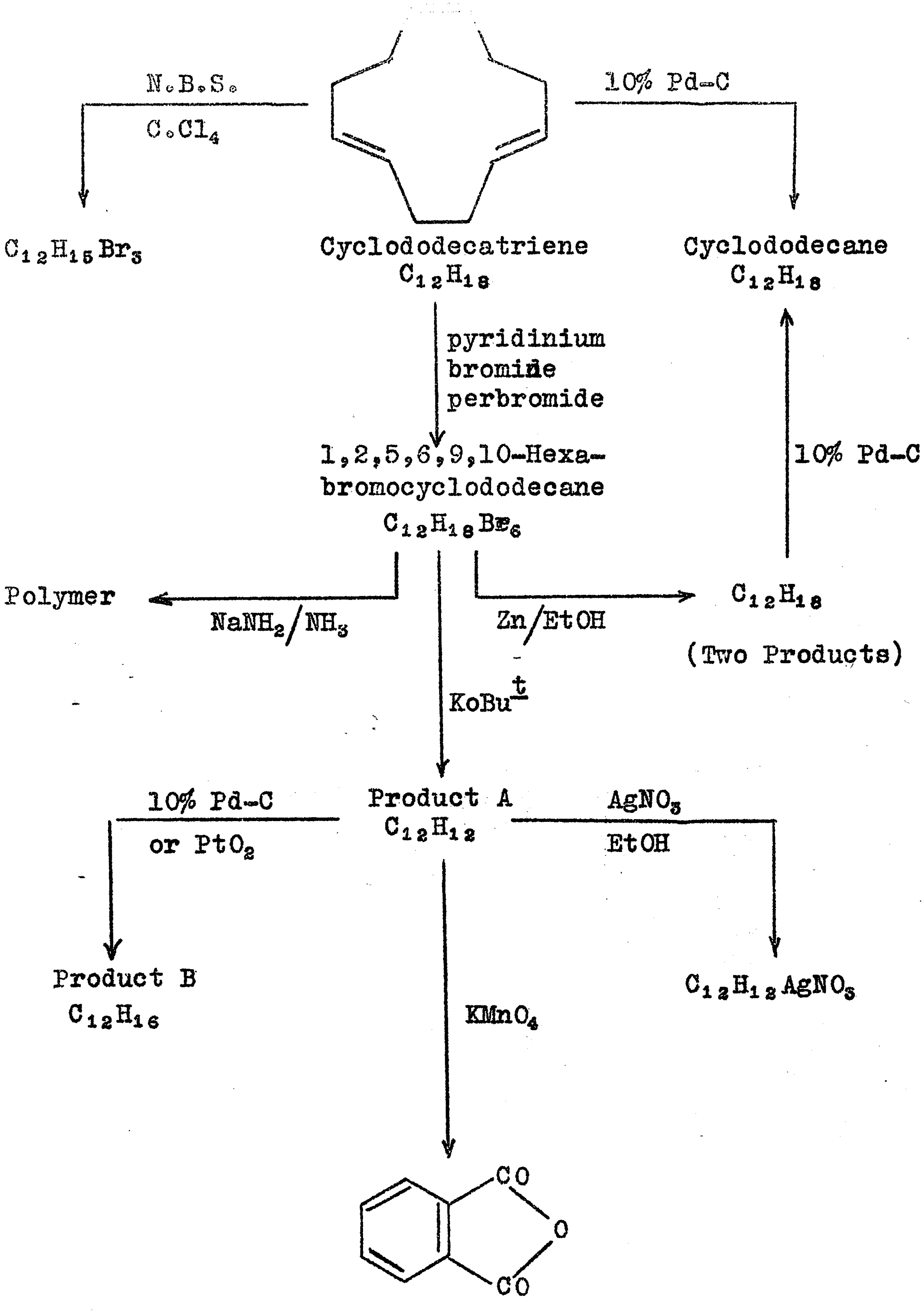

N.B.S.
C.Cl$_4$
$C_{12}H_{15}Br_3$
10% Pd-C
Cyclododecatriene
$C_{12}H_{18}$
Cyclododecane
$C_{12}H_{18}$
pyridinium
bromide
perbromide
1,2,5,6,9,10-Hexa-
bromocyclododecane
$C_{12}H_{18}Br_6$
10% Pd-C
Polymer
$NaNH_2/NH_3$
Zn/EtOH
$C_{12}H_{18}$
(Two Products)
KoBu$^{\underline{t}}$
10% Pd-C
or PtO_2
Product A
$C_{12}H_{12}$
$AgNO_3$
EtOH
Product B
$C_{12}H_{16}$
$C_{12}H_{12}AgNO_3$
$KMnO_4$
CO
O
CO

Figure 11.

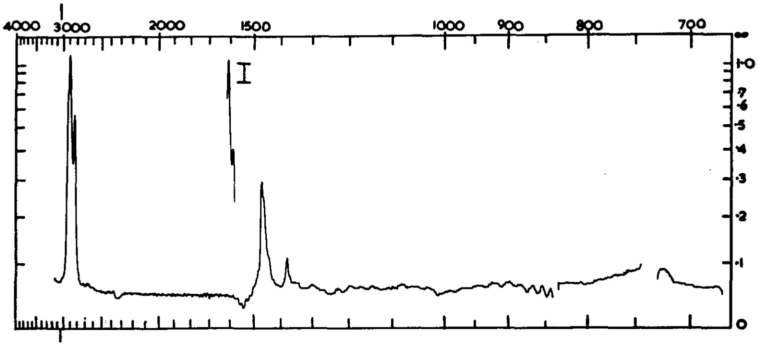
Synthetic Approaches to *Cyclododeca*-1,5,9-*triyne*.

An interesting direct formation of the twelve-membered carbocyclic ring system, has recently been acheived, in high yield, by the titanium tetrachloride-diethylaluminium chloride trimerisation of butadiene, to give cyclododeca-1,5,9-triene[158] (Figure 12c). The main product was reported to be the *cis-trans-trans* isomer together with a little of the all *trans* hydrocarbon; very recent work[159] has suggested the main constituent to be the *cis-cis-trans* isomer. As yet, little work has been done on this interesting hydrocarbon, though the all *trans* isomer has been reported to form a boron derivative[160] under conditions analogous to those used in the formation of trialkylboranes from simple olefins.[161] The ready availability of this triene[162] prompted an investigation into its potentialities as a starting material for the synthesis of cyclododeca-1,5,9-triyne, a hitherto unreported cyclic polyacetylene, which might be expected to have interesting properties.

