The synthesis and stereochemistry of allenee, acetylenes and related compounds

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The Synthesis and Stereochemistry of Allenes, Acetylenes and Related Compounds.

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ABSTRACT

(±)-Marasin, claimed to be the product from the reduction of non-2-en-4,6,8-triyn-1-ol with lithium aluminium hydride, has been shown to be a minor product only, the major product being the allenene. Reduction with dialkoxylithium aluminium hydride gave improved yields of allenynes together with allenenes whereas the lithium aluminium hydride-butane-2,3-diol complex gave allenynes only. Reduction with the asymmetric complexes of lithium aluminium hydride with menthol, and 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose gave the optically active allenynes. A consideration of the stereochemistry of these reductions enabled the configuration of the product to be predicted. The absolute configurations of four allenynes, including the naturally occurring marasin and its next higher homologue (9-methyl marasin) were determined. The lithium aluminium hydride-active amyl alcohol (2-methylbutan-1-ol) complex was found to be unsuitable for producing optically active allenynes. The kinetically controlled reduction of 4-chloro-2-yn-1-ols and the corresponding acetates with an asymmetric complex has been investigated.

The absolute configuration of (+)-hexa-3,4-dienol has been determined by application of the Claisen rearrangement to optically active (-)-chloroethyl but-1-yn-3-yl

ether. Trace impurities in 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose have been isolated and identified and the analytically pure compound prepared for the first time.

3,3,5-Trimethylcyclohexanone has been reduced with cyclic complexes of lithium aluminium hydride. The axial/equatorial ratio of the cyclohexanols obtained from these and other reductions has been interpreted by postulating the participation of the flexible form of the ketone in the reduction.

Bromopropargyl aldehyde has been synthesised for the first time and attempts to use this compound as an intermediate are described.

ACKNOWLEDGMENTS

The author wishes to acknowledge his gratitude to Professor S. R. Landor for his generous supervision of this work and for much stimulating discussion, to Dr. (Mrs.) P. D. Landor for her advice and encouragement, to his wife for typing the thesis and to Fourah Bay College, Freetown for a maintainance grant.

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I

INTRODUCTION

INTRODUCTION

Naturally Occurring Allenes

The discovery and isolation of penicillin from the mould Penicillium notatum just before the last war, stimulated great interest in the possibility of isolating other powerful antibiotics from mould and plant species. During the post war years, a great amount of effort has therefore been put into the screening of mould and plant extracts in the search for more potentially useful natural products.

The isolation of a naturally occurring diacetylene compound was reported by Sorensen and Stene[145] who obtained methyl dec-2-ene-4,6-diynoate from Matricaria indora L in 1941. By 1950 seven natural acetylenic compounds were known, and since then the number isolated, principally by the schools of Sir E. R. H. Jones and F. Bohlmann, has increased to about three hundred. The rapid increase in the rate of development in this field during the last seventeen years is a consequence of the introduction of automatic recording ultra-violet and, to a lesser extent, infra-red spectrophotometers. The polyacetylene system has a highly characteristic absorption pattern in the ultra-violet region and this, together with the high sensitivity of the ultra-violet spectrophotometer, makes its detection in plant or mould extracts relatively easy. After purification by counter-current distribution and

chromatography, the assignment of detailed structures to the compounds is made largely on the basis of spectral evidence.

(-)-Mycomycin (I), the first naturally occurring allene to be isolated, was discovered in 1947 by Johnson and Burdon[96] and shown to be active against the bacilli of human tuberculosis. In 1952 Celmer and Solomons[85] showed it to be the (-)-3(trans), 5(cis),7,8-trideca-tetraene-10,12-diynoic acid, (I).

$$HC\equiv C-C\equiv C-CH=C=CH-\overset{c}{CH}=\overset{t}{CH}-CH=CH-CH_2COOH \qquad (I)$$

The allenic system was shown to be present in this compound by absorption at 1930 cm.$^{-1}$ in the infra-red spectrum. The ultra-violet spectrum showed the presence of isolated triene, and endiyne chromophores and thus enabled the position of the allene grouping to be decided, since the central carbon in the allene separates the two conjugated systems. The compound is very unstable and shows the high optical activity characteristic of asymmetric conjugated allenes.

Under alkaline conditions mycomycin rearranges to trans-trans-trideca-3,5-diene-7,9,11-triynoic acid (isomycomycin) (II).

$$CH_3C\equiv C-C\equiv C-C\equiv C-\overset{t}{CH}=\overset{t}{CH}-CH=CH-CH_2COOH \qquad (II)$$

This compound was synthesised by Bohlmann and Viehe[86] in 1954.

Several synthetic routes to (±)-mycomycin were tried by Bohlmann and Sucrow[88] in 1964. They considered it necessary to use alkali free conditions to avoid rearrangement of the allene group,* and their approach was therefor somewhat limited. An attempt by these workers to apply the lithium aluminium hydride reduction of enynols to allenes[2] to the system

$$H(C{\equiv}C)_3(CH{=}CH)_2\text{-}\underset{\displaystyle OH}{\underset{|}{C}}H\text{-}CH_2R$$

failed for the naturally occurring allenynes although model compounds were successfully reduced to allenes.**

An attempt to apply the Chodkiewicz[89] method of extending compounds with terminal triple bonds, by coupling with bromopropiolic acid and then removing the carboxylic acid group by copper bronze in boiling dioxan was used as follows:‡

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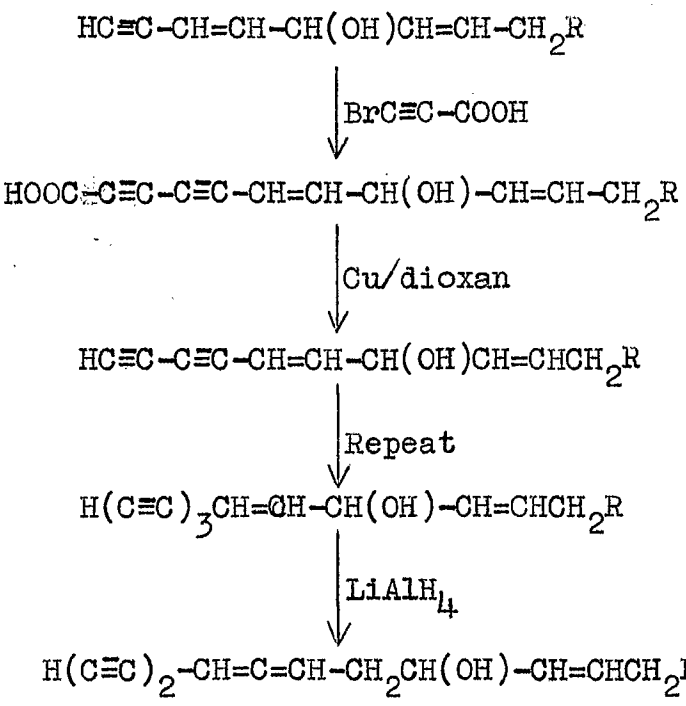
*It has been shown by Baker, Landor, and Landor[87] that allenynols can be prepared under basic conditions, however. This synthesis is mentioned later.

**It is reported in this thesis that allenynols cannot be prepared by lithium aluminium hydride reduction of enynols since further reduction to allenenol occurs (p.39).

‡The lithium aluminium hydride reduction in the last stage of this reaction sequence would again be expected to produce mainly allenenol.



(III)

It was hoped that elimination of water from (III) would give a certain amount of the 5-cis double bond. No elimination of water from (III) could be induced, however, using known acids and neutral reagents.

Kuhn and Winterstein[90] have reduced ω,ω-diphenyl-polyenes with aluminium amalgam in wet ether as follows:

$$Ph(CH=CH)_3Ph \longrightarrow PhCH_2(CH=CH)_2CH_2Ph$$

Bohlmann and Sucrow[88] tried to apply this reduction to the preparation of mycomycin as follows:

$$H(C{\equiv}C)_2\text{-}C{\equiv}C\text{-}CH{=}CH\text{-}CH{=}CH\text{-}CH{=}CH\text{-}COOR$$

$$\downarrow$$

$$H(C{\equiv}C)_2\text{-}CH{=}C{=}CH\text{-}(CH{=}CH)_2CH_2COOR \qquad \text{(IV)}$$

It was claimed that this method produced the methyl ester having spectra identical with the methyl ester of the naturally occurring material of Celmer and Solomons[85] but it could not be crystallised. In an attempt to produce crystallisable trans,trans-mycomycin the tert butyl ester of the precursor of (IV) was prepared* and the trans,trans,trans-isomer isolated by crystallisation. However, the tert-butyl ester produced by aluminium amalgam reduction (considered by Bohlmann and Sucrow to be the ester of mycomycin) could not be crystallised. Saponification with sulphuric acid in dioxan gave a solution considered to contain a small quantity of trans,trans-mycomycin. Attempts to crystallise this after purification by counter-current distribution were unsuccessful.** Two new polyacetylenic

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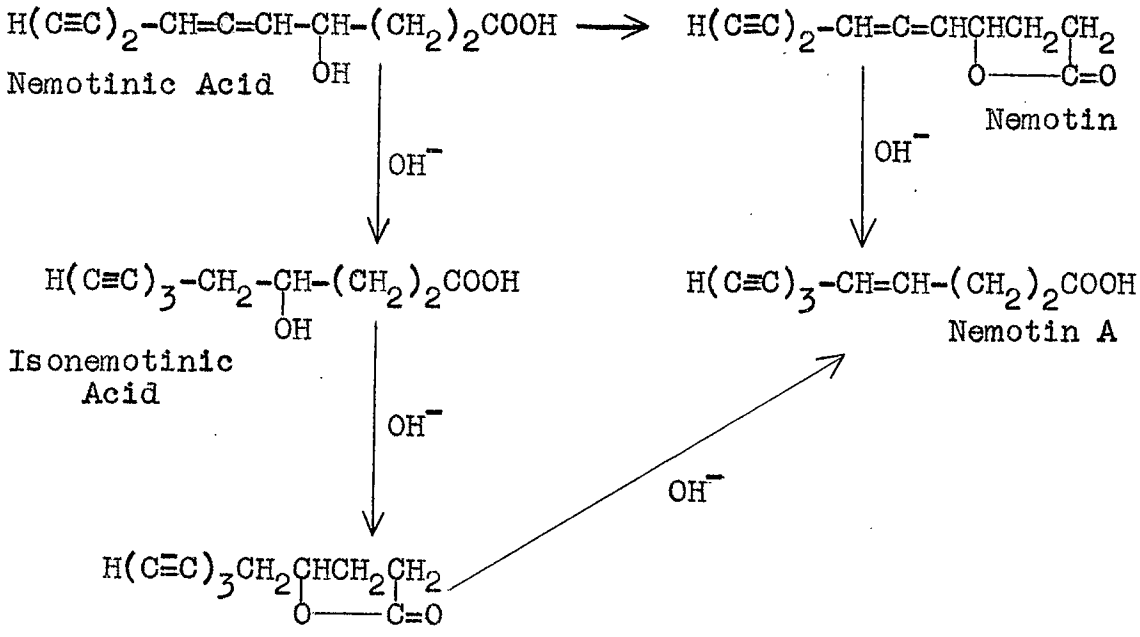
*Tert butyl esters are usually more stable than methyl esters.

**It has been shown in this thesis (p.48) that the ultraviolet spectra of allenene and allenyne are very similar. Attempts to separate mixtures of these compounds during the course of the present work and by other workers in these laboratories have proved unsuccessful (cf. Section II p.45). The inability of Bohlmann and Sucrow to crystallise their reduction product, even after attempted purification by the counter-current technique, suggests that the reducing agent used here had also caused further reduction of allenyne to allenene, and that these workers were unwittingly dealing with such a mixture.

antibiotics, nemotinic acid and nemotin, were isolated by Anchel, Palatnic, and Kavanagh[93] in 1950; the structures of these compounds were shown to be 4-hydroxyundeca-5,6-diene-8,10-diynoic acid and the corresponding lactone respectively by Bu'Lock, Jones, and Leeming.[94] These workers also isolated the related compounds odyssic acid and odyssin from the same source.[95] Nemotinic acid and nemotin undergo prototropic rearrangement on treatment with alkali with the loss of the allene groups to give (-)-4-hydroxyundeca-6,8,10-triynoic acid (isonemotinic acid), and undec-4-ene-6,8,10-triynoic acid (nemotin A) respectively. Nemotin A is also obtainable by treating the lactone of isonemotinic acid with alkali. These reactions are represented in the following scheme:



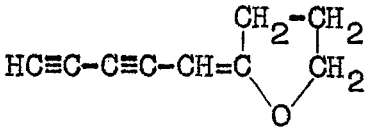
Isomerisations of this type in which the allene group is

lost are accompanied by a very large decrease in the optical activity which indicates that the allenic system with the highly polar diacetylene substituent is largely responsible for the high rotations observed.

In a study of some Marasmius species in 1959, G. Bendz[97] isolated marasin, an unstable, light-sensitive antibiotic, active in vitro against Staphylococcus aureous H, and Mycobacterium tuberculosis. He showed it to be nona-3,4-diene-6,8-diyn-1-ol, (V).

$$HC{\equiv}C\text{-}C{\equiv}C\text{-}CH{=}C{=}CH\text{-}CH_2CH_2OH \qquad (V)$$

The compound was separated from other polyacetylenes using the counter-current distribution technique, with carbon tetrachloride and water as the two liquid phases. Bendz[143] found that in the presence of alkali isomerisation to isomarasin (VI) occurred, the allene group being lost.



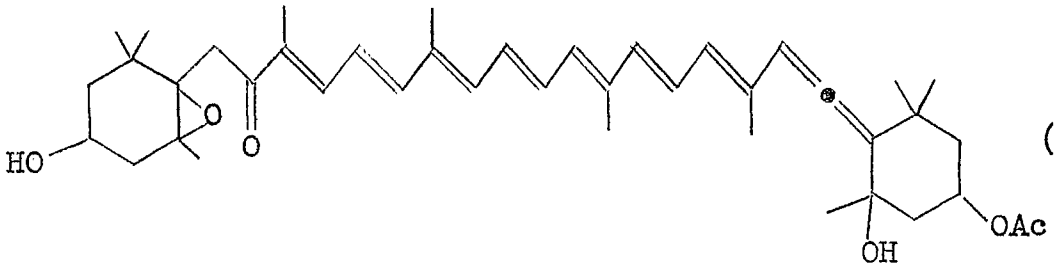
(VI)

This was accompanied by a loss in antibiotic activity and Bendz suggested that this activity was a property of the allene group in conjugation with the acetylene groups. Support for this suggestion came from Baker, Landor, and Landor[87] in 1963. A number of allenynes were synthesised by coupling 1-bromo- and 1-iodo-allenes with terminal acetylenic compounds in the presence of cuprous ions and

a suitable base, and found to exhibit a high level of activity in vitro against mycobacterium tuberculosis.

A synthesis of marasin in high yield was claimed by Bohlmann, Herbst, and Gleinig[5] in 1961, but work described in this thesis demonstrated that this synthesis yields mainly the dihyromarasin, having similar ultra-violet absorption spectra to marasin, and produces only traces of pure marasin. Other naturally occurring allenic poly-acetylenes which have recently been isolated are shown in Table I, (p. 16).

Recently (1964) Bonnett, Spark, Tee, and Weedon[98] have shown that the carotenoid pigment fucoxanthin, present in brown algae, is an allenic polyene, (VII).

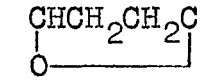
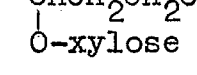
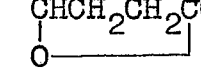
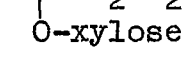


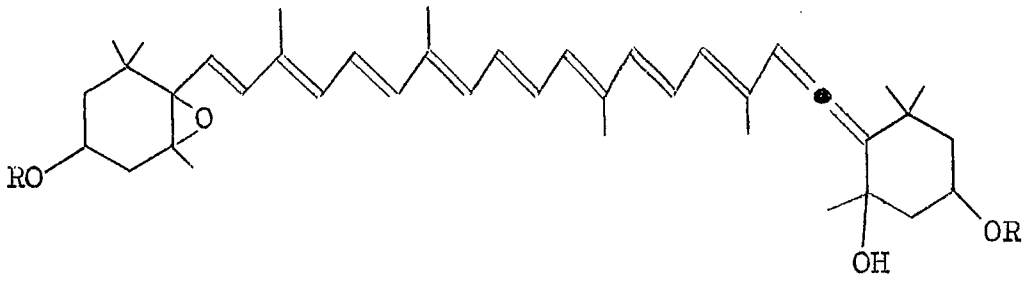
(VII)

In 1966 the same workers[99] showed that foliaxanthin which was first isolated from paprika[100] and has since been found in lucerne, maple and other leaves,[99] has structure (VIII). This is the first allenic carotenoid to be reported. Neoxanthin, first described by Strain[101] in 1938 has now been shown to be identical with foliaxanthin.[102]

TABLE I[92]

Natural Allenic Polyacetylenes

	$[\alpha]_D^{20}$
$HC\equiv CC\equiv CCH=C=CHX$	
X = CH_2OH	-380
CH_2CH_2OH	±385
$CH_2CH_2CH_2OH$	-290
$CH_2CH_2CH_2CH_2OH$	-300
$CH(OH)CH_2CH_2OH$	-210
$CH(OH)CH_2CH_2CH_2OH$	-
$CH_2CH(OH)CH_2CH_2OH$	-210
$CH_2COOMe(H)$	+285
$CH(OH)CH_2CH_2COOH(Me)$	+380
$CH=CH-CH\equiv CH\equiv CH_2COOH$	-
	+320
	+237
$CH_3C\equiv CC\equiv CCH=C=CHX$	
X = CH_2CH_2OH	+340
$CH(OH)CH_2CH_2COOH$	+360
	+300
	-
$H(C\equiv C)_2CH\equiv CC\equiv(CH)_2^{c}=(CH)_2^{t}=CHCH_2COOH$	-310
$H_2C=C=CHC\equiv CC\equiv CCH=^{c}CHCH_2COOH$	-



(VIII)

The first naturally occurring allenic fatty acid was isolated in 1964 from sapium sebiferum seed oil and was first believed to be the allenic cyclopropane carboxylic acid, 2,3-methylene-heptadeca-4,5-dienoic acid.[103] Later work showed it to be octadeca-5,6-dienoic acid.[104] (IX)

$$CH_3(CH_2)_{10}CH{=}C{=}CH(CH_2)_3COOH \qquad (IX)$$

This compound has just been synthesised and its absolute configuration determined by Landor and Punja.[105]

The Stereochemistry of Allenes

The stereochemical significance of the allenic system was first discussed by van't Hoff in his famous thesis of 1874. The original concept of van't Hoff was based on the representation of the carbon atom as a tetrahedron: double bonds between carbon atoms were shown by joining tetrahedra edge to edge, and this has been much discussed in elementary texts. The salient feature about such a model of the allenic system, is that the pairs of substituents on C_1 and C_3 lie in planes which are mutually perpendicular. Modern wave mechanics supports this feature of the early model, and indicates that the planes occupied by the two π bonds of the central carbon atom are also mutually perpendicular. A more up to date representation of the allene system is the following:

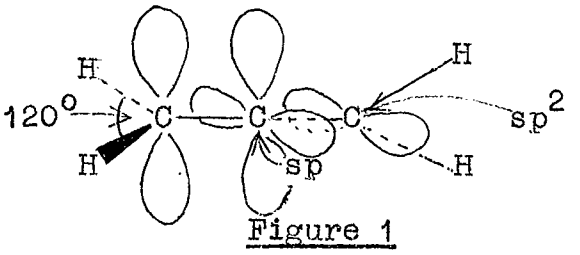
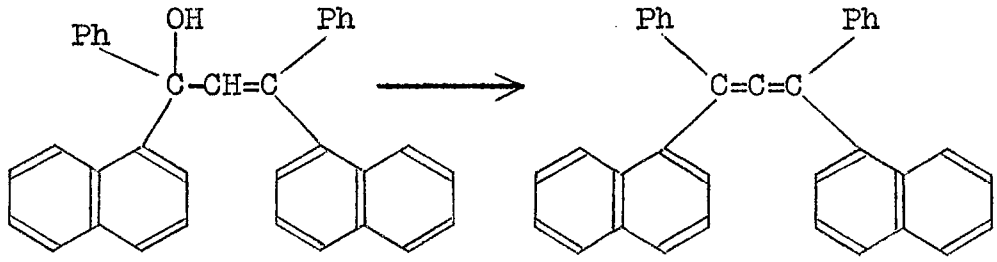


Figure 1

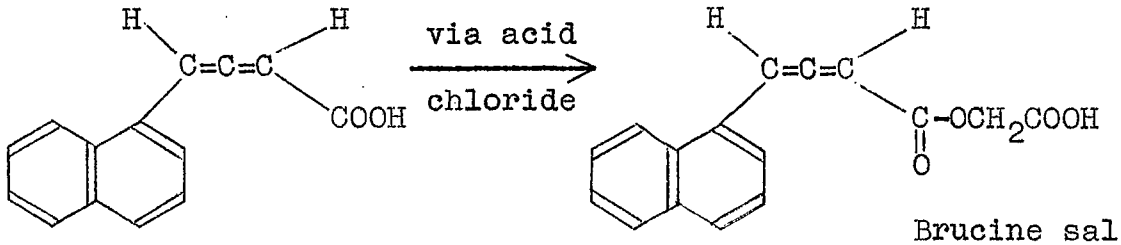
Van't Hoff realised that the orthogonal arrangement of the substituents on C_1 and C_3 of the allene system led to the possibility of optical activity in allenes if no one carbon contained the same two substituents. Although 1,1-dimethyl-allene was made three years later, sixty years elapsed

before Maitland and Mills[106] were able to prepare the first optically active allene although many other attempts had been made. These workers prepared the (+) and (-) enantiomers of 1,3-diphenyl-1,3-di-α-naphthylallene by dehydration of the corresponding prop-2-en-1-ol derivative with (+)- or (-)-camphor-10-sulphonic acid respectively.



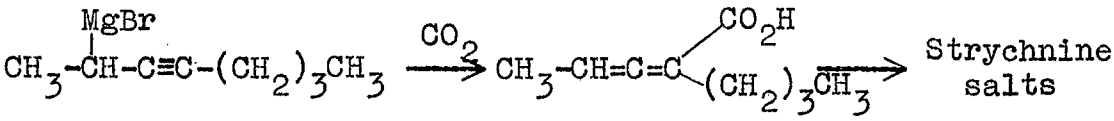
The product from the asymmetric dehydration was only slightly enriched in one enantiomer and this was increased by fractional crystallisation.

The first successful resolution of an allenic compound was carried out in 1935 by Kohler, Walker and Tischler.[107] These workers converted 1-α-naphthylallene-3-carboxylic acid into its glycollic acid ester, via the acid chloride and resolved this by forming the crystalline diastereoisomeric (-)-brucine salts which were separable by fractional crystallisation.



Brucine salt

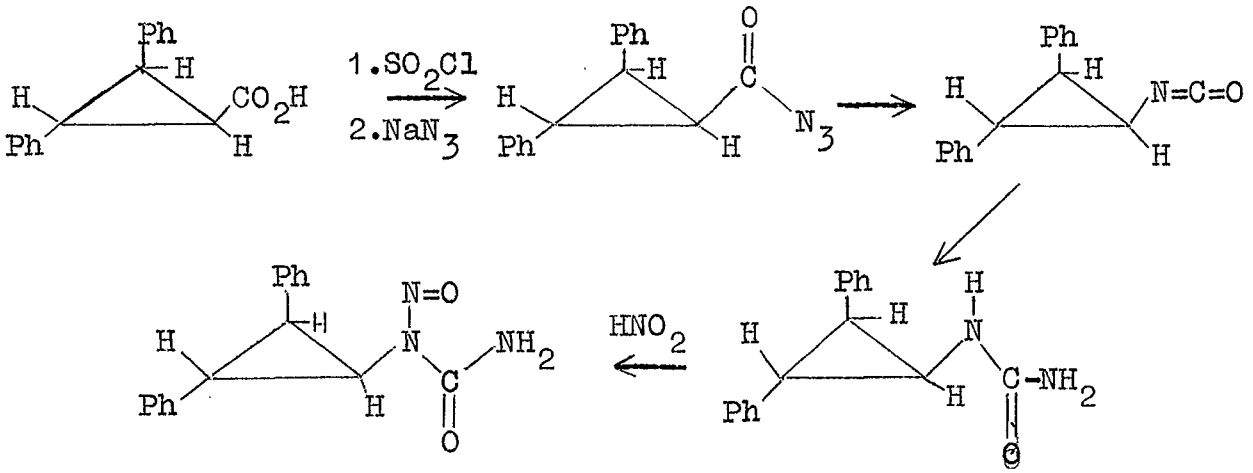
Resolution of an allenic acid was also accomplished by Watiz and Palchak[108] in 1951. Octa-2,3-dien-4-carboxylic acid was prepared by the reaction of the Grignard derivative of 2-bromo-oct-3-yne with carbon dioxide and this was resolved via its diastereoisomeric strychnine salts which were separable by fractional crystallisation.



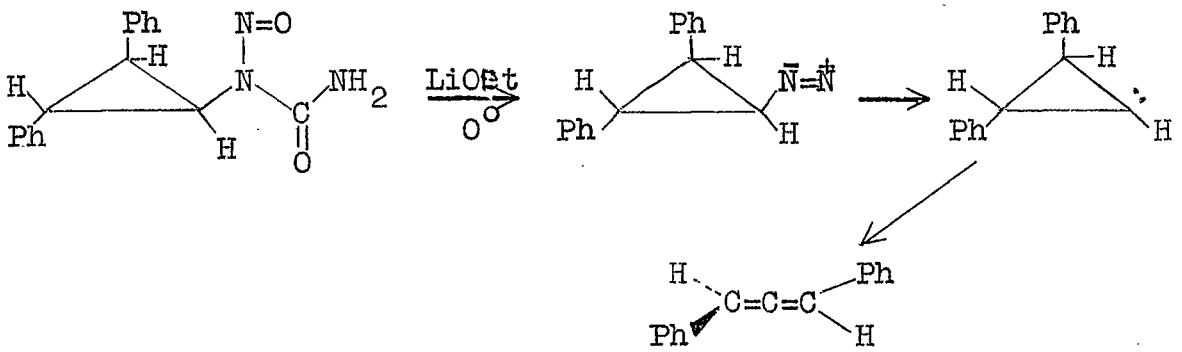
In 1957 Jacobs and Dankner[109] achieved an asymmetric synthesis of 1,3-diphenylallene and of 1-(p-biphenyl)-3-phenylallene, by prototropic rearrangement of their corresponding propynes with optically active bases adsorbed on alumina. The propynes were passed through columns containing the base impregnated alumina, pentane being used as the eluting solvent. The optically active allenic hydrocarbons were eluted and these were subsequently recrystallised to constant specific rotations. The stereoselectivity obtained by this method was low.

The (+)-enantiomer of 1,3-diphenylallene was also prepared in a much purer state than that obtained by the previous workers by Jones, Wilson, and Tutweiler.[110] These workers prepared the (+)-enantiomer by the action of lithium ethoxide on (+)-N-nitroso-N-(trans-2,3-diphenylcyclopropyl)-urea. The latter compound was prepared by

the following reaction sequence from (-)-trans-2,3-diphenyl-cyclopropane-carboxylic acid.



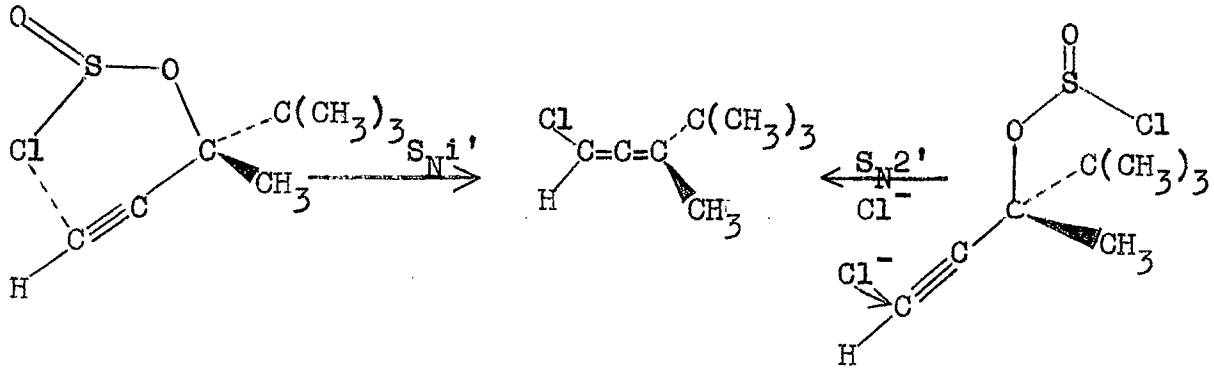
The reaction with lithium ethoxide may involve the intermediate formation of diazocyclopropane which decomposes to the allene either directly or via the carbene.[111]



The stereochemical course of this conversion has recently been analysed by Jones and Wilson[123] from which it was deduced that (+)-1,3-diphenylallene has the S configuration. This is in agreement with the result obtained recently by Mason and Vane[124] from a study of the electronic absorption and circular dichroism spectra of

the compound.

It was shown by Landor, Taylor-Smith, and Evans[112,113] that optically active 1-chloro-3,4,4-trimethylpenta-1,2-diene could be prepared from optically active 3,4,4-trimethyl-pent-1-yn-3-ol by reaction with thionyl chloride. These authors considered that this reaction could go by either an S_Ni' or an S_N2' mechanism. They found that under conditions favouring an S_Ni' mechanism, optically active allenic chloride, having the same sign of rotation as that obtained under conditions favouring an S_N2' mechanism, was produced from optically active acetylenic carbinol of given sign of rotation. The S_N2' mechanism requires the loss of oxygen at the asymmetric centre (C_3) and concerted attack by Cl^- at the terminal acetylenic carbon atom (C_1) from the same side of the molecule.* This appears quite reasonable on the basis of the stereo-electronic requirements[28a] of the system. (Cf. p. 90).

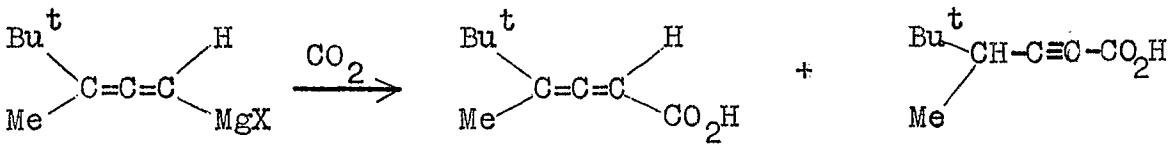


*Stork and White[114] observed the same effect in allylic rearrangements.

The absolute configuration of the acetylenic carbinol** was determined by Landor and Evans[117] as R(-) by relating it to S-(+)-2-t-butyl lactic acid which was synthesised by reacting menthyl pyruvate with t-butylmagnesium chloride (application of Prelog's rule[40]). It was shown that conversion of acetylenic alcohol to allenic chloride proceeds by an S_Ni' mechanism with retention of configuration and the absolute configuration of the allenic chloride was therefore assigned as S(-) by these workers.

Later work by Landor and Evans (unpublished) showed that the corresponding optically active allenic bromide could be prepared in good yield from the optically active acetylenic carbinol by use of a cuprous bromide-copper catalyst initially developed by Black, Landor, Patel, and Whiter.[118] The absolute configuration of 1-bromo-3,4,4-trimethylpenta-1,2-diene was assigned by a correlative method in which the (-)-chloroallene (S)- configuration and the (+)-bromoallene were converted by carbonation of their Grignard derivatives to mixtures of the allenic and acetylenic acids. These acids were separated by elution chromatography using silica gel and found in each case to be dextrorotatory. These results are summarised below.

** Subsequently deduced by Eliel[115] from a consideration of the polarisability of the substituents based on Brewster's theory.



2 : 1

X = Cl or Br ratio of products

R-(-)acetylenic alcohol ⟶ S-(-)allenic chloride ⟶ (+)-allenic acid and (+)-acetylenic acid

R-(-)acetylenic alcohol ⟶ (+)-allenic bromide ⟶ (+)-allenic acid and (+)-acetylenic acid

The configuration of the (+)-allenic bromide was therefore deduced to be S.*

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*It is at first sight surprising that the allenic chloride is S(-) whilst the corresponding allenic bromide is S(+). This observation is no doubt due to the optical rotatory dispersion curve of one (or possibly both) of these compounds crossing the zero axis of rotation, as in figure (a) or (b).

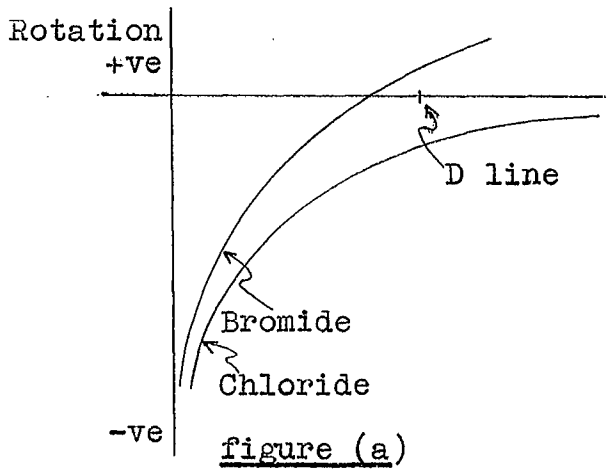


figure (a)

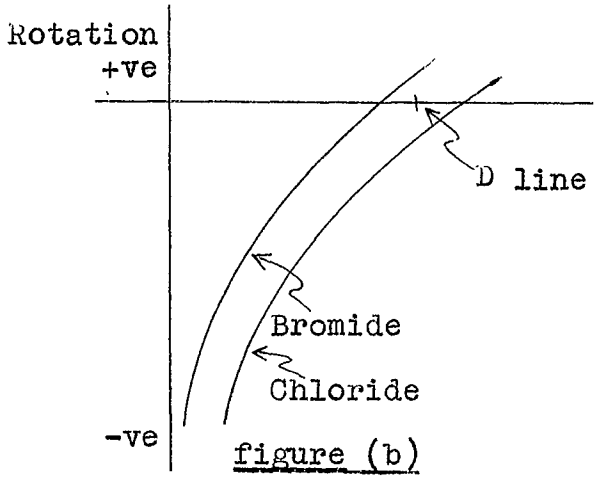
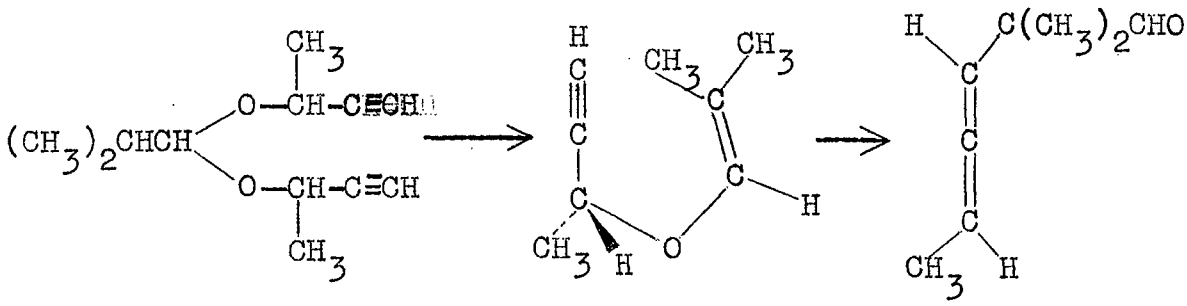


figure (b)

This situation is not unique. For example Sjoberg[119] observed that for a given configuration at the asymmetric carbon the meta- and para-iodophenyl ethers of lactic acid were dextrorotatory at the D line whilst the orthoisomer was laevorotatory.

In 1960, Jones, Loder, and Whiting[57] established the absolute configuration of 2,2-dimethylhexa-3,4-dienal by pyrolysis of optically active isobutyraldehydedibut-1-ynyl acetal. Elimination of but-1-yn-3-ol was postulated to give the vinyl ether which was not isolated and this by Claisen rearrangement gave the corresponding allenic aldehyde.



The absolute configuration of (+)-but-1-yn-3-ol was established by hydrogenation to (+)-butan-2-ol of known configuration and this was confirmed by the detailed work* of Baker, Landor, Landor, and Patel.[78]

In 1961 Gianni[120] synthesised the glycolic acid ester of 1,3-diphenyl-3-(1-naphthyl)allene-1-carboxylic acid (X) by the method of Kohler, Walker, and Tischler[107] and resolved this via the brucine salts. The glycolic acid ester

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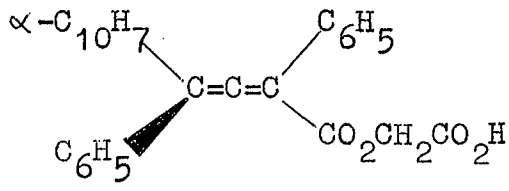
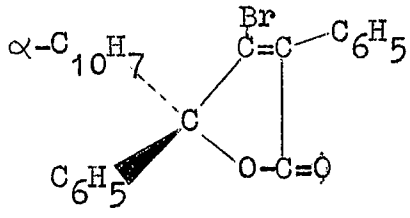
*In their preliminary account, Jones, Loder, and Whiting[57] state that they are "relating the butynol $[\alpha]_D^{20}$ -12.6° (homogeneous l=1 dm.) to the corresponding hydrogen phthalate $[\alpha]_D^{25}$-6.6° (c 10.0 in $CHCl_3$)." According to Baker, Landor, Landor, and Patel,[78] however, (+)-but-3-yn-2-yl hydrogen phthalate $[\alpha]_D^{20}$+7.7° gave (-)-but-3-yn-2-ol $[\alpha]_D^{20}$-17.4°.

was then converted stereospecifically by bromine to 1,3-diphenyl-3-(1-naphthyl)-2-bromocrotono lactone(XI).

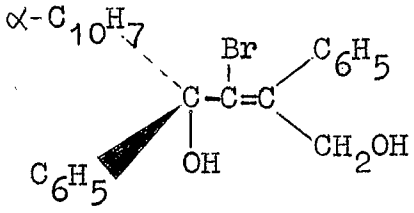


(X)

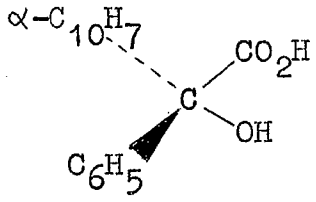


(XI)

Attempted ozonolysis of this lactone to α-naphthyl-mandelic acid (XIII) failed. The lactone was reduced to 1,3-diphenyl-1-(α-naphthyl)-2-bromo-2-butene-1,4-diol (XII), ozonolysis of which also failed to give α-napthyl-mandelic acid.



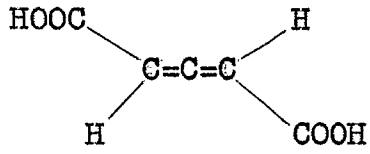
(XII)



(XIII)

The optical rotatory dispersion curves of the lactone (XI) and diol (XII) were compared with that of an authentic sample of R(+)-α-naphthylmandelic acid (XIII). It was found that the dextrorotatory isomers of all three compounds showed a single positive Cotton effect. On the basis of the R(+) assignment to (XIII), the R(+) configuration was assigned to (XI) and (XII). As (XI) was formed from the allene (X) stereospecifically, the R(+) configuration was assigned to the allene.

In 1962 Agosta[121] deduced the configuration of (+)-pentadiendioic acid (XIV) by forming a Diels Alder adduct with cyclopentadiene and converting this into the 2,4-dinitrophenylhydrazone of (+)-norcamphor of established configuration.



(XIV)

In 1965 it was shown by Lowe[125] that the absolute configuration of allenes could be predicted by an application of Brewster's[126] theory. According to Brewster[126] a centre of optical activity can be described as an asymmetric screw pattern of polarizability. Lowe applied this concept to allenes by viewing the allene system from one end so that the near substituents are in a vertical plane and the far substituents are then necessarily in a horizontal plane. Then, if when the more polarizable substituent in the vertical plane is uppermost and the more polarizable substituent in the horizontal plane is to the right, the polarizability will have a clockwise screw pattern and the enantiomer will be dextrorotatory. If the more polarizable substituent in the horizontal plane is to the left, the polarizability will have an anti-clockwise screw pattern

and the enantiomer will be laevorotatory.

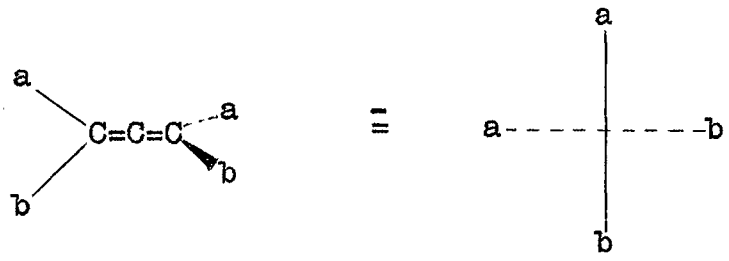


Figure 2

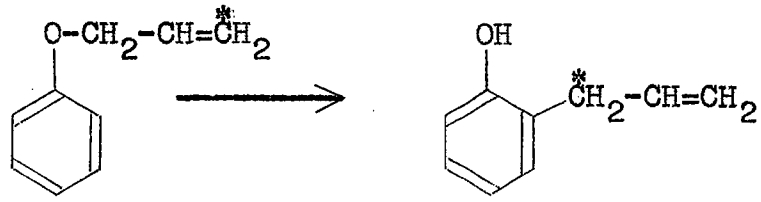
e.g. in Figure 2 if the polarizability of "a" is greater than that of "b", the compound is laevorotatory.

It follows therefore that the sign of rotation together with the above rule can be used to predict the absolute configuration of allenes.

On the basis of this rule, Lowe predicted that the naturally occurring fungal allenes containing the rigid diyne-allene system (R.C≡C-C≡C-CH=C=CHR') (where R = H or Me, and R' does not introduce conformational asymmetry) should have the R(-) and S(+) configuration. The determination of the absolute configuration of these compounds by a method described in this thesis has confirmed this prediction.

The Claisen Rearrangement

The Claisen rearrangement[41] was discovered in 1912 and has since undergone extensive investigation; it is the subject of several reviews.[59,63,64] Claisen and Tietze[67] put forward an intramolecular mechanism for the arrangement and this has now been well established. Thus Ryan and O'Conner[73] synthesised phenyl allyl ether with the terminal carbon marked by radioactive C^{14} and traced the path of C^{14} through the rearrangement by degradation of the product.



It was shown that migration with inversion of the allyl group was the only reaction which had occurred, thus supporting a cyclic mechanism.