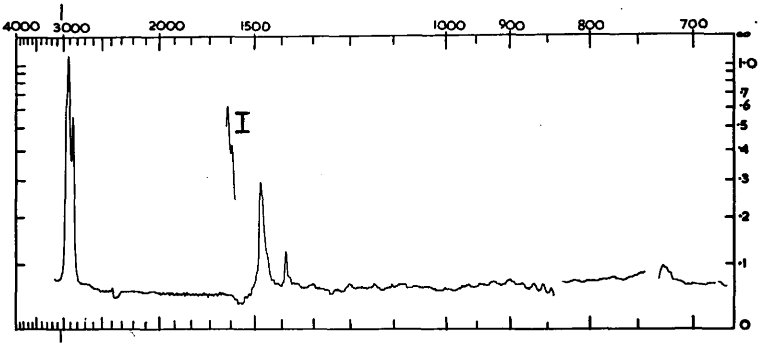
The obvious approach to this problem involved the bromination of the triene, followed by a dehydrobromination with strong base. Direct bromination of cyclododeca-1,5,9-triene was unsuccessful, the product being an intractable gum. Use of the reagent, pyridinium bromide

All spectra measured in carbon tetrachloride solution (75 mgs. [illegible] cell). Region 840–740 cm.$^{-1}$ – Film. (a), (b), and (c) clearly show the similarity between the spectra of straight chain hydrocarbons, (a) and (b), and the changes to be expected on the formation of a saturated aliphatic cyclic hydrocarbon (c).

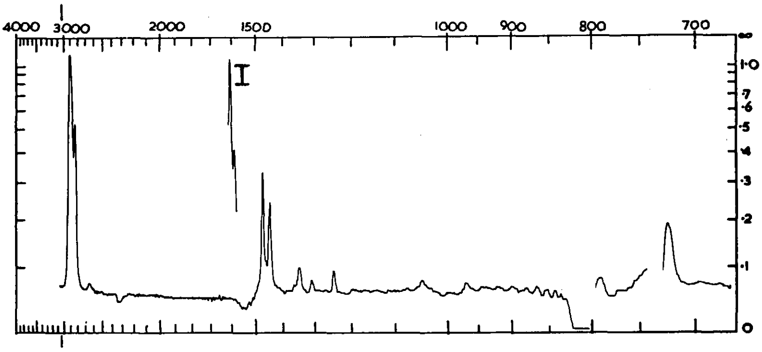
(a) n-Tetradecane.



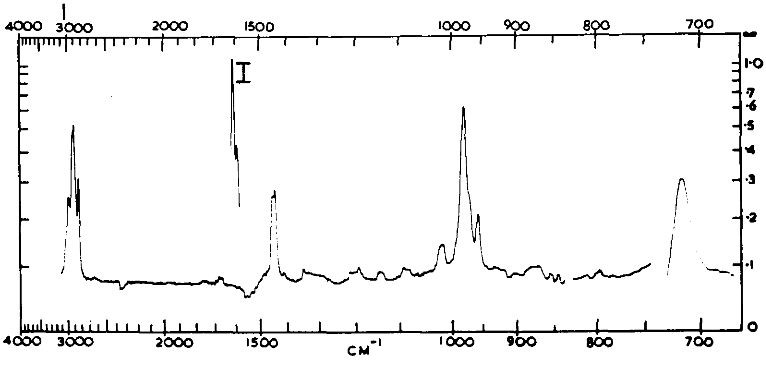
(b) n-Dodecane.



(c) Cyclododecane.



(d) Cyclododeca-1,5,9-triene.



I – polystyrene reference peak.

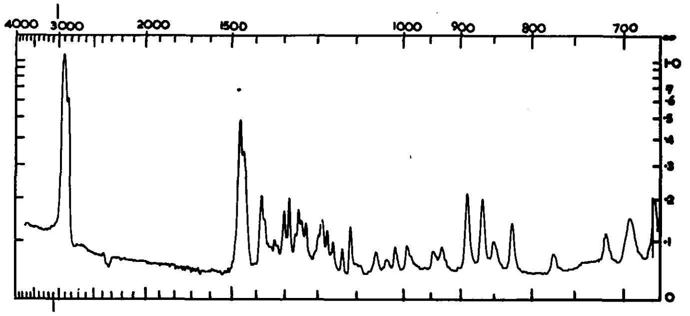
Figure 12.

perbromide,[120] however, in a benzene-methanol solution, yielded a crystalline hexabromide (Figure 13a) on which all subsequent reactions were performed. Treatment of this material with amalgamated zinc powder, in absolute ethanol, gave a colourless oil, which was shown by G.L.C. to contain two product, the retention time of the major product co-inciding with that of the starting cyclododeca-1,5,9-triene. A hydrogenation of a sample of the mixed product yielded cyclododecane only, shown by a G.L.C. examination and a mixed melting point with an authentic sample. The identity of the second product resulting from the debromination of the hexabromide has not yet been established but in view of the hydrogenation results it is certainly a monocyclic isomer of the triene.

Dehydrobromination of the hexabromide was first attempted using sodamide in liquid ammonia. If the reaction mixture was allowed to stand overnight before addition of ammonium chloride to destroy excess sodamide, the resultant gum showed no evidence of the presence of triple bonds, as evinced by the infra-red spectrum, whilst a G.L.C. examination of a hydrogenated sample failed to detect the presence of any cyclododecane. The addition of the ammonium chloride one hour after the start of the reaction, yielded a product which showed strong double bond peaks in the infra-red (1645, 974 and 853 cm.$^{-1}$) but still proved to be highly brominated. It would appear that the critical reaction time lay somewhere between the one hour and ten hours tried, prolonged contact with the sodamide resulting in polymer formation. In view of this, it was decided to abandon sodamide in favour of potassium tert-butoxide. The reactants in this case were held, in diglyme solution, at a temperature of 70° to 80° for 4.5 hours and the course of the reaction followed by an estimation (Volhard's method) of the bromide ion in the mixture. The product from this reaction was obtained as a yellow, mobile oil after alumina chromatography. This compound, termed temporarily product A (Figure 11), was shown by G.L.C. to be essentially pure; it proved to have a very interesting infra-red spectrum (Figure 13b) indicating strong aromatic character, (3000, 1500 and 760 cm.$^{-1}$), the presence of methylene groups (2900, 1450 cm.$^{-1}$) and cis double bonds (3040, 675 cm.$^{-1}$). Several microhydrogenations of A demonstrated the presence of two ethylenic double bonds and the ultra-violet spectrum of the resulting tetrahydro compound, product B, proved to be typically that

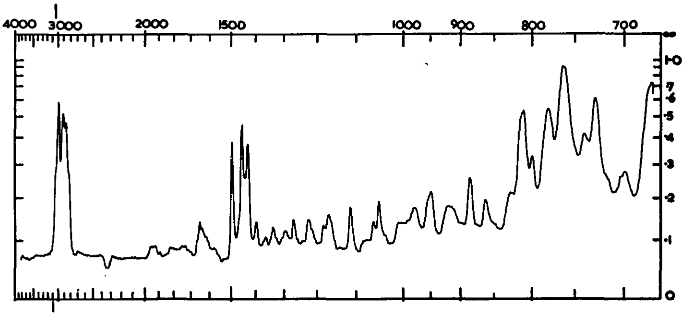
(a) 1,2,5,6,9,10-Hexabromocyclododecane.

(Nujol)



(b) Product A.

(Film)



(c) Product B.

(Film)

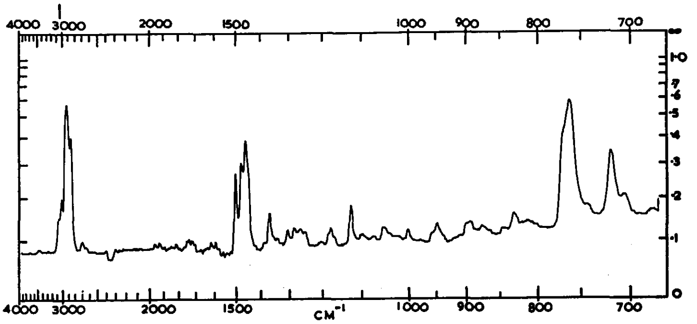
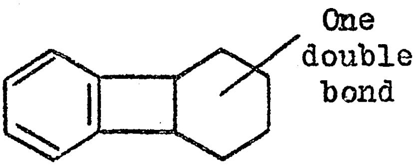
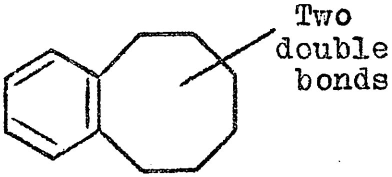


Figure 13.

of a simple *o*-disubstituted benzene (Figure 14b). Further confirmation of this benzene substitution pattern was obtained by the ready oxidation of A to phthalic anhydride in good yield. Since the analysis of A corresponded to a molecular formula of $C_{12}H_{18}$, the most probable structure for B is 1,2-benzocyclo-oct-1-ene. Such a product could be obtained by the hydrogenation of compounds of either type (Ia) or (Ib). Structure (Ia) might well undergo hydrogenolysis of the four-membered ring under the influence of platinum but such a ring fission would be most unlikely with palladium. The fact that the same product, B, was isolated when the hydrogenation was carried out in the presence of either platinic oxide or palladium charcoal would seem, therefore, to favour structure (Ib).

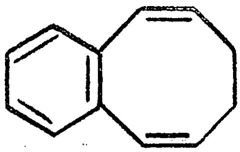


(Ia)



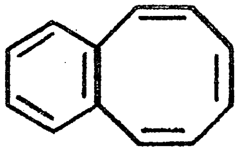
(Ib)

The only structural problem thus remaining in the case of product A, is the position of the two ethylenic double bonds in the eight membered ring. A series of compounds (II, III, IV, and V) closely related to this system has been recently reported by Wittig.[163] The infra-red spectrum of product A was strikingly similar to those of both (II) and (V); its ultra-violet spectrum, was entirely different from that of (II) but essentially similar to that of (V), (Figure 14a). A further comparison of product A, with Wittig's compound (II) is shown as follows.



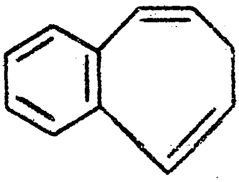
1,2-Benzocyclo-octa-1,3,7-triene.

(II)



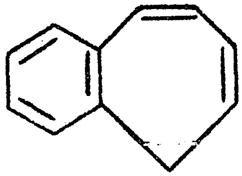
1,2-Benzocyclo-octa-1,3,5,7-tetraene.

(III)



1,2-Benzocyclohepta-1,3,6-triene.

(IV)



1,2-Benzocyclohepta-1,3,5-triene.

(V)

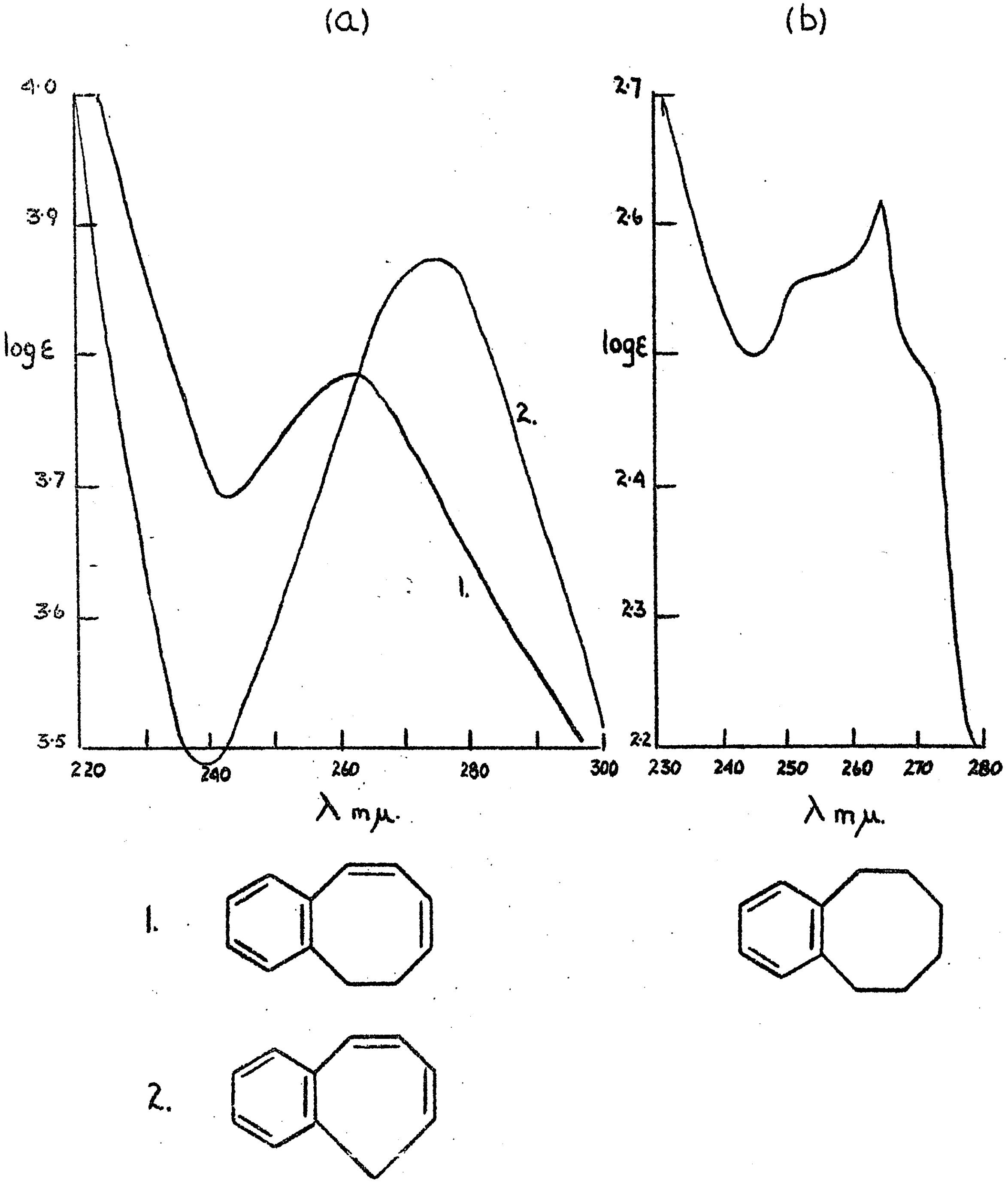
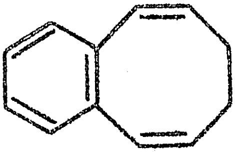
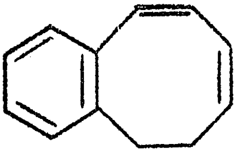