Kincaid and Tarbell,[65] studied the rearrangement of allyl 4-methylphenyl ether and confirmed that the reaction was strictly first order over a fivefold change in concentration in diphenyl ether solution, and that the initial rate in pure liquid was the same as the rate in solution. These results, as well as those of Alexander and Kluiber[134] in which high stereospecificity in the rearrangement of (-)-1,3-dimethylallyl ether was observed, also support

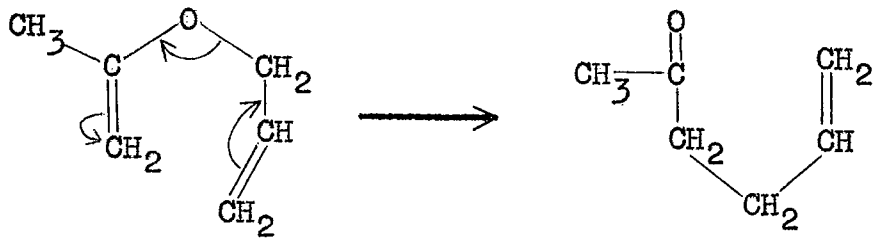
the cyclic mechanism.

The Claisen rearrangement is not confined to ethers of phenols. Thus vinyl allyl ether, first synthesised in 1938 by Hurd and Pollack[77a] was found to undergo rearrangement to pent-4-enol when heated in the liquid phase to 200-250°.

$$H_2C{=}CH{-}O{-}CH_2CH{=}CH_2 \longrightarrow CH_2{=}CH(CH_2)_2CHO$$

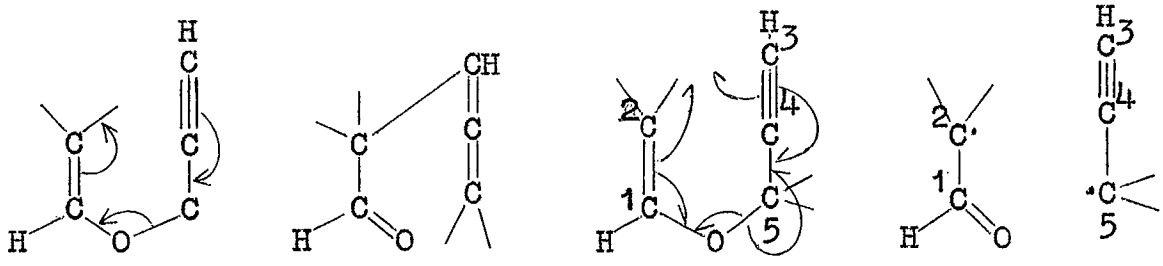
A similar rearrangement of 1-methylvinyl allyl ether was found to occur at a lower reaction temperature.

The kinetics of the rearrangement of vinyl allyl ether and <u>iso</u>-propenylallyl ether was studied by Murphy, Schuler[77b] and Stein[77c] during the early 1950s and it was concluded that the reactions were homogeneous, first order and accompanied by a large negative entropy of activation. The observations led to the proposal of a cyclic mechanism for these rearrangements.



It has recently been demonstrated by Landor and Black[54] that propargyl vinyl systems of type $RC{\equiv}C{-}CH_2{-}O{-}CH{=}CH_2$ can be rearranged to the allenic aldehydes by pyrolysis under special conditions. A series of these ethers were

rearranged and it was observed that as methyl substitution on the propargyl vinyl ether increased, the temperature at which rearrangement occurred decreased. Since increasing methyl substitution of the propargyl vinyl ether should not favour a two electron shift (I) ⟶ (II) Landor and Black rationalised this observation by postulating a one electron shift as in (III).



(I) (II) (III) (IV)

Partial radical formation at C_2 and C_5 (viz. (IV)) is helped by increasing substitution at these points.

An independent investigation by Jones, Loder, and Whiting[57] has established the direct conversion of isobutyraldehyde dipropargyl and dibut-1-ynyl acetals to the corresponding allenic aldehydes without isolation of the ether. Starting with optically active but-1-yn-3-ol of known absolute configuration, the absolute configuration of the optically active allenic aldehyde was deduced, postulating the ether as an intermediate (cf. p. 82).

The Stereochemistry of the Reduction of Cyclohexanones

It is well established that the reduction of alkylcyclohexanones gives mixtures of cis and trans alkylcyclohexanols.[36,146] The introduction of conformational concepts[147] permitted a detailed analysis of the mechanism of such reductions. All such analyses start with the assumption that cyclohexanones are predominantly in the chair form which is thermodynamically more stable than the boat (flexible) form. The attacking entity, e.g. a metal hydride, may then approach the carbonyl group either from the axial side or the equatorial side of the chair form of a cyclohexanone. Axial attack gives equatorial alcohols, whereas equatorial attack gives axial alcohols.[25] Although mixtures of the axial and equatorial alcohols are usually obtained, it has been observed that reduction of unhindered* ketones usually gives predominantly the more stable equatorial alcohols[36] whereas hindered ketones give predominantly the unstable axial alcohols.[25] This is at first sight surprising since the axial alcohols from hindered ketones are considerably less stable than the corresponding equatorial alcohols.

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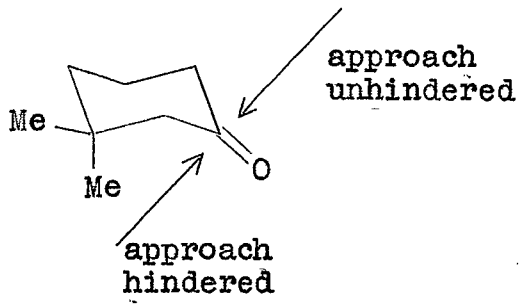
*The term "hindered ketone" is now accepted as meaning a cyclohexanone having an axial substituent (other than a hydrogen) in the 3 and/or 5 position of the ring.

Dauben[25] discussed this problem in 1956 and proposed that the ratio of equatorial to axial alcohol produced in the reduction of a cyclohexanone depended on the relative importance of two opposing effects. These he termed "steric approach control" and "product development control".

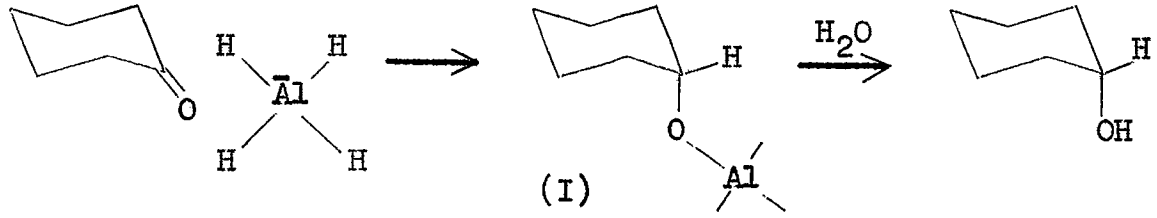
In the case of a hindered ketone, approach from the axial side of the ring is hindered by the axial substituent in the 3 and/or 5 position of the ring. This favours attack from the equatorial side and thus favours the formation of axial alcohol.



It is this effect that Dauben has termed "steric approach control".

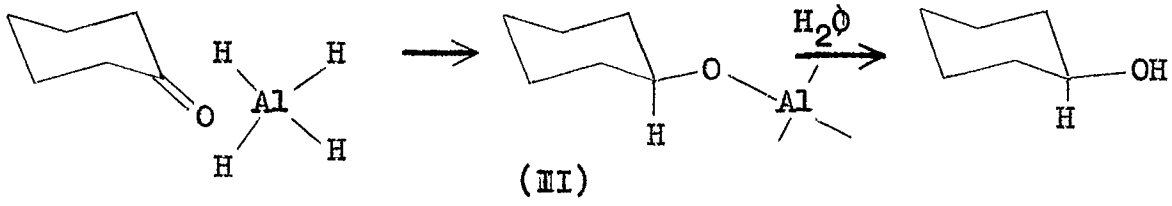
In describing the opposing effect, "product development control", Dauben made the assumption that for an unhindered ketone approach of the attacking entity is equally likely from either equatorial or axial side, and he accepted the earlier proposal by Cram and Green[38] that the first step in the reduction of ketones by lithium aluminium hydride is the formation of a co-ordination

complex between the hydride and the carbonyl oxygen atom. The formation of an axial alcohol thus requires the introduction of the O-Al-group into an axial position, (I).



(I)

The formation of equatorial alcohol, on the other hand, requires the introduction of the O-Al- group into an equatorial position, (II).



(II)

The formation of isomer (I) requires the expenditure of more energy than does the formation of isomer (II) due to the axial/axial interaction that is set up in the former, and this favours the formation of equatorial alcohol.

According to Dauben, therefore, the ratio of equatorial to axial alcohol in the product depends on the relative importance of steric approach control and product development control in the reduction of any substituted cyclohexanone. In this way he interpreted the product ratios

(axial/equatorial alcohol) produced in the reduction of menthone, 4-methylcyclohexanone and 2-methylcyclohexanone by metal hydrides as shown in Table II.

TABLE II[25]

Distribution of Isomers Formed by Reduction of Ketones

Reagent	Menthone		4-Methyl Cyclo-hexanone		2-Methyl Cyclo-hexanone	
	Menthol %	Neo-men-thol %	% trans	% cis	% trans	% cis
$LiAlH_4$	71	29	81	19	82	18
$NaBH_4$ in methanol	49	51	75	25	69	31
$NaBH_4$ in Pyridine	-	-	60	40	56	44
$Al(O\text{-}Pr^i)_3$	30	70	67	33	42	58
$NaBH(OCH_3)_3$	-	-	-	-	70	30
Equilibrium	mostly	-	88	12	99	1

In the light of Dauben's work, Haubenstock and Eliel[22,23] investigated the reduction of 3,3,5-trimethylcyclohexanone using alkoxy complexes of lithium aluminium hydride and sodium borohydride. They showed that there is some correlation (qualitative) between reagent size and axial/equatorial ratio of the alcohols produced and interpreted this on the basis of the concepts discussed by Dauben. However, some anomalous results with complexes of secondary

alcohols were obtained, which gave lower axial/equatorial ratios than expected. These were explained by postulating that lithium aluminium hydride complexes obtained from secondary alcohols disproportionate to give lithium aluminium hydride and lithium tetra-alkoxyaluminium so that some reduction was due to lithium aluminium hydride itself.

$$2LiAlH_2(OR)_2 \rightleftharpoons LiAl(OR)_4 + LiAlH_4$$

In the case of very bulky secondary alcohols and tertiary alcohols, however, the equilibrium lies well to the left.

Some of the results obtained by Haubenstock and Eliel are shown in Table III (p.112).

The concept of product development control has been attacked by Richer.[35] Richer maintains that as additions to acyclic ketones are regulated only by steric factors such as Cram's rule[39] and Prelog's rule,[40] there is no need to postulate the concept of product development control. Dauben postulated product development control in order to explain the relatively small amount of axial alcohols produced from unhindered ketones, but in other cases axial alcohols of low stability are produced in large amounts from highly hindered ketones. According to Richer, "the stereochemical results of all the additions to unhindered ketones by groups small enough not to interfere with the axial hydrogens in positions 3 and 5, will be directed exclusively by the presence of the axial hydrogens in

positions 2 and 6 which hinder attack from the equatorial side". Some of Richer's results are shown in Table IV (p. 126).

These conflicting views are further discussed later in this thesis, (p. 112).

Preparation of Allenynols with Deactivated Lithium Aluminium Hydride.

In 1960 an investigation was started in this laboratory[1,2] into the reduction of diynenols with lithium aluminium hydride as a potential route to naturally occurring allenynols. It was shown that simple alkyl- and aryl-penta-3,4-dienols of type $R-C\equiv C-CH=CH-CH_2OH$ of molecular weight similar to that of the naturally occurring allenes could be prepared pure, in good yield. Alkynylpenta-3,4-dienols (allenynols) of type $R-C\equiv C-CH=C=CH-CH_2CH_2OH$ underwent further reduction to allenenols, however, and since the complete separation of allenenol from allenynol was seldom possible, only very small yields of pure allenynol could be obtained by this procedure.

$$RC\equiv C-CH=C=CH-CH_2CH_2OH \xrightarrow{LiAlH_4} RCH=CH-CH=C=CHCH_2CH_2OH$$

The mechanism of the first stage of the reduction of an enynol to the corresponding allenic alcohol is now reasonably well established by deuteration experiments[3] and a seven-membered cyclic allene complex (I) has been used as a convenient representation of the reaction intermediate.[4*]

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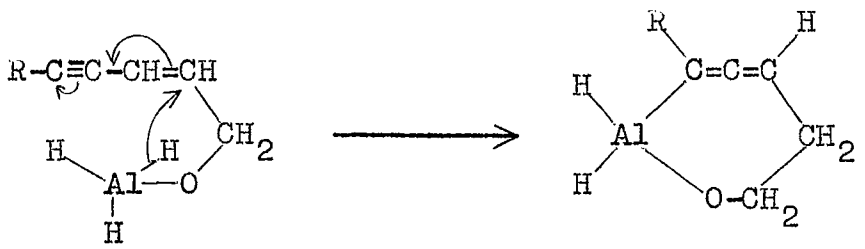
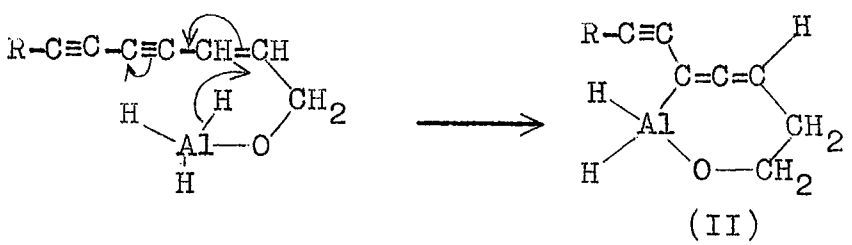
*See the later discussion of this, however, (p.55).



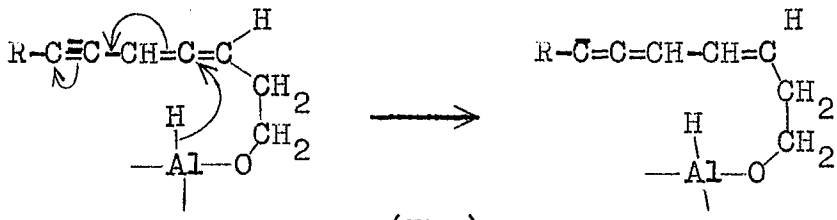
(I)

It had already been shown by Bohlmann, Enkelmann, and Plettner[122] that the reduction of the diynol, 6-phenyl-hexa-3,5-diyn-1-ol to the corresponding enynol by lithium aluminium hydride was prevented if the hydroxyl group was protected by formation of the tetrahydropyranyl ether. This indicated that the aluminium atom must be attached to the oxygen of the diynol in order to donate a hydride ion to C_2 of the latter. To establish whether or not this also applied to reduction of enynols 1-tetrahydropyranyl-oxypent-2-en-4-yne was treated with lithium aluminium hydride. No reaction occurred and the starting material was recovered quantitatively. This indicated that the aluminium atom must be attached to the oxygen of the enynol in order to facilitate hydride transfer to C_2 of a diynenol of type $R-C\equiv C-C\equiv C-CH=CH-CH_2OH$ with lithium aluminium hydride. The first stage of the reduction, therefore, is the formation of the allenic aluminium hydride complex which will be represented here as the seven-membered ring, (II).



(II)

It was considered likely that the next stage of the reduction which gives the allenene, was also likely to go by an intramolecular mechanism. Since transfer of another hydride ion to (II) would produce a double negatively charged complex ion, it was considered preferable to postulate that (II) picks up a proton first. Allenene could then be produced by intramolecular hydride ion transfer as in (III) to produce a new mesomeric allene anion.



(III)

It was reasoned that if this mechanism is correct then removal of two hydride ions from the lithium aluminium hydride by reaction with a suitable primary alcohol, should suppress the second stage of the reduction. Landor and Pepper[1] showed that reduction of alkynylpent-2-en-4-yn-1-ols with dimethoxy- and diethoxy-lithium aluminium hydride did give less reduction of allenyne to allenene, but did not suppress the formation of the latter completely.

At about this time, Bohlmann, Herbst, and Gleinig[5] claimed to have obtained (±)-nona-3,4-diene-6,8-diyn-1-ol ((±)-marasin) in 83% yield by the reduction of non-2-ene-4,6,8-triyn-1-ol with an excess of lithium aluminium hydride. Their product was described as showing a band at 968 $cm.^{-1}$

in the infra-red spectrum, typical of the trans-double bond in the allenene system,[1] and absent in natural marasin.[6] This work was repeated under the conditions described by the previous workers.

Non-2-en-4,6,8-triyn-1-ol was prepared by coupling 5-bromopent-2-en-4-yn-1-ol with diacetylene in the presence of base and cuprous ions* (p. 147), reduced with lithium aluminium hydride under the conditions specified by the previous workers[5] and isolated by the same procedure. The product was eluted from acid alumina in fractions 14 to 19 in approximately 85% theoretical yield (based on non-2-en-4,6,8-triyn-1-ol). This is similar to the yield obtained by Bohlmann, Herbst, and Gleinig. The approximate distribution of the product in these fractions was as follows: fraction 14, 34%; fraction 15, 18%; fraction 16, 15%; fraction 17, 11%; fraction 18, 4%; fraction 19, 0.6%.

The main fraction, fraction 14, and fraction 15 had maxima in the ultra-violet spectrum at λ_{max} 212 (Σ47,000), 265 mμ(15,000), λ_{sh} 253 (Σ12,400), 272 mμ(Σ12,600); (U.V.No. 2) and bands in the infra-red spectrum at ν_{max}3,450 m. (OH), 3,350 m (R-C≡CH), 2,210 m (R-C≡C-R), 1,950 w (-C=C=C-), 965 cm.$^{-1}$ m (trans-double bond in

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*Non-2-en-4,6,8-triyn-1-ol was prepared using the conditions specified by Bohlmann, Herbst, and Gleinig. A considerable improvement in yield was later achieved, however.

allenene system); (I.R. No. 1). The material absorbed five molar equivalents of hydrogen. The band at λ 265 in the ultra-violet spectrum was 2 mμ below the equivalent band (λ 263) in the marasin spectrum. Such a bathochromic shift in the ultra-violet spectra has been shown to accompany reduction of allenynes to allenenes.[1] The band at 965 cm.$^{-1}$ in the infra-red spectrum is also typical of allenenes,[1] and it seems reasonable on the above evidence to propose that fractions 14 and 15 consisted of an allenene. The presence of both terminal and internal acetylenes in the infra-red spectrum indicated that more than one allenene was present and mechanistic considerations led to the conclusion that two isomeric trienynols might be present, nona-3,4,8-trien-6-yn-ol (IV), and nona-3,4,6-trien-8-yn-1-ol (V).

$$CH_2=CH-C\equiv C-CH=C=CH-CH_2CH_2OH \qquad (IV)$$

$$HC\equiv C-CH=CH-CH=C=CH-CH_2CH_2OH \qquad (V)$$

The following mechanisms for formation of compounds (IV) and (V) seems plausible:

$$H(C\equiv C)_3-CH=CHCH_2OH \xrightarrow{LiAlH_4} H(C\equiv C)_2CH=C=CH(CH_2)_2OH$$

$$H(C\equiv C)_2CH=C=CH(CH_2)_2OH$$

$$\swarrow^{LiAlH_4} \qquad \searrow^{LiAlH_4}$$

$$HC\equiv C-CH=\bar{C}-CH=C=CH(CH_2)_2OH + CH_2=\bar{C}-C=C-CH=C=CH(CH_2)_2OH$$

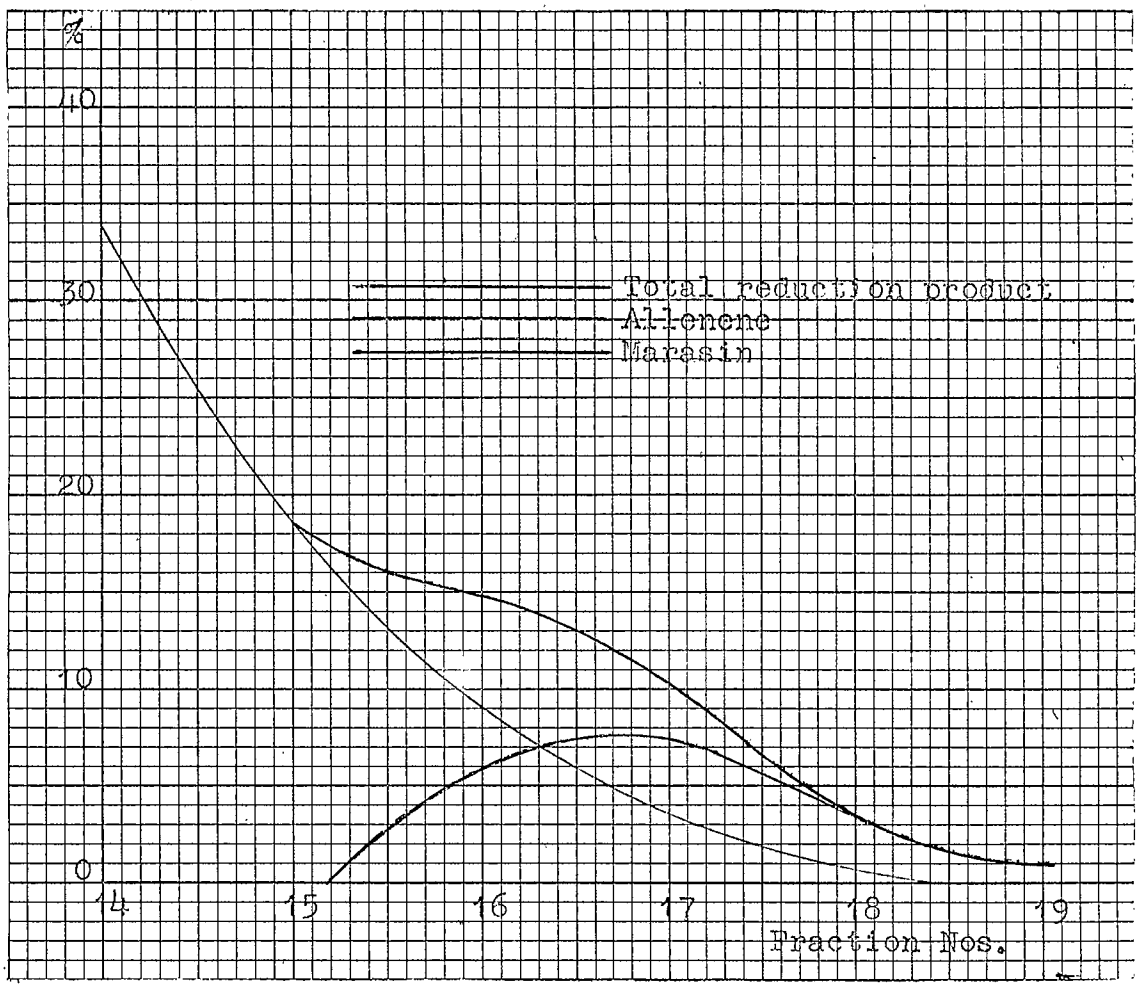
$$\downarrow H_2O \qquad \downarrow H_2O$$

$$HC\equiv C-CH=CH-CH=C=CH(CH_2)_2OH + CH_2=CH-C\equiv C-CH=C=CH(CH_2)_2OH$$

The ultra-violet spectra showed that fractions 16, 17 and

18 contained allenenes (IV) and (V) together with increasing quantities of marasin as shown by a shift in the ultra-violet band towards λ263 for successive fractions, (U.V. No. 3). The last fraction, fraction 19, contained a small amount (0.6%) of pure marasin with typical ultra-violet spectrum.

It was desirable to have some idea of the total quantity of marasin formed but which could not be separated from the allenene. This could not be computed from extinction coefficients as these are approximately the same for marasin and the allenenes, (cf. figure 1[a] p.48). A graphical method in which the percentage of reduction product in each fraction is plotted against the fraction number was therefore employed. Based on the fact that fraction 14 and fraction 15 contained only allenene and that fraction 19 contained no allenene, a fairly accurate curve representing percentage of allenene against fraction number could be drawn, (graph I). The percentages of reduction product in fractions 16, 17 and 18, representing the mixture of marasin and allenene, were also plotted on the curve enabling the percentages of marasin in these fractions to be computed. The total yield of marasin, obtained by the repetition of the procedure of Bohlmann, Herbst, and Gleinig, and computed in this way was approximately 16%; the yield of allenene was approximately 65%. Only a small quantity



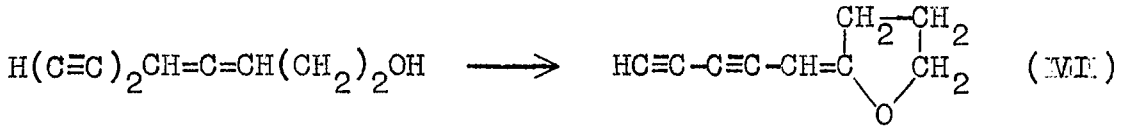
Graph I

Percentage of reduction product in each fraction is plotted against fraction number.

of marasin (0.6%) could be obtained pure by chromatography, however. Further chromatography of fractions 16-18 yielded small additional amounts of pure marasin (0.1% on non-2-en-4,6,8-triyn-1-ol) but the bulk of the marasin was still eluted as a mixture with allenene. This work was in

agreement with earlier work by Landor and Pepper,[1] these workers also being unable to effect complete separation of allenene and allenyne by chromatography. In the light of this work it is suggested that most of the material prepared by Bohlmann, Herbst, and Gleinig was in fact a mixture of allenenes (IV) and (V) and that this was mistaken for impure marasin by these workers.

As is well-known,[143] marasin undergoes isomerisation under alkaline conditions to produce isomarasin, (VII).



Bohlmann, Herbst, and Gleinig[5] claimed to have isomerised their product to isomarasin in 29% yield (based on marasin). Fraction 17, which from the graph was known to contain approximately 70% of marasin (based on the total reduction product in fraction 17 only) and 30% of allenene was subjected to the alkaline treatment specified by the previous workers and the products separated by their procedure using chromatography on acid alumina. Isomarasin in 45% yield (based on total reduction product in fraction 17 only)* was obtained having

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*Due to the volatility of isomarasin the amount obtained was calculated from the extinction coefficients due to Bendz. Bendz had calculated the extinction coefficients of this volatile compound by partially isomerising a number of samples of marasin solution. Knowing the extinction coefficients of marasin he calculated the quantity of isomarasin produced and hence was able to obtain the extinction coefficients of the compound as: λ_{max} 224 (20,900), 266 (10,700), 279.5 (14,500), 295 (11,200). Bohlmann, Herbst, and Gleinig give both the weight of material produced in their experiment and extinction coefficients which are very close to those of Bendz. They do not indicate how these were calculated, however.

ultra-violet spectrum similar to that obtained by Bendz.[143] This was a higher yield than was reported by Bohlmann, Herbst, and Gleinig (29%), and is no doubt due to the fact that the fraction containing the highest proportion of marasin was deliberately chosen for this experiment.

It was anticipated that the allenenes (dihydromarasin) would isomerise under basic conditions to the furan derivatives, having similar ultra-violet absorption spectra to that of isomarasin. In order to check this, fraction 14, containing only pure allenenes (i.e. no marasin), was subjected to the alkaline treatment as used for marasin and chromatographed as before on acid alumina. Surprisingly, no material having an ultra-violet spectrum similar to isomarasin was eluted. A material eluted in the fractions expected to contain the dihydroisomarasin (by analogy with the earlier chromatography of isomarasin) contained a compound having absorption maxima at λ 220 and at much lower intensity at λ 268, (U.V. No. 5). The experiment was repeated using fraction 15, containing only allenenes, and the isolation procedure described by Bendz.[143] Following Bendz the isomerisation product was subjected to a counter-current distribution in eight funnels between pentane as the stationary phase and ethanol containing 30% water as the mobile phase. After fifteen transfers the material previously described was found in the aqueous/ethanolic solutions

in funnels 2,3 and 4.* No material having an ultra-violet absorption spectrum similar to isomarasin was found, and it was concluded that the allenenes do not isomerise under basic conditions to the same type of conjugated furan derivative that is obtained with marasin. The isomerisation product obtained was probably a mixture since fractions 14 and 15 had contained two allenenes (IV) and (V). An attempt to obtain an infra-red spectrum of the material

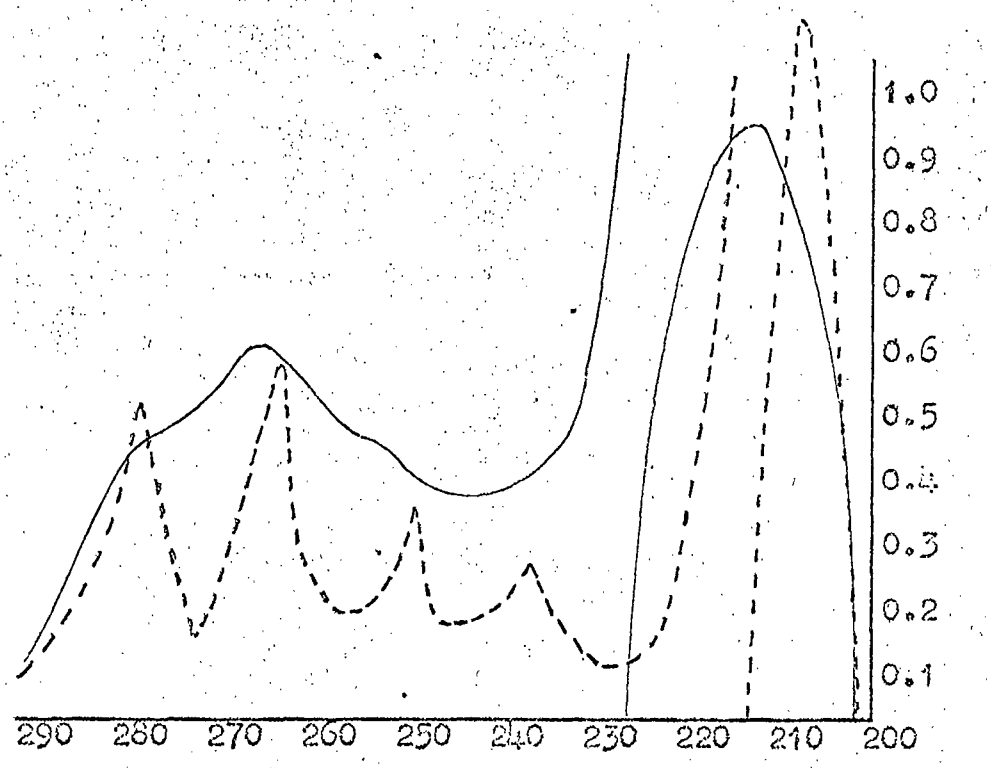

Figure 1[a]

The ultra-violet spectra of (-) marasin (- - - - -) and dihydromarasin (IV) and (V) (————).

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*Bendz had found isomarasin in the aqueous/ethanolic solutions in funnels 2, 3, 4 and 5.

was unsuccessful due to its volatility.*

An attempt was made to suppress the formation of allenene and increase the yield of marasin by using lithium diethoxy-aluminium hydride to reduce non-2-ene-4,6,8-triyn-1-ol. Preparation of the lithium diethoxyaluminium hydride complex was carried out by the dropwise addition of the calculated quantity of ethanol to a previously standardised[7] ethereal solution of lithium aluminium hydride, followed by heating of the reaction mixture under reflux for 1 hr. This procedure would be expected to give mainly diethoxy lithium aluminium hydride with a minimum of the triethoxy compound. The reduction of non-2-en-4,6,8-triyn-1-ol was then carried out for 2 hr. at room temperature and the aluminium complexes decomposed with 10% sulphuric acid to prevent isomerisation of the product under basic conditions. It was found that the yield of pure marasin obtained was increased to approximately 6% indicating that further reduction of marasin to allenene had been suppressed to some extent. Ultra-violet spectra showed that allenene formation was still occurring, however, and an estimate by the graphical method previously described showed that the yield of allenene was approximately 45% (based on non-2-en-4,6,8-triyn-1-ol) and marasin approximately 30%

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*The material was lost in attempting to concentrate the dilute solution from the chromatography and the counter-current experiment by evaporation.

(based on non-2-en-4,6,8-triyn-1-ol). Most of the marasin was thus not separated from the allenene by the chromatography.

It was considered likely that allenene formation was due to the presence of lithium monoethoxyaluminium hydride resulting from the initial formation of a mixture in preparing the reducing agent. A cyclic complex would be expected to be more stable than the acyclic complex* and it was therefore predicted that the use of a cyclic complex of lithium aluminium hydride should suppress allenene formation to a minimum. The cyclic complex chosen for investigation was the lithium aluminium hydride-butane-2,3-diol complex. The preparation of this complex and its use in the reduction of alka-4,6-diyn-2-en-1-ols was carried out as described for the diethoxy complex, (p. 49). Three molar equivalents of complex per mole of diynenol was used for the reduction. As marasin is very unstable and difficult to handle, two model compounds, trans-8,8-dimethylnon-2-en-4,6-diyn-1-ol[1] and trans-hept-2-en-4,6-diyn-1-ol,[10] were chosen for preliminary experiments. It was found that formation of allenene was completely suppressed; however, substantial amounts of the starting material were also recovered. This was completely separated from allenyne by chomatography on acid alumina. Pure

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*E.g. Cyclic acetals are more stable than acyclic ones.

8,8-dimethylnona-3,4-dien-6-yn-1-ol was obtained in 14% yield and pure hepta-3,4-dien-6-yn-1-ol in 9% yield. Both these compounds were shown to be free of allenene by the absence of bands in the region of 955 cm.$^{-1}$ in their infra-red spectra, (I.R. Nos. 8 and 10. This was in contrast to the earlier work of Landor and Pepper[1] in which the lithium dialkoxyaluminium hydride complex was used to reduce the above two model compounds. In both cases the formation of some allenene was observed, and although some hepta-3,4-dien-6-yn-1-ol was obtained pure by chromatography, the 8,8-dimethylnona-3,4-dien-6-yn-1-ol could not be completely freed from allenene, as shown by a band at 955 cm. $^{-1}$ in its infra-red spectrum, (cf. ref. 1).

It may thus be concluded that in the reduction of alka-4,6-diyn-2-en-1-ols with lithium aluminium hydride, the first product, the allenyne, is further reduced to an allenene. Formation of allenene can be partially suppressed by using a dialkoxyaluminiumhydride complex as the reducing agent, and may be completely eliminated by using a cyclic lithium aluminium hydride complex. In the latter case, however, a substantial quantity of unreduced alka-4,6-diyn-2-en-1-ol is recovered even though excess reducing agent is used. This may be completely separated from the allenyne by chromatography.

The Asymmetric Synthesis and Determination of the Absolute Configuration of Allenic Alcohols

The successful preparation of allenynols with deactivated lithium aluminium hydride complexes (pp. 50, 51) led to the interesting possibility that if an asymmetric complex of lithium aluminium hydride were used as the reducing agent, an asymmetric allenynol could be produced. Further, if it could be deduced theoretically whether the asymmetric reduction should give rise to the R or the S form of the allenic alcohol, it would be possible to determine the absolute configuration of these compounds. A preliminary investigation into the use of lithium dimenthoxyaluminium hydride as an asymmetric reducing agent was initiated by Evans and Landor,[11] and further work is described in this thesis.

The procedure used for preparing the complex was to add the calculated quantity of menthol in ether to the calculated quantity of an ethereal solution of lithium aluminium hydride and to heat the reaction mixture under reflux for 2 hr.; this was to ensure as far as possible that equilibration was complete and a dimenthoxyaluminium hydride complex had been formed. The enynol in ethereal solution was then added to the ethereal solution of the complex and stirred for 2 hr.; usually at room temperature. The complex was decomposed by dropwise addition of water,

or by pouring into dilute acid and, in the case of simple allenic alcohols, the products purified by careful fractionation under reduced pressure. The allenic alcohols were checked for the presence of traces of menthol by g.l.c. and rotations measured. Three preliminary experiments on these lines were carried out and the results are tabulated below:

Table I

Asymmetric Reduction of Alk-2-en-4-yn-1-ols with Menthoxyaluminium-hydride Complexes[11]

$LiAlH_4$ Mole	(-)-Menthol Mole	Alkenynol Mole	Allenic Alcohol $RCH=C=CHCH_2CH_2OH$ R=CH_3	R=C_2H_5
0.05	0.05	0.033	+1.68°	
0.13	0.26	0.065	+8.27	
0.125	0.25	0.075		+2.29°

Eliel[8] postulated disproportionation of complexes of lithium aluminium hydride with secondary alcohols, to explain his stereochemical results. The following equilibrium can occur, although in the case of bulky alcohols the equilibrium lies well to the left:

$$2LiAl(OR)_2H_2 \rightleftharpoons LiAl(OR)_4 + LiAlH_4$$

The production of optically active allenic alcohols (cf. Table I) by the dimenthoxyaluminium hydride complex indicates that the menthoxy groups are sufficiently large to inhibit disproportionation of the complex. A consideration of the stereochemistry of the complex ion is therefore appropriate.

Examination of a Dreiding model shows that the preferred conformation of the dimenthoxyaluminium hydride ion may be readily predicted. The most important interactions are between the two hydrogens on the aluminium atom and the equatorial hydrogens at C_2 and C'_2 and between the aluminium hydrogens and the hydrogens on the isopropyl groups. The menthyl chairs will also tend to position themselves so that the aluminium is staggered between the C_2 carbon and the axial hydrogen on C_1. Figure 1 represents the preferred conformation of the complex ion. The model shows that in this conformation the two remaining hydrogens on the aluminium are exactly equivalent and that each hydrogen is in an asymmetric environment

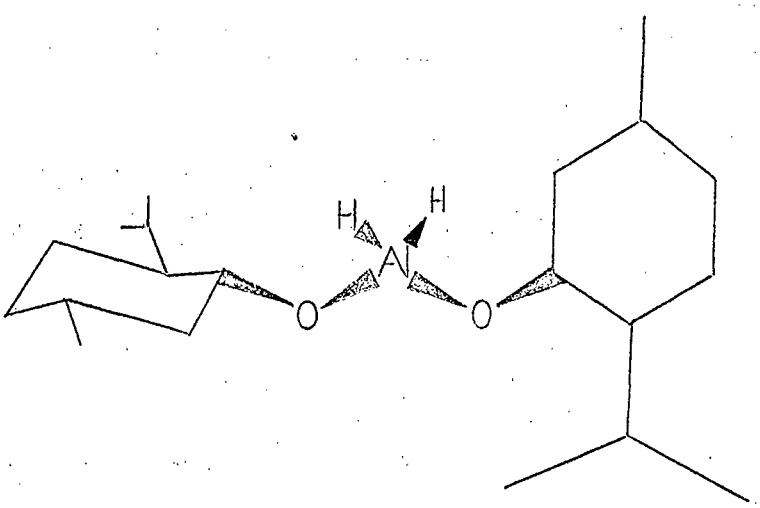

Figure 1
The dimenthoxyaluminium hydride complex in the preferred conformation.

being shielded on one side by an isopropyl group.

It has already been shown (p. 40) that the aluminium hydride ion must be attached to the oxygen of the enynol in order to transfer a hydride ion to C_2 of the enynol. After hydride ion transfer the aluminium is formally neutral but has the characteristics of a Lewis acid; at the same time an allenic mesomeric anion is formed. The allenic anion can co-ordinate with a trivalent aluminium either intramolecularly or intermolecularly. Intramolecular co-ordination would lead to the formation of a seven-membered cyclic allene complex (figure 2).

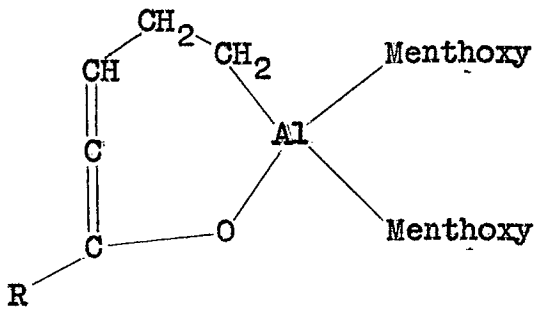

Figure 2
The seven-membered cyclic allene complex.

Intermolecular co-ordination could lead to either a polymeric complex (figure 3) or a dimeric fourteen-membered cyclic complex (figure 4).

The seven-membered cyclic allene complex is used as a convenient representation of the reaction intermediate although its formation in practice is doubtful

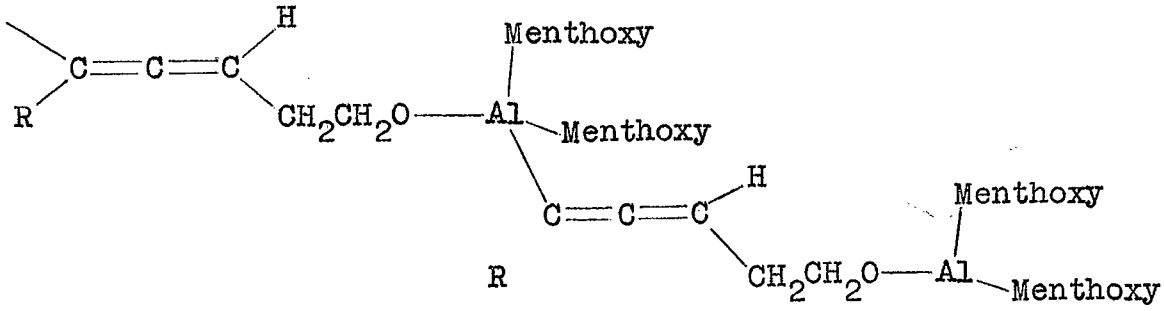

Figure 3
The polymeric complex.

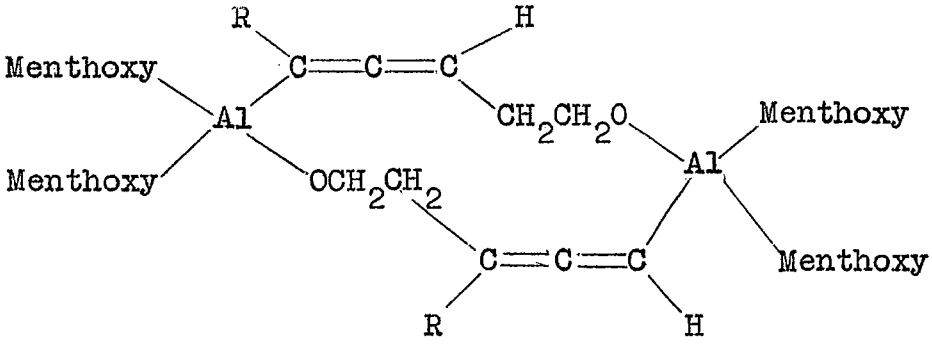

Figure 4
The dimeric fourteen-membered cyclic complex.

since seven- or eight-membered cyclic allene compounds are highly strained and not usually stable.[12] On the other hand, if a polymeric complex is formed it would be expected to precipitate* and no such precipitation has been observed during these reductions. It is for these reasons that the fourteen-membered cyclic allene complex is suggested as a third alternative. Such a complex appears to be unstrained and models can be readily constructed. In any

*Short polymer chains may be soluble, however.

case, an examination of models shows that whichever of these three possible intermediate complexes is formed, the stereochemistry of the reduction product will be the same.

Before discussing the stereochemistry of these intermediate complexes, it is pertinent to consider whether the reaction is under kinetic or thermodynamic control and any stereochemical consequences.

The concepts of kinetic control, and thermodynamic control may be conveniently explained by considering a chemical reaction in which two products, A and B are possible.* If A is formed faster than B, then if the reaction is stopped after a short time, A will predominate in the reaction products. Product A is then said to be the product of kinetic control, i.e., it is the product of the faster of the two reactions. It may happen, however, that the formation of A and B is reversible under the reaction conditions employed. In this event, if the reaction is allowed sufficient time to attain equilibrium, the thermodynamically more stable compound (say B) will predominate in the reaction products. Product B is then said to be the product of thermodynamic control.

If the observed optical activity of the products of this asymmetric reduction were a consequence of kinetic

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*For the present case the two possible products are the S and R forms of the allenic alcohol. The concepts are not restricted to the formation of enantiomeric forms, however.

control, then it would follow that the rate of formation of the R and the S forms of the allene must differ. An examination of models was therefore made to determine whether such a difference in rates would be expected. Since the enynol has a plane of symmetry, any asymmetry introduced into the reduction cannot involve the formation of the O-Al bond and this stage of the reduction will therefore be assumed to have taken place. In the second stage of the reduction, the donation of a hydride ion to C_2 of the enynol, however, two possible approach orientations are possible. Although one approach orientation may be favoured over the other, the anion produced is mesomeric* and this mechanism would therefore be expected to lead to a racemic product. Therefore a reduction under kinetic control should not give optically active allenic alcohols. The illustration of these arguments on paper is difficult, however, an attempt is made to demonstrate this point in figure 5.

After formation of the mesomeric anion a reversible co-ordination with a trivalent aluminium can occur as previously outlined. As no acetylene is formed on decomposition of the complex with water it is assumed that only the allenic anion participates in such a complex. If one form of the co-ordinated allene, i.e., R or S, is

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*In resonance terminology, the two canonical forms, i.e., the allenic anion and the propargylic anion are both linear.

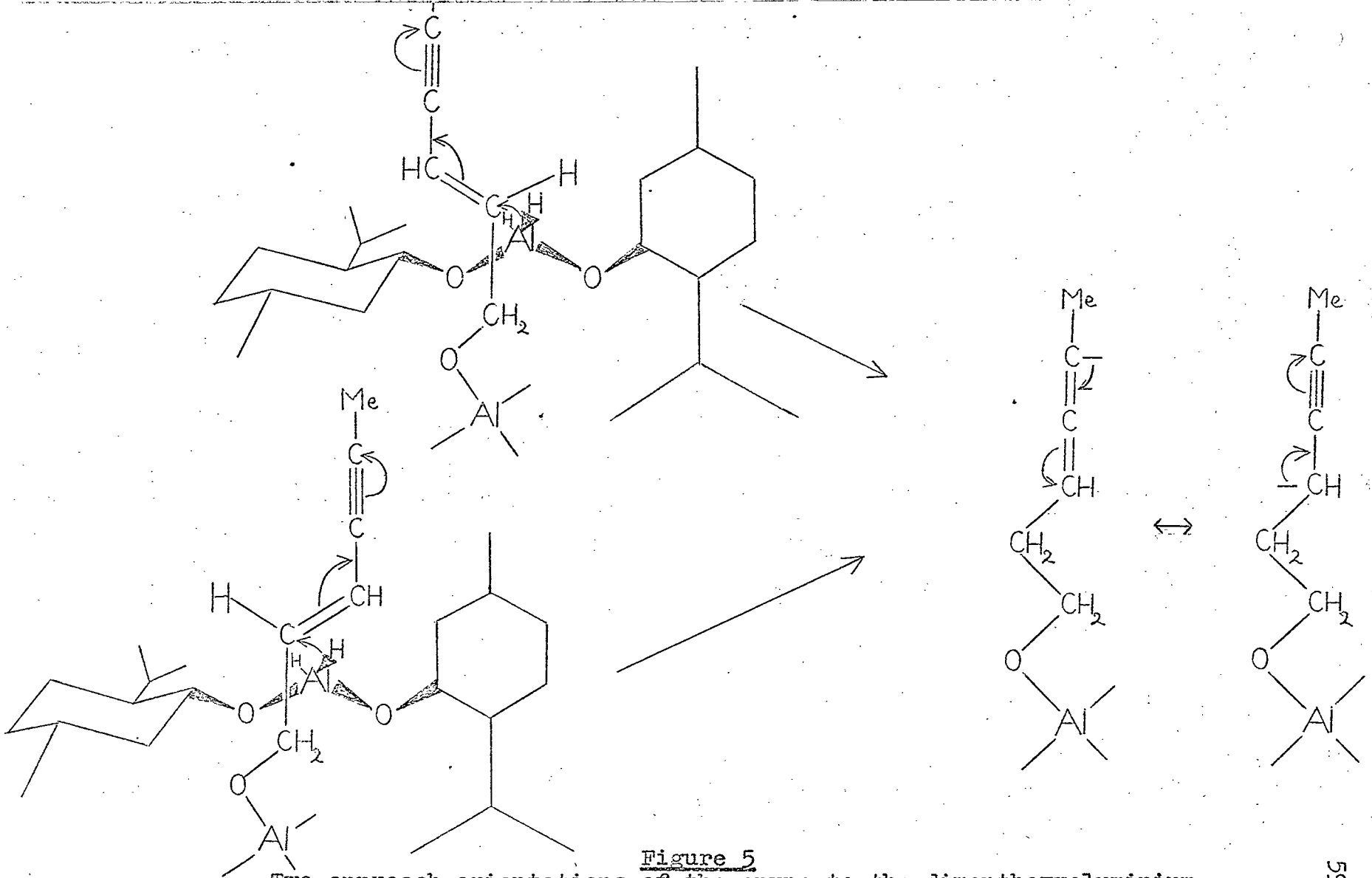

Figure 5
Two approach orientations of the enyne to the dimenthoxyaluminium hydride complex leading to the same mesomeric anion.

more thermodynamically stable than the other, then a preponderance of this enantiomer would be expected in the reduction products. An examination of models of the seven-membered cyclic allene complex, the fourteen-membered dimeric cyclic allene complex and the polymeric allene complex shows that in all cases the interactions between non-bonded atoms are at a minimum when the allene is in the S form. The S forms of these allenic complexes therefore have greater thermodynamic stability than the R forms. Thus thermodynamic control of this reduction would be expected to lead to an excess of the S form of the allenic alcohol in the product. This is illustrated in figures 6-8.

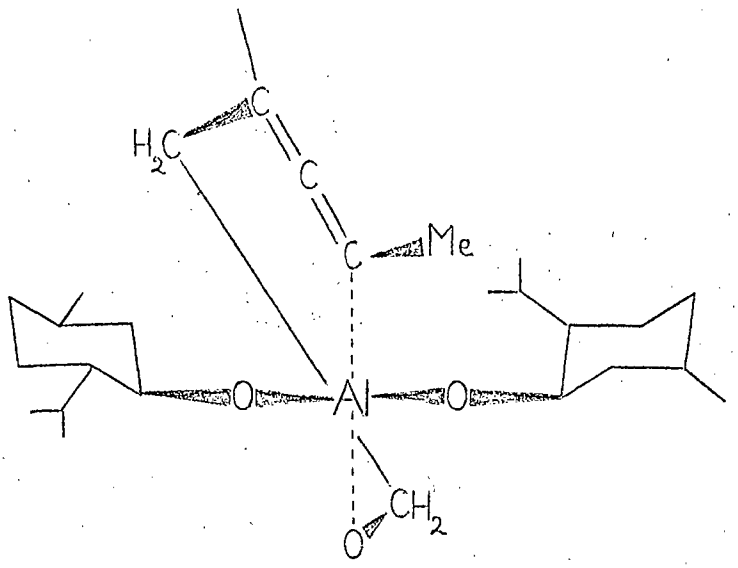

Figure 6
The seven-membered cyclic allene/dimenthoxyaluminium hydride complex in the more stable S form.

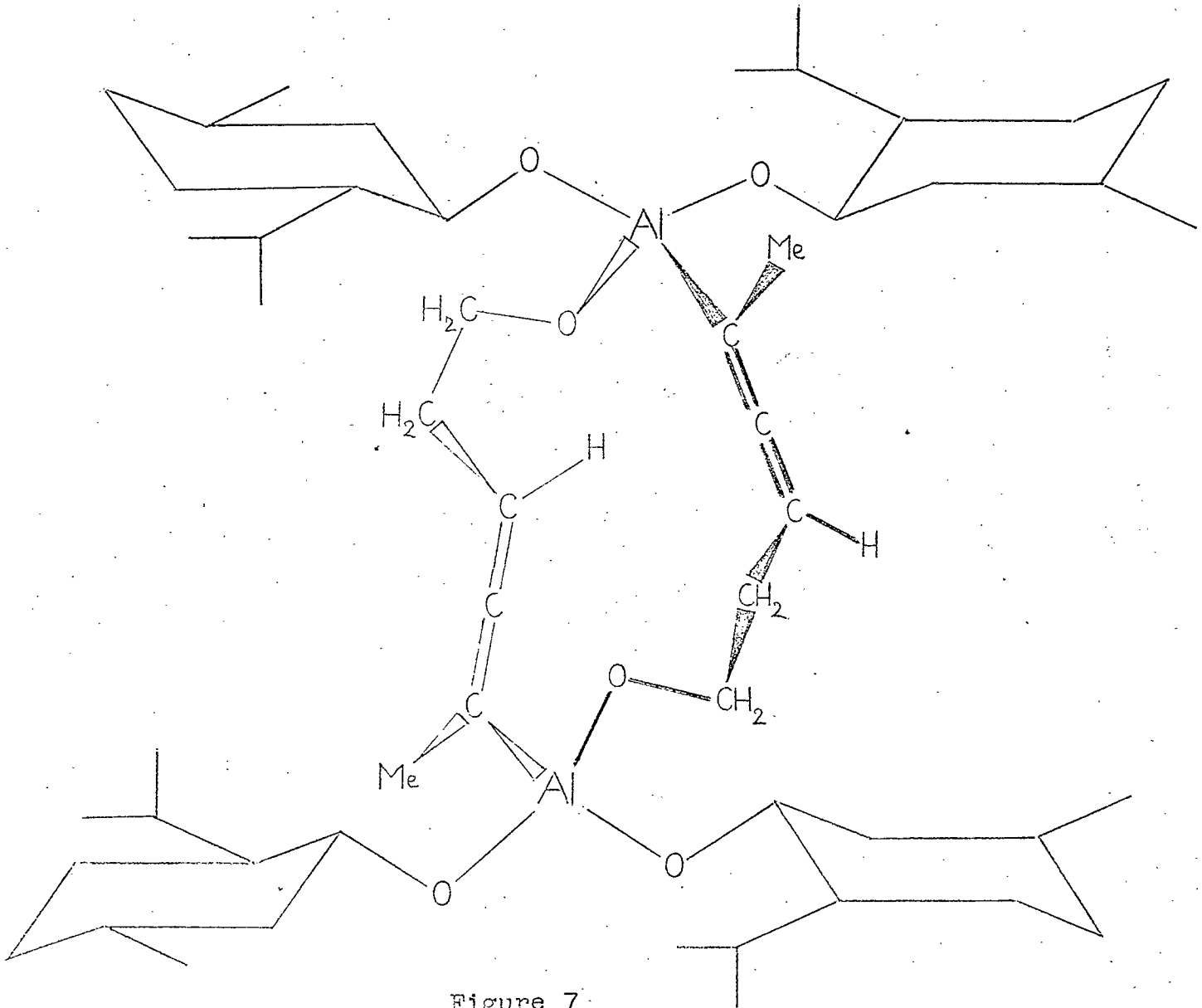

Figure 7

The fourteen membered dimeric cyclic allene-dimenthoxyaluminium hydride complex in the more stable S form.

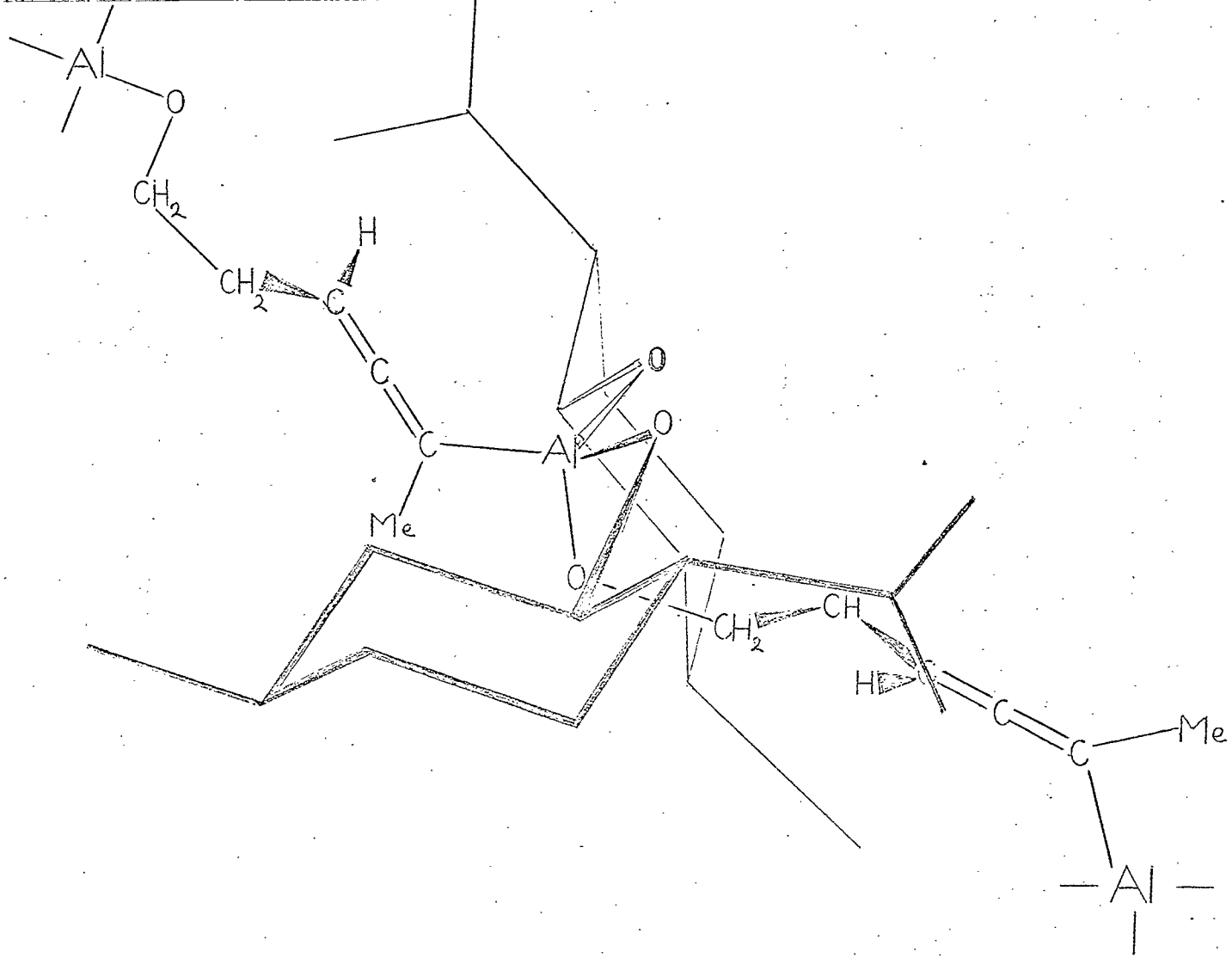

Figure 8
The polymeric allene–dimenthoxyaluminium hydride complex in the more stable S form.

The formation of an optically active product is therefore in no way connected with the actual reduction process (i.e. hydride transfer) of enynol to allenic alcohol. It was reasoned that if this was so, then addition of the optically active agent (e.g. menthol) after completion of the reduction stage should give an excess of the more stable S allene dimenthoxyaluminium complex and, after decomposition with water, excess S allenic alcohol just as it had done in the previous experiments with preformed menthylate complex. Accordingly, hex-2-en-4-yn-1-ol was stirred in ethereal solution with lithium aluminium hydride for 0.5 hr., an ethereal solution of menthol added and the reaction mixture stirred for a further 2 hr. After working up (+)hexa-3,4-dien-1-ol* $[\alpha]_D^{25}+9.3^\circ$ was obtained, thus supporting the conclusion that the reaction was thermodynamically controlled.

The theoretical prediction that reduction of an enynol of type $R-C\equiv C-CH=CH-CH_2OH$ with the lithium dimenthoxyaluminium hydride complex leads to excess of the S form of the corresponding allenic alcohol, constitutes a method for the determination of the absolute configuration of allenic alcohols. In principle, it is only necessary to prepare the allenic alcohol by use of the complex, observe its sign of rotation and assign the S configuration to the predominant

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*(+)Hexa-3,4-dien-1-ol prepared by adding hex-2-en-4-yn-1-ol to the previously formed lithium dimenthoxyaluminium hydride complex had $[\alpha]_D^{25}+8.27^\circ$.

enantiomorph. On this basis the configuration of the allenic alcohols listed in Table I (p. 53) is S(+).*

An attempt was made to use the lithium dimenthoxyaluminium hydride complex to determine the absolute configuration of the naturally occurring antibiotic nona-3,4-diene-6,8-diyn-1-ol (marasin). Preparation of non-2-ene-4,6,8-triyn-1-ol by the method used by Bohlmann, Herbst, and Gleinig[5,1] gave the pure product in only 5% yield. By modifying the reaction conditions (pp. 147-150) the yield was increased to 23.5%. The time-consuming chromatographic purification of the crude product was avoided by precipitating the compound as its silver salt in mildly basic solution. The highly explosive, shock-sensitive, silver salt was separated and washed several times with ether using a refrigerated centrifuge at -20°. Reduction of non-2-ene-4,6,8-triyn-1-ol was achieved by using a three-fold excess of lithium dimenthoxyaluminium hydride complex (prep. p. 52). About 0.1 g. of marasin was required for an accurate determination of rotation and this necessitated the use of approximately 7 g. of menthol in the preparation of the complex.**

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*The absolute configuration of these alcohols has also been assigned as S(+) by a completely independent method described in this thesis (p. 82). The S(+) configuration has also been predicted[125] by an application of Brewster's theory[126] (cf.p. 27)

**In this reduction only 10-15% of marasin (based on non-2-ene-4,6,8-triyn-1-ol) was obtained, the unreduced starting material being recovered. This was completely separated from the marasin by chromatography. No Allenene was formed.

Thus after decomposition of the complex with acid, the marasin had to be separated from this relatively large quantity of menthol. Although an exhaustive effort was made to achieve this, traces of this ten carbon alcohol persisted in the nine carbon marasin. Chromatography on Spence type H alumina deactivated with from 2-15% of 10% aqueous acetic acid and elution with ether/n-pentane mixtures was unsuccessful, as was chromatography on Woelm acid alumina deactivated with 3% water and elution with ether/n-pentane.

An attempt was also made to purify the marasin on a small hand-operated 50 tube counter-current apparatus (Quickfit) using 40-60° pet ether/butanol/water and carbon tetrachloride water systems (p. 152). Although separation was achieved using only 25 ml. of the dilute marasin solution, (∽0.05%) it was not practical to use the method for the separation of the large bulk of the marasin solution.*

During these experiments the photosensitive marasin was at all times protected from light by working in dim red light and by wrapping chromatography columns in brown paper. The traces of menthol in the marasin solution were readily detectable by gas/liquid chromatography on a silicon oil column.

By about this time, Landor, Miller, and Tatchell[13,14]

*The decomposition of marasin is rapid if the concentration is much above 0.6% (cf. G. Bendz[97]). Solutions were therefore necessarily very dilute, and optical rotations could not be determined.

had developed a method of asymmetric reduction using a complex prepared from lithium aluminium hydride and 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose. Attempts by these workers to obtain the monosaccharide analytically pure by chromatography had been unsuccessful and they had therefore used the slightly impure complex, containing approximately 1% of impurity, to reduce a series of ketones. The optically active alcohols produced were distilled from the high boiling monosaccharide which together with the impurities remained in the residue and was recovered for further use. During the course of this work, these workers introduced the use of titrated lithium aluminium hydride solutions[7] for the preparation of the complex so as to ensure accuracy in the stoichiometry. A number of alk-enynols were also reduced with the slightly impure complex and optically active allenic alcohols produced.[15] Thus for example, reduction of hex-2-en-4-yn-1-ol gave (-)-hexa-3,4-dien-1-ol $[\alpha]_D^{20}-10^o$, hept-2-en-4-yn-1-ol gave (-)-hepta-3,4-dien-1-ol $[\alpha]_D^{20}-8.9^o$, and non-2-en-4-yn-1-ol gave (-)-nona-3,4-dien-1-ol $[\alpha]_D^{20}-7.4^o$. The allenic alcohols could be distilled off and separated from the monosaccharide derivative without difficulty. It was therefore decided to attempt the preparation of optically active marasin using the complex prepared from the slightly impure monosaccharide derivative and lithium aluminium hydride.

The preparation of the monosaccharide complex and the reduction of enynols with this complex was carried out in a similar manner to that already described for the menthylate complex (p.52). Following Landor, Miller, and Tatchell, titrated solutions of lithium aluminium hydride[7] were used throughout this work.

After decomposition of the complex with acid and working up, the solution was chromatographed on Woelm acid alumina deactivated with 3% water using ether/n-pentane 1/4 as the eluting solvent. The marasin solution so obtained ($[\alpha]_D^{25}$-31°) was examined for the presence of traces of sugar derivatives by thin layer chromatography. After development of the t.l.c. plates with 2% methanol in benzene and spraying with a solution of naphthoresorcinol in ethanol/phosphoric acid the plates were placed in an oven at 110° for ½ hr. when monosaccharide derivatives showed as blue spots. Marasin gave a brownish spot at R_F 0.6. A second light blue spot at R_F 0.25 revealed the presence of an impurity suspected at the time of being a monosaccharide derivative due to the characteristic blue colour of the spot. Re-chromatography of the solution on deactivated alumina failed to remove this impurity. Examination of the 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose by thin layer chromatography showed a heavy blue spot at R_F 0.20 and faint blue spots at R_F values of 0.0, 0.25

and 0.95 and supported the conclusion that the impurity in the marasin was a monosaccharide derivative introduced as an impurity in the 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose.* As monosaccharide derivatives are optically active the optical rotation of marasin could not be determined in the presence of these impurities.

An unsuccessful attempt was made to remove the monosaccharide derivative by passing the marasin solution through a silica column impregnated with boric acid. This removes viscinal diols such as the 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose but did not remove the impurity having R_F 0.25 in the marasin solution, suggesting that it was probably a mono-ol. An attempt to hydrolyse the monosaccharide derivative contaminating the marasin solution with methanolic hydrochloric acid for 2 hr. at room temperature and then remove the hydrolysed sugar by further chromatography on silica impregnated with boric acid was successful. However, the marasin was apparently racemised by the acid treatment which defeated the purpose of the experiment.** As a last resort, an attempt was made to

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*This was later confirmed and the monosaccharide identified (pp. 99-106).

**Evans, Landor and Taylor Smith[113] had shown that optically active allenic chloride is racemised by hydrochloric acid.

separate the marasin as the silver salt, but as expected the marasin underwent rapid polymerisation and isomerisation under the mild alkaline conditions used.

It was realised at this point that a complete re-investigation of the preparation of the 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose would have to be undertaken with a view to removing the trace impurities. The separation of the trace impurities and their identification, and the preparation of 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose in an analytically pure form is described later in this thesis (pp. 99-106).

Using the pure glucofuranose, optically active (-)-marasin (11.5% on non-2-ene-4,6,8-triyn-1-ol) $[\alpha]_D^{25}$ -26.6° was obtained (p. 156) by the chromatography of the crude product on deactivated alumina and silica/boric acid. The marasin solution was shown to be free of monosaccharide derivatives by thin layer chromatography* and its ultra-violet spectrum was in agreement with those of Bendz[6,97] and Cambie, Hirschberg, Jones and Lowe[16] (U.V. No. 15). Since the lithium aluminium hydride-3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose complex gives allenes of the R configuration, (-)-marasin has the R configuration.

Having thus established a method for preparing optically active allenynols of known configuration, the method was

*Determination of the minimum quantity of monosaccharide detectable by t.l.c. (p. 178).

applied to three other examples. (-)-Deca-3,4-diene-6,8-diyn-1-ol ((-)-9-methylmarasin)[91] was prepared as follows: penta-1,3-diyne was prepared by a modification of the literature method[17] (p.157), and coupled under modified Chodkiewicz[18,1] (p.157) conditions with 5-bromopent-2-en-4-yn-1-ol[144] to give dec-2-ene-4,6,8-triyn-1-ol.[20] This was reduced with an excess of the lithium aluminium hydride-3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose complex (p.158) to give (-)-9-methylmarasin (14.0% on dec-2-ene-4,6,8-triyn-1-ol) $[\alpha]_D^{25}$-11.3°. (-)-9-Methylmarasin therefore has the R configuration.

7-Phenylhept-2-ene-4,6-diyn-1-ol was prepared by coupling phenylacetylene with 5-bromopent-2-en-4-yn-1-ol[144] (p.160) and reduction of this with excess of the lithium aluminium hydride-3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose complex gave (-)-7-phenylhepta-3,4-dien-6-yn-1-ol (14.4% on 7-phenylhept-2-ene-4,6-diyne-1-ol) $[\alpha]_D^{25}$-3.1° (p.161). (-)-7-Phenylhepta-3-4-dien-6-yn-1-ol therefore has the R configuration.

8,8-Dimethylnon-2-ene-4,6-diyn-1-ol was prepared by coupling of 3,3-dimethylbut-1-yne[21] with 5-bromopent-2-en-4-yn-1-ol[144] (p. 139) and reduction with the lithium aluminium hydride-3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose complex gave (-)-8,8-dimethylnona-3,4-dien-6-yn-1-ol (32% on 8,8-dimethylnon-2-ene-4,6-diyn-1-ol)

$[\alpha]_D^{25}$ -12.5°. (-)-8,8-Dimethylnona-3,4-dien-6-yn-1-ol therefore has the R configuration.

Samples of the above optically active allenynols were sent to Dr. L. Verbit at the State University of New York for optical rotatory dispersion measurements. Unfortunately, with the exception of the (-)-8,8-dimethylnona-3,4-dien-6-yn-1-ol, all the compounds had decomposed by the time they were received. The circular dichroism curve of (-)-8,8-dimethylnona-3,4-dien-6-yn-1-ol showed unambiguously the presence of a negative Cotton effect (p.221).

It has already been deduced theoretically that the configuration of allenic alcohols produced by the lithium dimenthoxyaluminium hydride complex is S(+). Since the monosaccharide complex produced laevorotatory allenic alcohols it follows that this complex produces predominantly the R(-) form of the allenic alcohol. If this conclusion could be confirmed by an independent consideration of the stereochemistry of reduction with the monosaccharide complex, then the force of the whole argument would be increased considerably. This may be demonstrated by an examination of models which predict that the monosaccharide complex should produce the R form of the allenic alcohol.

A Dreiding model of the lithium aluminium hydride-3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose complex in its preferred conformation is shown in figure 9.

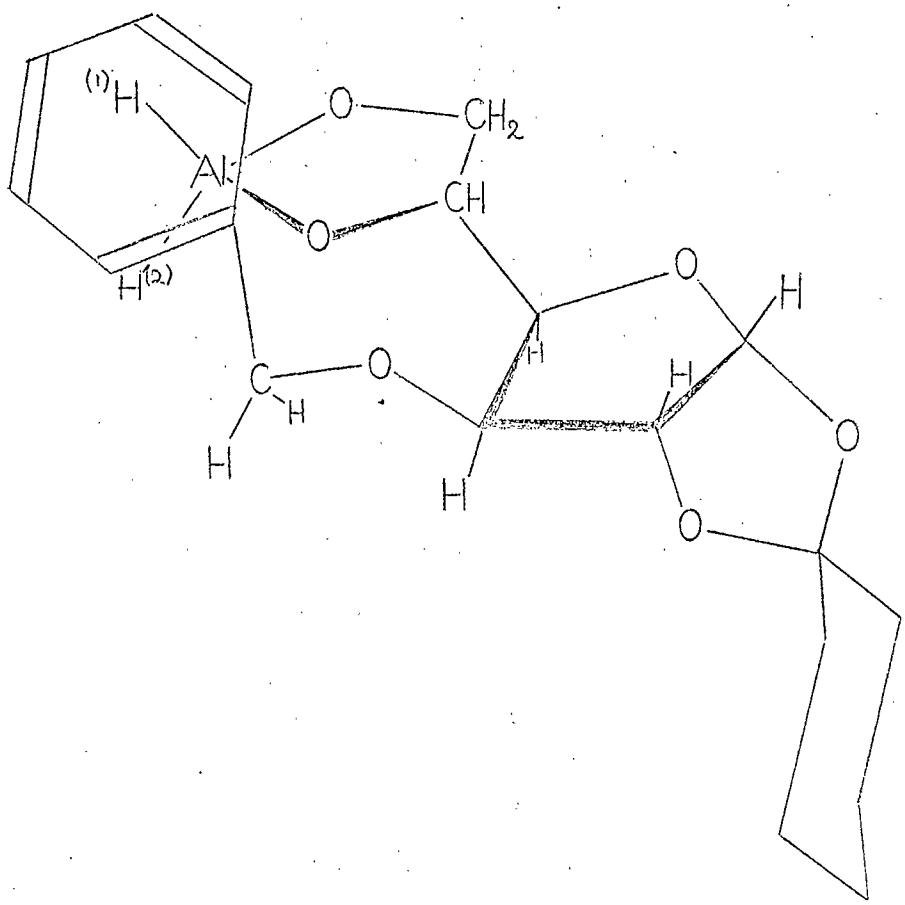

Figure 9
The 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose-aluminium hydride complex ion in the preferred conformation.

In this conformation the two hydrogens on the aluminium atom are shielded on one side by the benzyl group and it is clear from the model that H-1 (figure 9) is shielded more than H-2. H-2 would therefore be expected to react preferentially to H-1.*

*The validity of this theory has now been confirmed by Landor, Miller, and Tatchell.[24] These workers predicted the S configuration for alcohols obtained by the reduction of a series of ketones, on the basis that H-2 reacted preferentially with the ketone. It was then reasoned that if H-2 was removed by reaction with a primary alcohol H-1 would have to be utilised in the reduction, and this should lead to the R form of the alcohol. These predictions were realised experimentally.

The mechanism of the reduction of an enynol with the monosaccharide complex will be similar to that discussed for the dimenthoxy complex (p. 55). The seven-membered cyclic allene complex will again be used as the most convenient demonstration of the stereochemical argument, although the polymeric allene complex or the fourteen-membered dimeric allene complex are more realistic possibilities.

The possibility that the reduction was under kinetic control was rejected on the same theoretical grounds as before (p. 58) and an experiment (cf. p. 63) in which hex-2-en-4-yn-1-ol was first reduced with lithium aluminium hydride and monosaccharide was then added to the mixture gave optically active hexa-3,4-dienol* $[\alpha]_D^{25}$ -8.2° and confirmed that the formation of optically active alcohol was due to a thermodynamic control of the reaction.

In considering the stereochemistry of the monosaccharide/allenic complexes an important difference between these and the previously considered dimenthoxy/allenic complexes is immediately apparent. Whereas in the earlier case the two hydrogens on the aluminium were equivalent to each other, in the present case H-1 is not equivalent to H-2.

The initial reaction of the monosaccharide complex

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*Preformed complex produced hexa-3,4-dien-1-ol $[\alpha]_D^{20}$ -10°.

with the hydroxyl group on the enynol will undoubtedly involve H-2, the more reactive hydrogen. After donation of the hydride ion and formation of the mesomeric allene anion, however, the formally neutral aluminium atom will adopt a planar arrangement. In co-ordinating with this aluminium atom to form the seven-membered cyclic complex, therefore, the anion can approach from either side of the planar aluminium.

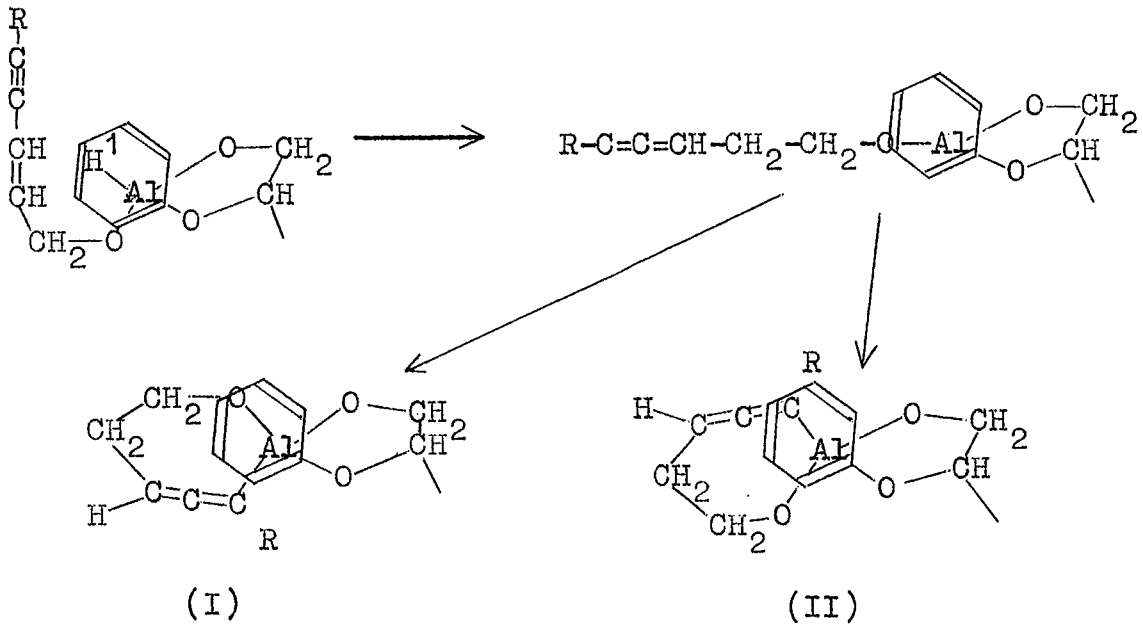


Figure 10
Only partial glucofuranose structures are shown.

Two factors favour approach such that in the final cyclic complex the oxygen of the enynol will replace H-1 as shown in figure 10 (I). The first factor is steric approach control. Approach from the H-2 side of the aluminium is

easier than approach from the H-1 side due to differential shielding by the benzyl group, (cf. Landor, Miller, and Tatchell[14]). The second factor is the greater thermodynamic stability of the complex in which the oxygen replaces H-1 indicated by fewer interactions between non-bonded atoms in this complex compared with the alternative. With the seven-membered cyclic allene complex no conformational variations are possible, the only other variant being whether the allene is in the R or the S configuration. There is no doubt that the R configuration is subject to less steric interference by the benzyl group than the S configuration and the R form would therefore be expected to predominate in the reaction products. This is illustrated in figure 11, (p. 76).

In considering the fourteen-membered cyclic complex and the polymeric allene complex the arguments used for the seven-membered cyclic complex also apply but are further complicated by the greater flexibility of the system. There are six possible conformations for the R allene and six for the S allene; these are represented schematically in figure 12 (p. 77). Steric interactions with the benzyl group make conformations b_1, b_2, c_1, and c_2 unfavourable and these may be ignored. A model of conformation a_1 shows that the R form of the allene would be thermodynamically more stable and a model of conformation a_2 shows that the

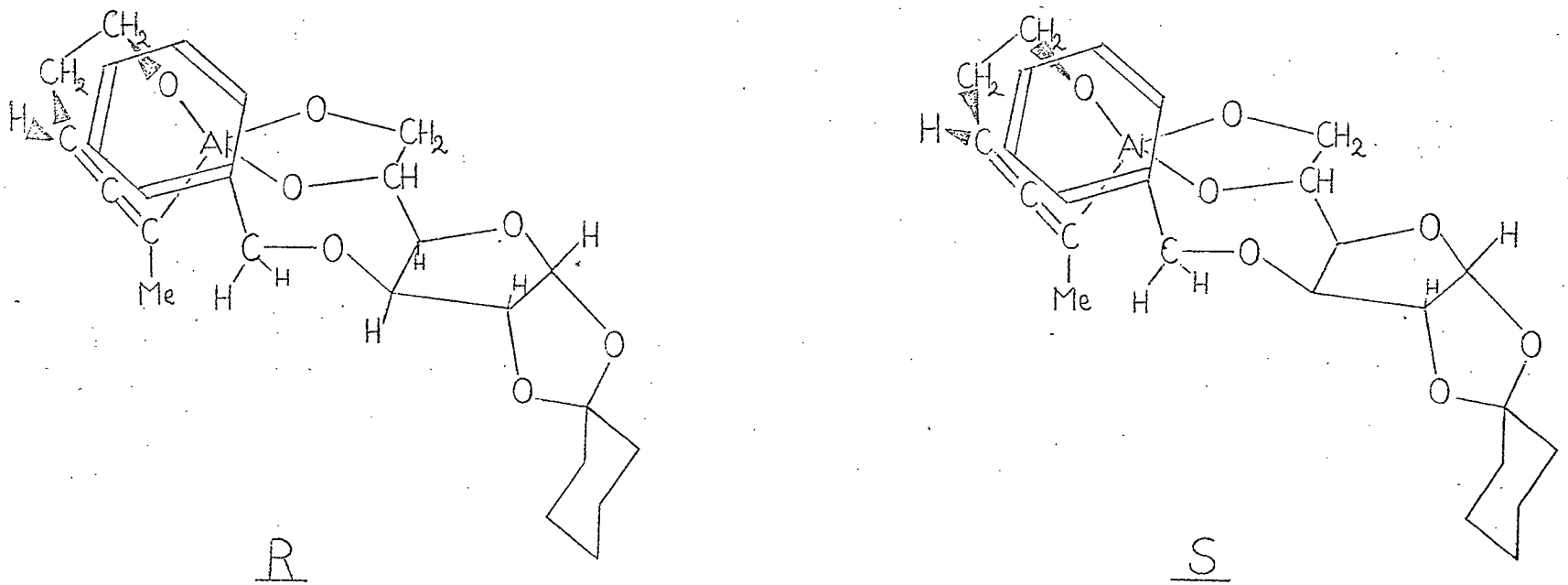
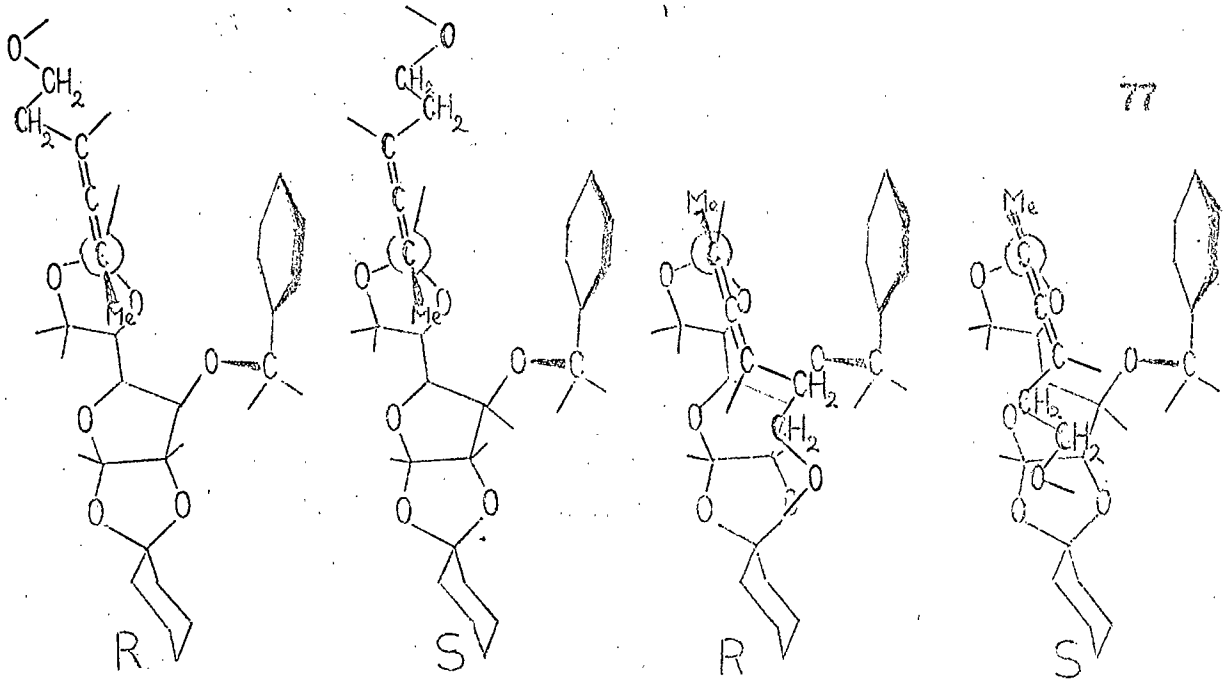
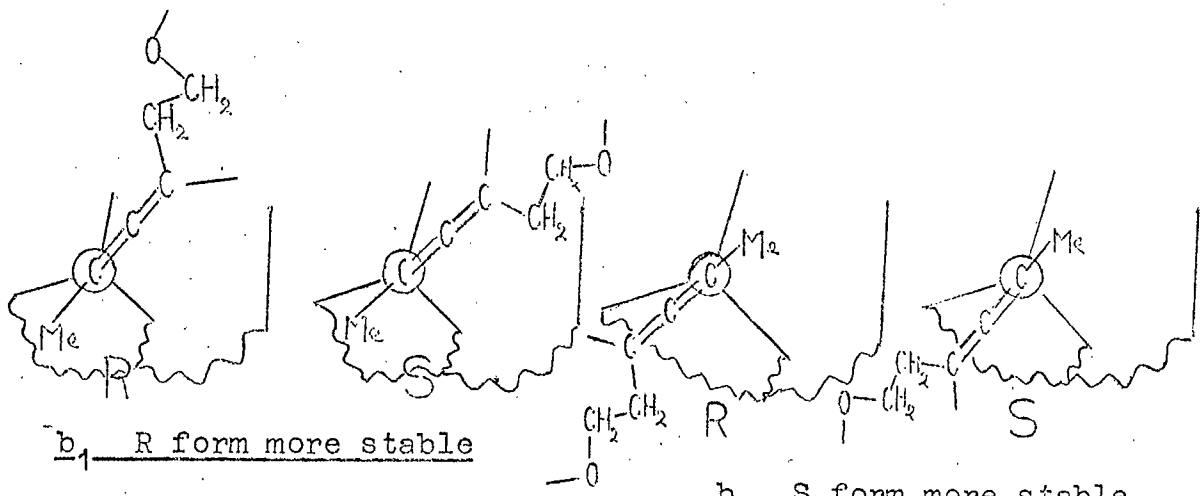


Figure 11
Drelding model of the seven-membered cyclic allene-monosaccuride complex in the R and S forms.