(a)
(b)
4·0
3·9
3·7
3·6
3·5
log ε
220
240
260
280
300
λ mμ.
1.
2.
2·7
2·6
2·4
2·3
2·2
230
250
270

Figure 14

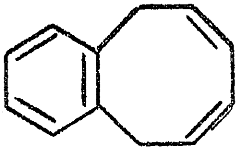


		Product A
1.5983	n_D^{20}	1.5980
74–75°/0.8 m.m.	b.p.	~70°/0.8 m.m.
163–165	$AgNO_3$ adduct m.p.	140–141 (dec.)
226 mμ	$\lambda_{max.}$	264 mμ
4.65	log ε	3.78

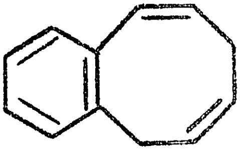
The remaining three isomers of the 1,2-benzocyclooctatriene series not discussed by Wittig are shown below.



(VI)



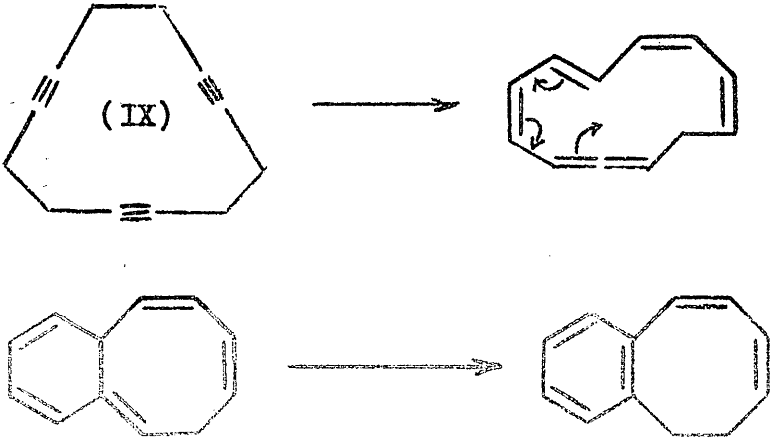
(VII)



(VIII)

A Rudloff oxidation of A, designed to restrict the oxidation to the double bonds only, was followed by a methylation of the products and the resultant methyl esters examined by G.L.C.; a peak coincident with that given by dimethyl oxalate was obtained. This would seem to point to the presence of a conjugated diene and thus, would eliminate structure (VIII). The resistance of product A to attempted acid isomerisation would seem also to argue against structure (VII), in which the ethylenic double bonds would have a strong tendency to migrate into conjugation with the benzene nucleus; further, the ultra-violet spectrum of A was not in accord with this chromophore. The above comparison with Wittig's isomer (II) clearly showed that product A did not possess this structure. Thus, by elimination 1,2-benzocyclo-octa-1,3,5-triene was considered to be the most likely constitution for A, this conclusion being supported by the previously mentioned resemblance between the ultra-violet spectra of A and the analogous 1,2-benzocyclohepta-1,3,5-triene (V).

The mechanism of the formation of this compound, 1,2-benzocyclo-octa-1,3,5-triene, is obscure. It is not unlikely that the expected product cyclododeca-1,5,9-triyne - (IX), was first formed and then, in a series of base catalysed prototropic shifts, rearranged to the bicyclic molecule obtained. A similar mechanism has



1,2-benzo-cyclo-octa-1,3,5-triene.

already been suggested to account for the rearrangement of diacetylenes to aromatic compounds.[164]

A further bromination of cyclododecatriene was attempted, using N-bromosuccinimide, with the intention of brominating all six allylic centres. Reflux of the reactants in carbon tetrachloride, for 7 hours yielded an unstable gum, the analysis of a semi-crystalline sample of which clearly showed that only three bromine atoms had entered the molecule. An infra-red spectrum of this material showed pronounced double bond peaks (3030, 1660 and 960 $cm.^{-1}$) but little else. In the hope of obtaining some transannular reactions this material was refluxed with zinc powder in absolute ethanol for 10 hours. The oil obtained still contained bromine but had an infra-red spectrum essentially similar to that of cyclododecatriene. This material was not further examined.

PART 3.

EXPERIMENTAL

Cyclododeca-1,5,9-triene.

The colourless oil had b.p. 115° 20 m.m., n_D^{20} 1.5078 (Found: C,86.5; H,14.6% $C_{12}H_{18}$ requires C,86.4; H,14.6%). $\nu_{max.}^{film}$ 3010 (CH=CH) and 970 cm.$^{-1}$ (*trans* CH=CH)(Figure 12d). $\lambda_{max.}^{hexane}$ 200 mμ. (ε 7,000).