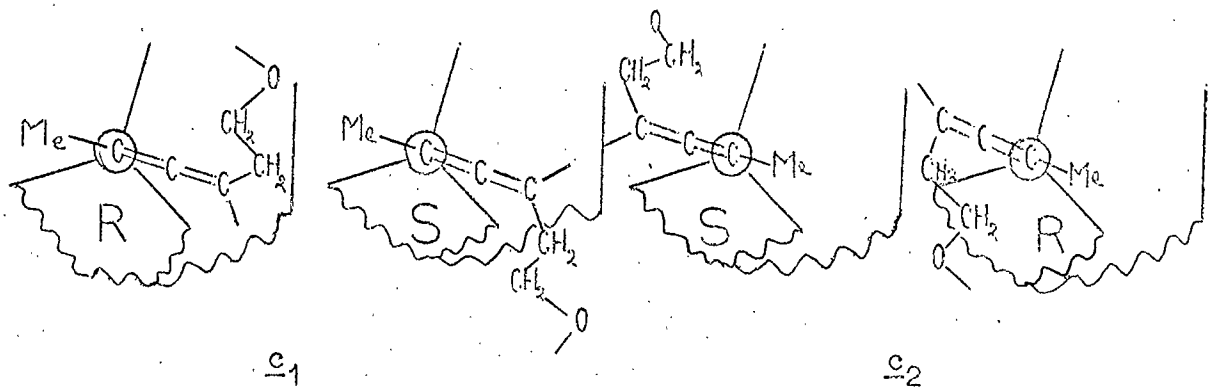
a_1 R form more stable

a_2 S form more stable



b_1 R form more stable

b_2 S form more stable



c_1 c_2

Figure 12
Conformations of the monocationic complex Cr,Cm
in Newman projections.

S form of the allene would be more stable. Models of conformation a_2 cannot be constructed for the dimeric fourteen-membered cyclic complex. Models of conformation a_1 are readily constructed for this complex and the dimeric fourteen-membered cyclic complex would therefore be expected to give an excess of the R form of the allene. Models of conformation a_2 can be constructed for the polymeric complex although it appears less stable than conformation a_1 due to interference of the two monosaccharide molecules. The polymeric complex would also be expected to give excess of the R form of the allene therefore. The stereochemistry of the dimeric fourteen-membered cyclic complex and the polymeric allene complex are shown in figures 13 and 14, (pp. 79 and 80).

To summarise, it has been deduced theoretically in this section that reduction of alkenynols with the lithium dimenthoxyaluminium hydride complex should produce predominantly S allenic alcohols. As all the allenic alcohols which have so far been prepared by this method are dextrorotatory they must have the S(+) configuration. Independent theoretical deductions led to the conclusion that reduction of alkenynols with the lithium aluminium hydride-3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose complex should give predominantly the R form of the allenic alcohols. The observation that all allenic alcohols produced in this

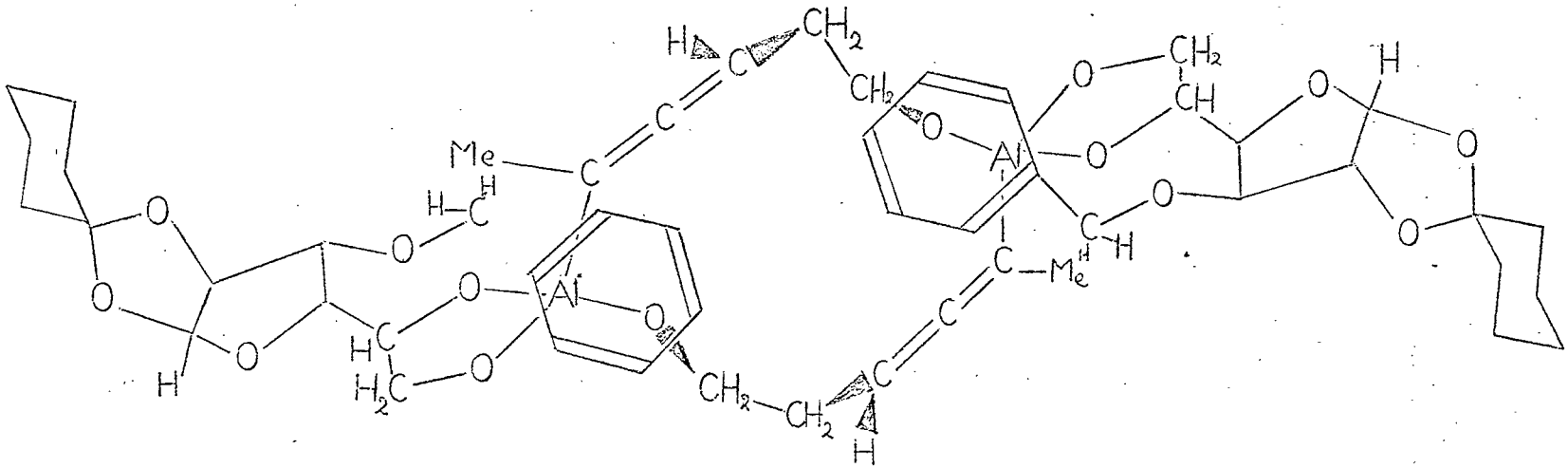


Plate 13

Building model of the dimeric form of the proposed cyclic alkano-monosaccharide complex in the crystallization.

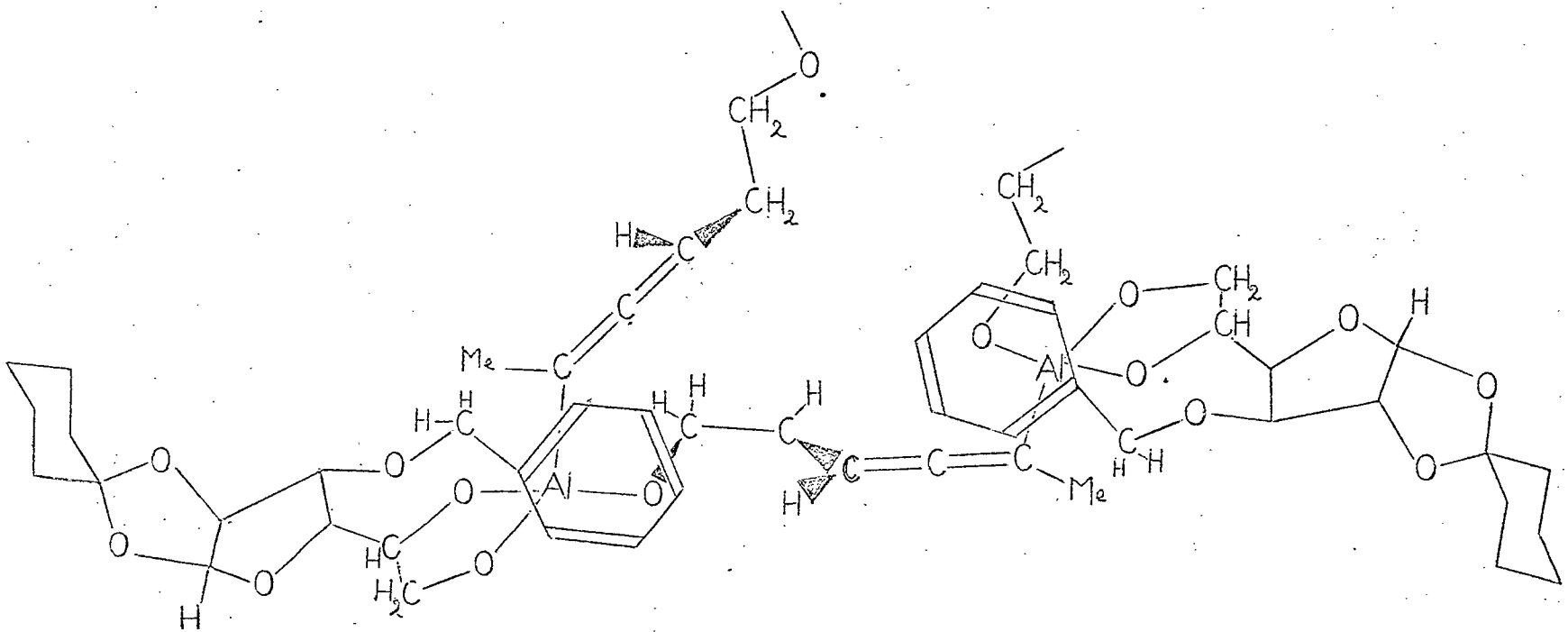


Figure 14

Building model of the polymeric allene-monosaccharide complex in the R configuration.

way are laevorotatory confirms that they have the R(-) configuration.

The configuration of an allenic alcohol has also been assigned as S(+) by a completely different experimental method described later in this thesis (p. 82).

An application of Brewster's theory[126] predicts that allenynols (e.g. marasin) should have the S(+) configuration.[125]

The Determination of the Absolute Configuration of Allenic Alcohols by use of the Claisen Rearrangement

There is considerable evidence[77] (p.30) that the Claisen rearrangement of allyl vinyl ethers involves a six-membered cyclic transition state, C-C bond formation occurring simultaneously with C-O bond fission. With propargyl vinyl ethers, the formation of a cyclic transition state is less favourable since the group C-C≡C- must be linear. It has been demonstrated[54] that under suitable conditions, however, these systems can be made to undergo Claisen type rearrangements and by analogy with the allyl vinyl systems it seems reasonable to suppose that this rearrangement also goes via a cyclic transition state. The rearrangement of optically active propargyl vinyl ethers described in this thesis and the independent work by Jones, Loder and Whiting[76] on the direct conversion of optically active isobutyraldehyde dibut-1-ynyl acetal to the corresponding optically active allenic aldehydes,* corroborates this conclusion.

On the basis of a cyclic transition state for this rearrangement, Jones, Loder and Whiting deduced the absolute configuration of 2,2-dimethylhex-3,4-dienal by using

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*These workers postulated the ether as a necessary intermediate although this was not isolated.

optically active but-1-yn-3-ol of known configuration[‡] in the preparation of the acetal and converting[*] this to the optically active allenic aldehyde.

By similar argument, it was proposed to deduce the absolute configuration of straight chain allenic aldehydes, and of the corresponding allenic alcohols. The argument depends on the fact that in the cyclic transition state, rotation about bonds is not possible. In the transition state the molecule takes up the conformation shown in figure 15 and as indicated there, if S-but-1-yn-3-ol is used in the preparation of the ether the S form of the allenic aldehyde should be produced.

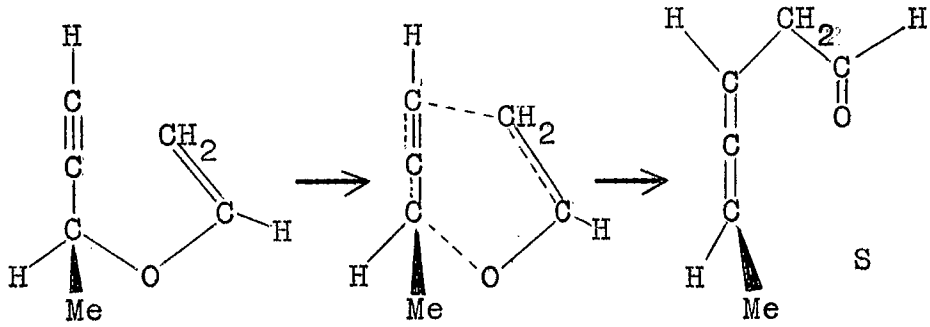


Figure 15

[‡]The absolute configuration of but-1-yn-3-ol was shown to be S(-) by Jones, Loder and Whiting[76] by reducing (-) but-1-yn-3-ol to (+)-butan-2-ol of known absolute configuration.[78] This was confirmed in our laboratories.

[*]These workers postulated an elimination of but-1-yn-3-ol to give the isobutenylbut-1-yn-3-yl ether as a necessary intermediate although this was not isolated. It was proposed that this intermediate then rearranged intramolecularly to the optically active allene.

The absolute configuration of the allenic aldehyde may thus be determined and by reducing this to the corresponding alcohol with lithium aluminium hydride, which does not affect the π bond system, the absolute configuration of the allenic alcohol too, may be deduced.

Black and Landor[56] have prepared a number of 1-chloro-alkyl and vinyl ethers, and the preparation of α-chloroethyl but-1-yn-3-yl ether was undertaken by the method introduced by these workers. The procedure used was as follows (cf. p. 165): a mixture of freshly redistilled dry acet-aldehyde (1 equiv.) and dry but-1-yn-3-ol (2 equiv.) was added dropwise with stirring under anhydrous conditions to boron trichloride (1.3 equiv.), cooled to -15° and stirred for 3 hr. at -15°. The mixture was then allowed to warm to room temperature, stand for 3 days and the chloro ether distilled in vacuo into a cold trap. After refractionation the required 1-chloro ether was obtained.

Following the procedure of Black and Landor, the chloro ether was treated in dry diethyl ether solution at 0° with excess anhydrous triethylamine to give the corresponding quaternary ammonium salt as a hygroscopic solid. This was decomposed at 120° in vacuo to give the impure vinyl ether, having identical infra-red spectrum, (ν_{max} 3,320 (C≡CH), 2,110 (C≡C), 1,680 and 1,630 $cm.^{-1}$ (C=C)), to that obtained by the previous workers, but the

gas liquid chromatogram of this material showed three peaks (t=14 min. 60%), (t=9 min. 2%) and(t=85 min. 38%) (dinonylphthalate 84°, nitrogen 2 l/h). On distillation only a very small amount of pure vinyl ether was obtained and a large residue. The infra-red spectrum of the residue was similar to the crude product and its g.l.c. showed that the peak at (t=85 min.) had increased in size to represent 70% of the material.

It is well-known that vinylic ethers dimerise[81] and Landor and Black[79] have previously observed that 3-carboxylpropargyl vinyl ether undergoes a ready dimerisation, viz.

$$CH_2{=}CH{-}O{-}CH_2C{\equiv}C{-}COOH \longrightarrow \begin{matrix} CH_2{-}CH{-}O{-}CH_2C{\equiv}C{-}COOH \\ | \quad\quad | \\ CH_2{-}CH{-}O{-}CH_2C{\equiv}C{-}COOH \end{matrix}$$

It is therefore probable that a similar dimerisation (or polymerisation) had occurred with the 1-methylprop-2-ynyl vinyl ether. (This being responsible for the g.l.c. peak at t=85 min.) Attempts to purify the vinyl ether were therefore abandoned.

The pyrolysis of the impure ether gave as main product hexa-2,4-dienal identified from its infra-red spectrum ν_{max} 1,750 (C=O), 1,640 and 1,680 cm.$^{-1}$ (C=C) and its ultra-violet spectrum λ_{max} 273 mμ(ε14,400) (pure hexa-2,4-dienal λ_{max} 271 mμ(ε 25,000)).[80] It is probable that traces of base in the impure vinyl ether had caused

rearrangement of the hexa-3,4-dienal to the conjugated hexa-2,4-dienal during the pyrolysis.

It is known that α-chloro ethers eliminate HCl on pyrolysis,[82] and Black and Landor[54] had shown that a number of α-dichloroalkyl propargyl ethers could be converted directly to allenic aldehydes by heating under reflux. It was therefore considered, that under carefully controlled conditions, pyrolysis of the α-chloroethyl but-1-yn-3-yl ether should result in elimination of HCl followed by the Claisen rearrangement. This was achieved by passing the chloro ether in a stream of nitrogen through an electrically heated glass tube packed with glass wool at 200°. The unstable hexa-3,4-dienal together with some hexa-2,4-dienal was collected in a trap at -60° (I.R. No. 16). The amount of conjugated diene in the mixture was estimated to be 20-50% from the ultra-violet spectrum (U.V. No. 20). The mixture of aldehydes was added to an excess of lithium aluminium hydride and stirred at room temperature overnight. Excess lithium aluminium hydride was destroyed with dilute sulphuric acid and the mixture of alcohols produced was ether extracted, dried and separated by chromatography on alumina to give pure hexa-3,4-dienol (I.R. No. 17).

Repetition of this procedure using optically active (-)-α-chloroethyl but-1-yn-3-yl ether, $[\alpha]_D^{20}$ -44.5°

(prepared from acetaldehyde, boron trichloride and S-(-)-but-1-yn-3-ol $[\alpha]_D^{20}$ -5.3°) gave (+)-hexa-3,4-dienol, $[\alpha]_D^{20}$ $+5.3^{\circ}$. (+)-Hexa-3,4-dienol therefore has the S configuration.

The Attempted Asymmetric Reduction of Acetophenone with the Lithium Aluminium Hydride-Active Amyl Alcohol Complex.

The preparation of a complex of lithium aluminium hydride with active amyl alcohol (2-methylbutan-1-ol) and its use in reducing acetophenone to 1-phenylethyl alcohol was carried out as previously described (p. 52); experimental details (p. 170) for the menthoxy complex. After decomposition of the complex with dilute acid, ether extraction, drying and fractionation on a spinning band fractionating column, the 1-phenylethyl alcohol was still contaminated with traces of active amyl alcohol. This was readily shown by gas liquid chromatography on silicon oil. The last trace of active amyl alcohol was removed by dissolving the impure 1-phenylethyl alcohol in n-pentane/ether (4/1) and passing water through the solution in a continuous extraction apparatus overnight. Evaporation of solvent and redistillation gave the pure 1-phenyl ethyl alcohol. This compound was found to be optically inactive, ($\pm 0.001^{\circ}$ Bendix photoelectric polarimeter.)

In the light of this it was considered most unlikely that other ketones would undergo asymmetric reduction with this complex since the difference in bulk between the phenyl group, and the methyl group on acetophenone is quite substantial.

An examination of a model of the lithium aluminium hydride-active amyl alcohol complex shows that the lack of asymmetric reduction with this complex is not surprising. The asymmetric centres are too far from the aluminium atom to play an important part in the shielding of the remaining two hydrogens on the aluminium atom, (figure 16). The approaching ketone molecule thus sees these hydrogens in an approximately symmetrical environment and the reduction product is therefore racemic.

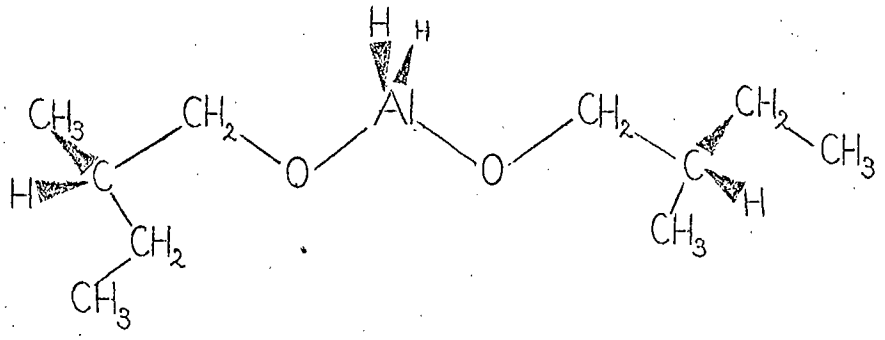
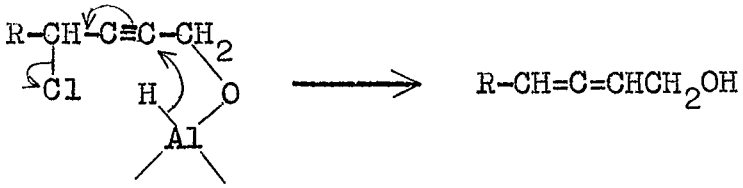


Figure 16
The lithium aluminium hydride-active amyl alcohol complex in the preferred conformation.

Preparation of 4-Cholorhept-2-yn-1-ol and 4-Chlorohept-2-ynyl acetate and the Reduction of These Compounds with the Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose Complex.

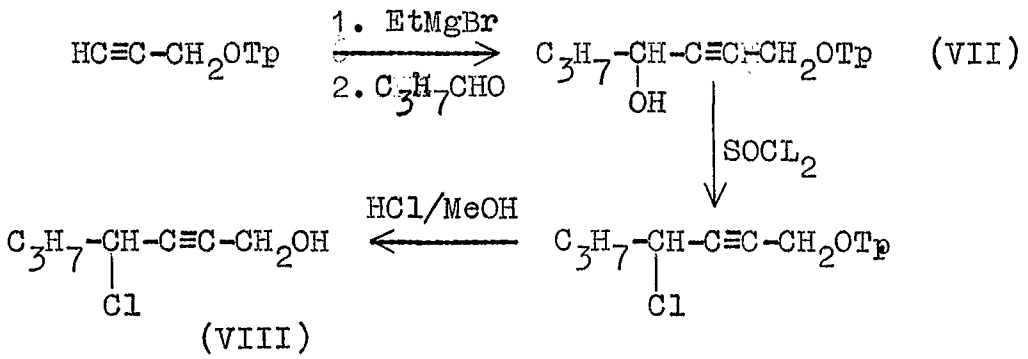
Following the work of Landor, Landor, and Pepper[72] on the preparation of allenic alcohols by the reduction of propynyl halides with lithium aluminium hydride, it was of interest to carry out the reduction using the lithium aluminium hydride-monosaccharide complex. An unconjugated chloracetylenic alcohol would be expected to be reduced to the allene by the following mechanism (cf. ref. 72):



Due to stereoelectronic[28a] requirements (i.e. trans movement of electrons) the elimination of the chlorine would normally be expected to take place from the same side of the propynyl halide as the hydride ion is introduced, (cf. p. 22). If an asymmetric reducing agent is used, such as the lithium aluminium hydride monosaccharide complex, the two stereoisomers would not be expected to undergo reduction at the same rate, since the R group on one enantiomorph would give rise to more steric interaction with the benzyl

group on the monosaccharide than would the R group on the other enantiomorph. This is illustrated in figure 17, p. 92. If the reduction was stopped before completion, optically active allenic alcohol should therefore be obtained. This would constitute an example of a kinetically controlled asymmetric reduction.

An examination of models showed that the stereospecificity of the reaction was likely to increase with increasing size of the R group on the acetylenic halide since this would increase interference with the benzyl group on the monosaccharide (cf. figure 17). 4-Chlorohept-2-yn-1-ol was considered a suitable compound for investigation. Preparation of this compound was carried out by the following method. 3-Tetrahydropyranyloxyprop-1-yne was reacted with ethyl magnesium bromide in tetrahydrofuran, and the resulting Grignard reagent reacted with n-butyraldehyde to give 1-tetrahydropyranyloxyhept-2-yn-4-ol, (VII). Chlorination of (VII) with thionyl chloride in the presence of pyridene followed by hydrolysis of the OTp derivative with methanolic hydrochloric acid afforded the required 4-chlorohept-2-yn-1-ol, (VIII).



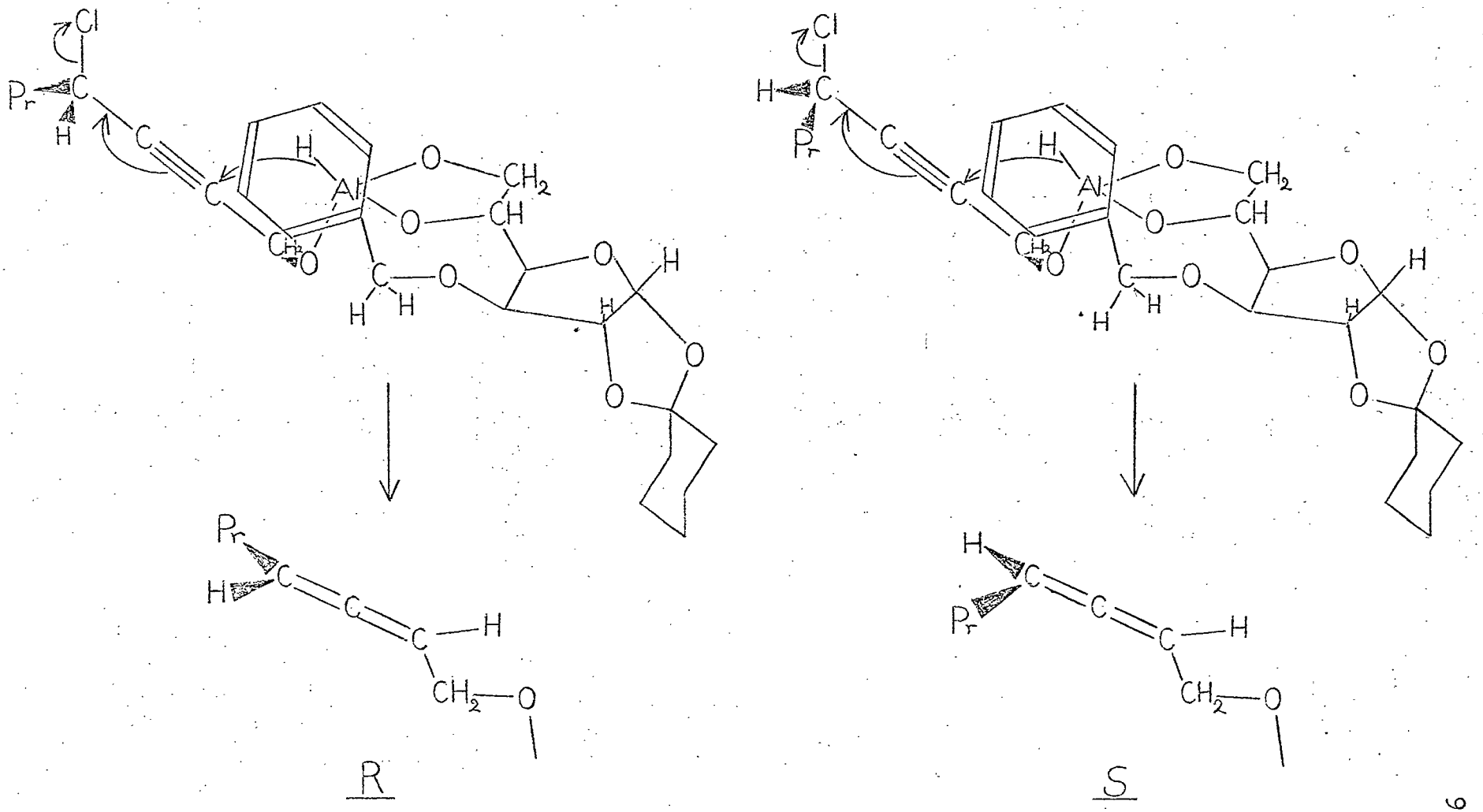


Figure 17

Reduction of the chloracetylenic alcohol with the lithium aluminium hydride-monosaccharide complex. Both chloracetylenic alcohol enantiomorphs are shown.

The compounds prepared in the course of this synthesis were identified by infra-red spectra and analysis.

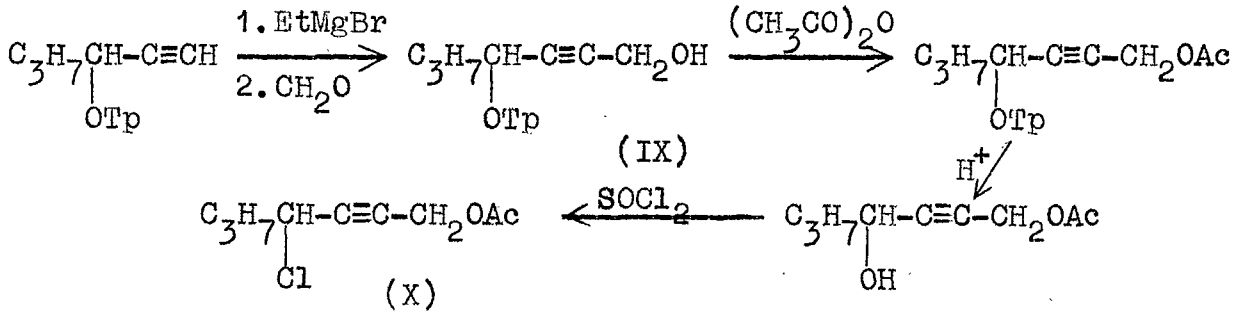
The lithium aluminium hydride-monosaccharide complex (.01 mole in ether) was prepared as described earlier in this thesis (p. 67) and the 4-chlorohept-2-yn-1-ol (.01 mole) added in one portion at room temperature and stirred for 0.5 hr. The product showed a single peak on g.l.c. (silicon oil) and was optically inactive ($\pm 0.001^{\circ}$). It was identified as hept-2,3-dien-1-ol by its infra-red spectrum. Clearly the reduction to the allenic alcohol had gone to completion.

The reduction was repeated using a deficiency of the reducing complex, but it was found that although some starting material was recovered, the allenic alcohol produced was still optically inactive.

Repetition of the reduction at -40° for 10 min. with one equivalent of reducing complex still resulted in complete reduction of the acetylenic chloride to allenic alcohol, and it was concluded that this reaction was too fast for kinetic control to be effective.

In view of the rapidity of the reduction of the chloracetylenic alcohol it was decided to try reducing the corresponding acetate since it was considered that this reduction might be a slower process, and kinetic control might then be effective. 4-Chlorohept-2-ynyl

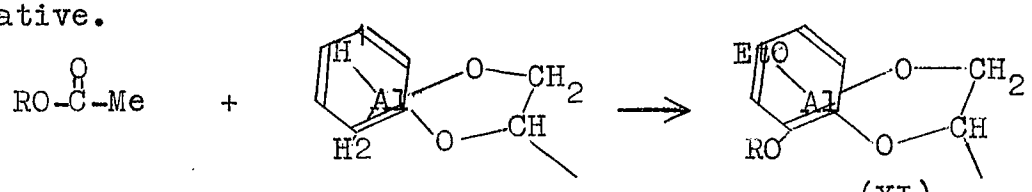
acetate was prepared by the following method. 3-Tetrahydropyranyloxyhex-1-yne was converted to the Grignard reagent by reaction with ethyl magnesium bromide in tetrahydrofuran, and this reacted with formaldehyde gas to give 4-tetrahydropyranyloxyhept-2-yn-1-ol, (IX). Acetylation of (IX) with a mixture of acetic anhydride and dry pyridene gave 4-tetrahydropyranyloxyhept-2-ynyl acetate and hydrolysis of the OTp derivative followed by chlorination with thionyl chloride in the presence of dry pyridene afforded the required 4-chlorohept-2-ynyl acetate (X) identified by infra-red spectrum and analysis.



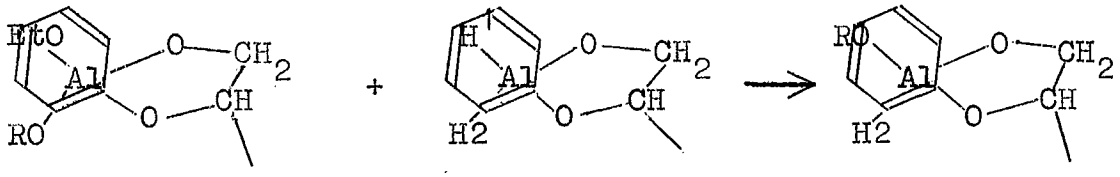
4-Chlorohept-2-ynyl acetate (0.01 mole) added in one portion to lithium aluminium hydride-monosaccharide complex (0.01 mole) in ether and stirred for 0.5 hr. at room temperature gave hepta-2,3-dien-1-ol $[\alpha]_D^{25}+1.6^\circ$, identified by its infra-red spectrum, and gas/liquid chromatography.

The production of dextrorotatory allenic alcohol was somewhat unexpected. Examination of models show that if the hydride ion is donated by an aluminium already.

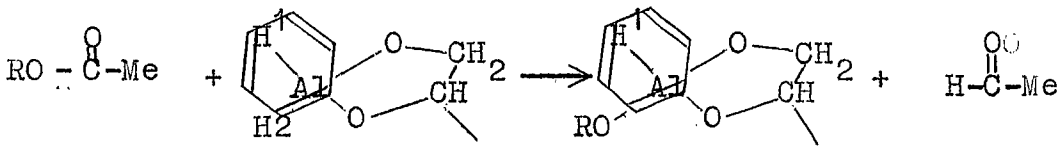
attached to the oxygen of the chloracetylenic alcohol in the usual way then the R form of the allenic alcohol should be formed more rapidly than the S form (cf. figure 17, p. 92). If the reaction is interrupted before completion the product would therefore be expected to be laevorotatory.* It may be inferred from this that the mechanism of the reduction of the chloracetate (X) is more complex than is indicated on p. 90** and the following scheme is put forward as a plausible alternative.



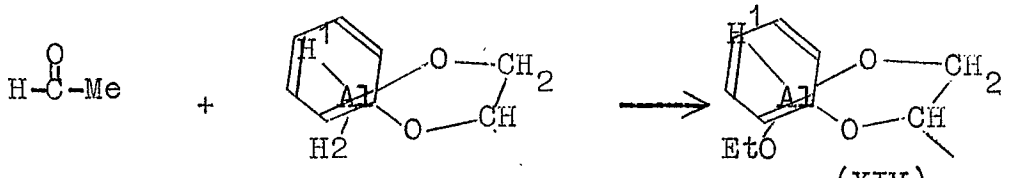
(XI)



(XII)



(XIII)



(XIV)

Only partial monosaccharide structures are shown.

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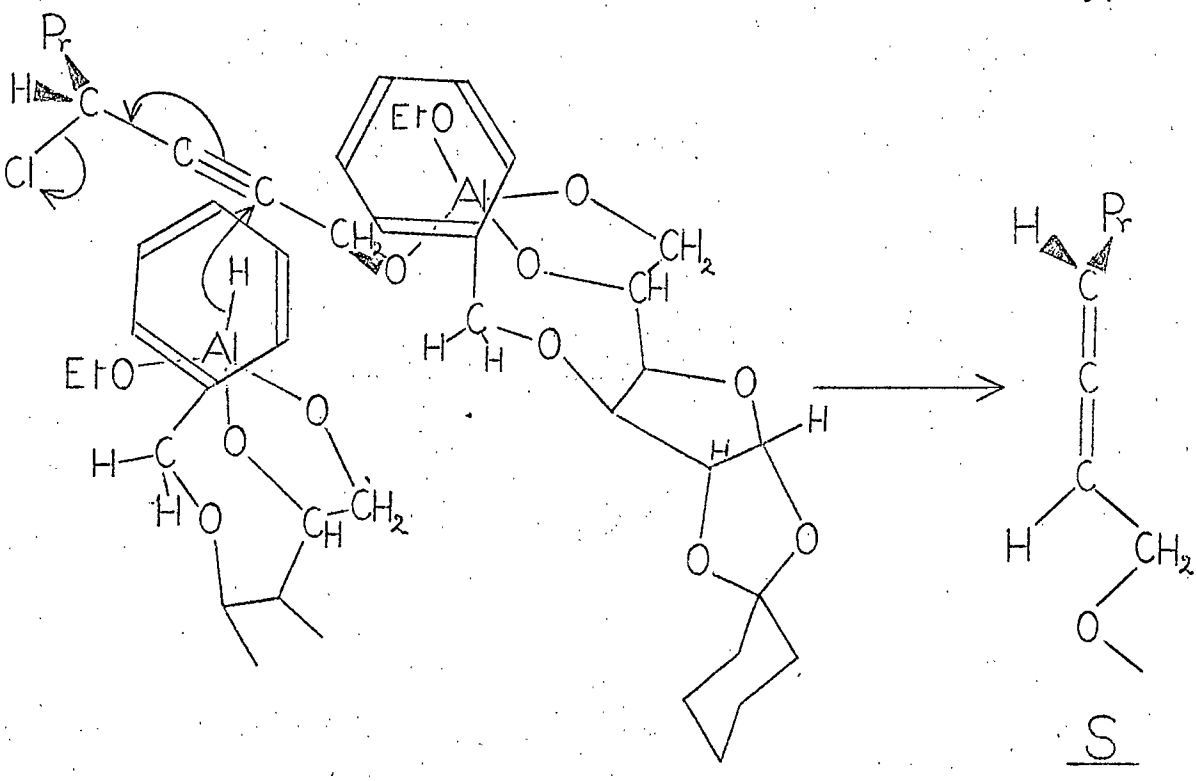
*The absolute configuration of allenic alcohols has been shown to be R(-) earlier in this thesis (p. 52 et seq.)

**The mechanism depicted on p. 90 is still considered to apply to the reduction of the corresponding alcohol.

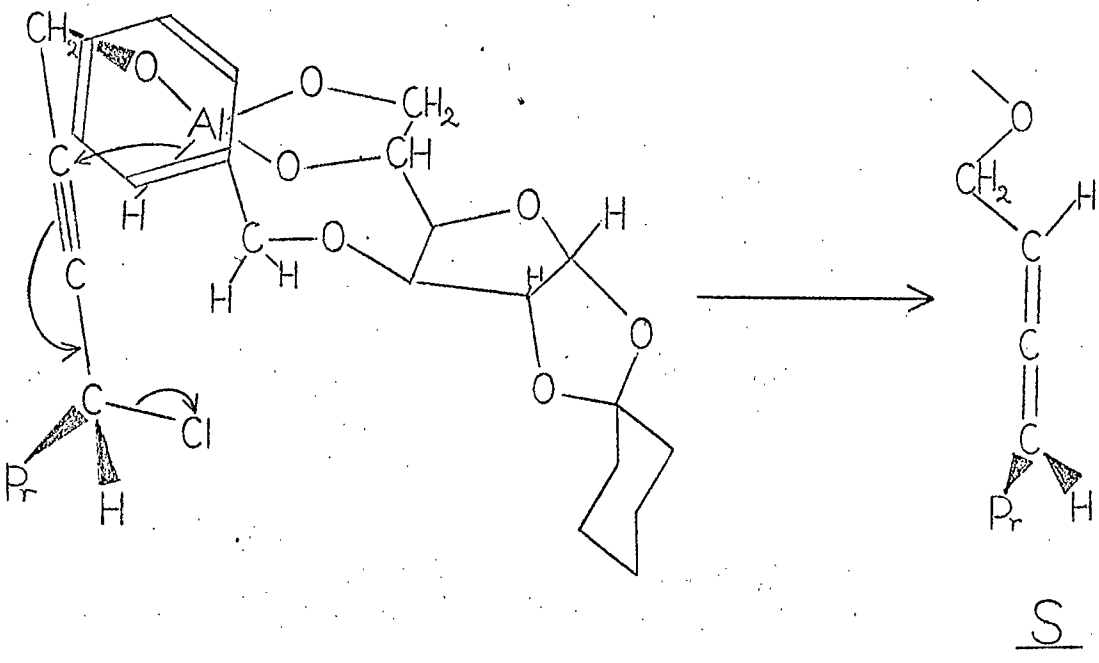
Reaction of the lithium aluminium hydride-monosaccharide complex with the chloracetate may give rise to species (XI), (XII) or (XIII). Species (XI) can react by intermolecular reduction only. Since a deficiency of reducing complex was used in these experiments this must involve the less active hydrogen H-1 (cf. p. 72) on the attacking complex molecule as H-2 will already have been used up preferentially in formation of species such as (XIV). A model shows that if such a reduction was interrupted before completion, the S form of the allenic alcohol (i.e. dextrorotatory) should predominate in the products. This is illustrated in figure 18.

The larger OR group would be expected to predominate in the less shielded position, i.e. replacing H-2, in species (XI) with the smaller OEt group replacing H-1 (cf. p. 74). If hydride exchange occurs between another molecule of complex and species (XI) attack will be predominantly from the H-2 side of the aluminium in species (XI) (cf. p. 74). This will be accompanied by inversion of the aluminium to give species (XII) with the OR group predominating in the more shielded position, replacing H-1.

Species (XII) can undergo intramolecular reduction and a model shows that, if interrupted before completion, this would also result in a predominance of the S form of the allenic alcohol in the products. This is illustrated in figure 18, p. 97.



Intermolecular reduction of species (XI).



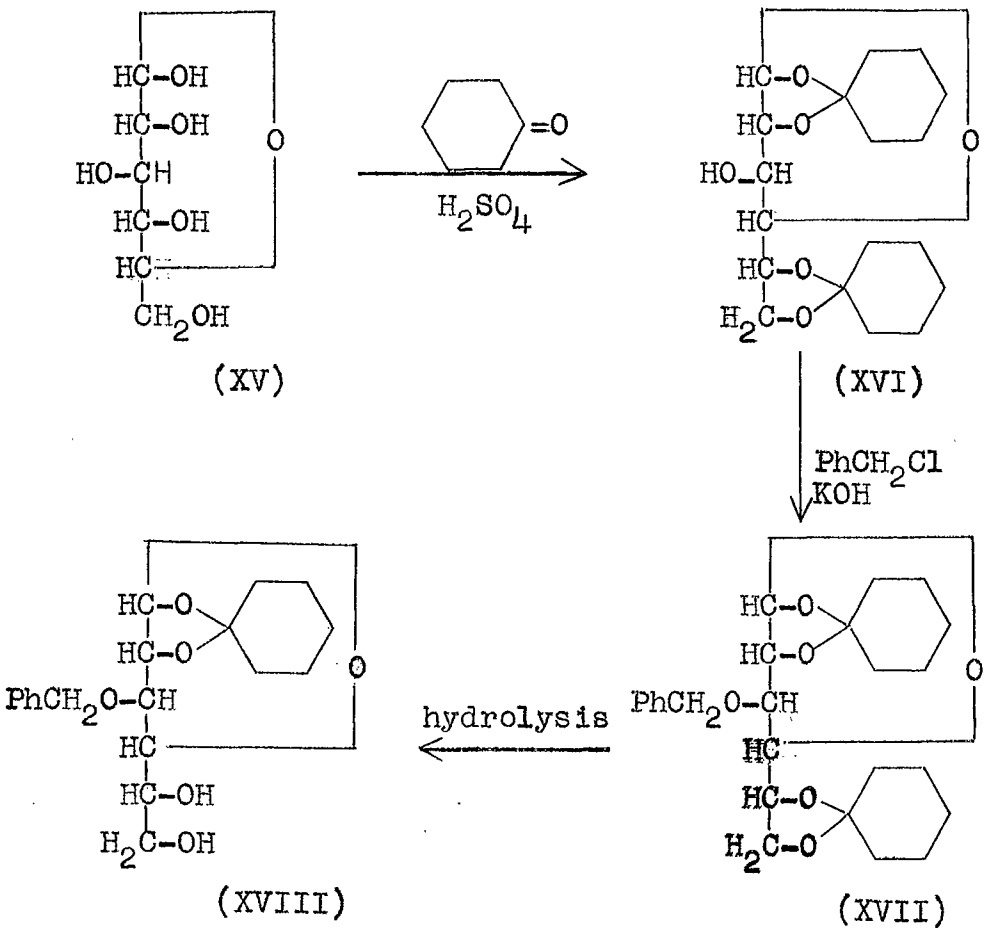
Intramolecular reduction of species (XII).

Figure 18

Species (XIII) in which the OR group replaces the less shielded hydrogen could also be formed as shown on p. 95. Intramolecular reduction of (XIII) would lead to the R form of the allenic alcohol (cf. figure 17, p. 92), but since the S form (dextrorotatory) is found to predominate experimentally, species (XIII) must play a minor part.

The Isolation and Identification of Trace Impurities in 3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose and the Preparation of the Pure Compound.

The method introduced by Landor, Miller, and Tatchell[13] for the preparation of 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose is represented very briefly by the following reaction scheme:



These workers had shown by thin layer chromatography on silica gel, using 2% methanol in benzene as

eluant,* that their product contained small amounts of impurities. Attempts to purify the compound by chromatography on activated alumina using benzene/chloroform (3/1) as eluant had been unsuccessful.[83] They therefore used the slightly impure monosaccharide to prepare the complex with lithium aluminium hydride, and used this in the preparation of optically active alcohols and simple allenic alcohols by reduction of ketones and enynols.[13,14] The impurities did not interfere in these reductions, and, being high boiling, were easily removed from the products by distillation.

The monosaccharide was prepared by the method of Landor, Miller, and Tatchell and thin layer chromatography confirmed the presence of trace amounts of impurities. Attempts to remove the impurities by chromatography on activated alumina, or silica gel impregnated with boric acid solution using benzene/chloroform or n-pentane/ether solvent mixtures as eluant were unsuccessful. It was therefore decided to go back to the start of the synthesis and to check each stage by thin layer chromatography to establish where the impurities were introduced.

1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranose was

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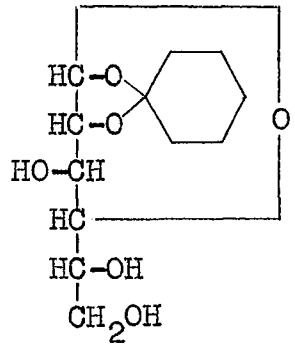
*After development the plates were sprayed with a 0.2% solution of naphthoresorcinol in ethanol to which 0.1 vol. of H_3PO_4 had been added for every volume of ethanol. Monosaccharides show up as light blue spots on heating at 110° for 0.5 hr.

prepared by the literature method,[84] (p.179) and after three recrystallisations from n-heptane, melted sharply at 132° (lit. 132°). Thin layer chromatography of this material, however, revealed the presence of a minute quantity of impurity at R_F 0.10; the main spot was at R_F 0.20. The impurity was not removed by further recrystallisation.

Glucose, on thin layer chromatography, gave a single spot at R_F 0.00. It was considered probable, therefore, that the impurity at R_F 0.10 was 1,2-O-cyclohexylidene-α-D-glucofuranose (XIX) or an isomer of this.



(XIX)

It was realised that in the next stage of the synthesis the free -OH groups would become benzylated and then be resistant to hydrolysis in the final stage. It was considered likely that these benzylated derivatives were the impurities encountered in the final product, and it was therefore imperative to remove the monosaccharide derivative (XIX) at this stage. This was achieved by dissolving the crystals in the minumum volume of hot heptane (60°)

and washing the resulting solution repeatedly with hot water (60°) in which the monosaccharide derivative (XIX) is slightly soluble. On refrigeration of the heptane solution the required 1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose crystallised out and showed only one spot R_F 0.20 on t.l.c.; the crystals had m.pt. 132.0°.

Benzylation of the 1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose was carried out with excess benzyl chloride at 150° in the presence of potassium hydroxide. The reaction was followed by withdrawal of small portions at 1 hr. intervals and t.l.c. examination of these. After 4 hr. the reaction was complete as shown by obtaining one spot on t.l.c. R_F 0.95. The solution was allowed to cool and the organic layer separated from solid inorganic salts. Distillation using a mercury vapour pump gave 3-O-benzyl-1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose, $[\alpha]_D^{20}$ -17.4° (c. 19.68 in $CHCl_3$), as a brittle glass identified by its infra-red spectrum and analysis. The compound showed one spot on t.l.c. R_F 0.95.

The final stage of the synthesis, hydrolysis of one of the cyclohexylidene groups, was carried out using 75% acetic acid at 80° in a water bath. The reaction was followed by withdrawing small samples at 0.5 hr. intervals and examining these by t.l.c. as before. The formation of the required monocyclohexylidene derivative was marked by the

gradual appearance of a spot at R_F 0.25 accompanied by a corresponding diminishing of the spot at R_F 0.95 for successive samples. Before hydrolysis of the dicyclohexylidene derivative was complete, however, the gradual appearance of a third spot at R_F 0.00 was observed. This clearly corresponded to the formation of 3-O-benzylglucose by hydrolysis of the second cyclohexylidene group. To prevent substantial hydrolysis of the 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose it was necessary to stop the hydrolysis with a small amount (ca. 4%) of the dicyclohexylidene derivative still remaining. The solution was cooled, water and chloroform added, the organic layer separated and the aqueous layer extracted several times with chloroform. The combined chloroform layers were washed with sodium bicarbonate solution to remove acetic acid and with hot water (60°) to remove 3-O-benzylglucose. T.l.c. on the chloroform solution showed only two spots, R_F 0.25 (3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose) and R_F 0.95 (unhydrolysed 3-O-benzyl-1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose).

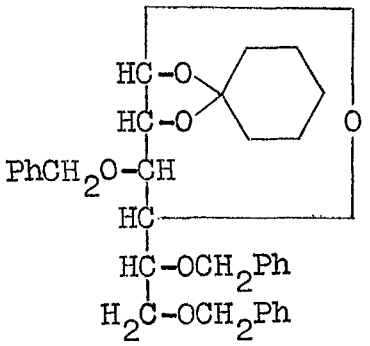
Removal of the unhydrolysed material was achieved on a small scale (ca. 1. g.) by chromatography* on acid alumina

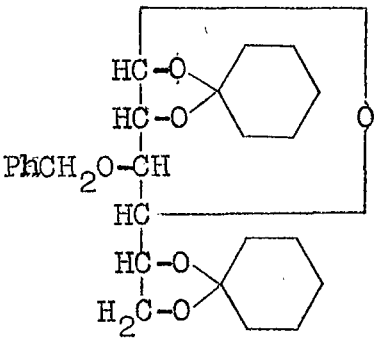
*This is not the same impurity that was present in the 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose prepared by Landor, Miller and Tatchell.

identification of the impurities present in the monosaccharide prepared by the original method of Landor, Miller, and Tatchell. A sample of the slightly impure monosaccharide that had been used in early attempts at preparing optically active marasin (p. 67 et seq.) was available and was used for this purpose.

Preparative size t.l.c. plates of silica gel were prepared, a 10% solution of the impure monosaccharide in chloroform applied using an automatic applicator (supplied by Desaga Ltd.), and the plates developed with 2% methanol in benzene. The bands were located by spraying just the ends of the t.l.c. plates with the naphthoresorcinol spray mentioned earlier (p. 100), each band removed and extracted with chloroform. Evaporation of the solvent gave the monosaccharide derivatives which were identified by infra-red spectra and analysis. The compounds present in the monosaccharide prepared by the method of Landor, Miller, and Tatchell, and the R_F values are listed on p. 106. The compound at R_F 0.25 which could not be removed from marasin solution by chromatography, was found to be a mono-ol as suspected earlier (cf. p. 68). The impurities in the 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose amounted to approximately 1% by weight.

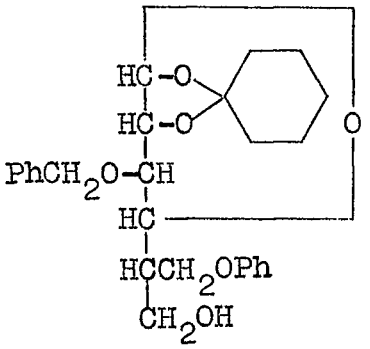
R_F 0.95





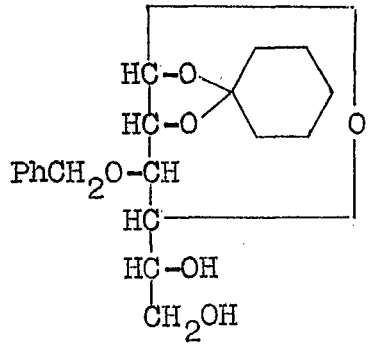
mixture

R_F 0.25

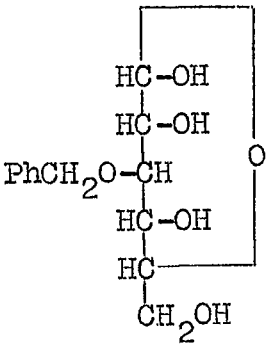


or isomers

R_F 0.20



R_F 0.00



Preparation and Reactions of Bromopropargyl Aldehyde

Propargyl aldehyde was prepared in 1950 by Wille and Saffer[130] and their method has since been considerably improved by Landor and Pepper.[131] The method consists of oxidizing propargyl alcohol to the aldehyde which is distilled from the reaction sphere under reduced pressure as it is formed to prevent further oxidation.

$$HC{\equiv}CH_2OH \xrightarrow{[O]} HC{\equiv}C\text{-}CHO$$

Landor and Pepper prepared one acetylenic alcohol and two diacetylenic alcohols from propargyl aldehyde via the Grignard reagents, (table II).[131]

TABLE II[131]

Reagent	Product	Yield %
$(CH_3)_3CMgCl$	$(CH_3)_3C\text{-}CH(OH)\text{-}C{\equiv}CH$	25
$HC{\equiv}CMgBr$	$HC{\equiv}C\text{-}CH(OH)\text{-}C{\equiv}CH$	66
$(CH_3)_3C\text{-}C{\equiv}CMgBr$	$(CH_3)_3C\text{-}C{\equiv}C\text{-}CH(OH)\text{-}C{\equiv}CH$	72

Penta-1,4-diyn-3-ol had been previously prepared by a different method by Jones, Skattebol, and Whiting,[132] and since Landor and Pepper's work, Wille and Strasser[133] have also used propargyl aldehyde to prepare the compound.

One of the disadvantages of using propargyl aldehyde in syntheses is the high reactivity of the acetylenic hydrogen which is often involved in side reactions. Thus

Landor and Pepper attributed the low yield of 4,4-dimethyl-pent-1-yn-3-ol in Table II to side reactions of type:

$$(CH_3)_3CMgCl + HC{\equiv}C\text{-}CHO \longrightarrow (CH_3)_3CH + ClMgC{\equiv}C\text{-}CHO.$$

It was considered possible that these side reactions could be inhibited by the use of bromopropargyl aldehyde instead of propargyl aldehyde. The preparation of bromo-propargyl aldehyde and an examination of its properties was therefore undertaken.

The first attempted synthesis was to convert propargyl aldehyde to the diethyl acetal and to brominate this with sodium hypobromite. Accordingly, propargyl aldehyde was prepared by the method of Landor and Pepper (p.185) and this was added to an ice cold mixture of anhydrous calcium chloride and ethyl alcohol. The propargyl aldehyde underwent rapid polymerisation under these conditions, however, and none of the required acetal could be prepared by this method. A similar result was obtained when hydrochloric acid was used as the catalyst, and an alternative approach was therefore tried.

Bromopropargyl alcohol was prepared by the action of sodium hypobromite on propargyl alcohol, (p. 185). This was oxidised to the aldehyde by the slow addition of an acidic solution of chromium trioxide. During the addition nitrogen was bubbled through the reaction mixture and the pressure reduced to 4 mm. Hg. The volatile

bromopropargyl aldehyde was thus swept from the oxidising mixture and collected in a trap at -60° as it was formed. Further oxidation of the aldehyde was thus reduced to a minimum. After drying ($MgSO_4$), the material was identified as bromopropargyl aldehyde (11%) by comparison of its infra-red spectrum with that of an authentic sample of propargyl aldehyde, (I.R. No.4 and 2). An attempt to distil the compound resulted in an explosion after a small amount of distillate had been collected. The infra-red spectrum of the distillate (I.R. No.26) was much more complex than that of the undistilled material and it was concluded that polymerisation had occurred.

In view of the low yield (11%) obtained by the previous method, an alternative synthesis was sought. Propargyl aldehyde diethylacetal had been prepared in 1949 by a rather roundabout route by Sheehan and Robinson.[129] It was decided to prepare this compound by their method and to try brominating it with sodium hypobromite solution. The synthesis of propargyl aldehyde diethylacetal is represented very briefly by the following reaction scheme (experimental details p.187 et seq.).

$$CH_2{=}CH{-}CHO \xrightarrow{Br_2} CH_2(Br)CH(Br){-}CHO$$

$$CH_2(Br)CH(Br){-}CHO \xrightarrow{EtOH/HCl} CH_2(Br)CH(Br){-}CH(OEt)_2$$

$$CH_2(Br)CH(Br){-}CH(OEt)_2 \xrightarrow{KOH/EtOH} HC{\equiv}C{-}CH(OEt)_2$$

Bromination of the acetylenic acetal was carried out

with sodium hypobromite and the brominated acetal obtained, hydrolysed to the aldehyde with dilute sulphuric acid, ether extracted, and dried. Removal of the ether gave bromopropargyl aldehyde (45% on acrolein) identified by its infra-red spectrum as before. Another attempt to distil the compound, again resulted in an explosion and it was therefore decided to use the compound without further purification. The material polymerised in a few hours at room temperature and throughout this work was prepared in small batches as required.

Bromopropargyl aldehyde was reacted with one equivalent of tbutylmagnesium chloride (experimental details p.189). A large amount of polymer was formed during the reaction. After working up, an attempt to distil the material resulted in further polymerisation and only a small quantity of distillate was obtained. The infra-red spectrum of the distillate showed bands at ν_{max} 3,450 (OH), 2,220 and 2,185 (RC≡CR) and 1,700 cm.$^{-1}$ (C=O), (I.R. No.36). The absence of a band in the region of 685 cm.$^{-1}$ indicated that the bromine had been lost and it was therefore considered that the acetylenic bromine had undergone reaction with the Grignard reagent, and that the product was probably a mixture of tBuC≡C-CH(OH)tBu and tBuC≡C-CHO. Since the primary object of this work was to inhibit reaction at the acetylene and the yield of distillate was so low (ca. 6%)

the experiment was abandoned at this stage.

An attempt was made to react bromopropargyl aldehyde with 2-tetrahdropyranyloxyethyl lithium. A large amount of polymeric material was again formed during the reaction and only a very small amount of material could be distilled after working up the reaction products. The infra-red spectrum of the distillate showed bands at ν_{max} 3,400 (OH) and 2,220 cm.$^{-1}$ (RC≡CR), (I.R. No. 37). Absence of a band in the region 685 cm.$^{-1}$ indicated that the acetylenic bromine had again been lost and the small quantity of distillate obtained was probably $TpO(CH_2)_2C{\equiv}C\text{-}CH(OH)(CH_2)_2OTp$. This experiment was also abandoned.

An attempt to carry out a Reformatsky reaction between bromopropargyl aldehyde and ethyl bromoacetate was also unsuccessful. Difficulty was caused by a very rapid polymerisation of the bromopropargyl aldehyde under reaction conditions.

In the light of this work it was concluded that bromination of the acetylene in propargyl aldehyde was of no advantage in inhibiting reactions of the acetylene group.

The Stereochemistry of the Reduction of Cyclohexanones

Reductions with cyclic complexes of lithium aluminium hydride have been described earlier in this thesis (pp. 50, 66 et seq.). To obtain further information on the mechanism of these reductions, 3,3,5-trimethylcyclohexanone was reduced with the complexes shown in table III and the ratio of axial/equatorial alcohol produced determined by g.l.c. on "Tide" detergent. Results obtained by Haubenstock and Eliel[22,23] (cf. p. 35) are also included in table III for convenience.

TABLE III

The reduction of 3,3,5-trimethylcyclohexanone with lithium aluminium hydride complexes

	Addend	Moles addend / Mole $LiAlH_4$	Moles of complex / Mole ketone	Axial alcohol %(Trans)
1	$CH_2(OH)CH_2(OH)$	1	3	54
2	$CH_3CH(OH)CH(OH)CH_3$	1	3	53
3	3-O-Benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose	1	2	58
4	3-O-Benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose/EtOH	1/1	2	70
5	EtOH	3	3	85
6	EtOH	2	3	81
7	EtOH[22]	3	1.20	83
8	t-Butyl alc.[22]	3	1.07	73
9	None[22]	-	1.24	52
10	None[22]	-	8.40	55

Reagent	Solvent	Mole Reagent Mole ketone	Axial alcohol % (Trans)
11 $NaBH_4$ [23]	Anhyd. isopropyl alc.	0.53	55
12 $NaBH_4$ [23]	Anhyd. isopropyl alc.	0.25	56
13 $NaBH_4$ [23]	Anhyd. t-butyl alc.	0.52	55
14 $NaBH_4$ [23]	Anhyd. diglyme	0.52	55

As described earlier in this thesis, in the preparation of allenynols by reduction of enynols, further reduction of the product to allenene was prevented by using a cylic complex of lithium aluminium hydride as the reducing agent (p. 50). Reduction of enynols with the cyclic 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose complex with lithium aluminium hydride, gave optically active allenic alcohols (p. 66 et seq.). These observations led to the conclusion that the cyclic complexes used were stable under the experimental conditions; the other cyclic complexes shown in table III would also be expected to be stable under the conditions used. It was found that reduction of 3,3,5-trimethylcyclohexanone with the cyclic complexes listed gave products with similar axial/equatorial ratios as did lithium aluminium hydride and sodium borohydride.

Prior to the present work, the reduction of cyclohexanones was assumed to involve only the chair form of the ketone, and in the case of 3,3,5-trimethylcyclohexanone the reduction was considered to be subject to steric approach

control[25,26] (cf. p. 33). It was shown by Landor, Miller, and Tatchell[24] that in the asymmetric reduction of ketones with optically active complexes of lithium aluminium hydride, the stereochemistry of the resulting alcohols was correctly predicted if the approach of the ketone towards the complex occurred so that minimum interaction of the non-bonded oxygen atoms occurred.

An examination of Dreiding models shows that the experimental results obtained (table III) are inconsistent with these points. It is clearly untenable that a cyclic complex of lithium aluminium hydride should experience roughly the same steric interaction by the axial methyl group during its approach from the axial side to the carbonyl of 3,3,5-trimethylcyclohexanone as does lithium aluminium hydride and the sodium borohydride complexes. This therefore leads to the conclusion that axial attack of 3,3,5-trimethylcyclohexanone by lithium aluminium hydride or its complexes, and by sodium borohydride or its complexes, does not occur.* An examination of a Catalin model of 3,3,5-trimethylcyclohexanone shows that this conclusion is quite reasonable, since the carbonyl group is effectively shielded to attack from the axial side.** The only way of producing the equatorial

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*If axial attack did occur the reaction would be subject to steric approach control and results 1, 2, 3, 10, 11, 13 and 14 in table III would be much more divergent.

**This applies to any hindered cyclohexanone (cf. footnote p. 32).

alcohol by reduction of 3,3,5-trimethylcyclohexanone, therefore, is by equatorial attack on the flexible form of the ketone with nearly simultaneous flip to the chair form. It is proposed that this reaction competes with equatorial attack of the chair form. The ratio axial/equatorial alcohols produced in the products thus depends on the relative rates of these two competing reactions. A re-examination of some results cited in the literature which have up to the present time appeared anomalous, may also be rationalised by assuming the participation of flexible forms.

Although flexible forms have not previously been considered to be of importance in this type of reaction, it has been estimated that in cyclohexanone the energy difference between the chair and flexible forms is only 2.7 K cal/mole,[27] i.e. about half as much as in cyclohexane. This means that about 1% of the ketone is in the flexible form.[28a] Attempts have been made to measure the barrier height to chair-chair and chair-flexible forms in cyclohexanones[26] from low temperature NMR spectra of cyclohexanone and some of its simple alkyl derivatives down to -75^{o}, but it has not yet been possible to reach sufficiently low temperatures to freeze the conformational inversions. It may be implied from this that the barrier is substantially lower than in cyclohexane. It seems a reasonable proposal, therefore, that a ketone with an axial methyl group such

as 3,3,5-trimethylcyclohexanone should be capable of existing to considerably greater than 1% in the flexible form. Consideration of some observations reported in the literature leads to the conclusion that even for ketones having no axial substituents, flexible forms can be important participants in reactions. It will be shown that in some cases, the participation of the flexible form in a reaction of a ketone may have a marked affect on the stereochemistry of the products, even though the concentration of flexible form in the chair-flexible form equilibrium is extremely low.

The equation derived by Eliel, Ro and Lukach[28a,29] for reactions of equatorial and axial conformers present in an equilibrium mixture, may be applied to reactions of chair-flexible form mixtures:

$$k=(k_cK+k_f)/(K+1)$$

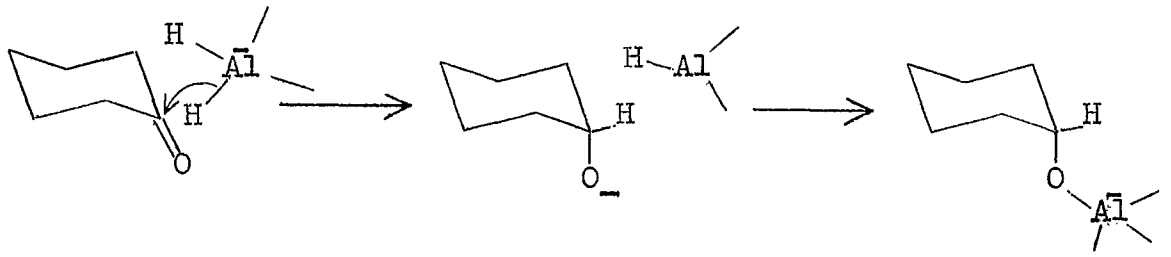
where k is the overall rate constant, k_c is the rate constant of reaction of the chair form and k_f is the rate constant of reaction of the flexible form. If about 5% of the flexible form* is present at 25° then K = 19 and we must assume that $k_f = 17k_c$ to account for the formation of about equal amounts of equatorial and axial alcohol with

---

*For a 95:5 equilibrium the difference in energy between chair and flexible form is 1.7 K cal/mole; it is assumed that the energy due to relief of axial Me:H interaction is about 1 K cal/mole which seems not unreasonable.

lithium aluminium hydride.* Such a difference in reaction rate of chair and flexible form may be accounted for by a detailed consideration of the mechanism of the reduction process.

A broad-side attack of the carbonyl group (i.e. simultaneous donation of the hydride ion and formation of the new O-Al bond) by the aluminium hydride complex ion is unlikely since this would involve an unstable four centred cyclic transition state. The reduction is more likely to go in two stages, the initial donation of hydride ion by the complex being followed by formation of the oxygen-aluminium bond, possibly by reaction with a different molecule of complex.†



Clearly, the concept of product development control as originally introduced by Dauben,[25,26] in which the bulk of the group being introduced into the axial position

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* $\frac{\text{axial}}{\text{equatorial}} = \frac{k_c \times 95}{k_f \times 5} = \frac{k_c \times 95}{17k_c \times 5} = \frac{95}{85} = 1.117$

†Such a mechanism is consistent with the observed stereochemical results. This mechanism is also supported by the work of Landor, Miller, and Tatchell[44] on the asymmetric reduction of ketones.

was considered to exert a retarding effect on the reaction, must be modified in the present case. If the proposed mechanism for this reaction is correct, the substituent being introduced into the axial position is always a negatively charged oxygen atom, no matter what lithium aluminium hydride complex is used. In the case of attack of the flexible form this might lead to interaction (i.e. attraction) between flagpole hydrogen and O^- and between the isoclinal* methyl group on C_3 and O^-. This would thus cause an acceleration of the reaction (i.e. a lowering of the activation energy of the reaction) and this reaction could thus be regarded as being subject to "positive product development control".* This is shown in figure 19, p. 119.

In the case of equatorial attack of the chair form, the O^- being introduced into the axial position could interact (attraction) with the axial methyl group on C_3, so that this reaction too is subject to positive product

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*The classical boat form of 3,3,5-trimethylcyclohexanone may be twisted so that the two methyl groups on C_3 are orientated at equal angles above and below the plane of the ring. Following a suggestion by Professor M. C. Whiting, methyl groups thus orientated have been called isoclinal. Interactions in the boat (flexible) form appear to be at a minimum in this conformation.

*The type of effect envisaged by Dauben in which the bulk of the substituent (uncharged) being introduced into the axial position causes steric crowding of axial substituents (thus increasing the activation energy) could be termed "negative product development control".

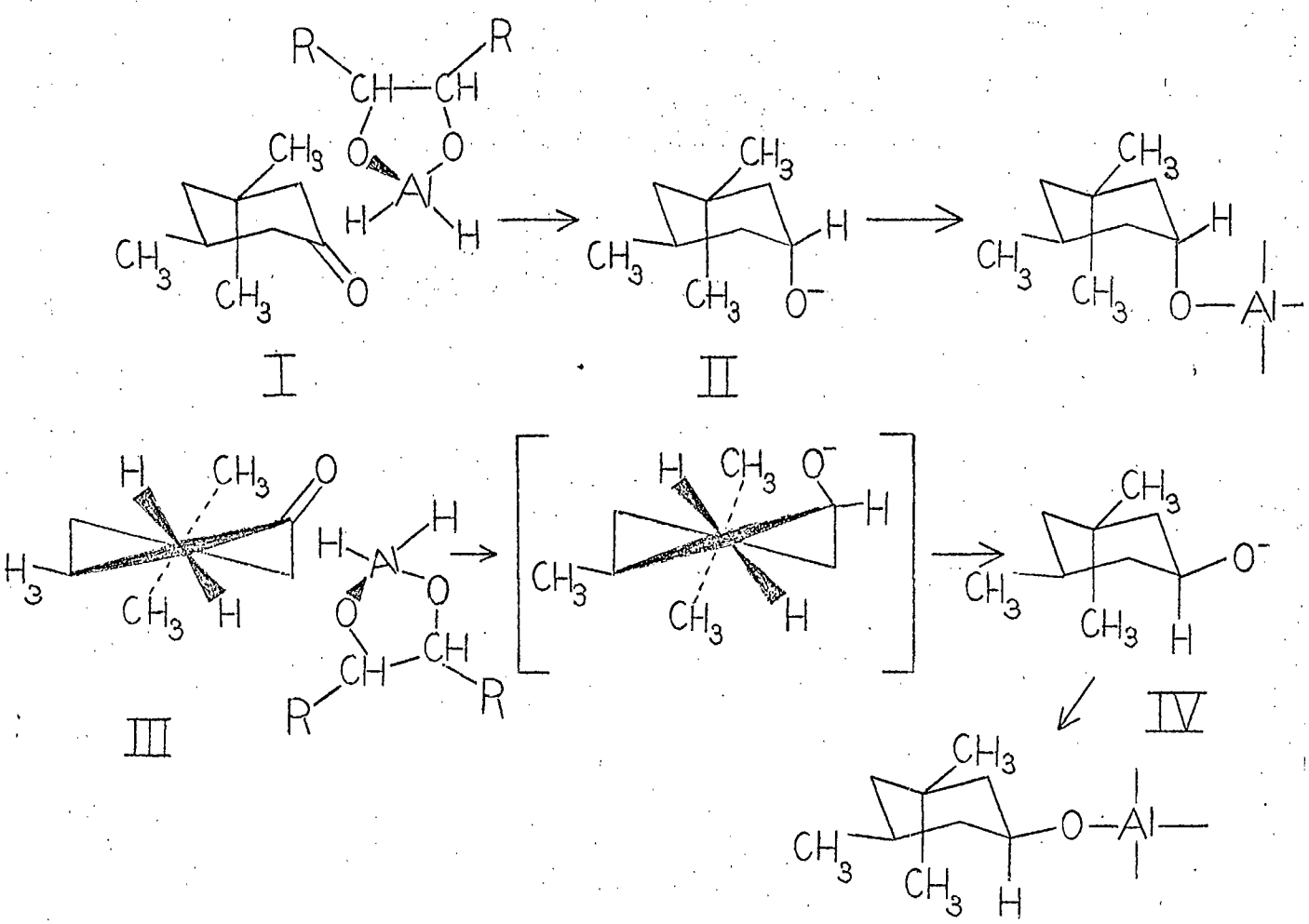

Figure 19

development control. The difference in reaction rates of flexible and chair forms of 3,3,5-trimethylcyclohexanone may thus be attributed to a difference in the magnitude of the positive product development control in the two cases.

Examination of models show that during equatorial attack of both chair and flexible forms of 3,3,5-trimethyl-cyclohexanone by lithium aluminium hydride or sodium

borohydride, and by moderately sized complexes of these hydrides in which not more than two of the aluminium hydrogens have been replaced, steric interactions between reactants are comparitively unimportant. The axial/equatorial ratios of alcohols produced by these complexes are therefore insensitive to the size of the reducing complex (cf. table III). With a very bulky complex of this type however, (and a critical size seems to be reached with the monosaccharide complex) equatorial attack on the flexible form experiences more steric retardation both by the 2,6-hydrogens and the isoclinal 3-methyl group, than does equatorial attack on the chair form, and this leads to slightly more axial alcohol in the product.

When the third hydrogen on the complex hydride is replaced by an alkoxy group, approach of the complex hydride towards the carbonyl is much more unfavourable (if overlap of non-bonded oxygens is kept at a minimum, cf. p. 114). This causes the reaction to be much more sensitive to steric interactions. Models show that reaction of flexible form is retarded more than reaction of chair form by steric interactions of the 2,6-hydrogen and isoclinal 3-methyl and more axial alcohol is therefore observed in the products, (cf. results 3 and 4, table III).

The result obtained by Haubenstock and Eliel for the triethoxyaluminiumhydride complex, and confirmed during

the present work, indicates that this effect is more enhanced with a non-cyclic tri-alkoxy complex. This may be due to the fact that an alkoxy modified cyclic complex is a more rigid structure than the non-cyclic tri-alkoxy complex. Random movements of the three alkoxy groups on the non-cyclic tri-alkoxy complex may increase the interference with the 2,6-hydrogens and isoclinal 3-methyl group as attack occurs. Reduction with the tri-t-butoxy aluminium hydride complex gives a lower amount of axial alcohol in the products than would be expected. It has recently been suggested[30] that tri-t-butoxyaluminium hydride may not be the operative reducing agent however, and this may account for this result.

The participation of flexible forms in reactions of some cyclohexanones enables some observations reported in the literature to be rationalised, which prior to the present work have appeared anomalous. Thus it is reported by Lansbury and MacLeay[31] that reduction of 4-t-butylcyclohexanone with both lithium aluminium hydride and sodium borohydride gives predominantly the equatorial alcohol and is influenced only very slightly by temperature differences, the amount of equatorial alcohol increasing slightly at lower reaction temperature. Similar reductions of 3,3,5-trimethylcyclohexanone give substantially larger amounts of axial alcohol at lower temperature, however.

Normally, in a system in which two reaction paths are

possible, the proportion of the product derived from the reaction path of lower activation energy increases as the reaction temperature is lowered. Thus in the present case, lowering the reaction temperature should increase the proportion of equatorial alcohol produced (from equatorial attack of flexible form). Opposing this effect however, is the fact that as reaction temperature is lowered, the amount of flexible form present in the flexible form/chair form equilibrium decreases. This second temperature effect thus tends to decrease the proportion of equatorial alcohol produced at lower reaction temperature. The net result observed thus depends on which of these two opposing temperature effects is dominant for the particular compound concerned. In the case of 4-t-butylcyclohexanone the first effect is dominant and in the case of 3,3,5-trimethylcyclohexanone the second effect is dominant. The observations of Lansbury and MacLeay are thus explained.

The stereochemistry of catalytic reduction may also be interpreted on the basis of flexible form participation. Such reductions have been considered to involve steric approach control (absorption on the catalyst and approach of hydrogen from the less hindered equatorial side) and yield mainly axial alcohols (von Auwers-Skita hydrogenation rule[28a]). The equatorial alcohols produced in smaller quantities in these reductions were considered to result

from absorption on catalyst and approach of hydrogen from the axial side. Examples are the reduction of cholestan-3-one over active platinum to give cholestan-3-α- and -3β-ol[32] in a ratio of 3:1 and reduction of 4-t-butylcyclohexanone[33] over platinum in acetic acid-hydrochloric acid to give cis and trans-4-t-butylcyclohexanol in a ratio of 4:1. These reductions are not completely stereoselective and it has been observed that catalytic hydrogenation gives the greatest amount of axial alcohol when carried out under conditions where hydrogenation is fast. Thus hydrogenation of 4-t-butylcyclohexanone[33] is more stereoselective in the presence of hydrochloric acid (4:1) than in its absence (2:1); use of an aged and not very active platinum catalyst reduces selectivity even more (1.2:1).

If the equatorial alcohols produced in these catalytic reductions resulted from reduction of chair forms of the ketones, then absorption of ketone onto the catalyst would have to take place from the axial side. If this were the mechanism of the formation of equatorial alcohol, then slowing down the reaction by use of old catalyst should lead to more axial alcohol, not less, as the less active catalyst would be more selective in absorbing molecules in favourable orientation (i.e. from the equatorial side). The observed decrease in the amount of axial alcohol produced

with the use of old catalyst therefore implies that another mechanism must be operative. This conclusion is supported by an examination of models which show that absorption of these ketones onto a catalyst surface from the axial side is very difficult due to the angle of the carbonyl group. It is proposed therefore, that in these catalytic reductions no axial absorption of ketone onto the catalyst occurs. Any equatorial alcohol produced in the reductions must therefore be a result of the equatorial absorption of flexible forms onto the catalyst surface. Use of an aged catalyst (with a not very active surface) results in preferred absorption of flexible form* from the equatorial side, and will thus give larger amounts of equatorial alcohol in the products as observed.

An exception to the hydrogenation rule is the reduction of cholestan-1-one[34] which is reduced to the (equatorial) 1-β-ol over platinum in acetic acid in over 90% yield. This observation would be predicted since in cholestan-1-one equatorial absorption of the ketone when the A ring has the chair conformation is prevented by the methyl group in the C_{10} position. The reduction therefore goes completely

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*Models show that equatorial absorption of flexible form takes up less room on the catalyst surface than does equatorial absorption of chair form. With an aged and not very active catalyst the surface is presumably contaminated and the slightly different spatial requirements of chair and flexible forms become important.

by the equatorial absorption and reduction of the flexible form to give the equatorial alcohol. This is illustrated in figure 20.

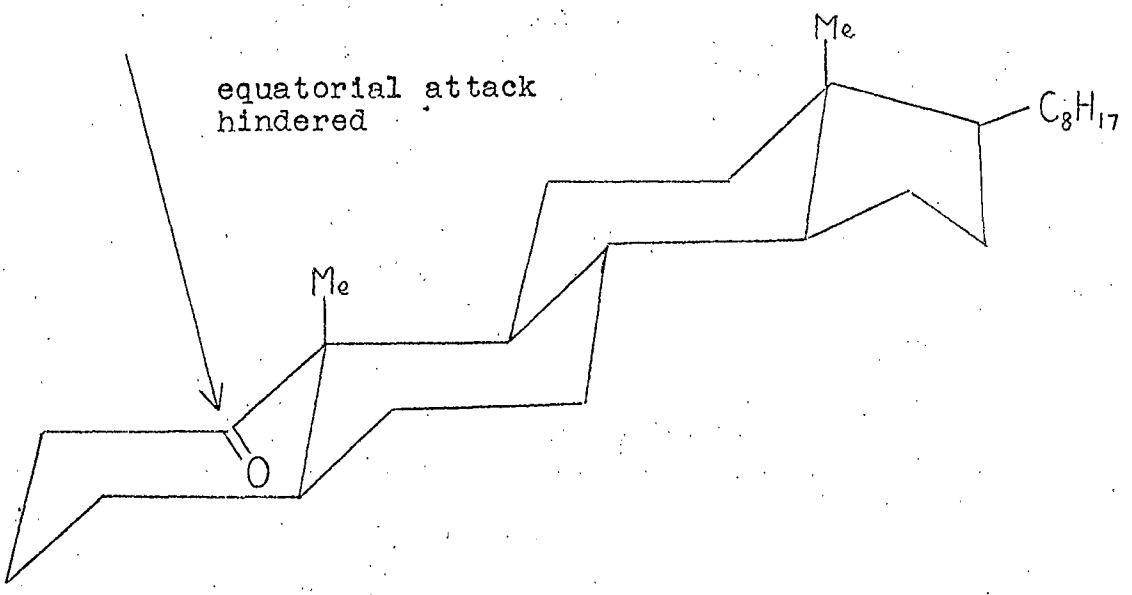


Figure 20

The proposal by Richer[35] (cf. p. 36) that "the stereochemical results of all the additions on unhindered ketones by groups small enough not to interfere with the axial hydrogen in positions 3 and 5, are directed exclusively by the axial hydrogens on positions 2 and 6 which hinder attack from the equatorial side", appears dubious on examination of models. Due to the angle of the carbonyl group, approach to the carbonyl appears to be always easier from the equatorial side no matter what size the attacking entity.

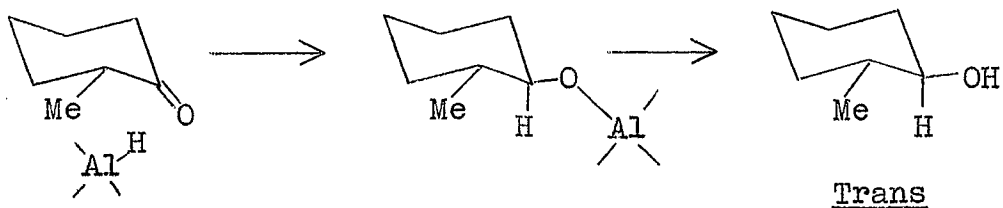
Richer's[35] results from reductions of different substituted cyclohexanones with lithium tri-t-butoxy aluminium hydride (table IV) may be interpreted by postulating the participation of chair and flexible forms. (There is some doubt whether the reducing entity is tri-t-butoxy aluminium hydride[30]).

TABLE IV[35]

Reduction of cyclic ketones by $LiAlH(O\text{-}t\text{-}Bu)_3$ in tetrahydrofuran.

	Ketone	% Stable Isomer
1.	2-Methylcyclohexanone	63.2
2.	3-Methylcyclohexanone	86.0
3.	4-Methylcyclohexanone	82.6
4.	4-t-Butylcyclohexanone	89.7
5.	4-t-Butyl-2,2-dimethylcyclohexanone	100.0
6.	3,3,5-Trimethylcyclohexanone	12.2

1. 2-Methylcyclohexanone gives less of the stable (trans) isomer than any of the other monosubstitued cyclohexanones in table IV. Axial attack on chair* produces the stable (trans)isomer:



Trans

equatorial attack on chair gives the cis isomer, but so does equatorial attack on flexible form in this case.

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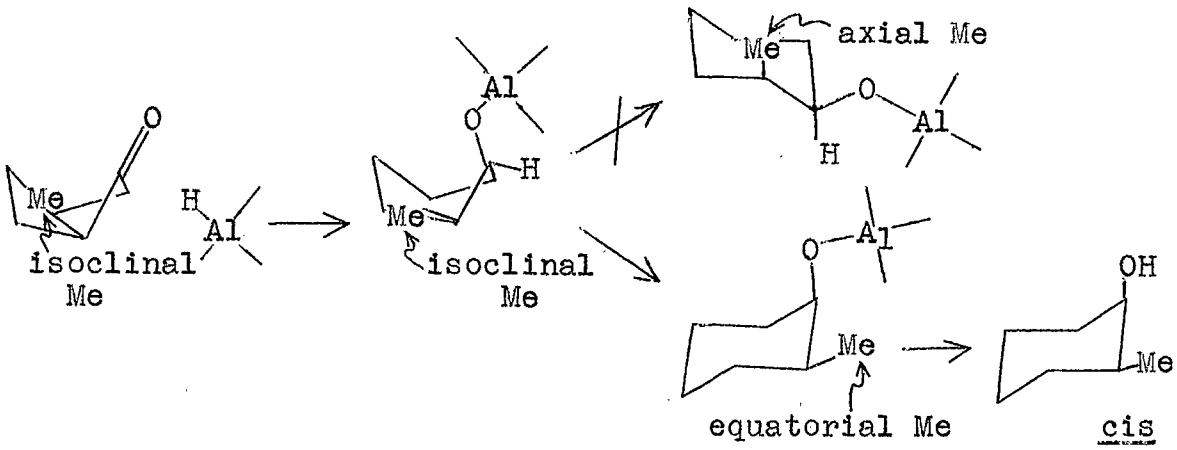
*Axial attack on chair is possible in this case since there are no axial substituents in positions 3 and 5.



2, 3 and 4. Both axial attack on chair form and equatorial attack on flexible form give the more stable isomer. Equatorial attack on the flexible form would be expected to play a bigger part with tri-t-butoxy aluminium hydride as reducing agent than with lithium aluminium hydride.

5. Equatorial attack on both chair and flexible form is prevented by the 2,2-dimethyl group. Axial attack on chair* form gives only the stable (trans) isomer. The fact that no axial alcohol is formed indicates that axial attack of flexible form does not occur. This may be due to shielding by the flagpole hydrogen.

6. Equatorial attack by the bulky reagent on the flexible form experiences steric interference from the 2,6-hydrogens and isoclinal 3-methyl group and gives the equatorial

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*Axial attack on chair is possible in this case since there are no axial substituents on positions 3 and 5.

cyclohexanol. Equatorial attack on the chair form gives the axial cyclohexanol which predominates in the product.

There are therefore four possible reaction paths to be considered for reductions of cyclohexanones:

(a) axial attack of chair form to give equatorial alcohol, (for unhindered cyclohexanones);

(b) equatorial attack of chair form to give axial alcohol;

(c) axial attack of flexible form to give axial alcohol (appears to be relatively unimportant due to steric hindrance of the flagpole hydrogen);

(d) equatorial attack of flexible form to give equatorial alcohol.

The axial/equatorial ratio of products from these four reaction paths should be interpreted in the light of steric approach control and product development control for the particular compound concerned; e.g. in the case of a hindered cyclohexanone having no substituents in positions 2 and 6 (such as 3,3,5-trimethylcyclohexanone) mechanism (a) is eliminated by steric approach control. Mechanisms (b) and (d) are both favoured by positive product development control and the relative magnitude of this factor in the two cases is important in determining the axial/equatorial ratio of products.

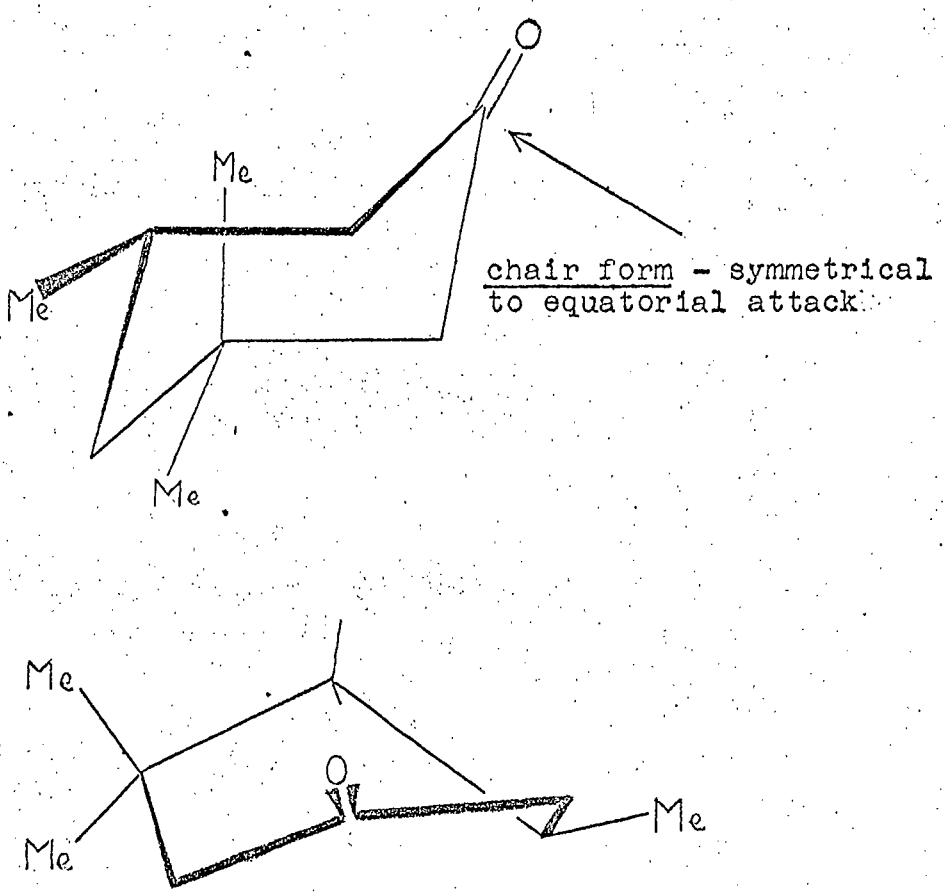
In a different cyclohexanone, however, e.g. 4-t-butyl-2,2-dimethylcyclohexanone (table IV) mechanisms (b) and (d) are eliminated by steric approach control and the

reaction goes entirely by mechanism (a). Mechanism (c) appears to be unimportant, possibly due to shielding of the carbonyl by the flagpole hydrogen.