Cyclododecane.

Cyclododeca-1,5,9-triene (1.0 g.) in ethyl acetate (25 c.c.) was hydrogenated over 10% palladium on charcoal (100 mgs.) The uptake of hydrogen stopped after 7 hours, when 32 c.c. had been absorbed. The solution was filtered and the solvent removed, under vacuum to give crystalline cyclododecane, which crystallised from methanol as long needles, m.p. 60-61° (0.96 g., 90%).
(Found: C,85.4; H,14.2% $C_{12}H_{24}$ requires C,85.7; H,14.3%).

1,2,5,6,9,10-Hexabromocyclododecane.

(i) Bromination with Liquid Bromine.

Cyclododecatriene (4.05 g.) in benzene (100 c.c.) was cooled to 10° and a solution of liquid bromine, (12.0 g.) in benzene (50 c.c.) slowly added over 45 minutes. After 80% of the bromine had been added a yellow colour persisted, the final solution being deep red.

This solution was allowed to stand overnight and the excess bromine destroyed by addition of sodium metabisulphite solution. The benzene solution was then washed with bicarbonate, water, dried over magnesium sulphate and evaporated.

The resultant brown gum (8.0 g.) was chromatographed on alumina (Grade 3, 60 g.). No separation into clear cut fractions was possible and since the gum could not be crystallised and still showed evidence of double bonds ($\nu_{max.}$ 970 cm.$^{-1}$) this procedure was abandoned.

(ii) Bromination with Pyridinium Bromide Perbromide.[120]

Cyclododecatriene (15.0 g.) in benzene-methanol (1:1, 200 c.c.) was stirred at room temperature and a solution of pyridinium bromide perbromide (90 g.) in pyridine-methanol (4:1, 200 c.c.) added over 5 hours. The final mixture was allowed to stand overnight, then poured into a large volume of water (2 l.). The precipitated bromo-compound was separated from the aqueous solution and dissolved in ethyl acetate (200 c.c.). This solution was combined with the ethyl acetate extracts of the aqueous layer and the whole washed with dilute sulphuric acid, bicarbonate, water and dried over magnesium sulphate. The solvent was removed under suction to give asemi-crystalline colourless gum, which was dissolved in the minimum of hot ethyl acetate to give, on cooling, 1,2,5,6,9,10-<u>hexabromocyclododecane</u> as white plates, m.p. 199-200° (30.1 g.). This yield constituted an 80% conversion, since 5.5 g. of the cyclododecatriene were recovered from the mother liquors. The infra-red absorption curve of this compound is shown in Figure 13a.

(Found: C, 22.7; H, 2.7; Br, 74.5% $C_{12}H_{18}Br_6$ requires
C, 22.5; H, 2.8; Br, 74.7%).

<u>Tribromocyclododeca</u>-1,5,9-<u>triene.</u>

Cyclododecatriene (3.0 g.) and <u>N</u>-bromosuccinimide (20 g. - theoretical quantity for bromination of the six allylic centres) were stirred in refluxing carbon tetrachloride (200 c.c.) for 7 hours. The final mixture was freed of suspended solid by filtration and the filtrate evaporated to give a gum which partially crystallised from an ether-petrol mixture in small plate crystals, m.p. 124-125° (5.8 g., 87%). The analysis indicated that only three of the allylic centres had been brominated.

(Found: C, 36.3; H, 3.6; Br, 59.9% $C_{12}H_{15}Br_3$ requires
C, 36.1; H, 3.8; Br, 60.1%).

A sample of the above tribromocyclododecatriene (2.0 g.) was refluxed with amalgamated zinc powder in absolute ethanol for 10 hours. On working up in the usual manner, the product proved to be a colourless oil which still contained halogen. This oil was not further examined.

$\nu^{\text{film}}_{\text{max.}}$ 3050 (CH=CH) 1660 and 960 cm.$^{-1}$ (<u>trans</u> CH=CH).

<u>Debromination of</u> 1,2,5,6,9,10-<u>Hexabromocyclododecane</u>.

The hexabromocyclododecane (3.0 g.) was refluxed in absolute ethanol (100 c.c.) with amalgamated zinc (5.0 g.) for 6 hours. The solution was filtered to remove excess zinc and zinc bromide and the filtrate evaporated to give a colourless oil (0.5 g., 78%). This oil was examined by G.L.C. (column temperature 115° and Argon flow rate 42 c.c./minute) and shown to consist of two products; the major portion (68%) corresponded to the original cyclododeca-1,5,9-triene.

A sample of this mixture (0.1 g.) was hydrogenated over 10% Pd-C (10 mgs.) in ethyl acetate solution with uptake of 38 c.c. of hydrogen (theoretical). The resultant product, a crystalline solid, sublimed at 100° 20 m.m. to give needle crystals, which were shown by G.L.C. to be identical with cyclododecane, m.p. and mixed m.p. 59-60°.

Dehydrobromination of 1,2,5,6,9,10-Hexabromocyclododecane.

(i) Sodamide in Liquid Ammonia.

Sodium (2.0 g.) was dissolved in 500 c.c. of liquid ammonia to give sodamide. The hexabromide (3.2 g.) in tetrahydrofuran (200 c.c.) was added over 10 minutes and the mixture vigorously stirred overnight. The residue was treated with solid ammonium chloride, then saturated ammonium chloride solution, the mixture poured into ice-cold dilute sulphuric acid (0.05$\bar{N}$ 200 c.c.) and ether extracted. The extracts were washed with water till neutral, dried over magnesium sulphate and evaporated to give a brown gum (0.62 g.).

A sample of this gum (100 mgs.) on hydrogenation (in ethyl acetate over 10% Pd-C) absorbed 32 c.c. of hydrogen but a G.L.C. of the product failed to detect the presence of any cyclododecane. A second dehydrobromination attempt, using sodamide in liquid ammonia, was also unsuccessful. In this case the ammonium chloride was added one hour after the addition of the hexabromide was completed. On working up as above, a viscous oil was obtained which still contained bromine. $\nu_{\text{max.}}^{\text{film}}$ 1645 (CH=CH) 974 (*trans* CH=CH) and 853 cm.$^{-1}$ (CH=C<).

(ii) Potassium tert-Butoxide in Diglyme.

Potassium *tert*-butoxide (from 5.0 g. of potassium) was vigorously stirred in diglyme (250 c.c.) and a solution of the hexabromide (6.24 g.) in the same solvent (50 c.c.) rapidly added. The mixture was then heated to 70-80° and at prescribed periods, samples were taken, and the bromide ion content estimated.