The products from the reduction of 3,3,5-trimethylcyclohexanone with the lithium aluminium hydride-monosaccharide complex were found to be optically inactive. Whilst the chair form of 3,3,5-trimethylcyclohexanone is undergoing equatorial attack, the axial methyl group on C_3 is on the side of the ring remote from the attacking complex hydride. From the point of view of the attacking entity, therefore, the ketone appears to be symmetrical. A model of the flexible form of 3,3,5-trimethylcyclohexanone shows that the steric interference of the two isoclinal methyl groups on C_3 with the benzyl group on the monosaccharide, is about the same as that of the lone methyl group on C_5 with the benzyl group of the monosaccharide. (This is illustrated in figure 20.) Optically inactive alcohol would therefore be expected from both these mechanisms. The observation that optically inactive alcohol is obtained experimentally is further support for the proposal that axial attack of the chair form of 3,3,5-trimethylcyclohexanone does not occur. If axial attack did occur the steric interaction of the axial methyl group on C_3, with the benzyl group of the monosaccharide, would differ

for the two ketone enantiomorphs. (This is illustrated in figure 22). The alcohol produced would thus be optically active.

Attempts to measure experimentally the relative rates of formation of axial and equatorial alcohol were unsuccessful due to the rapidity of the reactions. Even at -40° the reaction was found to be complete after about two minutes.



Flexible form - 3,3-isoclinal methyl groups cause about the same steric interference to the benzyl group as the 5-equatorial methyl group.

Figure 21

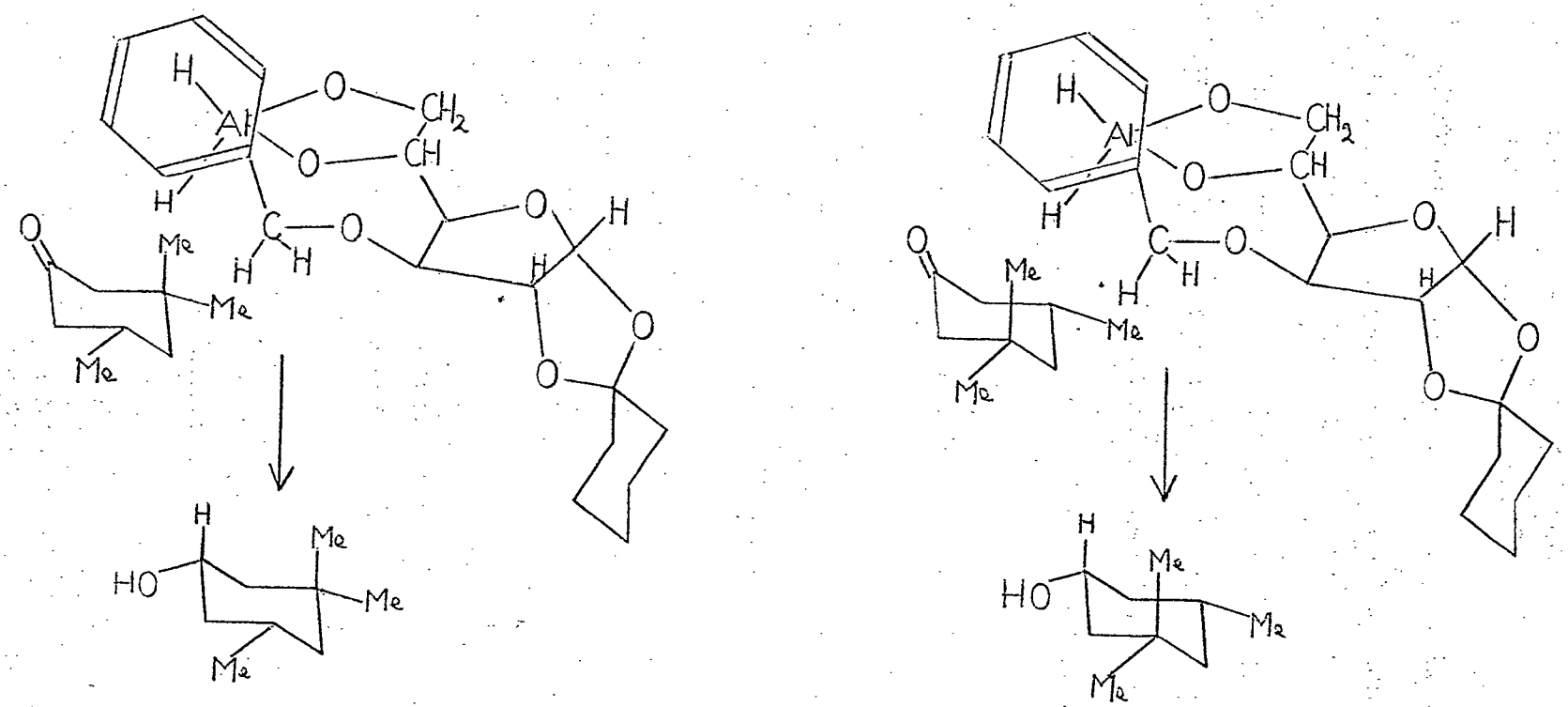


Figure 22

If axial attack occurred as shown, the rate of reduction of the two ketone enantiomorphs would differ.

III

EXPERIMENTAL

5-Bromopent-2-en-4-yn-1-ol[19].-Sodium hydroxide (60 ml. 10 N. 0.6 mole) and ice (100 g.) were placed in a 250 ml. two-necked flask cooled in an ice bath and bromine (40 g., 0.24 mole) added dropwise with stirring over 0.5 hr. The solution was stirred for 0.5 hr. at 0° after the addition of bromine was complete. The sodium hypobromite so produced was then added dropwise with stirring over 1 hr. to pent-2-en-4-yn-1-ol[19] (16.4 g., 0.2 mole) contained in a second 250 ml. two-necked flask cooled in an ice bath. Stirring was continued for 3 hr. at 0° after completion of the sodium hypobromite addition. The cream-coloured precipitate was filtered off using a cooled sintered glass filter, and recrystallised from chloroform/40°-60° pet ether (1/4) to yield whitish crystals (25 g., 78%) m.p. 38°-39°. The material was identified as 5-bromopent-2-en-4-yn-1-ol by its infra-red spectrum,[2,19] ν_{max} 3,350 s (OH), 2,220 m (RC≡CR).

Buta-1,3-diyne(diacetylene)[127].-1,4-Dichlorobut-2-yne (46 g., 0.38 mole) was placed in a 500 ml. flask with potassium hydroxide (45 g., 0.80 mole,) dioxan (20 ml.) and water (300 ml.). Nitrogen was bubbled through the reaction mixture which was heated to reflux temperature with rapid stirring. The diacetylene vapour evolved was passed through two double surface condensers in series, dried by passing

over anhydrous calcium chloride and collected in a trap at -60° (13.7 g., 73%), identified by its infra-red spectrum in chloroform, I.R. No. 5. (One sample of this material exploded violently and throughout this work was used immediately after preparation, being diluted with dimethyl formamide at -60°).

Non-2-ene-4,6,8-triyn-1-ol (Bohlmann Procedure)[5].-Hydroxylamine hydrochloride (0.6 g.) and aqueous ethylamine solution (12 ml., 50%) followed by cuprous chloride (0.1 g.) were added to a solution of diacetylene (1.4 g., 0.03 mole) in dimethyl formamide (50 ml.) and methanol (40 ml.) at 0°. This was immediately followed by the addition of a solution of 5-bromopent-2-en-4-yn-1-ol (1.6 g., 0.01 mole) in dimethyl formamide (40 ml.). The reaction mixture was stirred for 2 hr. at 0° and then the complex decomposed by the addition of potassium cyanide (5 g.) in water (50 ml.), followed by extraction with ether (3 x 200 ml.). The combined ethereal extracts were washed with water (2 x 100 ml.), 2.5 N. HCl (2 x 100 ml.) and water (3 x 100 ml.) and dried ($MgSO_4$). The ultra-violet spectrum of the crude solution showed peaks clearly discernable at λ 231, 240, 271, 288, 306, 327 mμ (U.V. No. 1a). The ethereal solution was evaporated down to 50 ml. in vacuo without heating, 100 ml. n-pentane added and the solution again evaporated to 50 ml.

After three repetitions of this procedure the solution (50 ml.) was chromatographed on Woelm acid alumina (200 g.,), deactivated with water (6 ml., 3%), eluted with n-pentane (5 x 400 ml.) and then ether/n-pentane 1/4 (20 x 400 ml.). Non-2-ene-4,6,8-triyn-1-ol was eluted in fractions 14 to 16 (0.053 g., 4.7% on 5-bromopent-2-en-4-yn-1-ol) λ_{max} 229 (Σ62,500), 240 (Σ86,600), 272 (Σ6,400), 288 (Σ12,400), 306.5 (Σ16,250) and 328 mμ (Σ11,150) (U.V. No. 1).

Nona-3,4-6-trien-8-yn-1-ol, Nona-3,4,8-trien-6-yn-1-ol and Nona-3,4-dien-6,8-diyn-1-ol (Bohlmann Procedure[5]).-A solution of non-2-ene-4,6,8-triyn-1-ol (1.070 g.) in ether (50 ml.) was added at room temperature over 0.25 hr. with stirring, to a standardised ethereal solution of lithium aluminium hydride (75.5 ml. of 0.4 molar solution 0.03 mole). The reaction mixture was stirred for 2 hr. at room temperature and then the complex decomposed by pouring into 10% sulphuric acid (150 ml.) with rapid stirring, and extracted into ether (3 x 200 ml.). The combined extracts were washed with water (3 x 100 ml.) and dried ($MgSO_4$). The ultra-violet spectrum of this crude solution is shown (U.V. No. 2a). The ethereal solution was evaporated to 50 ml. in vacuo without heating, 100 ml. n-pentane added and the solution again evaporated

to 50 ml. After three repetitions of this procedure the solution (50 ml.) was chromatographed on Woelm acid alumina (200 g.) deactivated with water (6 ml. 3%), eluted with n-pentane (5 x 400 ml.) and then ether/n-pentane 1/4 (21 x 400 ml.). Fraction 14 contained a mixture of nona-3,4,8-trien-6-yn-1-ol (IV) and nona-3,4,6-trien-8-yn-1-ol (V) (0.36 g., 33.7%) λ_{max} 212 (Σ47,500), 265 mμ(Σ15,200), λ_{sh} 253 (Σ12,400), 272 mμ(Σ12,600)(U.V. No. 2) ν_{max} 3,500, 3,300, 2,210, 1,950, 1,650, 965 and 935 cm.$^{-1}$ (I.R. No. 1). The product 0.11 g. absorbed hydrogen (102.6 ml., 5 mole (PtO_2)). Fraction 15 (0.19 g., 18%) also contained a mixture of (IV) and (V), having the same ultra-violet and infra-red spectra as before. Fractions 16 (0.17 g., 15%), 17 (0.12 g., 11%), and 18 (0.05 g., 4%) consisted of (IV) and (V) with increasing proportions of nona-3,4-dien-6,8-diyn-1-ol; (U.V. No. 3). Fraction 19 gave nona-3,4-dien-6,8-diyn-1-ol (±marasin) (0.006 g., 0.6%) λ_{max} 208 (Σ51,000), 237 (Σ5,000), 239.5 (Σ8,900), 263 (Σ14,100) 278 mμ(Σ12,500) (cf. U.V. No.15); ν_{max} 3,450, 3,320, 2,210, 1,950 cm.$^{-1}$ (I.R. No. 6).

Use of lithium diethoxyaluminium hydride.-Similarly, 0.4 M lithium aluminium hydride solution (75.5 ml., 0.03 mole) with added ethanol (2.76 g., 0.06 mole) and non-2-ene-4,6,8-triyn-1-ol (0.26 g., 0.002 mole) at room temperature for 2 hr. gave a mixture of (IV) and (V) with (±)marasin, and

pure (±) marasin (0.016 g., 6%) with the same ultra-violet and infra-red spectra as before.

2-(Penta-2,4-diyn-1-ylidene)-Tetrahydrofuran (isomarasin).[143] Fraction 17 from the preceeding experiment (containing 0.08 g. marasin and 0.04 g. dihydromarasin) was repeatedly evaporated to 50 ml. with addition of methanol. Sodium hydroxide (50 ml. 4 N.) was then added and the solution allowed to stand for 24 hr. in the dark. The solution was then extracted with n-pentane (4 x 10 ml.), the combined extracts washed with water (1 x 10 ml.) and dried ($MgSO_4$). Chromatography on Woelm acid alumina (100 g.) deactivated with water (3 ml., 3%) and eluted with n-pentane (6 x 100 ml.) gave isomarasin in fraction 4 (0.054 g., 45% based on total weight of fraction 17 - calculated from extinction coefficients, cf. p. 46) identified by its ultra-violet spectrum λ 224, 266, 279.5, 295[143] (U.V. No. 6).

Isomerisation of Nona-3,4,6-trien-8-yn-1-ol and Nona-3,4,8-trien-6-yn-1-ol.-(a) Sodium hydroxide (50 ml., 4 N.) was added to a mixture of nona-3,4,6-trien-8-yn-1-ol and nona-3,4,8-trien-6-yn-1-ol (total 0.36 g.) in methanol (50 ml.) and the solution allowed to stand for 24 hr. in the dark. The solution was then extracted with n-pentane (4 x 10 ml.) the combined extracts washed with water

(1 x 10 ml.),dried ($MgSO_4$) and chromatographed on Woelm acid alumina (100 g.) deactivated with water (3 ml., 3%) and eluted with n-pentane (12 x 100 ml.) and then ether (3 x 100 ml.). The product λ_{max} 220, 268 (U.V. No. 5) was eluted in fraction 4.

(b) The experiment was repeated on a fresh solution of the allenenes but the isolation procedure described by Bendz[143] was used. The isomerisation product was subjected to a counter-current distribution in eight 500 ml. funnels between n-pentane as the stationary phase and ethanol containing 30% water as the mobile phase (200 ml. of each phase in each funnel). After fifteen transfers the product λ_{max} 220,268 (as before) was found in the aqueous ethanolic solutions in funnels 2, 3 and 4.

2,2-Dichloro-3,3-dimethylbutane and 2-chloro-3,3-dimethylbut-1-ene[21].-Pinacolone (48 g., 0.48 mole) was added with stirring over 1 hr. to phosphorous pentachloride (100 g., 0.48 mole) with ice cooling. Stirring was continued for 6 hr., and the reaction mixture allowed to stand overnight. It was then poured onto crushed ice and the solid produced was filtered off, washed with water and dried in a dessicator giving 2,2-dichloro-3,3-dimethylbutane (40 g., 54%).

The filtrate consisted of two layers, a lower aqueous layer which was separated and rejected, and an upper

organic layer, which was dried (Mg SO_4) to give crude 2-chloro-3,3-dimethylbut-1-ene (24 g., 41%). The combined yield of products was 95% (lit. 91%).

3,3-Dimethylbut-1-yne[21].-Potassium hydroxide pellets (102.8 g.) were crushed using a pestle and mortar in a dry box and mixed thoroughly with 2,2-dichloro-3,3-dimethylbutane (30 g., 0.2 mole);the powder was transferred to a 1 litre two-necked flask fitted with two double surface reflux condensers and a trap at -50° in series. Absolute ethanol (10.2 ml.) was added, the flask heated in an oil bath over 1 hr. to 165° and maintained at this temperature for 5 hr. The reflux condensers were then replaced by a still head and condenser fitted for distillation, and the reaction flask heated in the oil bath to 200°. A colourless distillate was collected which on refractionation gave 3,3-dimethylbut-1-yne (13 g., 82%) ν_{max} 3,330 s (C≡C-H), 2,110 m (C≡CH), 1,390 m and 1,360 s (CMe_3 doublet) (I.R. No. 7).

The compound was obtained in a similar manner from 2-chloro-3,3-dimethylbut-1-ene.

trans-8,8-Dimethylnon-2-en-4,6-diyn-1-ol.-Cuprous chloride (1.65 g., 0.016 mole), hydroxylamine hydrochloride (20 mg.), dimethylformamide (20 ml.) and 70% aqueous ethylamine

(2.68 ml., 0.033 mole) were placed in a dropping funnel under oxygen free nitrogen and shaken for 0.5 min. The light green suspension was then immediately added in one portion to a solution of 3,3-dimethylbut-1-yne (8.2 g., 0.1 mole) in dimethylformamide (20 ml.) contained under nitrogen and cooled in an ice bath. The reaction mixture remained light green in colour. After 0.5 min. a solution of trans-5-bromopent-2-en-4-yn-1-ol (2.68 g., 0.017 mole) in dimethylformamide (15 ml.) was added in one portion and the mixture stirred under nitrogen for 2 hr. The complex was then decomposed by addition of a solution of potassium cyanide (20 g.) in water (50 ml.) and extracted with ether (3 x 75 ml.). The combined extracts were washed with water (2 x 50 ml.), 2.5 N. HCl (2 x 75 ml.), water (3 x 200 ml.) and dried ($MgSO_4$). A band at λ_{max} 230 mμ in the ultra-violet spectrum (U.V. No. 7) showed that the product contained 5-bromopent-2-en-4-yn-1-ol. The solution was therefore evaporated in vacuo without heating, to 50 ml. and pet ether (100 ml., 40-60°) added, resulting in precipitation of 5-bromopent-2-en-4-yn-1-ol. This was removed by filtration and the filtrate washed with water (6 x 100 ml.). Methanol (100 ml.) was then added and the solution evaporated in vacuo to 100 ml. Ammoniacle silver nitrate solution (75 ml., 10%*) was

*Preparation of ammoniacle silver nitrate solution: 17 g. silver nitrate was dissolved in 100 ml. water and 0.880 ammonium hydroxide solution added until the initial dark brown precipitate had just redissolved. This solution was used immediately.

then added and the solution refrigerated for 1 hr. with occasional shaking. Excess 3,3-dimethylbut-1-yne was filtered off as the silver salt and rejected. The filtrate contained trans-8,8-dimethylnon-2-en-4,6-diyn-1-ol (1.1 g., 41% on bromopentenynol) λ_{max} 207 (Σ33,000), 212 (Σ38,000), 229 (Σ3,000), 240 (Σ5,100), 252 (Σ12,100), 267 (Σ18,000) and 282 mμ (Σ14,000) (U.V. No. 11). (Found C 81.5, H 8.9; $C_{11}H_{14}O$ requires C 81.6, H 8.7%).

In subsequent preparations purification was also carried out by chromatography on Woelm acid alumina (100 g.) deactivated with water (3 ml., 3%) eluted with n-pentane (5 x 200 ml.) and then ether/n-pentane 1/4 (10 x 200 ml.). trans-8,8-Dimethylnon-2-ene-4,6-diyn-1-ol was eluted in fractions 9 and 10 and had the same ultra-violet spectrum as before.

8,8-Dimethylnona-3,4-dien-6-yn-1-ol (Use of Lithium Aluminium Hydride-Butane-2,3-diol Complex).-Butane-2,3-diol (3.6 g., 0.04 mole) was added dropwise with stirring to a standardised solution of lithium aluminium hydride (0.04 mole) in ether (100 ml.) and the reaction mixture heated under reflux for 2 hr. The reaction mixture was then allowed to cool to room temperature, a solution of 8,8-dimethylnon-2-ene-4,6-diyn-1-ol (1.62 g., 0.01 mole) in ether (40 ml.) was added and the mixture stirred at

room temperature for a further 2 hr. The complex was then decomposed by pouring into 10% sulphuric acid extracted into ether (3 x 150 ml.), washed with water (3 x 100 ml.) and dried ($MgSO_4$). Ether was removed in vacuo and the yellowish oil remaining distilled using a mercury vapour pump to give 8,8-dimethylnona-3,4-dien-6-yn-1-ol (0.7 g., 43%) b.p. 60°/ 5 x 10^{-3} mm. λ_{max} 219 mμ(Σ14,700) (U.V. No. 8) ν_{max} 3,400 m (OH), 2,120 w (C≡C-R), 1,950 mμ (C=C=CH) and 868 $cm.^{-1}$ m (allene CH deformation) (I.R. No. 8).

Trans-hept-2-en-4,6-diyn-1-ol and 1-(2-Furyl)prop-1-yne[10].- 1,4-Dichlorobut-2-yne (123.0 g., 1.00 mole) was added dropwise to a suspension of sodamide prepared from sodium (69.0 g., 3.00 g-atom) in liquid ammonia (3 litres) and a crystal of ferric nitrate. This was immediately followed by the dropwise addition of epichlorohydrin (46.3 g., 0.50 mole). The mixture was stirred for 3 hr. and left to stand overnight. The complex was then decomposed by the addition of ammonium chloride (53.5 g., 1.00 mole) with stirring and the ammonia allowed to evaporate off. The residue was extracted with ether (4 x 150 ml.) and the combined extracts dried ($MgSO_4$). The ethereal solution was then evaporated to 60 ml. in vacuo without heating, petroleum ether (100 ml., 40-60°) added and the solution again evaporated to 60 ml. After repetition of this

procedure a further two times the material was chromatographed on Spence type H alumina (750 g.,) deactivated with acetic acid (37.5 ml., 10% aqueous solution) eluted with 40-60° petroleum ether (17 x 350 ml.) and then ether/40-60° pet ether 1⁄3 (5 x 350 ml.). 1-(2-Furyl)prop-1-yne (13.4 g., 25%) having infra-red spectrum identical to that of the known compound was eluted in fractions 1 to 7. Trans-hept-1-en-4,6-diyn-1-ol was eluted in fractions 10 to 18. Removal of solvent gave the crystalline material (2.4 g., 5%) m.p. 48° (lit.[149] 48-49): λ_{max} 279 (ε14,300), 264 (ε18,600), 250 (ε12,800), 238 (ε6,500), 227 (ε3,300) and 211 mμ(ε39,800) and 205.5 $_{sh}$ (ε32,300) (U.V. No. 9) and I.R. spectrum in chloroform: ν_{max} 3,400 m (OH), 3,300 m (C≡C-H), 2,050 w, 1,630 w (C=C), and 948 m (trans CH=CH) (I.R. No. 9).

Hepta-3,4-dien-6-yn-1-ol (use of the Lithium Aluminium Hydride-Butane-2,3-diol Complex).-Butane-2,3-diol (3.6 g., 0.04 mole) was added dropwise with stirring to a standardised solution of lithium aluminium hydride (0.04 mole) in ether (100 ml.) and the reaction mixture heated under reflux for 2 hr. The reaction mixture was then allowed to cool to room temperature and a solution of trans-hept-2-en-4,6-diyn-1-ol (1.06 g., 0.01 mole) in ether (40 ml.) added dropwise with stirring and the reaction mixture stirred

at room temperature for 2 hr. The complex was then decomposed by pouring into 10% sulphuric acid (150 ml.), ether extracted (3 x 150 ml.) and washed with water (3 x 150 ml.) and dried ($MgSO_4$). The ethereal solution was then evaporated down in vacuo without heating to 50 ml., 40-60° pet ether (100 ml.) added and the solution again evaporated to 50 ml. After repetition of this procedure three times the material was chromatographed on Spence type H alumina (200 g.) deactivated with acetic acid (10 g., of 10% solution) eluted with 40-60° pet ether (7 x 200 ml.) and then ether/pet ether 1/4 (7 x 200 ml.). Unchanged starting material was eluted in fractions 6 to 8, identified by its ultra-violet spectrum. Fraction 10 contained hepta-3,4-dien-6-yn-1-ol (0.896 g., 9%) identified by its infra-red spectrum (in $CHCl_3$): λ_{max} 3,450 s (OH), 3,300 v s (C≡C-H), 2,100 m (C≡CH), 1,955 s (C=C=C) and 868 cm.$^{-1}$ m (allene CH deformation (I.R. No. 10 cf. ref. 10) and λ_{max} 211 m (11,00) (U.V. No. 10).

1-Tetrahydropyranyloxypent-2-en-4-yne (Action of Lithium Aluminium Hydride (a).-Concentrated hydrochloric acid (1 ml.) was added to a mixture of pent-2-en-4-yn-1-ol (8.2 g., 0.1 mole) and 2,3-dihydropyran (10.9 g., 1.3 mole) with ice cooling, the mixture allowed to warm to room temperature over 1 hr. and then heated to 70° in a water bath for 3 hr.

Ether (100 ml.) was added and the solution washed with water (50 ml.), saturated sodium bicarbonate solution (50 ml.) and dried ($MgSO_4$). Solvent was removed and the material distilled to give 1-tetrahydropyranyloxypent-2-en-4-yne (13.6 g., 82%) b.p. 66°/3 mm., identified by its infra-red spectrum ν_{max} 3,250 m (-C≡C-H), 2,110 w (RC≡CH). The compound gave one peak on g.l.c. (silicone oil 120°) t = 9.5 min.

Action of Lithium Aluminium Hydride (b).-1-Tetrahydropyranyloxypent-2-en-4-yne (1.7 g., 0.01 mole) was added dropwise over 0.25 hr. to a standardised solution of lithium aluminium hydride (0.02 mole) in ether (104 ml.) and the reaction mixture stirred at room temperature for 2 hr. The complex was then decomposed by addition of water, the precipitated solids removed by filtration, the filtrate extracted with ether (3 x 25 ml.) and the combined extracts dried ($MgSO_4$). Removal of solvent gave 1-tetrahydropyranyloxypent-2-en-4-yne (1.7 g., 100% recovery) identified by its infra-red spectrum as before (I.R. No. 11). G.l.c. (silicone oil 120°) gave one peak t = 9.5 min.

Hex-2-en-4-yn-1-ol.-1-Tetrahydropyranyloxypent-2-en-4-yne (16.6 g., 0.1 mole) was added dropwise to sodamide prepared from sodium (4.6 g., 0.2 g. atom) liquid ammonia (700 ml.) and ferric nitrate (0.1 g.) and stirred for 1 hr.

Dimethyl sulphate(25.3 g., 0.2 mole) was then added dropwise over 0.5 hr. and the mixture stirred for a further 3 hr. and left overnight. Ammonium chloride (11 g., 0.2 mole) was then added and the ammonia allowed to evaporate. The solid was extracted with ether (4 x 100 ml.) and the combined extracts heated under reflux for 0.5 hr. with added methanol (50 ml.) and concentrated hydrochloric acid (2 ml.). The solution was then washed with water (2 x 50 ml.), saturated sodium hydrogen carbonate solution (1 x 50 ml.), and dried. Solvent was removed and the residue distilled to give hex-2-en-4-yn-1-ol (5.5 g., 58%) b.p. 90°/20 mm. identified by its infra-red spectrum. ν_{max} 3,500 s (OH), 2,200 m (RC≡CR).

(±)-Hexa-3,4-dien-1-ol (Menthol added at end of Reaction).- A solution of hex-2-en-4-yn-1-ol (1.0 g., 0.01 mole) in ether (50 ml.) was added dropwise over 0.5 hr. at room temperature, with stirring, to a standardised solution of lithium aluminium hydride (0.015 mole) in ether (67.2 ml.) and the reaction mixture then heated under reflux for 2 hr. A solution of menthol (5.1 g., 0.03 mole) in ether (50 ml.) was then added dropwise over 0.5 hr. and the refluxing continued for a further 2 hr. The complex was then decomposed by pouring into 10% sulphuric acid (150 ml.), ether extracted (3 x 100 ml.), washed with water (2 x 50 ml.)

and dried ($MgSO_4$). Solvent was removed and the material distilled to give hexa-3,4-dien-1-ol (0.7 g., 70%). G.l.c. on silicone oil at 120° showed two peaks at t = 4.5 min. (menthol) and t = 7 min. The material was refractionated using a 12" column packed with Fenske rings, giving hexa-3,4-dien-1-ol $[\alpha]_D^{20}$ + 9.3° (0.3 g., 30%) having infra-red spectrum identical with an authentic sample. ν_{max} 3,340 s (OH), 1,960 w (C=C=C) and 1,040 cm.$^{-1}$ (cf. I.R. No.17). The material gave one peak on g.l.c. t = 7 min.

Non-2-ene-4,6,8-triyn-1-ol[5](a).-Cuprous chloride (1.2 g., 0.012 mole) was placed in a 250 ml. three-necked flask under oxygen free nitrogen. Hydroxylamine hydrochloride (0.02 g.) was added followed by dimethylformamide (4 ml.), 70% aqueous ethylamine solution (2.0 ml., 0.024 mole) and a solution of diacetylene (4.4 g., 0.88 mole) in dimethylformamide (40 ml.). A solution of 5-bromopent-2-en-4-yn-1-ol (2.0 g., 0.012 mole) in dimethylformamide (4 ml.) was then added and the mixture stirred for 0.5 hr. The complex was decomposed by addition of a solution of potassium cyanide (10 g.) in water (100 ml.) and the solution was extracted with ether (3 x 100 ml.), washed with 2.5 N. HCl (3 x 100 ml.) water (3 x 100 ml.), and dried ($MgSO_4$). The crude product (0.16 g., 10%) showed

λ_{max} 229 (ε26,900), 240 (ε31,500), 257 (ε4,100), 272 (ε4,100), 288 (ε5,000), 306 (ε5,800) and 327 mμ(ε4,500) (U.V. No. 12).

(b) Attempt to Increase Yield of Non-2-en-4,6,8-triyn-1-ol.-Cuprous chloride (1.2 g., 0.012 mole) was placed in a 250 ml. three-necked flask under oxygen free nitrogen. Hydroxylamine hydrochloride (0.02 g.) was added followed by dimethylformamide (4 ml.), 70% aqueous ethylamine solution (2.0 ml., 0.024 mole), and a solution of diacetylene (4.4 g., 0.88 mole) in dimethylformamide (40 ml.). A solution of 5-bromopent-2-en-4-yn-1-ol (2.0 g., 0.012 mole) in dimethylformamide (4 ml.) was then added and the mixture stirred for 0.5 hr.

A second flask was prepared containing cuprous chloride (1.2 g., 0.012 mole), hydroxylamine hydrochloride (0.02 g.) dimethylformamide (4 ml.), 70% aqueous ethylamine solution (2.0 ml., 0.024 mole), and a solution of diacetylene (4.4 g., 0.88 mole) in dimethylformamide (40 ml.) under oxygen free nitrogen. The contents of the first reaction flask were then added to the second (keeping the reaction mixture under oxygen free nitrogen during the transfer) and the reaction mixture stirred for a further 0.5 hr. The complex was decomposed by addition of a solution of potassium cyanide (10 g.) in water (100 ml.). The solution was extracted with ether (3 x 100 ml.), washed with 2.5 N. HCl (3 x 100 ml.), water(3 x 100 ml.) and dried ($MgSO_4$).

The ultra-violet spectrum of the crude product (0.15 g., 10%) was the same as before (a). No improvement in yield was obtained.

(c) Cuprous chloride (4.95 g., 0.05 mole), hydroxylamine hydrochloride (0.02 g.), dimethylformamide (40 ml.) and 70% aqueous ethylamine solution (8.05 ml., 0.1 mole) were placed in a dropping funnel under oxygen free nitrogen and shaken for 0.5 min. The light green suspension was then immediately added in one portion to a solution of diacetylene (13.7 g., 0.27 mole) in dimethylformamide (80 ml.) contained under nitrogen in a 500 ml. three necked flask fitted with stirrer and nitrogen inlet and cooled in an ice bath. A deep red precipitate formed which started to darken in colour almost immediately. After 0.5 min. a solution of 5-bromopent-2-en-4-yn-1-ol (8.05 g., 0.05 mole) in dimethylformamide (30 ml.) was added in one portion and the mixture stirred under nitrogen at 0° for 2 hr. The complex was decomposed by addition of a solution of potassium cyanide (30 g.) in water (150 ml.), extracted with ether (3 x 200 ml.) and the combined extracts washed with water (2 x 100 ml.), 2.5 N. HCl (2 x 100 ml.), water (3 x 200 ml.) and dried ($MgSO_4$). The ultra-violet spectrum of the crude material (2.01 g., 31%) showed peaks clearly defined at λ230, 240, 272, 288, 306 and 328 mμ.

Silver Salt Separation.-The solution was evaporated to 200 ml. (without heating) methanol (100 ml.) added followed by ammoniacle silver nitrate solution* (100 ml.) and the mixture refrigerated for 1 hr. with occasional shaking. The silver salt formed was separated by refrigerated centrifuge at -20° and washed with ether (3 x 100 ml.). It was shock-sensitive and detonated violently if allowed to dry. The solid salt was decomposed by shaking with potassium cyanide (30 g.) in water (200 ml.) and ether (200 ml.). The ether layer was separated and the aqueous layer extracted with ether (2 x 75 ml.). The combined ethereal extracts were washed with water (2 x 50 ml.), dilute HCl (2 x 50 ml.), water (3 x 100 ml.) and dried ($MgSO_4$). The solution contained non-2-ene-4,6,8-triyn-1-ol (1.52 g., 23.5% based on bromopentenynol). λ_{max} 229 (Σ61,000), 240 (Σ86,500), 271.5 (Σ7,100), 288 (Σ13,200), 306.5 (Σ17,000) and 327.5 mμ (Σ12,600) U.V. No. 13) (cf. Jones and Stephenson's values for the naturally occurring product: λ_{max} 229 (Σ60,500), 239.5 (Σ86,500), 271.5 (Σ6,500), 288 (Σ13,000), 306 (Σ17,000) and 327.5 mμ (Σ12,500).

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*See footnote on p. 140;

(+)-Nona-3,4-dien-6,8-diyn-1-ol ((+)-Marasin) with the Dimenthoxyaluminium Hydride Complex.-Lithium aluminium hydride (0.4 g., 0.01 mole) was suspended in ether (100 ml.) and a solution of menthol (3.3 g., 0.02 mole) in ether (10 ml.) added dropwise with stirring at room temperature over 0.5 hr. The reaction mixture was heated under reflux with stirring for 1 hr. and then allowed to cool to room temperature. A solution of non-2-ene-4,6,8-triyn-1-ol (0.3 g., 0.002 mole) in ether (60 ml.) was added and the reaction mixture stirred for 2 hr. at room temperature. The complex was decomposed by adding water dropwise from a burette, followed by dilute sulphuric acid until all the precipitated solid had dissolved. The ether layer was separated and the aqueous layer extracted with ether (2 x 75 ml.), the combined extracts were washed with water (4 x 100 ml.). The solution of the crude product gave λ_{max} 238 (Σ2,000), 250.5 (Σ4,400), 264 (Σ10,100), and 279 mμ (Σ6,100).

Attempts to remove menthol from the marasin by chromatography on Woelm acid alumina (200 g.) deactivated with water (3; 4; 5; and 6 ml.) or on Spence type H alumina (200 g.) deactivated with 10% aqueous acetic acid (2; 4; 6; 8; 10; 15; 20; and 30 ml.) eluting with n-pentane or ether/n-pentane (1/10; 1/8; 1/6; 1/4) were unsuccessful; mixtures were invariably obtained. The following experiment

is typical: the solution of marasin and menthol was repeatedly evaporated to 50 ml. with addition of n-pentane and then chromatographed on Woelm acid alumina (200 g.) deactivated with water (6 ml., 3%) (column wrapped in brown paper). The polarity of the eluting solvent was increased very slowly, the total continuous chromatography taking 54 hr., however, the marasin eluted in fractions 60-69 still contained menthol as shown by g.l.c. (silicone oil 110° menthol t = 9.5 min.).

Counter-Current Distribution.-Attempts were also made to remove the menthol by counter-current distribution using a hand-operated 50 tube (each tube 50 ml.) apparatus. In a typical experiment a small sample (25 ml.) of the solution of marasin and menthol was placed in tube 19 and using water/carbon tetrachloride as the two phases the apparatus was worked by the "steady state method" (upper and lower phases transferred in opposite directions). After forty transfers the marasin (0.005 g.) was found in tubes 16-32 and was shown to be free of menthol by g.l.c. on silicone oil at 110° (menthol t = 9.5 min.).

Attempts to separate the bulk of the marasin solution using carbon tetrachloride/water and ether/butanol/water systems were unsuccessful as marasin was washed from the apparatus before removal of menthol was complete.

(-)-Nona-3,4-dien-6,8-diyn-1-ol ((-)-Marasin) with the Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose Complex (a).-A solution of the slightly impure 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (11.2 g., 0.032 mole) in ether (50 ml.) was added dropwise with stirring to lithium aluminium hydride (1.67 g., 0.044 mole) in ether (50 ml.) and the reaction mixture heated under reflux for 2 hr. The solution was then allowed to cool to room temperature and a solution of non-2-ene-4,6,8-triyn-1-ol (1 g.) in ether (60 ml.) added dropwise and stirring continued for 2 hr. at room temperature. The complex was decomposed by pouring into 10% sulphuric acid (140 ml.) with rapid stirring, ether extracted (3 x 100 ml.), washed with water (3 x 100 ml.) and dried ($MgSO_4$). The ethereal solution was repeatedly evaporated down to 50 ml., n-pentane (100 ml.) added, and again evaporated to 50 ml. The solution was then chromatographed on Woelm acid alumina (200 g.) deactivated with water (6 ml., 3%) and eluted with n-pentane (5 x 400 ml.) and then ether/n-pentane 1/4 (20 x 400 ml.). Marasin (0.098g., 10%) was eluted in fractions 12 to 16 and was detected by ultra-violet scanning of each fraction. Fractions 12 to 16 were combined and evaporated down to 20 ml. and the rotation of the solution found to be $[\alpha]_D^{25}$ -31°(c 0.49 in n-pentane).

Examination of the solution by thin layer chromatography,* showed two spots, R_F 0.25 (blue - monosaccharide derivative) and R_F 0.6 (brown - marasin). The solution was diluted to 50 ml. with n-pentane and rechromatographed on alumina as before. The marasin (0.030 g., 3.2%) solution obtained was examined by t.l.c. and showed two spots, R_F 0.25 (blue) and R_F 0.6 (brown) as before.

(b) Chromatography on Boric Acid-Silica.-Marasin was prepared by the method described in (a). After the chromatography on acid alumina the fractions containing marasin (12-16) were evaporated to 50 ml. and chromatographed on silica (400 g.) impregnated with boric acid (120 ml. of 0.1 M solution) eluted with n-pentane (10 x 100 ml.) Marasin (0.1 g., 10%) was eluted in fractions 4-8. Examination by t.l.c. as before showed two spots R_F 0.25 (blue) and R_F 0.6 (brown).

(c) Attempt to Remove Traces of Monosaccharide by Hydrolysis and Chromatography.-The preparation of marasin was repeated by the method described in (a). Before the chromatography on alumina, however, an attempt was made to hydrolyse the monosaccharide by the following procedure: to the ethereal solution of marasin was added methyl alcohol (100 ml.) and the solution evaporated to 100 ml. without heating. Concentrated hydrochloric acid (60 ml.) was then added

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*Details of thin layer chromatography p.178 .

and the solution stirred for 2 hr. at room temperature. Water (400 ml.) was added, the mixture extracted with ether (5 x 100 ml.), and the combined extracts dried ($MgSO_4$). The solution was then repeatedly evaporated down with n-pentane to 50 ml. and chromatographed on alumina as in (a) to yield pure marasin (0.1 g., 10%) identified by its ultra-violet spectrum: λ_{max} 208 (ε51,000), 224 (ε3,200), 327 (ε5,000), 249.5 (ε8,900), 263 (ε14,100) and 278 mμ (ε12,500), (U.V. No. 15) (cf. ref. 97). On evaporation to 20 ml. t.l.c. as before gave one spot R_F 0.6 (brown). The solution was optically inactive however ($\pm 0.001^{\circ}$).

The above experiment was repeated four times in an attempt to increase the rotation without success. It was concluded that the acid hydrolysis of the monosaccharide was also causing racemisation of the marasin.

(d) Attempt to Purify Marasin by Precipitation as the Silver Salt.-Marasin was prepared by the procedure described in (a) and repeatedly evaporated down to 50 ml. with added methanol. Ammoniacle silver nitrate solution* (75 ml.) was added and the solution refrigerated for 1 hr. with occasional shaking. The precipitated silver salt was separated and washed with ether using a refrigerated centrifuge at -20°. A solution of potassium cyanide (10 g.)

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* See footnote on Page 140.

in water (100 ml.) and ether (100 ml.) was added, the ether layer separated and the aqueous layer extracted with ether (3 x 75 ml.). The combined ethereal extracts were washed with water (2 x 50 ml.), dilute HCl (2 x 50 ml.) and water (3 x 100 ml.) and dried ($MgSO_4$). The ultra-violet spectrum of this solution showed end absorption and a broad band centred on 280 mμ .

(e) A solution of the complex of lithium aluminium hydride with analytically pure 3-O-benzyl-1,2-cyclohexylidene-α-D-glucofuranose was prepared and used to reduce non-2-ene-4,6,8-triyn-1-ol (1 g.) in ether (60 ml.) as described in (a). Chromatography on Woelm acid alumina as previously described in (a) was followed by chromatography on Boric acid-silica as described in (b) to yield a solution of marasin (0.12 g., 12%), λ_{max} 208 (Σ51,000), 224 (Σ3,200) 237 (Σ5,000), 249.5 (Σ8,900), 263 (Σ14,100) and 278 mμ (Σ12,500) (U.V. No. 15); ν_{max} 3,330, 2,220, and 1,960 $cm.^{-1}$; (I.R. No. 12). The solution was evaporated to 20 ml., without heating, and the rotation found to be $[\alpha]_D^{20}$-26.6° (c, 0.6 in n-pentane) (Stanley visual polarimeter). After further evaporation to 2 ml. the rotation was found to be $[\alpha]_D^{20}$-20.301° (c, 0.6 in n-pentane) (Bendix photoelectric polarimeter ±0.001°). This concentrated solution was examined by t.l.c. and gave one spot R_F 0.6 (brown).

Penta-1,3-diyne[17].-1,4-Dichlorobut-2-yne (29.6 g., 0.24 mole) was added dropwise with stirring to a suspension of sodamide in liquid ammonia prepared from sodium (16.56 g., 0.72 g.atom), liquid ammonia (600 ml.) and a crystal of ferric nitrate. After stirring for 0.25 hr., methyl iodide (34.08 g., 0.24 mole) was added dropwise, and the reaction mixture stirred for 3 hr. The solution was then allowed to evaporate to 200 ml. and n-pentane (300 ml.) was cautiously added. The remaining ammonia was then allowed to evaporate from the solution overnight, and this solution then used without further purification for the preparation of dec-2-ene-4,6,8-triyn-1-ol.

Dec-2-ene-4,6,8-triyn-1-ol[20].-Cuprous chloride (1.66 g., 0.016 mole) hydroxylamine hydrochloride (0.02 g.), dimethyl-formamide (40 ml.) and 70% aqueous ethylamine solution (2.8 ml., 0.032 mole) were placed in a dropping funnel under oxygen free nitrogen and shaken for 0.5 min. The light green suspension was then added in one portion to the solution of penta-1,3-diyne prepared in the preceding experiment and contained in a 500 ml. three necked flask fitted with stirrer and nitrogen inlet and cooled in an ice bath. A bright yellow precipitate formed. After 0.5 min. a solution of 5-bromopent-2-en-4-yn-1-ol (8.05 g., 0.05 mole) in dimethyl formamide (30 ml.) was added in

one portion. The mixture was stirred under nitrogen at 0^{o} for 2 hr. The complex was then decomposed by addition of a solution of potassium cyanide (30 g.) in water (150 ml.), extracted with ether (3 x 200 ml.) washed with water (2 x 100 ml.), 2.5 N. HCl (2 x 100 ml.) and water (3 x 200 ml.) and dried ($MgSO_4$). The solution was repeatedly evaporated down to 60 ml. without heating with added n-pentane and chromatographed on Woelm acid alumina (200 g.) deactivated with water (6 ml., 3%) eluted with n-pentane (6 x 400 ml.) and then ether/n-pentane 1/4 (20 x 400 ml.). Fractions 13 to 16 contained dec-2-ene-4,6,8-triyn-1-ol (2.05 g., 28.6% on bromopentenynol) λ_{max} 205 (ε99,500), 230 (ε67,000), 241.5 (ε87,000), 272 (ε6,800), 288.5 (ε12,500), 307.5 (ε17,000), 329 mμ (ε12,000).

(-)-Dec-3,4-diene-6,8-diyn-1-ol ((-)-9-Methylmarasin) [91] with the Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose Complex.-A solution of analytically pure 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (12.36 g., 0.035 mole) in ether (50 ml.) was added dropwise with stirring to a standardised solution of lithium aluminium hydride (0.035 mole) in ether (57.6 ml.) over 0.5 hr. and the reaction mixture heated under reflux for 2 hr. The solution was then allowed to cool to room temperature and dec-2-ene-4,6,8-triyn-1-ol (1.05g., 0.007 mole)

in ether (60 ml.) added over 0.5 hr. and stirring continued at room temperature for a further 2 hr. The complex was decomposed by pouring into 10% sulphuric acid (200 ml.) with rapid stirring, ether extracted (3 x 200 ml.) and the combined extracts washed with water (2 x 50 ml.) and dried ($MgSO_4$). The ethereal solution was repeatedly evaporated down to 60 ml. in vacuo with added n-pentane and chromatographed on Woelm acid alumina (200 g.) deactivated with water (6 ml., 3%) eluted with n-pentane (4 x 400 ml.) and then ether/n-pentane 1/4 (25 x 400 ml.). 9-Methylmarasin was eluted in fractions 19 to 21. These fractions were combined, evaporated to 60 ml. and the solution chromatographed on silica gel (200 g.) impregnated with boric acid (120 ml. of 0.1 M solution) eluted with n-pentane (10 x 100 ml.). Fractions 2 and 3 contained 9-methylmarasin (0.15 g., 10%) λ_{max} 208 (ε56,000), 224.5 (ε3,900), 237 (ε6,500), 250.5 (ε12,100), 264 (ε16,000) and 280 mμ (ε12,900) (U.V. No. 16). The solution was evaporated to 20 ml. and the rotation found to be $[\alpha]_D^{25}$-11.3° (c 0.75, n-pentane). (Stanley visual polarimeter). After further evaporation to 2 ml. the rotation was $[\alpha]_D^{25}$-11.012° Bendix photoelectric polarimeter ±0.001°). Examination of this concentrated solution by t.l.c.* showed one spot R_F 0.6 (brown).

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*Details of thin layer chromatography p. 178.

7-Phenylhept-2-en-4,6-diyn-1-ol.-Cuprous chloride (1.65 g., 0.016 mole), hydroxylamine hydrochloride (0.02 g.), dimethylformamide (20 ml.) and 70% aqueous ethylamine solution (2.68 ml., 0.033 mole) were placed in a dropping funnel under oxygen free nitrogen and shaken for 0.5 min. The light green suspension was then added in one portion to a solution of phenylacetylene (10.2 g., 0.1 mole) in dimethylformamide (40 ml.) under nitrogen at 0°. A bright yellow precipitate formed. After 0.5 min. a solution of 5-bromopent-2-en-4-yn-1-ol (8.05 g., 0.05 mole) in dimethylformamide (30 ml.) was added in one portion. The solution turned a light green colour. The mixture was stirred under nitrogen at 0° for 2.5 hr. and the complex then decomposed by addition of a solution of potassium cyanide (30 g.) in water (150 ml.), extracted with ether (3 x 200 ml.), washed with water (2 x 200 ml.) and dried ($MgSO_4$). The solution was repeatedly evaporated to 50 ml. with added n-pentane and chromatographed on Spence type H alumina (100 g.) deactivated with 10% aqueous acetic acid (5 ml.), eluted with n-pentane (4 x 400 ml.) and then ether/n-pentane 1/4 (6 x 400 ml.). 1,4-Diphenyldiacetylene, having infra-red spectrum identical to an authentic sample was eluted in fraction 1. Fraction 5 gave 7-phenylhept-2-en-4,6-diyn-1-ol (5.8 g., 70%) λ_{max} 210 (Σ55,000), 230 (Σ37,800),

240 (Σ36,000), 252 (Σ27,000), 265 (Σ15,000), 299 (Σ31,800) and 319 mμ (Σ25,600) (U.V. No. 17).

(-)-7-Phenylhepta-3,4-dien-6-yn-1-ol with the Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose Complex.-A solution of analytically pure 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (8.5 g., 0.024 mole) in ether (25 ml.) was added dropwise with stirring over 0.5 hr. to a standardised solution of lithium aluminium hydride (0.024 mole) in ether (41 ml.) and the reaction mixture heated under reflux with stirring for 2 hr. The solution was then allowed to cool to room temperature and a solution of 7-phenylhept-2-en-4,6-diyn-1-ol (0.9 g., 0.005 mole) in ether (50 ml.) added over 0.5 hr. and stirring continued for 2 hr. at room temperature. The complex was then decomposed by pouring into 10% sulphuric acid (200 ml.) with rapid stirring, and ether extracted (3 x 100 ml.). The combined extracts were washed with water (3 x 50 ml.) and dried ($MgSO_4$). The ethereal solution was repeatedly evaporated to 50 ml. with added n-pentane and chromatographed on Spence type H alumina (100 g.) deactivated with 10% aqueous acetic acid solution (5 ml.) eluted with n-pentane (4 x 200 ml.) and then ether/n-pentane 1/4 (6 x 200 ml.). Ultra-violet scanning of each fraction

showed that 7-phenylhepta-3,4-dien-6-yn-1-ol was eluted in fractions 8 to 10. These were combined and evaporated without heating to 60 ml. and chromatographed on silica gel (200 g.) impregnated with boric acid (60 ml. of 0.1 M solution). 7-Phenylhepta-3,4-dien-6-yn-1-ol (0.13 g., 14.4% on 7-phenylhept-2-ene-4,6-diyne-1-ol) having λ_{max} 205 (Σ41,500), 257 (Σ13,600), 273.5 (Σ19,300), 288 mμ (Σ14,800) λ_{sh} 218 mμ (Σ29,000) (U.V. No. 18) and ν_{max} 3,300 m (OH) and 1,950 m (C=C=C) (I.R. No. 13). The solution was evaporated to 20 ml. and the rotation found to be $[\alpha]_D^{25}$ -3.1° (c 0.65, n-pentane) (Stanley visual polarimeter). After further evaporation to 2 ml. the rotation was found to be $[\alpha]_D^{20}$ -2.805° (Bendix photo-electric polarimeter ±0.001°). This concentrated solution gave one spot on t.l.c. R_F 0.75 (yellow).

<u>(-)-8,8-Dimethylnona-3,4-dien-6-yn-1-ol with the Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose Complex</u>.-A solution of analytically pure 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (9 g., 0.026 mole) in ether (50 ml.) was added dropwise with stirring over 0.5 hr. to a standardised solution of lithium aluminium hydride (0.026 mole) in ether (62.5 ml.) and the reaction mixture heated under reflux with stirring for 2 hr. The solution was allowed to cool to room temperature, a

solution of 8,8-dimethylnon-2-ene-4,6-diyn-1-ol (1.67 g., 0.01 mole) (preparation, p. 139) in ether (50 ml.) added over 0.5 hr. and stirring continued at room temperature for 2 hr. The complex was then decomposed by pouring into 10% sulphuric acid (200 ml.) with rapid stirring, and ether extracted (3 x 150 ml.). The combined extracts were washed with water (2 x 50 ml.) and dried ($MgSO_4$). Ether was removed and the residual yellowish oil distilled to give 8,8-dimethylnona-3,4-dien-6-yn-1-ol (0.55 g., 32%) b.p. 79°/2 x 10^{-3} mm. λ_{max} 219 (ε14,690), (U.V. No. 19); ν_{max} 3,300 m (OH) 2,200 w (C≡C) and 1,600 w (C=C=C) (I.R. No. 14). (Found C, 80.51; H, 9.80 $C_{11}H_{16}O$ requires C, 80.60; H, 9.82%); $[\alpha]_D^{25}$ -12.5° (neat) (Stanley visual polarimeter).

(-)-Hexa-3,4-dien-1-ol (Monosaccharide added at end of Reaction).-A solution of hex-2-en-4-yn-1-ol (1.0 g., 0.01 mole) in ether (50 ml.) was added dropwise over 0.5 hr. at room temperature, with stirring to a standardised solution of lithium aluminium hydride (0.015 mole) in ether (59.0 ml.) and the reaction mixture heated under reflux for 2 hr. A solution of analytically pure 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (5.3 g., 0.015 mole) in ether (50 ml.) was then added dropwise over 0.5 hr. and the refluxing continued for a further 2 hr. The complex

was then decomposed by pouring into 10% sulphuric acid (150 ml.), ether extracted (3 x 100 ml.) washed with water (2 x 50 ml.) and dried ($MgSO_4$). Solvent was removed and the material distilled to give hexa-3,4-dien-1-ol (0.4 g., 40%) $[\alpha]_D^{25}$ -8.2° (neat) b.p. 60°/4 mm. having infra-red spectrum identical with an authentic sample ν_{max} 3,340 s (OH), 1,960 w (C=C=C) and 1,040 $cm.^{-1}$ (cf. I.R. No. 17). The compound was shown to be free of monosaccharide derivatives by examination on t.l.c.

Claisen Rearrangement

1-Chloroethyl but-1-yn-3-yl ether.-[56] A mixture of but-1-yn-3-ol (28.0 g., 0.40 mole) and freshly distilled acetaldehyde (8.8 g., 0.20 mole) was added dropwise with stirring to boron trichloride (31.2 g., 0.27 mole) cooled to -15° in an ice salt bath. After stirring for 3 hr. at -15° the reaction mixture was allowed to warm to room temperature and left to stand for 2 days. The product was distilled in vacuo (1 mm.), using a 12 cm. column packed with Fenske rings to give 1-chloroethyl but-1-yn-3-yl ether (9.5 g., 36%) b.p. 64-68°/120 mm. ν_{max} 3,320 (C≡C) 2,130 (C≡C), 1,135 (C-O-C)(I.R. No. 15.)

Hexa-3,4-dienal and Hexa-2,4-dienal.- 1-Chloroethyl but-1-yn-3-yl ether (0.3 ml.) was injected into a stream of nitrogen passing through an electrically heated glass tube clamped vertically and packed with glass wool at 200°. The pyrolysis products having ν_{max} 3,300 (C≡C-H), 2,112 (C≡CH), 1,960 (C=C=C) (I.R. No. 16) and λ_{max} 228 (Σ23,000) and 271 mμ (Σ12,000) (U.V. No. 20) were collected in a trap at -60° and contained approximately 50% of hexa-3,4-dienal and 50% of hexa-2,4-dienal.*

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*From absorption coefficient; pure hexa-2,4-dienal has λ_{max} 271 mμ (Σ25,000).[80]

Hexa-3,4-dien-1-ol.-The mixture of aldehydes resulting from the pyrolysis of 1-chloroethyl but-1-yn-3-yl ether (1.5 g.) was rapidly transferred to a solution of lithium aluminium hydride (2 g.) in ether (30 ml.) and stirred at room temperature overnight. Excess lithium aluminium hydride was decomposed by the dropwise addition of water, the ether layer separated and the aqueous layer extracted with ether (2 x 50 ml.). The combined ether extracts were evaporated to 5 ml., 40-60° petroleum ether (10 ml.) added and the solution chromatographed on Spence type H alumina (100 g.), deactivated with acetic acid (10 ml. of 10% aqueous solution). Elution with ether/40-60° petroleum ether (1/4) (12 x 100 ml.) gave hexa-3,4-dien-1-ol (0.4 g., 26%) in fraction 9. ν_{max} 3,350 (OH) 1,960 (C=C=C) (I.R. No. 17) identical with the infra-red spectrum of an authentic sample.

(+)-Hexa-3,4-dien-1-ol.-The procedure given in the preceeding three experiments was repeated starting with (-)-but-1-yn-3-ol $[\alpha]_D^{20}$-5.3°. Reaction of this with acetaldehyde in the presence of boron trichloride as before gave (-)-1-chloroethyl but-1-yn-3-yl ether $[\alpha]_D^{20}$-44.5°. Pyrolysis of this and reduction of the unstable allenic aldehyde, followed by chromatography of the alcohol as before gave (+)-hexa-3,4-dienol $[\alpha]_D^{20}$+5.3°.

Resolution of But-1-yn-3-ol[127]

But-1-yne-3-hydrogenphthalate.-But-1-yn-3-ol (28 g., 0.4 mole) and recrystallised phthalic anhydride* (88.8 g., 0.60 mole) were placed in a conical flask and ice cold 10% sodium hydroxide solution (240 ml., 0.6 mole) was added in three portions with vigorous shaking. The reaction mixture became warm and after shaking for a further 5 minutes was transferred to a beaker and carefully rendered acid by the addition of 5 N hydrochloric acid. The crude phthalate separated as an oil, and on extraction with chloroform (200 ml.) phthalic acid (12 g.,) was precipitated. After filtration the chloroform layer was separated, dried ($MgSO_4$) evaporated in vacuo and the crude phthalate recrystallised from chloroform/40-60° petroleum ether giving a small residue of phthalic acid and but-1-yne-3-hydrogenphthalate (67 g., 77%) m.p. 92°.

Brucine Salt of But-1-yne-3-hydrogenphthalate.- Anhydrous brucine (157 g., 0.4 mole) was added to a solution of but-1-yn-3-hydrogenphthalate (86.1 g., 0.4 mole) in acetone (1,150 ml.), the mixture refluxed for 3 hr. and allowed to cool. No crystallisation occurred. Acetone (300 ml.) was distilled off and the solution again cooled

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*Recrystallised from chloroform.

when heavy crystallisation occurred. A small sample of the crystals were debasified (cf. next experiment) and the phthalate (20% solution in ether) examined in the polarimeter and found to be optically inactive. The bulk of the brucine salt was therefore again recrystallised from acetone* until a small sample when debasified produced but-1-yne-3-hydrogenphthalate $[\alpha]_D^{20}+5.3^\circ$ (c 4.3 in ether). The bulk of the brucine salt (49 g.) was then debasified.

Debasification of the Brucine Salt of (+)-but-1-yne-3-hydrogenphthalate.-The brucine salt of (+)-but-1-yne-3-hydrogenphthalate (49 g.) was shaken with hydrochloric acid (100 ml., 2.5 N) and ether (400 ml.), and the ether layer separated and dried ($MgSO_4$). Ether was removed in vacuo and the crude but-1-yne-3-hydrogenphthalate recrystallised from chloroform/40-60° petroleum ether (1/4) giving a small residue of phthalic acid and (+)-but-1-yne-3-hydrogenphthalate (8.1 g., 45%) m.p. 91° $[\alpha]_D^{20}+5.3^\circ$ (c 3.4 in ether).

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*It was found difficult to obtain the right conditions to precipitate the brucine salt of (+)-but-1-yne-3-hydrogenphthalate the first time. In subsequent preparations, however, the solution was seeded with the optically active salt and no trouble was experienced.

Recovery of Brucine.-The acid solution from hydrolysis was made alkaline by the addition of potassium hydroxide solution and the precipitated brucine filtered and washed with water. After drying in a dessicator for one week the brucine hydrate was dissolved in benzene and the water separated by azeotropic distillation using a Dean and Stark apparatus. On removal of 70% of the benzene by distillation the anhydrous brucine crystallised on cooling. Recovery was 85%.

(-)-But-1-yn-3-ol from (+)-But-1-yne-3-hydrogenphthalate.- But-1-yn-3-hydrogenphthalate (25 g., 0.1 mole) was dissolved in 40% sodium hydroxide solution (25 ml., 0.25 mole) and continuously extracted with ether for 48 hr. The ether layer was removed, dried ($MgSO_4$), and the solvent removed by distillation. Distillation of the residue gave (-)-but-1-yn-3-ol (4.0 g., 47%) b.p. $50^{\circ}/120$ mm.

$[\alpha]_D^{20}$ -5.3° (neat) ν_{max} 3,300 (OH) 2,130 cm.$^{-1}$ (C≡C).

Reduction of Acetophenone with the Lithium Aluminium Hydride-Active Amyl Alcohol Complex.-Active amyl alcohol (5.3 g., 0.06 mole) was added dropwise over 0.5 hr. to a standardised solution of lithium aluminium hydride (0.03 mole) in ether (120 ml.) and the resulting solution heated under reflux for 2 hr. Acetophenone (1.2 g., 0.01 mole) in dry ether (10 ml.) was then added, the solution refluxed for a further 2 hr., allowed to cool to room temperature, poured into 10% sulphuric acid, and ether extracted (3 x 50 ml.). After drying ($MgSO_4$) and removal of ether, the residue was distilled using a spinning band column. 1-Phenylethyl alcohol (1.0 g.) b.p. $74^{\circ}/10$ mm. was obtained. G.l.c. on silica at 110° showed two peaks t = 7 minutes (amyl alcohol 10%) and t = 12 minutes (1-phenylethyl alcohol 90%). The mixture of alcohols was added to a mixture of n-pentane (30 ml.) and ether (5 ml.) and washed with water for 48 hr. on a continuous extraction apparatus. Evaporation of solvent gave 1-phenylethyl alcohol (0.8 g.) identical with an authentic sample. The compound was examined on visual and photoelectric polarimeters ($\pm 0.001^{\circ}$) and found to be optically inactive.

3-Tetrahydropyranyloxyprop-1-yne.-Concentrated hydrochloric acid (1.1 ml.) was added to propargyl alcohol (56.0 g., 1.0 mole) and 2,3-dihydropyran (109 g., 1.3 mole), with ice cooling, the mixture allowed to warm to room temperature with stirring over 1 hr. and then heated at 70° in a water bath for 2 hr. Ether (100 ml.) was added and the resulting solution washed with saturated sodium hydrogen carbonate solution (50 ml.), water (50 ml.), dried and the solvent removed in vacuo. The residue was distilled to give 3-tetrahydropyranyloxyprop-1-yne (120 g., 86%) b.p. 90°/29 mm. ν_{max} 3,300 and 2,110 cm.$^{-1}$ (C≡CH).

1-Tetrahydropyranyloxyhept-2-yn-4-ol.- 3-Tetrahydropyranyloxyprop-1-yne (120 g., 0.86 mole) dissolved in dry tetrahydrofuran (120 ml.) was added dropwise, with ice cooling, to ethylmagnesium bromide (prepared under nitrogen from ethyl bromide (98 g., 0.90 mole), magnesium (21.8 g., 0.90 g. atom), and dry tetrahydrofuran, (300 ml.)). After stirring for 1.5 hr., n-butyraldehyde (67.7 g., 0.94 mole) dissolved in dry tetrahydrofuran (60 ml.) was added dropwise to the reaction mixture at 0°. Stirring was continued for 3 hr., then the ice bath was removed and the stirring continued at room temperature overnight. The mixture was then poured into saturated ammonium chloride solution (200 ml.), ether extracted (4 x 100 ml.), washed

with saturated sodium chloride solution (2 x 50 ml.), and dried. Solvent was removed in vacuo and the residue distilled to give 1-tetrahydropyranyloxyhept-2-yn-4-ol (108 g., 60%), b.p. 136-140°/4 mm. (I.R. No. 18).

4-Chloro-1-Tetrahydropyranyloxyhept-2-yne.-Thionyl chloride (80.0 g., 0.63 mole) was added dropwise over 1 hr. to a stirred mixture of 1-tetrahydropyranyloxyhept-2-yn-4-ol (117.9 g., 0.56 mole), dry pyridene (53.0 g., 0.63 mole) and dry ether (150 ml.) cooled to 0°. The mixture was stirred to room temperature for 3 hr. and left to stand over the weekend. The mixture was then washed with water (100 ml.), dilute hydrochloric acid (100 ml.), saturated sodium hydrogen carbonate solution (100 ml.), dried, the solvent removed and the residue distilled to give 4-chloro-1-tetrahydropyranyloxyhept-2-yne (85.0 g., 70%), b.p. 110-115/1.5 mm. ν_{max} 700 cm.$^{-1}$ (C-Cl) (I.R. No. 19).

4-Chlorohept-2-yn-1-ol.- 4-Chloro-1-tetrahydropyranyl-oxyhept-2-yne (30 g., 0.8 mole) in absolute methanol (60 ml.) and concentrated hydrochloric acid (3 ml.) was refluxed for 3 hr. After cooling the mixture was added to water (200 ml.), the aqueous layer extracted with ether (3 x 40 ml.), the combined organic layers treated with potassium carbonate, dried, and the solvent removed.

Distillation of the residue gave 4-chlorohept-2-yn-1-ol (7 g., 60%), b.p. 70°/1 mm. (Found C, 57.49; H, 7.60% $C_7H_{11}OCl$ requires C 57.40 H 7.56%). ν_{max} 3,300 (OH) 700 cm.$^{-1}$ (C-Cl) (I.R. No. 20).

3-Tetrahydropyranyloxyhex-1-yne.-Concentrated hydrochloric acid (0.6 ml.) was added to hex-1-yn-3-ol (50.0 g., 0.51 mole) and 2,3-dihydropyran (59.5 g., 0.71 mole), with ice cooling, the mixture stirred for 2 hr. and allowed to warm to room temperature. The mixture was then heated at 70° for 2 hr., ether (100 ml.) was added, the resulting solution was washed with saturated sodium hydrogen carbonate solution (50 ml.), water (50 ml.), dried ($MgSO_4$), the solvent removed and the residue distilled to give 3-tetrahydropyranyloxyhex-1-yne (66.8 g., 78%), b.p. 70-75°/3 mm. ν_{max} 3,300 (C≡CH), 2,100 cm.$^{-1}$ (C≡C) (I.R. No. 21).

4-Tetrahydropyranyloxyhept-2-yn-1-ol.- 3-Tetrahydropyranyloxyhex-1-yne (66.8 g., 0.34 mole) in dry tetrahydrofuran (60 ml.) was added dropwise with stirring and ice cooling to ethylmagnesium bromide (prepared under nitrogen from ethyl bromide (43.0 g., 0.4 mole), magnesium (9.0 g., 0.4 g. atom) and dry tetrahydrofuran (200 ml.). The reaction mixture was allowed to warm to room temperature and formaldehyde gas, generated by heating paraformaldehyde

(18.0 g.), was passed through a heated glass tube onto the surface of the well stirred reaction mixture. Stirring was continued overnight, and the reaction mixture was poured into saturated ammonium chloride solution, ether extracted, and dried. The solvent was removed and the residue distilled to give 4-tetrahydropyranyloxyhept-2-yn-1-ol (55.0 g., 70%) b.p. 140°/3 mm. (Found, C, 67.73; H, 9.67 $C_{12}H_{20}O_3$ requires C, 67.80; H, 9.48%) ν_{max} 3,400 (OH) 2,200 cm.$^{-1}$ (-C≡C-) (I.R. No. 22).

4-Tetrahydropyranyloxyhept-2-ynyl Acetate.-A mixture of acetic anhydride (23.4 g., 0.23 mole), and dry pyridene (18.2 g., 0.23 mole), was added to 4-tetrahydropyranyloxyhept-2-yn-1-ol (45.7 g., 0.23 mole) at 0°. The resulting solution was heated at 70° for 3 hr., diluted with ether (200 ml.), washed with dilute hydrochloric acid (3 x 50 ml.), water (3 x 50 ml.), saturated sodium hydrogen carbonate solution (3 x 50 ml.), dried, and the solvent removed. The residue was distilled to give 4-tetrahydropyranyloxyhept-2-ynyl acetate (33 g., 60%) b.p. 135-140°/3 mm. (Found C, 65.97; H, 8.70; $C_{14}H_{22}O_4$ requires C, 66.1; H, 8.72%) ν_{max} 2,240 (-C≡C-) 1,760 cm.$^{-1}$ (C=O) (I.R. No. 23).

1-Acetoxyhept-2-yn-4-ol.- 4-Tetrahydropyranyloxyhept-2-ynyl acetate (35.2 g., 0.15 mole) and 5 N hydrochloric acid

(100 ml.), were mechanically shaken for 0.5 hr., extracted several times with ether, the combined ether extracts dried and the solvent removed. Distillation of the residue gave 1-acetoxyhept-2-yn-4-ol (12.0 g., 47%) b.p. 119°/4 mm.

4-Chlorohept-2-ynyl Acetate.-Redistilled thionyl chloride (8.33 g., 0.07 mole) was added dropwise with stirring, to a mixture of 1-acetoxyhept-2-yn-4-ol (11.6 g., 0.07 mole), dry pyridine (5.5 g., 0.07 mole) and anhydrous ether (50 ml.) cooled in ice. Stirring was continued for 1 hr. and the mixture left overnight. Pyridinium chloride was filtered off, washed with ether, and the filtrate washed with dilute hydrochloric acid (3 x 50 ml.), water (3 x 50 ml.), saturated sodium hydrogen carbonate solution (2 x 50 ml.), dried and the solvent removed to give 4-chlorohept-2-ynyl acetate (11.7 g., 70%) ν_{max} 2,210 (-C≡C-), 1,750 cm.$^{-1}$ (C=O) (I.R. No. 24).

Reduction of 4-Chlorohept-2-yn-1-ol with the Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose Complex (a).- 4-Chlorohept-2-yn-1-ol (1.46 g., 0.01 mole) in ether (10 ml.) was added as rapidly as possible to the lithium aluminium hydride-monosaccharide complex (prepared from lithium aluminium hydride (0.01 mole) in ether (93.5 ml. standardised) and 3-O-benzyl-1,2-O-

cyclohexylidene-α-D-glucofuranose (3.5 g., 0.01 mole) by the method described on p. 153) at room temperature and stirred for 0.5 hr. The complex was decomposed by the dropwise addition of water, filtered, ether extracted and dried. The solution on g.l.c. on silica at 70° gave solvent peaks and a single peak at t = 7.5 minutes. Removal of solvent from the bulk of the solution and distillation of the residue gave hepta-2,3-dien-1-ol (1.0 g., 89%) b.p. 60°/20 mm. (Found C, 74.5; H, 10.8; $C_7H_{12}O$ requires C, 74.90: H, 10.78%). ν_{max} 3,350 (OH) 1,970 cm.$^{-1}$ (-C=C=C-) (I.R. No. 25). The compound was optically inactive (±0.001°).

(b).-The above reduction was repeated at -40° for 10 min. After decomposition of the complex as in (a), g.l.c. on the ether solution on silica at 70° gave solvent peaks and a single peak at t = 7.5 minutes. Removal of solvent and distillation of the residue gave the optically inactive hepta-2,3-dien-1-ol as in (a).

(c).-The reaction was again repeated using 4-chlorohept-2-yn-1-ol (2.92 g., 0.02 mole) and lithium aluminium hydride-monosaccharide complex (0.01 mole prepared as in (a)). After decomposition of the complex as in (a), g.l.c. on the ethereal solution as before showed solvent peaks, a peak at t = 7.5 minutes (hepta-2,3-dien-1-ol) and a peak at t = 11 minutes. Fractionation gave hepta-2,3-dien-1-ol b.p. 60°/20 mm. and 4-chlorohept-2-yn-1-ol as residue

identified by its infra-red spectrum. The hepta-2,3-dien-1-ol was optically inactive ($\pm 0.001^{\circ}$).

Reduction of 4-Chlorohept-2-ynyl Acetate with the Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose Complex.- 4-Chlorohept-2-ynyl acetate (3.6 g., 0.02 mole) in ether (10 ml.) was added as rapidly as possible to the lithium aluminium hydride-monosaccharide complex (prepared from lithium aluminium hydride (0.017 mole) in ether (56.6 ml. standardised) and 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (5.9 g., 0.017 mole) by the method described on p. 153). After decomposition of the complex and work up as in (a) (p. 175), g.l.c. on silica at 70° gave solvent peaks, a peak at t = 7.5 minutes (hepta-2,3-dien-1-ol) and a peak at t = 8 minutes (4-chloro-hept-2-ynyl acetate). Fractionation gave pure hepta-2,3-dien-1-ol (0.9 g., 40%) b.p. $60^{\circ}/20$ mm. identified by its infra-red spectrum. This material had $[\alpha]_D^{25} = +1.6^{\circ}$ (neat).

The Isolation and Identification of Trace Impurities in 3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose and the Preparation of the Pure Compound.

Preparation and use of Thin Layer Chromatography Plates.- Silica gel* (30 g.,) was made into a paste with distilled water (60 ml.) and spread on five 20 x 20 cm. plates to a thickness of 250 μ . The solution of the monosaccharide in chloroform or ether was applied using a glass capilliary and the solvent allowed to evaporate from the spot before placing the plate in the development solvent (2% methanol in benzene). After development (a 10 cm. run was used in all cases) the plates were sprayed with a 0.2% solution of naphthoresorcinol in ethanol to which 0.1 volume of phosphoric acid had been added for every volume of ethanol. The plates were then placed in an oven at 110° for 15 minutes when the monosaccharides showed up as blue spots.

Determination of Minimum Quantity of Monosaccharide Detectable.-The impure monosaccharide (5 g.) was dissolved in chloroform and made up to 10 ml. in a standard flask. 1 ml. of this solution was diluted with chloroform to 10 ml. in a second standard flask. Repetition of this procedure gave a range of solutions of concentrations

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*"Kieselgel G" - suppliers: E. Merck AG., Darmstadt.

ranging from 0.5 g./ml. to 0.0005 g./ml. These were applied to a t.l.c. plate, developed and sprayed. The monosaccharide could just be detected as a blue smudge on the solution of strength 0.0005 g./ml. On application of allenyne solutions to t.l.c. plates, several spots (up to 10) were superimposed so as to increase the sensitivity.

1,2:5,6-Di-O-Cyclohexylidene-α-D-Glucofuranose.-[84]

Cyclohexanone (400 ml., 4.0 mole) was placed in a 1 l. flask cooled in an ice bath and concentrated sulphuric acid (26 ml.) added over 10 minutes with rapid stirring. This was immediately followed by the rapid addition of D-glucose (180 g., 1.0 mole). The mixture was allowed to warm up to room temperature over 1 hr. with stirring and stirring continued until the mixture solidified (ca 6 hr.). n-Heptane (600 ml.) was added and the mixture heated in a water bath to 80° when two layers formed. The lower dark coloured layer was separated and rejected and the upper n-heptane layer refrigerated overnight when heavy crystallisation occurred. The crystals were removed by filtration, dissolved in the minimum volume of near boiling n-heptane and the solution washed with hot water (5 x 200 ml. at 60°) and dried ($MgSO_4$). Refrigeration of the n-heptane layer overnight gave 1,2:5,6-di-O-cyclohexylidene-α-D-

glucofuranose as white crystals, (272 g., 80%) m.p. 132° giving one spot on t.l.c. R_F 0.20.

3-O-Benzyl-1,2:5,6-Di-O-Cyclohexylidene-α-D-Glucofuranose.- Potassium hydroxide (74 g.) was added to freshly redistilled benzyl chloride (110 ml.) followed by 1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose (32 g., 0.09 mole) with stirring, and the temperature of the reaction mixture increased to 150° over 1.5 hr. The temperature was maintained at 150° and a small sample of the reaction mixture withdrawn at intervals of 1 hr. and examined by t.l.c. After 4.0 hr. only one spot, R_F 0.95, was obtained, and the reaction mixture was allowed to cool to room temperature. The organic layer was separated from solid inorganic salts. Water (150 ml.) was then added to dissolve the inorganic salts and the resulting solution extracted with chloroform (3 x 50 ml.). The organic layer and chloroform extracts were combined and dried ($CaCl_2$). Chloroform and benzyl chloride were then distilled off to leave a light amber coloured viscous oil (43 g.). Distillation of this on a mercury vapour pump gave 3-O-benzyl-1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose as a brittle glass, (30 g., 82%) b.p. 190-195°/ 2 x 10^{-3} mm. $[\alpha]_D^{20}$ -17.4° (C 19.68 in $CHCl_3$), (Found: C, 69.7; H, 7.8 $C_{25}H_{34}O_6$ requires C, 69.7; H, 7.9%); t.l.c. gave one component R_F 0.95. (I.R. No. 27).

3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose.- 3-O-Benzyl-1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose (16 g.) was added to acetic acid (62 ml. of 75% v.v) and the solution heated to 70-80° in a water bath with stirring. Small samples were withdrawn at intervals of 0.5 hr. and examined by t.l.c. After 3.0 hr. blue spots showed at R_F 0.95 (light), R_F 0.25 (heavy), and R_F 0.0 (faint). After 4.0 hr. t.l.c. showed spots as follows: R_F 0.95 (faint), R_F 0.25 (heavy), R_F 0.0 (light). The reaction mixture was cooled, water (50 ml.) added and chloroform extracted (5 x 75 ml.). The combined chloroform extracts were shaken with saturated sodium hydrogen carbonate solution till no further effervescence was observed, washed with hot water (60°, 4 x 100 ml.), and dried ($MgSO_4$). Removal of chloroform and distillation of the residue gave 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (9.8 g., 75%) as a pale coloured very viscous oil, b.p. 195-200°/5 x 10^{-3} mm. (Found: C, 66.0; H, 7.8 $C_{19}H_{26}O_6$ requires C, 65.1; H, 7.4%). T.l.c. showed one main component at R_F 0.25 and a minor component at R_F 0.95.

Analytically pure 3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose (cf. p. 104).-The slightly impure monosaccharide (40 g.) was stirred for 2 hr. with chloroform/n-heptane

1/20 (200 ml.). A portion of the monosaccharide remained undissolved. After refrigerating overnight the solvent was removed by decanting and the remaining oil washed with n-heptane (2 x 50 ml.) by decanting and distilled to give 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (11.5 g., 29%) b.p. $200^{\circ}/5 \times 10^{-3}$ mm. $[\alpha]_D^{20} -34.8^{\circ}$ (C 4.3 in $CHCl_3$). (Found: C, 65.3; H, 7.6 $C_{19}H_{26}O_6$ requires C, 65.1; H, 7.4%) as a pale yellow brittle glass (I.R. No. 28).

Identification of Trace Impurities in 3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose.-Preparative t.l.c. plates (20 x 40 cm.) were prepared as previously described (p. 178). The impure monosaccharide (5 g.) was dissolved in chloroform (30 ml.), the whole of this solution applied to ten t.l.c. plates using an automatic applicator* and the plates eluted with 2% methanol in benzene. The bands were located at R_F values 0.00; 0.20; 0.25; and 0.95 by spraying just the ends of the plates, then each band was removed, the silica slurried with chloroform to dissolve the monosaccharide and the silica removed by filtration. Evaporation of the chloroform afforded the monosaccharide. Earlier work had inferred that the impurities were benzylated

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*Supplied by Desaga Ltd.

glucose derivatives (cf. p. 101).

(a) Band at R_F 0.00.-The infra-red spectrum of this material showed a strong band at 3,400 cm.$^{-1}$ (OH) (I.R. No. 29) and the low R_F value indicated more than two -OH groups.* Analysis gave C, 57.56; H, 6.97%. These facts are best accounted for if the material at R_F 0.00 is 3-O-benzyl-glucose (requires C, 56.40 H, 6.61).

(b) Band at R_F 0.25.-The infra-red spectrum of this material showed extremely weak absorbance in the 3,400 cm.$^{-1}$ region (I.R. No. 30) and the R_F value indicated that less than two hydroxyl groups were present.** Analysis gave C, 70.90; H, 7.69%. These facts are best accounted for if the material at R_F 0.25 is a di-O-benzylated-1,2-O-cyclo-hexylidene glucose derivative (requires C, 70.20; H, 7.24%). An example is shown on page 106, but the position of the free -OH group cannot be definitely decided.

(c) Band at R_F 0.95.-The infra-red spectrum of this material showed no absorbance in the 3,400 cm.$^{-1}$ region(I.R.No.31) indicating a complete absence of hydroxyl groups, a

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*By comparison with analytically pure 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose of R_F 0.20.

**By comparison with analytically pure 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose of R_F 0.20.

conclusion supported by the high R_F value.* Analysis gave C, 72.88; H, 7.63%. These facts are best accounted for if the material at R_F 0.95 is a mixture of 3-O-benzyl-1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose (requires C, 69.70; H, 7.90%.) and 3,5,6-tri-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (requires C, 73.8; H, 7.14%).

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*By comparison with analytically pure 3-O-benzyl-1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose of R_F 0.95.

Propargyl Aldehyde.[130,131] A solution of chromium trioxide (105 g.), concentrated sulphuric acid (68 ml.) and water (165 ml.) was added dropwise to a mixture of concentrated sulphuric acid (68 ml.), water (100 ml.) and propargyl alcohol (60 g., 1.07 mole) cooled in an ice bath. During the addition, the reaction flask was evacuated to 50-20 mm. pressure by a vacuum pump connected via two traps at -60° in series. A mixture of propargyl aldehyde, water, and propargyl alcohol collected in the traps. The total trap contents were fractionated using a 25 cm. column filled with Raschig rings, to give propargyl aldehyde (21 g.) b.p. 54-55°/760 mm. from which all the propargyl alcohol and most of the water had been removed. Drying ($CaCl_2$) gave pure propargyl aldehyde (18.0 g., 31%), ν max 3,320, 2,130 (C≡C-H) 1,700 (C=O) (I.R. No. 2).

Bromopropargyl Alcohol.-Bromine (11 ml., 0.2 mole) was added dropwise to sodium hydroxide (50 ml. 1 ON.) and ice (100 g.) cooled in an ice bath and stirred at 0° for 0.5 hr. The sodium hypobromite solution so formed was added dropwise over 3 hr. to propargyl alcohol (11.2 g., 0.2 mole) cooled in an ice bath and stirred for 1 hr. The mixture was then extracted with chloroform (3 x 100 ml.) and dried ($MgSO_4$). Evaporation of solvent gave bromopropargyl

alcohol* (11.5 g., 48%) ν_{max} 3,360 (OH), 2,260 cm.$^{-1}$ (R-C≡C-R). (I.R. No. 3).

Bromopropargylaldehyde.-A solution of chromium trioxide (4.2 g.) and concentrated sulphuric acid (2.7 ml.) in water (20 ml.) was added dropwise to a stirred mixture of bromopropargyl alcohol (5.0 g.), concentrated sulphuric acid (2.6 ml.) and water (9.0 ml.), cooled in an ice salt bath. During the addition the reaction flask was evacuated to 4 mm. pressure and nitrogen bubbled through the reaction mixture. Bromopropargylaldehyde (0.6 g., 11%) was collected by means of a trap cooled to -60°, and dried ($MgSO_4$). ν_{max} 2,200 (RC≡CR), 1,680 (C=O) and 685 cm.$^{-1}$ (C-Br) (I.R. No. 4).

2,3-Dibromopropanaldehyde Diethyl Acetal.-^{128}Bromine (32.0 g., 0.4 mole) was added dropwise with ice cooling to redistilled acrolein (11.0 g., 0.2 mole) in chloroform (50 ml.) and the reaction mixture stirred for 1 hr. Solvent was removed in vacuo and the residue distilled to give 2,3-dibromopropanal (28.0 g., 0.13 mole, 65%) b.p. 63°/5 mm. (I.R. No. 32).

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*A previous attempt to distil bromopropargyl alcohol resulted in an explosion.

(a).-This was added to absolute ethyl alcohol (30 g., 0.65 mole) containing hydrogen chloride (1% by weight)* and allowed to stand with occasional shaking for three days. The acid was then neutralised by the addition of sodium hydrogen carbonate, water added, and the acetal ether extracted, dried ($MgSO_4$), solvent removed and the residue distilled to give 2,3-dibromopropanaldehyde diethyl acetal (28.0 g., 77%) b.p. $80^{\circ}/2$ mm.(I.R. No. 33).

(b).-The acetal was also prepared as follows: anhydrous calcium chloride (10.0 g.) was added to absolute ethyl alcohol (23.0 g., 0.5 mole) and stirred for 0.5 hr., 2,3-dibromopropanal (21.6 g., 0.1 mole) was then added and the reaction mixture allowed to stand for two days with occasional shaking. Sodium hydrogen carbonate solution (100 ml., 10%) was then added and the acetal ether extracted and dried ($MgSO_4$). Evaporation of ether and distillation gave 2,3-dibromopropanaldehyde diethyl acetal (16.2 g., 75%) as before.

Propargyl Aldehyde Diethyl Acetal.-[129] 2,3-Dibromoprop-analdehyde diethyl acetal (17.5 g., 0.06 mole) was added dropwise to a solution of potassium hydroxide (8.5 g)

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*Dry HCl gas was bubbled into the absolute alcohol until its weight had increased by 1%.

in absolute ethyl alcohol (58 ml.) the temperature being allowed to rise to 50-55°. The reaction mixture was cooled to 10°, precipitated potassium bromide removed by filtration and washed with absolute alcohol (10 ml.). The combined filtrate and washings was heated under reflux for 2.5 hr. cooled to 20° and the pale yellow solution containing crystallised potassium bromide was poured into water (500 ml.) and extracted with chloroform (3 x 60 ml.). The chloroform solution was washed with water (2 x 20 ml.), dried ($MgSO_4$) solvent removed and the residue distilled to give propargyl aldehyde diethyl acetal (6.4 g., 83%) b.p. 139-142°/750 mm. ν_{max} 3,320 (C≡CH), 2,140 (C≡CH), 1,060 (C-O-C) (I.R. No. 34).