Each 10 c.c. sample was diluted with distilled water and acidified with dilute nitric acid. An excess of standard silver nitrate solution was then added and the excess back titrated against standard potassium thiocyanate, using a ferric alum solution as indicator.

Time (hours)	1	2	3	4
% reaction	68	76	83	92

After 4.5 hours the mixture was acidified and poured into a large volume of water (2 l.). This aqueous solution was ether extracted several times and the combined extracts washed with water and dried over magnesium sulphate.

The bulk of the ether was removed by a fractional distillation at atmospheric pressure and the remainder at 20 m.m. pressure, the distillate in this case being collected in a liquid air-cooled trap. Both distillates were pure ether (n_D^{20} 1.3540) and no other fractions were obtained under these conditions. The final residue, a brown oil (0.92 g.) was chromatographed on alumina (Grade 5., 40 g.), elution with petrol giving an aromatic hydrocarbon (0.5 g.) b.p. 70° 0.8 m.m., n_D^{20} 1.5980. (Found: C, 92.1; H, 7.9% $C_{12}H_{12}$ requires C, 92.3; H, 7.7%). $\nu_{max.}^{film}$ 3040 (CH=CH) 3000 and 1500 (aromatic C-H) 2900 and 1450 cm.$^{-1}$ ($-CH_2-$) and a complex region 800-700 cm.$^{-1}$ (Figure 13b). $\lambda_{max.}^{hexane}$ 264 mμ (ε 6,100).

Hydrogenation of this material (17.5 mgs.) with Adam's catalyst or 10% Pd-C resulted in the absorption of two molar equivalents of hydrogen to give an oil, b.p. 70°/0.5 m.m., n_D^{20} 1.5362. $\lambda_{max.}^{hexane}$ 265 mμ. (ε 408) A G.L.C. examination of both the unsaturated and hydrogenated materials (products A and B respectively) showed them to be mainly pure compounds. (Column temperature 165°, Argon flow rate 36 c.c./min. Retention time (mins.) A, 6.6; B, 5.0). Product B should be 1,2-benzo-cyclo-oct-1-ene; Wittig reported for this compound, b.p. 64°/0.8 m.m., n_D^{20} 1.5398. However, despite repeated alumina chromatography and distillation the value of the refractive index for product B could not be raised above that given.

Rudloff Oxidation of Product A.

The aromatic hydrocarbon, A, (100 mgs.) was shaken for 10 hours in an aqueous *tert*-butanol solution (1:1, 120 c.c.) containing sodium metaperiodate (214 mgs.) potassium permanganate (68 mgs.) and potassium carbonate (560 mgs.). The *tert*-butanol was largely removed under suction, the residue strongly acidified and ether extracted continuously over 24 hours. The extract, after drying over magnesium sulphate, was treated with excess diazomethane and the resultant esters examined by G.L.C. Under the conditions of the chromatogram only one peak was obtained. (Column temperature 120°, Argon flow rate 40 c.c./min. Peak retention time 0.93 mins.). Under the same conditions, dimethyl oxalate had a retention time of 0.92 mins.

Permanganate Oxidation of Product A.

Product A (20 mgs.) in aqueous *tert*-butanol (1:1, 20 c.c.) was refluxed with potassium carbonate (30 mgs.) and excess potassium permanganate for 6 hours. The mixture was treated with sodium metabisulphite solution to remove the precipitated manganese dioxide, acidified and ether extracted. The extract was washed with water (4 x 50 c.c.), dried and evaporated to give a crystalline solid. This material was sublimed by heating on a steam bath at 12 m.m. pressure to give white needles (16.2 mgs., 85%), m.p. 130-131°, undepressed on mixing with a sample of phthalic anhydride.

Silver Nitrate Adduct of Product A.

Finely powdered silver nitrate (20 mgs.) was partially dissolved in boiling absolute ethanol (5 c.c.) and product A (15.6 mgs.) in ethanol (1 c.c.) added. The residual silver nitrate dissolved after a further 30 seconds reflux and the solution, on cooling, deposited small plate crystals (20 mg., 66%). Crystallisation from the minimum of boiling ethanol gave plates, m.p. 140-141° with decomposition. (Found: C, 44.9; H, 4.1% $C_{12}H_{12}AgNO_3$ requires C, 44.2; H, 3.7%).

REFERENCES

1. Barton and Cohen, *Festschrift*, Arthur Stoll, p. 117, (Birkhauser, Basel, 1957).
2. Glaser, *Ber.*, 1869, *2*, 422.
3. Baeyer, *Ber.*, 1882, *15*, 50.
4. Nieuwland, *et al.*, *J. A. C. S.*, 1931, *53*, 4197.
5. Salkind and Fundyler, *Ber.*, 1936, *69*, 128.
6. Bowden, Heilbron, Jones and Sargent, *J.*, 1947, 1579.
7. Heilbron, Jones and Sondheimer, *J.*, 1947, 1586.
8. Armitage, Cook, Entwistle, Jones and Whiting, *J.*, 1952, 1998.
9. Bruun, Haug and Sorensen, *Acta Chem. Scand.*, 1950, *4*, 850.
10. Sorensen, *et al.*, *ibid*, 1951, *5*, 1244.
11. Christensen and Sorensen, *ibid.*, 1952, *6*, 602, 893. Also Sorensen, *et al.*, *ibid*, 1954, 8, 26, 1757.
12. Shaw and Whiting, *Chem. and Ind.*, 1953, 409.
13. Black and Weedon, *J.*, 1953, 1785.
14. Bohlmann and Viehe, *Chem. Ber.*, 1955, *88*, 1245, 1347.
15. Bohlmann, Mannhardt and Viehe, *ibid.*, 1955, *88*, 361.
16. Crombie and Manzoor-i-Knuda, *Chem. and Ind.*, 1956, 409.
17. Bohlmann and Inhoffen, *Chem. Ber.*, 1956, *89*, 21.
18. Bell, Jones and Whiting, *Chem. and Ind.*, 1956, 548.
19. Chicoisne, Dupont and Dulou, *Bull. Soc. Chim.*, 1957, 1232.
20. Ashworth, *et al.*, *J.*, 1958, 950.
21. Cameron and Bennett, *J. Org. Chem.*, 1957, *22*, 557.
22. Milas and Mageli, *J. A. C. S.*, 1953, *75*, 5970.

23. Salkind and Fundyler, *J. Gen. Chem.*, (U.S.S.R.), 1939, *9*, 1725.

24. Bohlmann, *Chem. Ber.*, 1953, *86*, 657.

25. Vaitiekunas and Nord, *J. A. C. S.*, 1954, *76*, 2733.

26. Armitage, Jones and Whiting, *J.*, 1952, 2014.

27. Cook, Jones and Whiting, *J.*, 1952, 2883.

28. Armitage, Entwistle, Jones and Whiting, *J.*, 1954, 147.

29. Scharnberg, *Ber.*, 1938, *71*, 569.

30. Akhtar, Richards and Weedon, *J.*, 1959, 933.

31. Jones, Lee and Whiting, *J.*, 1960, 341.

32. Epstein and Marszak, *Compt. rend.*, 1956, *243*, 283.

33. Arens, *et al.*, *Rec. Trav. Chim.*, 1956, *75*, 1459.

34. Bohlmann, Inhoffen and Politt, *Ann.*, 1957, *604*, 210.

35. Chodkiewicz, *Ann. Chim.*, 1957, *2*, 819.

36. Eglinton and Galbraith, *J.*, 1959, 889.

37. Reppe, *Ann.*, 1955, *596*, 1.

38. Bohlmann and Sinn, *Chem. Ber.*, 1955, *88*, 1869.

39. Lespieau, *Ann. Chim. Phys.*, 1897, *11*, 281.

40. Dupont, *Compt. rend.*, 1909, *148*, 1522.

41. Reich, *Chem. Abs.*, 1918, *12*, 1877.

42. Moureau and Bongrand, *Ann. Chim.*, 1920, *14*, 47.

43. Rose and Weedon, *J.*, 1949, 782.

44. Noyes and Tucker, *Am. Chem. J.*, 1897, *19*, 123.
Strauss and Kollek, *Ber.*, 1926, *59*, 1664.
Nakagawa, *J. C. S. Japan*, 1951, *72*, 561.

45. Danielly and Nieuwland, *J. A. C. S.*, 1936, *58*, 1609.
Schlubach and Franzen, *Ann.*, 1951, *572*, 116.

46. Westcott, Ph.D. Thesis, Manchester 1954.

47. Eglinton and Galbraith, *Chem. and Ind.*, 1956, 737.

48. Organic Synth. Coll. Vol. 1., 1941, p.87 (Wiley and Sons).
See also Fieser's " Experiments in Organic Chemistry"
p.311 (Heath and Co. 1955).

49. Bohlmann, *et al.*, *Chem. Ber.*, 1957, *90*, 130, 1661.

50. Sondheimer, *J. A. C. S.*, 1960, *82*, 754, 755, also 1959, *81*, 6301 and earlier papers.

51. Akiyama and Nakagawa, *Chem. and Ind.*, 1960, 346.
Toda and Nakagawa, *Bull. Chim. Soc. Japan*, 1960, *33*, 223.

52. Bohlmann, unpublished results.

53. Sondheimer, *et al.*, *J. A. C. S.*, 1957, *79*, 4247.

54. Carnduff, B.Sc. Thesis, Glasgow, 1959.

55. Jones and Whiting, unpublished observation.

56. Hay, *J. Org. Chem.*, 1960, *25*, 1275.

57. Galbraith, Ph.D. Thesis, Glasgow, 1958.

58. Strauss, *Ann.*, 1905, *342*, 190.

59. Akhtar and Weedon, *Proc. Chem. Soc.*, 1958, 303.

60. Skattebol, *Acta Chem. Scand.*, 1959, *13*, 198.

61. Behr, unpublished results.

62. Behr, Eglinton and Raphael. *Chem. and Ind.*, 1959, 69.

63. Chodkiewicz and Cadiot, *Compt. rend.*, 1959, *248*, 116.

64. Chodkiewicz, Alhuwalia, Cadiot and Willemart,
Compt. rend., 1957, *245*, 322 and earlier references.

65. Jones and Stephenson, *J.*, 1959, 2197.

66. Gardiner, Jones, Leeming and Stephenson, *J.*, 1960, 691.

67. Bohlmann, *et al.*, *Chem. Ber.*, 1958, *91*, 1631 also 1960, *93*, 981.

68. Meier, Chodkiewicz, Cadiot and Willemart, *Compt. rend.*, 1957, *245*, 1634.

69. Grignard and Tcheofaki, *Compt. rend.*, 1929, *188*, 359.

70. Skattebol and Sorensen, *Acta Chem. Scand.*, 1953, *7*, 1388,

71. Black, Horn and Weedon, *J.*, 1954, 1704.

72. Lepedeva, *Chem. Abs.*, 1945, *39*, 4287.

73. Coates, *J.*, 1946, 838.

74. Piganiol " Acetylene, Homologues et Derives" , p.263, (Masson, Paris, 1945).

75. Schlubach and Wolf, *Ann.*, 1950, *568*, 141.

76. Salkind and Gverditseli, *J. Gen. Chem.*, (U.S.S.R.), 1939, *9*, 971.

77. Mkryan and Papazyan, *Doklady Akad. Nauk Armyan.*, *S.S.R.*, 1953, *16*, No.1, 17.

78. Klebanski et al., *J. Gen. Chem.*, (U.S.S.R.), 1957, *27*, 2977.

79. Brackmann, " International Conference on Co-ordination Chemistry" p.128 (The Chemical Society, London, 1959).

80. Crawford, *Nature*, 1950, *165*, 728.

81. Ahrland, Chatt and Davies, *Quart. Rev.*, 1958, *12*, 265.

82. Nyholm, *et al.*, *J.*, 1954, 332.

83. Latimer, " Oxidation Potentials" , pp.186, 226 and 213 (Prentice-Hall, Inc., New York, 1952).

84. Waters, _Quart. Rev._, 1958, _12_, 277.

85. Nogaideli and Shvangiradze, _Zhur. Obshchei. Khim._, 1954, _24_, 1025.

86. Ruzicka and Stoll, _Helv. Chim. Acta_, 1928, _11_, 1159.

87. Stoll and Rouve, _Helv. Chim. Acta_, 1934, _17_, 1283.
Polak and Swarz's Essence fabrieken, Dutch Patent, 1951, _Chem. Abs._, 1951, 9076i.
Hunsdieker and Erlbach, _Chem. Ber._, 1947, _80_, 129.
Stoll, _Helv. Chim. Acta_, 1947, _30_, 1393.
Stoll and Bolle, _ibid._, 1948, _31_, 98.

88. Ruggli, _Ann._, 1912, _392_, 92.
Ziegler, _Ann._, 1933, _304_, 44.

89. Svadkovskaya, Voitkevich, Smolyaninova and Belov, _J. Gen. Chem._ (U.S.S.R.), 1957, _27_, 2204.

90. Carnduff, Eglinton, McCrae and Raphael, _Chem. and Ind._, 1960, _20_, 559.

91. Eglinton and Galbraith, _J._, 1959, 889.

92. Riley, _J._, 1953, 2193.

93. Rudloff, _Can. J. Chem._, 1956, _34_, 1413, 1714 and earlier references.

94. Gillam and Stern, " Electronic Absorption Spectra" , p.96 (Arnold, London, 1954).

95. Cadiot and Chodkiewicz, unpublished observation.

96. Bergelson _et al._, _Chem. and Ind._, 1960, 20, 558.

97. Raphael " Acetylenic Compounds in Organic Synthesis" , p.203 (Butterworth, London, 1955).

98. _Idem_, _ibid._, p.15.

99. Chaudarv, Paul and Handa, _Ind. Soap J._, 1959, _23_ 288.

100. Strauss, Kollek and Heyn, _Ber._, 1930, _63_, 1868.

101. Vaughn, _et al._, _J. Org. Chem._, 1938, _2_, 1.

102. Johnson and McEwen, *J. A. C. S.*, 1926, *48*, 469.
Elsner and Paul, *J.*, 1951, 893.

103. Bowers, Halsall, Jones and Lemin, *J.*, 1953, 2548.

104. Johnson, Schwartz and Jacobs, *J. A. C. S.*, 1938, *60*, 1882.

105. Hill and Tyson, *J. A. C. S.*, 1928, *50*, 172.

106. Evans, *J.*, 1953, 3055.

107. Young, Vogt and Nieuwland, *J. A. C. S.*, 1936, *58*, 55.

108. Jacobsen and Carothers, *ibid.*, 1933, *55*, 4667.

109. Vaughn, *ibid.*, 1933, *55*, 3453.

110. McCusker and Vogt, *ibid.*, 1937, *59*, 1307.

111. Iositsch, *Bull. Soc. Chim.*, 1905, *34*, 181.
Iositsch and Orielkine, *J. Russ. Phys. Chem. Soc.*, 1910, *42*, 728.

112. Grignard, Bellet and Courtot, *Ann. Chim.*, 1915, *4*, 30.

113. Nef, *Ann.*, 1899, *308*, 264.

114. Lespieau, *Bull. Soc. Chim.*, 1908, *3*, 638.

115. Vaughn and Nieuwland, *J. A. C. S.*, 1932, *54*, 787.

116. Prevost *et al.*, *Compt. rend.*, 1935, *200*, 942; 1937, *204*, 989.

117. Armitage, Jones and Whiting, *J.*, 1952, 1993.

118. Truchet, *Ann. Chim.*, 1931, *16*, 309.

119. Viehe, *Chem. Ber.*, 1959, *92*, 1270.

120. McElvain and Morris, *J. A. C. S.*, 1951, *73*, 206.

121. Kosolapoff, *J. A. C. S.*, 1953, *75*, 3596.

122. Porter and Stelle, *J. A. C. S.*, 1920, *42*, 2650.
Kharasch and Reynolds, *ibid.*, 1943, *65*, 501.

123. Goebel and Marvel, ibid., 1933, 55, 1593.

124. Kroeger and Nieuwland, ibid., 1936, 58, 1861.

125. Dobson, Ph.D. Thesis, Belfast, 1957.

126. Walling and Buckler, J. A. C. S., 1955, 77, 6032.

127. Lawesson et al., J. A. C. S., 1959, 81, 4230; Acta Chem. Scand., 1959, 13, 1716.

128. Hawthorne, J. Org. Chem., 1957, 22, 1001.

129. Sheverdina and Kocheschkov, J. Gen. Chem., (U.S.S.R.), 1938, 8, 1825.

130. Brown and Jones, J., 1946, 781.

131. Rollefson and Aldershaw, J. A. C. S., 1932, 54, 977.

132. Andrewes, King and Walker, Proc. Roy. Soc. London, 1946, 133B, 20-62.

133. Fuller and King, J., 1947, 965.

134. Linnemann and de Zotta, Ann., 1871, 159, 247.

135. Faworsky, J. Russ. Phys. Chem. Soc., 1894, 26, 559.

136. Jacquier, Bull. Soc. Chim., 1950, D35.

137. Aston and Greenberg, J. A. C. S., 1940, 62, 2590.

138. Marker and Wagner, ibid., 1942, 64, 1273.

139. Marker, Crookes and Wagner, ibid., 1942, 64, 213, 817.

140. Wagner and Moore, ibid., 1950, 72, 974.

141. Faworsky, Chem. Zentr., 1915, 85, 984.

142. Faworsky, J. prakt. Chem., 1913, 88, 658.

143. Marker, Wagner and Wittbecker, J. A. C. S., 1942, 64, 2093.

144. Wagner, ibid., 1949, 71, 3214.

145. Wagner and Moore, ibid., 1950, 72, 3655.

146. Loftfield, ibid., 1951, 73, 4707.

147. Aston and Newkirk, ibid., 1951, 73, 3900.

148. Burr and Dewar, J., 1954, 1201.

149. Romo and de Vivar, J. A. C. S., 1957, 79, 1118.

150. Salamon and Reichstein, Helv. Chim. Acta, 1947, 30, 1616.

151. Raphael, J., 1949, 544.

152. Nazarov and Akhrem, J. Gen. Chem., (U.S.S.R.), 1956, 26, 1186; 1958, 28, 1838.

153. Braud and Waight, Nature, 1949, 164, 241.

154. Di Modica and Spriano, Ann. Chim., 1951, 41, 64.

155. Bruyland and Fonteyn, Bull. Classe Sci., Acad. roy. Belg., 1933, 19, 689.

156. Raphael and Roxburgh, J., 1955, 3405.

157. Jacobs, Cramer and Hanson, J. A. C. S., 1942, 64, 223.

158. Wilke, Angew. Chem., 1957, 69, 397,

159. Greenwood and Morris, J., 1960, 2922.

160. Koster, Angew. Chem., 1957, 69, 684.

161. Brown and Subba Row, J. A. C. S., 1956, 78, 5694.

162. Kindly supplied by I. C. I. Billingham.

163. Wittig, Eggers and Duffner, Chem. Ber., 1958, 619, 10.

164. Eglinton, Raphael and Willis, Proc. Chem. Soc., 1960, 247.