Bromopropargylaldehyde Diethyl Acetal.-Bromine (5.5 ml., 0.1 mole) was added dropwise with stirring to sodium hydroxide (25 ml., 1 0N solution) and ice (50 g.) with ice cooling and the mixture stirred at 0° for 0.5 hr. The sodium hypobromite solution so formed was added dropwise over 1.5 hr. to propargyl aldehyde diethyl acetal (12.8 g., 0.1 mole) with ice cooling and the reaction mixture stirred at 0° for 2 hr. and extracted with ether (3 x 75 ml.), dried ($MgSO_4$) and the solvent evaporated to yield bromopropargylaldehyde diethyl acetal (16.5 g., 80%) ν_{max} 2,220 (RC≡CR), 1,060 (C-O-C) (I.R. No. 35).

Bromopropargylaldehyde.-Bromopropargylaldehyde diethyl acetal (18.0 g.) was stirred for 2 hr. with 10% sulphuric acid (150 ml.) at 35° and ether extracted using a continuous extraction apparatus. The ether solution was dried ($MgSO_4$), and ether removed in vacuo to give crude bromopropargylaldehyde (11.0 g., 95%). ν_{max} 2,200 (RC≡CR), 1,680 (C=O) and 685 cm.$^{-1}$ (C-Br). (I.R. No. 4). The material was distilled at 42°/1.5 mm. Polymerisation occurred in the distilling flask. Infra-red spectrum of distillate ν_{max} 2,200 (RC≡CR, 1,700, 1,660 and 1,580 cm.$^{-1}$ (I.R. No. 26).

Reaction of Bromopropargylaldehyde with t-Butylmagnesium Chloride.-Bromopropargylaldehyde (6.6 g., 0.05 mole) in dry ether (8.0 ml.) was added dropwise with stirring and cooling in an ice salt bath to t-butylmagnesium chloride (prepared from magnesium (1.2 g., 0.05 g. atom) and t-butylchloride (4.6 g., 0.05 mole) in dry ether (14 ml.)). The reaction mixture was stirred for 0.25 hr. and then poured onto crushed ice (18.0 g.), ether extracted and dried ($MgSO_4$). Removal of solvent and distillation gave the product (0.6 g.) b.p. 40°/1.2 mm. ν_{max} 3,450 (OH), 2,230 and 2,170 (RC≡CR) and 1,700 cm.$^{-1}$ (C=O) (I.R. No. 36).

2-Tetrahydropyranyloxyethylbromide.-Ice cold 2,3-dihydropyran

(10.8 g., 0.12 mole) was added portionwise to ice cold ethylene bromohydrin (12.5 g., 0.1 mole) and shaken with cooling in an ice bath for 0.25 hr. Concentrated hydrochloric acid (1 drop) was then added and the mixture allowed to warm up to room temperature and stand overnight. The mixture was shaken with sodium hydroxide solution (20 ml., 10%), ether extracted (3 x 100 ml.), washed with water (2 x 50 ml.) and dried ($MgSO_4$). Removal of solvent and distillation gave 2-tetrahydropyranyloxyethylbromide (16.5 g., 75%), b.p. 86°/6 mm.

Reaction of Bromopropargylaldehyde with 2-Tetrahydropyranyloxyethyl Lithium.-Bromopropargylaldehyde (5.0 g., 0.4 mole) in dry ether (20 ml.) was added with ice cooling to 2-tetrahydropyranyloxyethyl lithium (prepared from lithium (0.56 g., 0.08 g. atom) and 2-tetrahydropyranyloxyethyl bromide (8.6 g., 0.04 mole) in dry tetrahydrofuran (30 ml.)) and the reaction mixture stirred for 3 hr. The complex was decomposed with iced ammonium chloride solution (100 ml.), ether extracted, and dried ($MgSO_4$). Removal of solvent in vacuo and distillation gave the product (0.5 g.) b.p. 71-74°/2 mm. ν_{max} 3,400 (OH) and 2,210 cm.$^{-1}$ (RC≡CR') (I.R. No. 37).

Reduction of 3,3,5-Trimethylcyclohexanone with Lithium Aluminium Hydride Complexes.

Reactions were carried out using titrated solutions of lithium aluminium hydride[7] and the reaction mixtures heated under reflux for 3 hr. Solvents were removed from the products which were analysed directly by gas chromatography (g.l.c.) using a 12 ft. "Tide" detergent column at 167°. Ether was dried (Na wire) and distilled from lithium aluminium hydride before use. All alcohols and diols were distilled from calcium hydride.

Reduction of 3,3,5-Trimethylcyclohexanone with the Lithium Aluminium Hydride-Ethylene Glycol Complex.-Ethylene glycol (1.86 g., 0.03 mole) was added to an ethereal solution of lithium aluminium hydride (120 ml. containing 0.03 mole) and the mixture heated under reflux for 2 hr., 3,3,5-trimethylcyclohexanone (1.4 g., 0.01 mole) in ether (20 ml.) was then added and the mixture refluxed for a further 3 hr. Excess complex was destroyed with 10% sulphuric acid and the aqueous layer extracted with ether. The combined ether solution was washed with saturated sodium bicarbonate solution, salt solution, and dried ($MgSO_4$). Distillation of ether gave the product; g.l.c. on "Tide" detergent at 167° gave two components t = 105 min. (54% axial alcohol,

identical with an authentic specimen) and t = 175 min. (46% equatorial alcohol identical with an authentic specimen).

Reduction of 3,3,5-Trimethylcyclohexanone with the Lithium Aluminium Hydride-Butane-2,3-diol Complex.* Butane-2,3-diol (2.7 g., 0.03 mole) in dry ether (20 ml.) was added dropwise to an ethereal solution of lithium aluminium hydride (120 ml. containing 0.03 mole) and the mixture heated under reflux for 2 hr. 3,3,5-Trimethylcyclohexanone (1.4 g., 0.01 mole) in dry ether (20 ml.) was then added and the mixture refluxed for a further 3 hr. The excess complex was decomposed and the material worked up as before. G.l.c. gave two components t = 105 min. (53% axial alcohol and t = 175 min. (47% equatorial alcohol).

Reduction of 3,3,5-Trimethylcyclohexanone with the Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose Complex.- 3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-glucofuranose (7 g., 0.02 mole) in dry ether (20 ml.) was added dropwise to an ethereal solution of lithium aluminium hydride (80 ml. containing 0.02 mole) and the mixture heated under reflux for 2 hr; 3,3,5-trimethyl-

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*Technical grade supplied by the British Drug Houses.

cyclohexanone (1.4 g., 0.01 mole) in dry ether (20 ml.) was then added and the mixture refluxed for a further 3 hr. The excess complex was decomposed and the material worked up as before. G.l.c. gave two components t = 105 min. (58% axial alcohol) and t = 175 min. (42% equatorial alcohol). The products, separated from monosaccharide derivative by distillation, showed no optical activity ($\pm 0.001^{\circ}$).

Reduction of 3,3,5-Trimethylcyclohexanone with the Ethanol Modified Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose Complex. - 3-O-Benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (7 g., 0.02 mole) in dry ether (20 ml.) was added dropwise to an ethereal solution of lithium aluminium hydride (66.6 ml. containing 0.02 mole) and the mixture heated under reflux for 1.5 hr. Dry ethyl alcohol (0.92 g., 0.02 mole) was then added and heating continued for a further 1 hr. 3,3,5-Trimethylcyclohexanone (1.4 g., 0.01 mole) was added and heating continued for a further 3 hr. The excess complex was decomposed and the material worked up as before. G.l.c. gave two components t = 105 min. (70% axial alcohol) and t = 175 min. (30% equatorial alcohol). The products, separated from the monosaccharide derivative by distillation, showed no optical activity ($\pm 0.001^{\circ}$).

Reduction of 3,3,5-Trimethylcyclohexanone with the Lithium Aluminium Hydride-Diethoxy Complex.-Ethyl alcohol (2.76 g., 0.06 mole) in dry ether (10 ml.) was added to an ethereal solution of lithium aluminium hydride (99.9 ml. containing 0.03 mole) and the mixture heated under reflux for 2 hr. 3,3,5-Trimethylcyclohexanone (1.4 g., 0.01 mole) in dry ether (20 ml.) was then added and the mixture heated for a further 3 hr. The excess complex was decomposed and the material worked up as before. G.l.c. gave two components t = 105 min. (81% axial alcohol) and t = 175 min. (19% equatorial alcohol). A repeat experiment gave 82% axial alcohol and 18% equatorial alcohol.

Reduction of 3,3,5-Trimethylcyclohexanone with the Lithium Aluminium Hydride-Triethoxy Complex.-Ethyl alcohol (4.1 g., 0.09 mole) in dry ether (10 ml.) was added to an ethereal solution of lithium aluminium hydride (120 ml. containing 0.03 mole) and the mixture heated under reflux for 2 hr. 3,3,5-Trimethylcyclohexanone (1.4 g., 0.01 mole) in dry ether (20 ml.) was then added and the mixture heated for a further 3 hr. The excess complex was decomposed and the material worked up as before. G.l.c. gave two components t = 105 min. (85% axial alcohol) and t = 175 min. (15% equatorial alcohol).

Standardisation of Lithium Aluminium Hydride Solution[7]

Solutions (a).-Lithium aluminium hydride (10 g.) was stirred with dry ether (400 ml.) for 2 hr. and the solution filtered at the pump. The residue was decomposed with absolute alcohol.*

(b).-Iodine (50 g.) was dissolved in analar benzene (1,000 ml., Na dried) to give an approximately 0.4 N solution. This solution was standardised against standard sodium thiosulphate solution (0.1 N) as follows: iodine solution (10 ml.) pipetted into water (50 ml.) and glacial acetic acid (1 ml.) and titrated against standard thiosulphate using starch indicator.

Titration of Lithium Aluminium Hydride Solution.-Lithium aluminium hydride solution (5 ml.) was added to iodine solution (50 ml.) and the flask shaken for 4 minutes. Water (50 ml.) and acetic acid (1 ml.) was added and the excess iodine titrated with standard thiosulphate using starch indicator.

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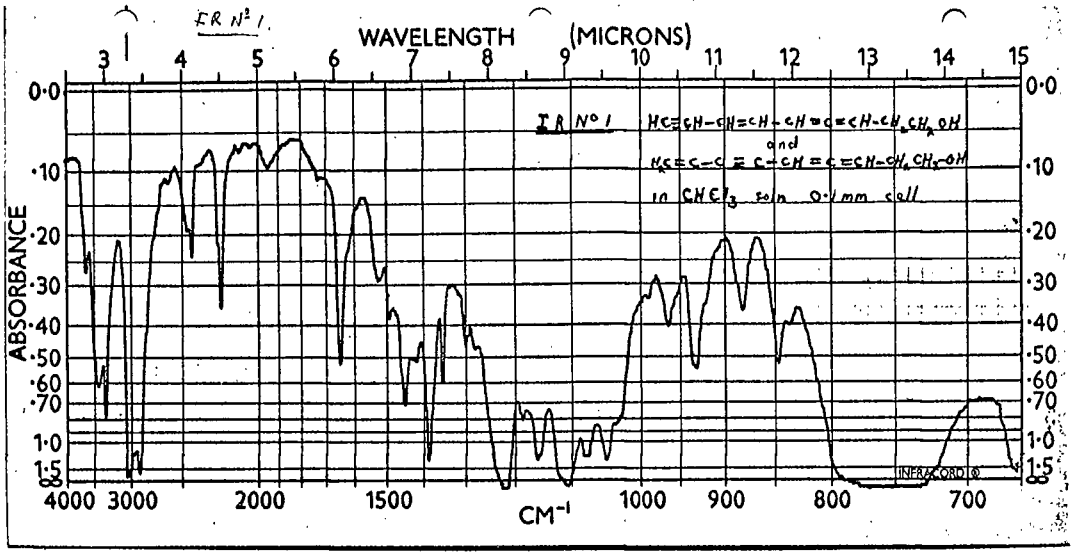
*Residue sometimes catches fire on being decomposed.

SPECTRA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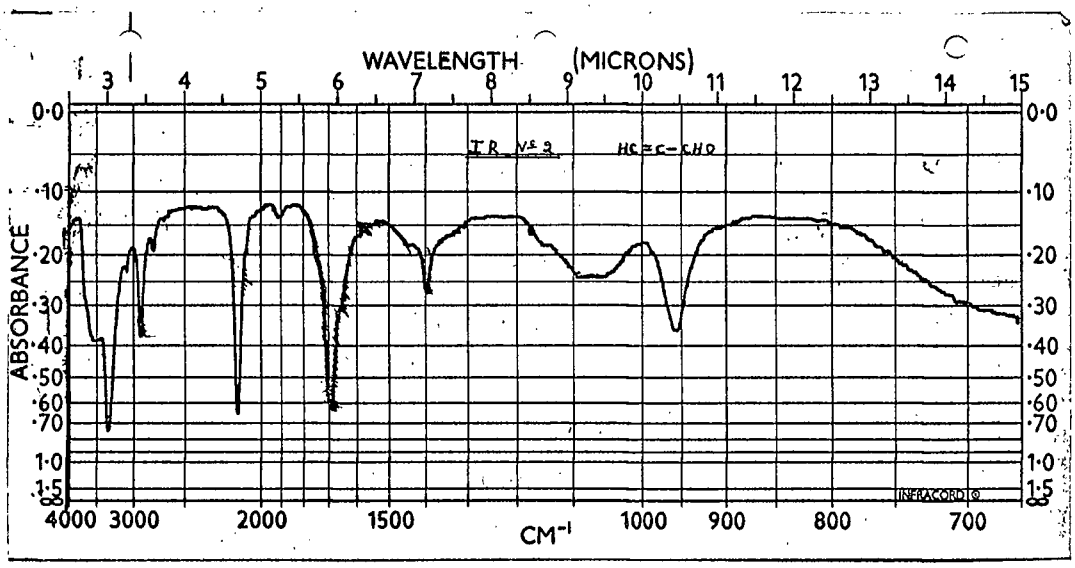
CM⁻¹
INFRACORD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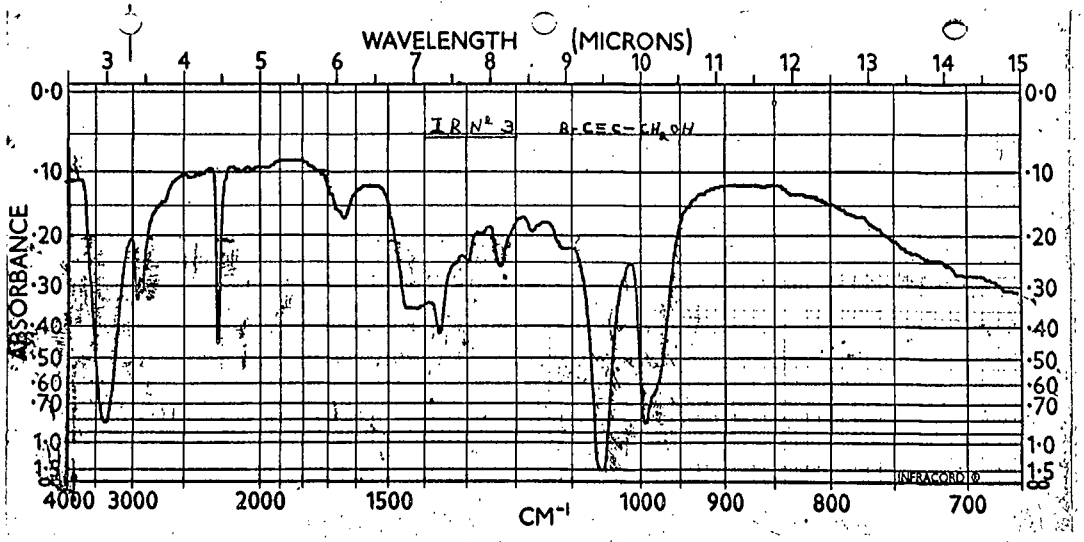
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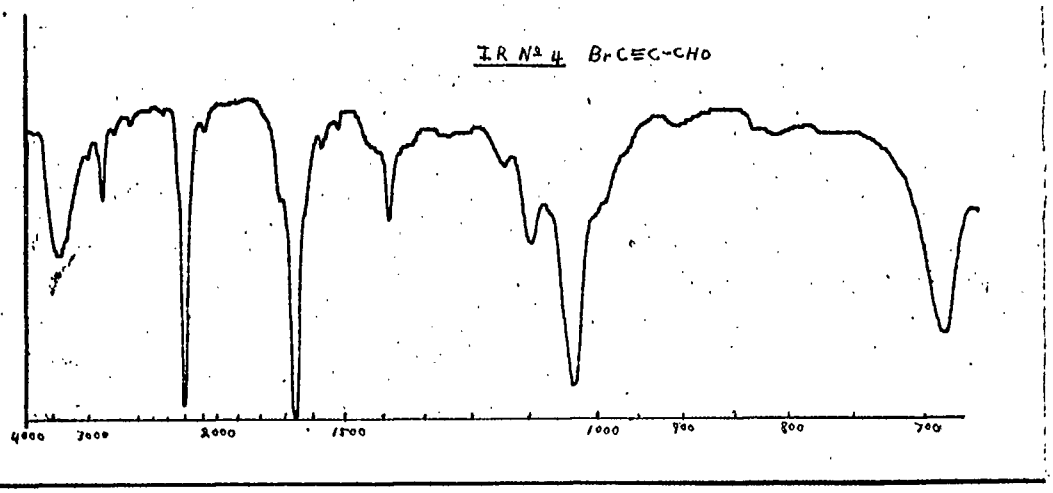
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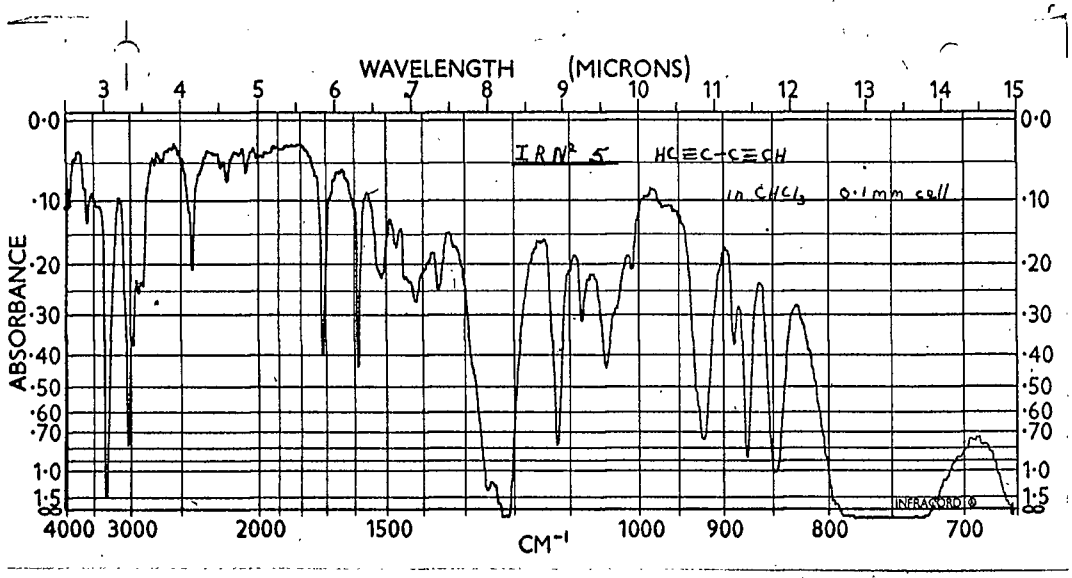
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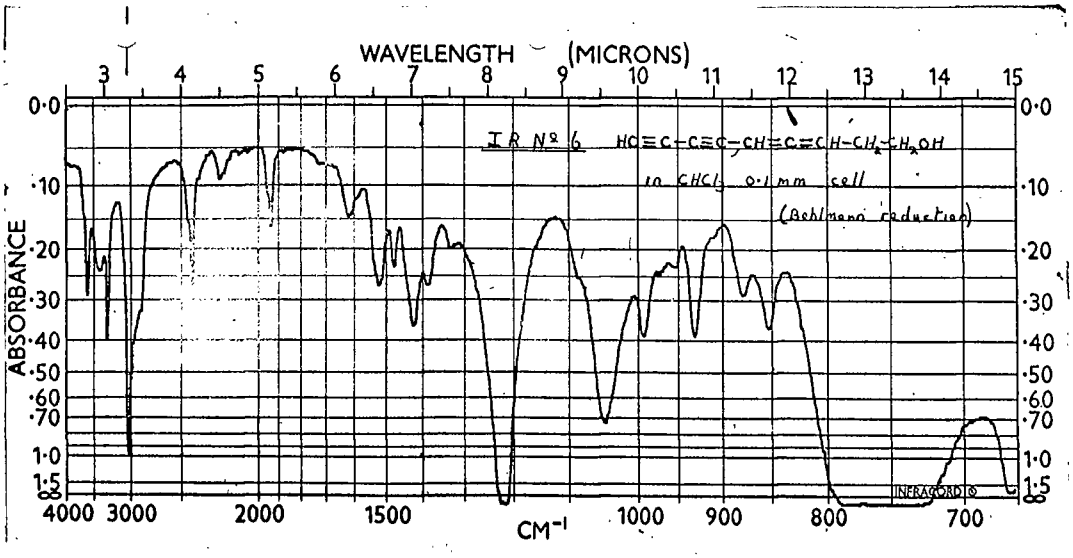
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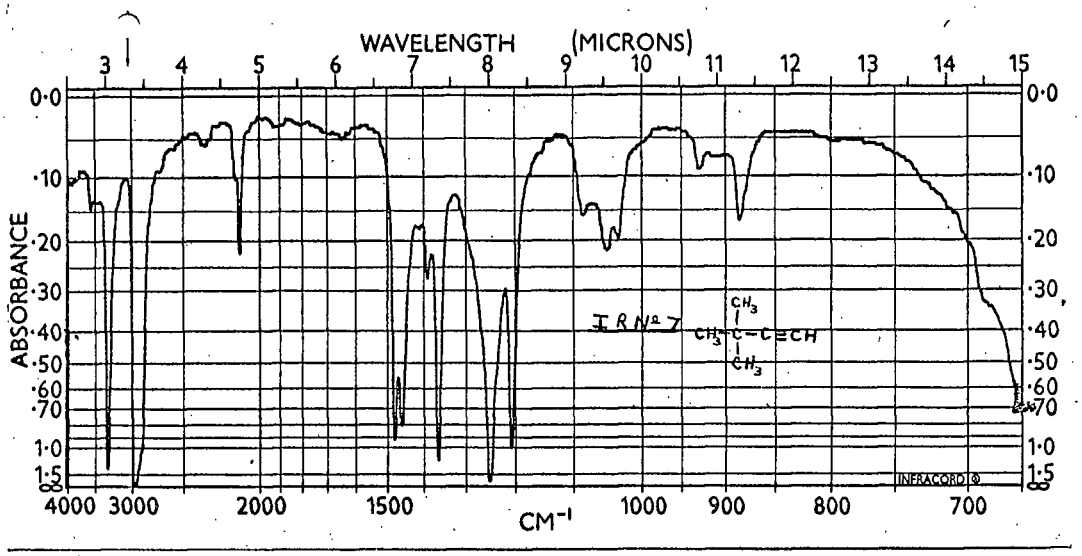
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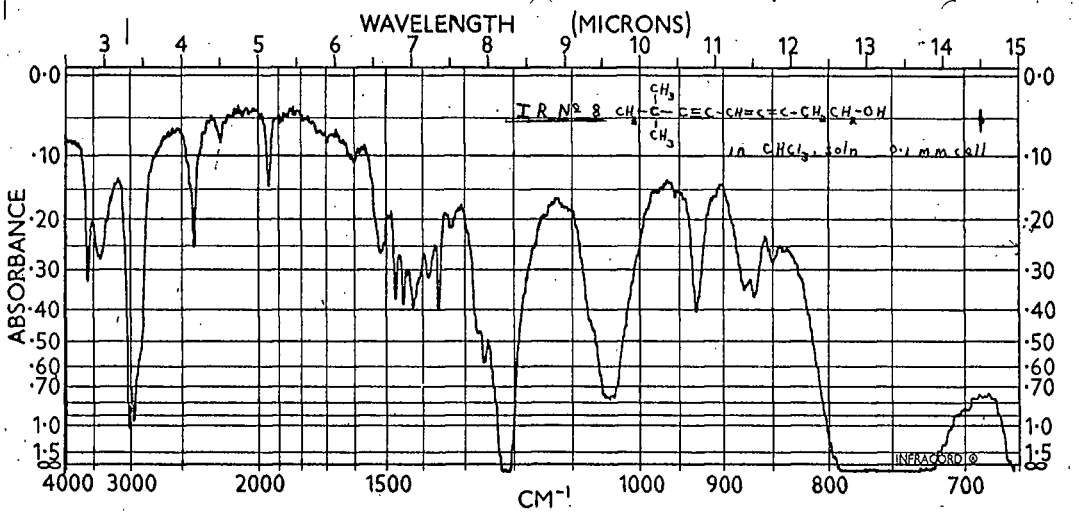
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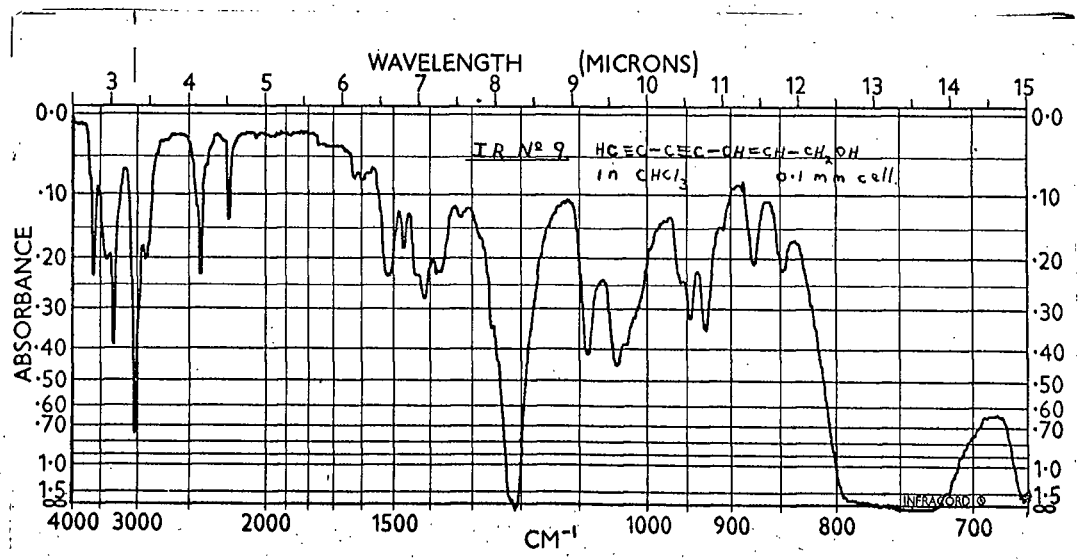
INFRACORD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0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
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CM⁻¹
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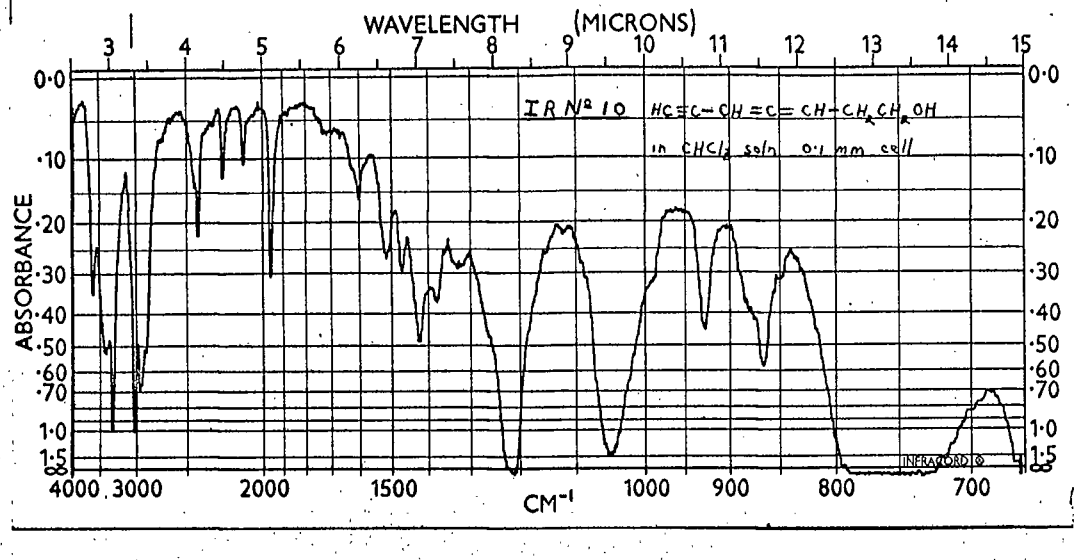
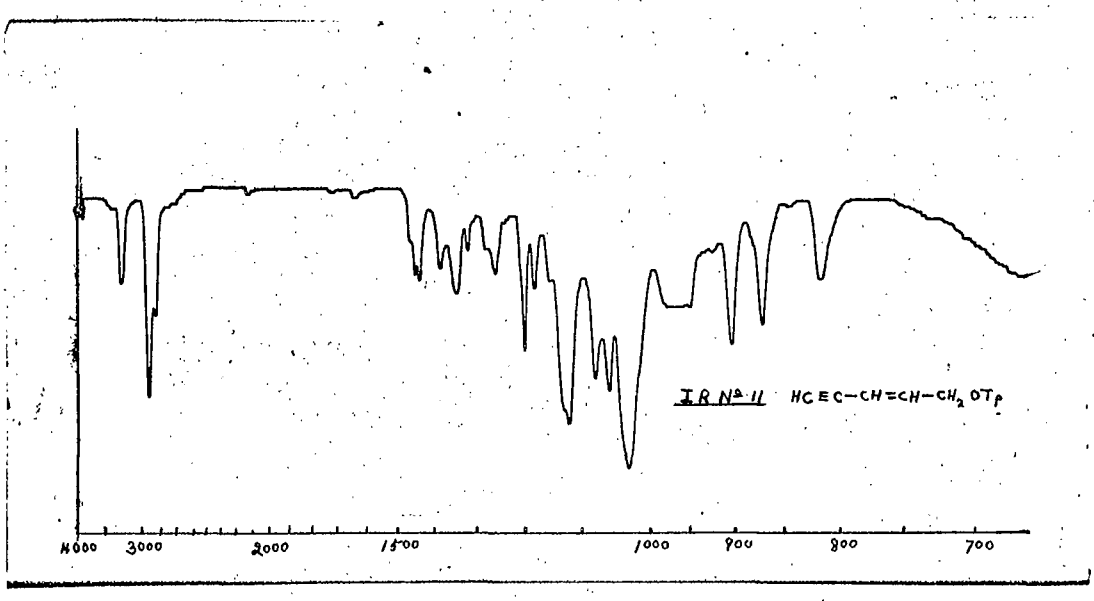
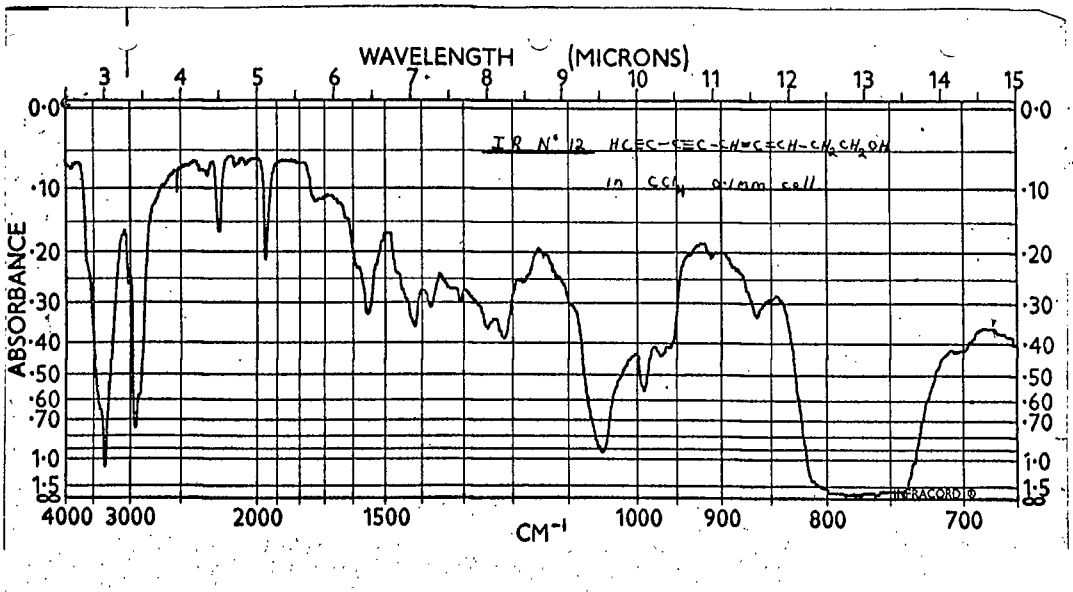
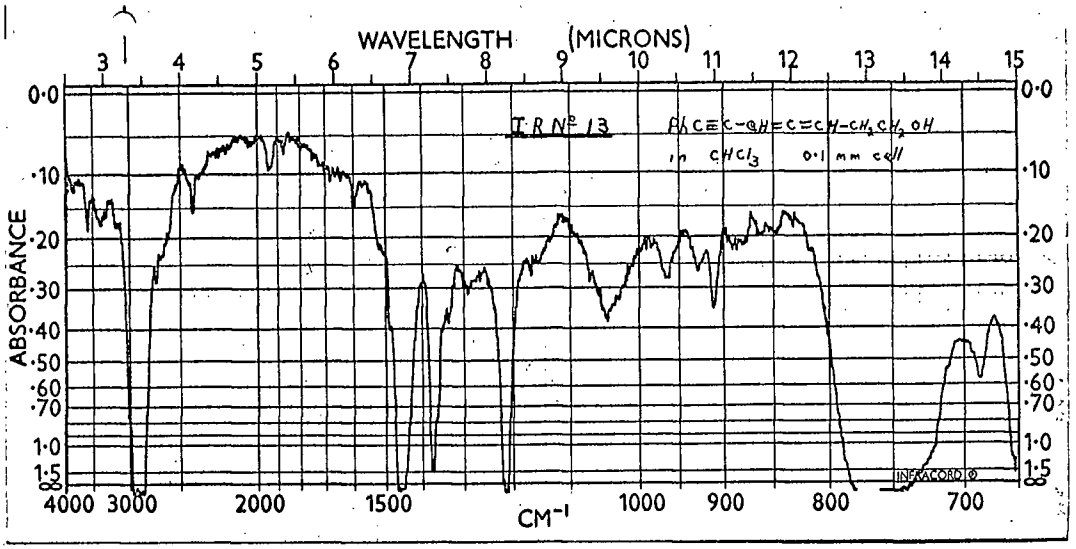
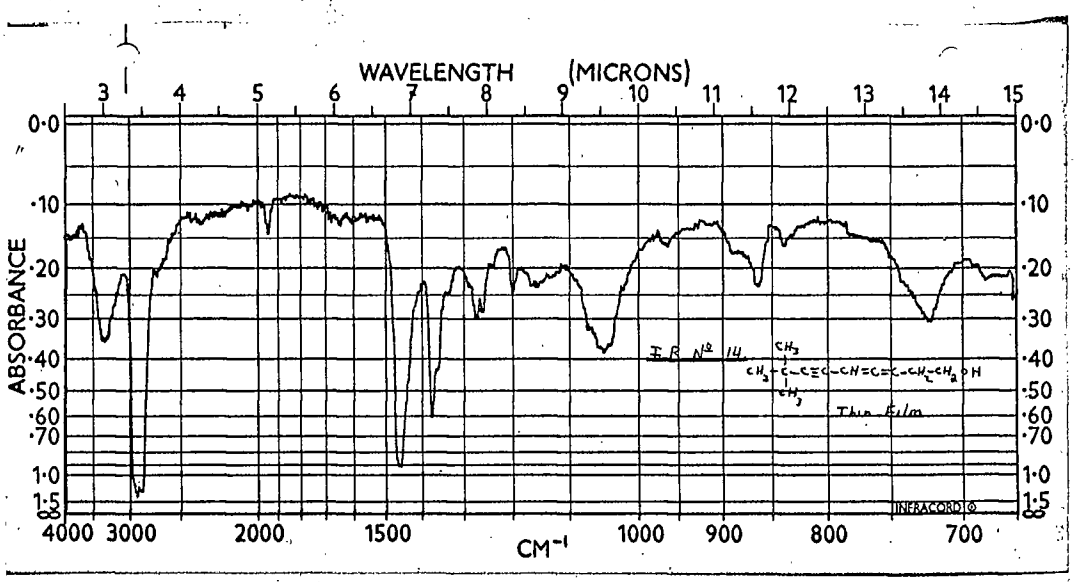
in CHCl3
0·1 mm cell
INFRACORD

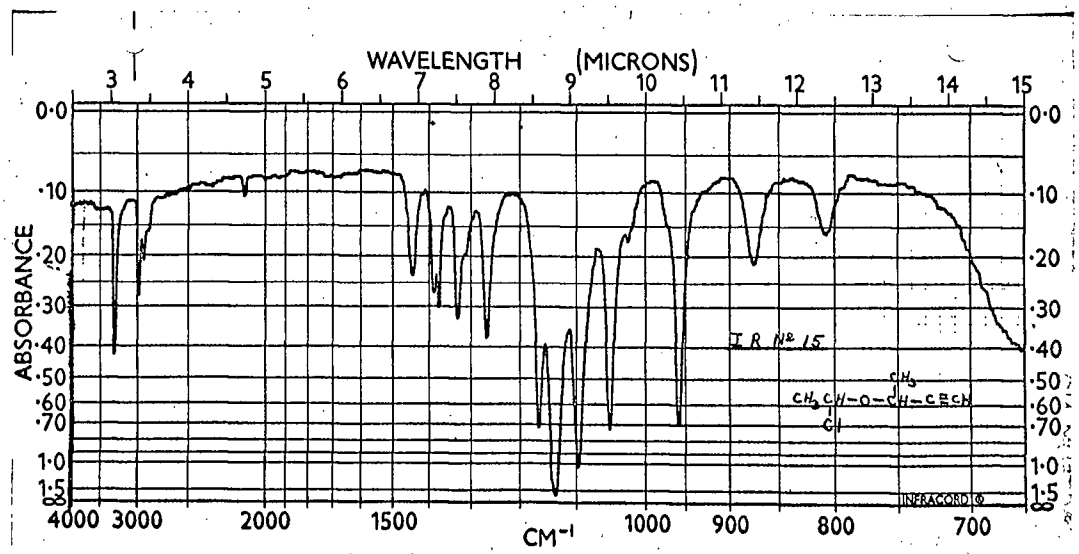

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
IR Nº 10 HC≡C-CH=C=CH-CH2CH2OH
in CHCl3 soln 0·1 mm cell
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
4000 3000 2000 1500 1000 900 800 700
CM-1
INFRACORD

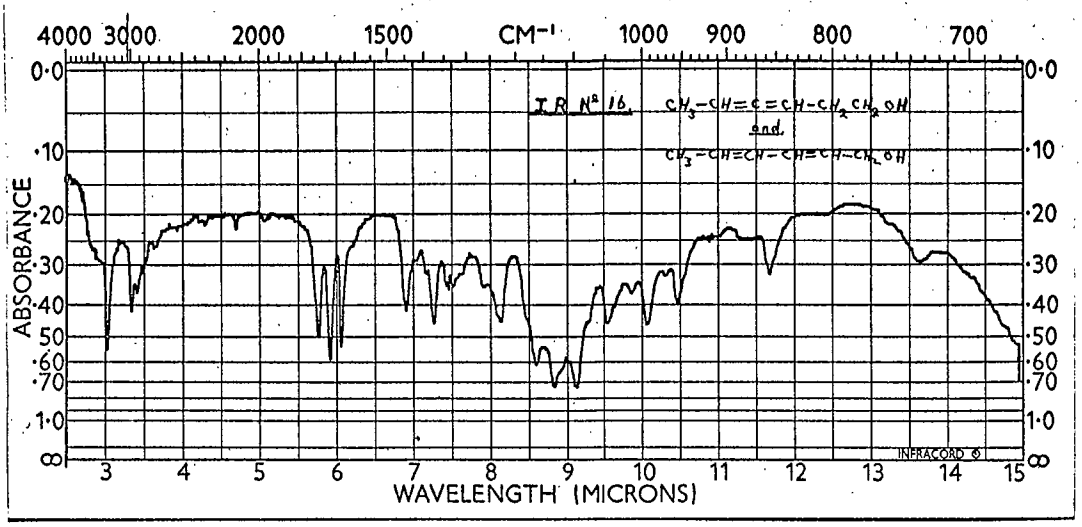

IR Nº 11 HC≡C-CH=CH-CH2OTp
4000 3000 2000 1500 1000 900 800 700

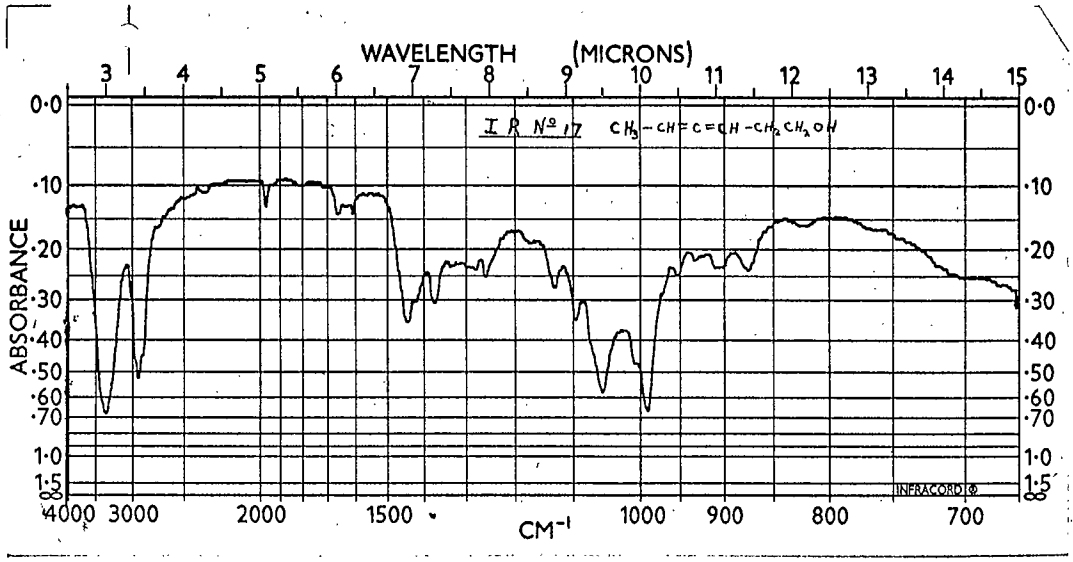

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
IR N° 12 HC≡C-C≡C-CH=C=CH-CH2CH2OH
in CCl4 0·1mm cell
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
4000 3000 2000 1500 1000 900 800 700
CM-1
INFRACORD

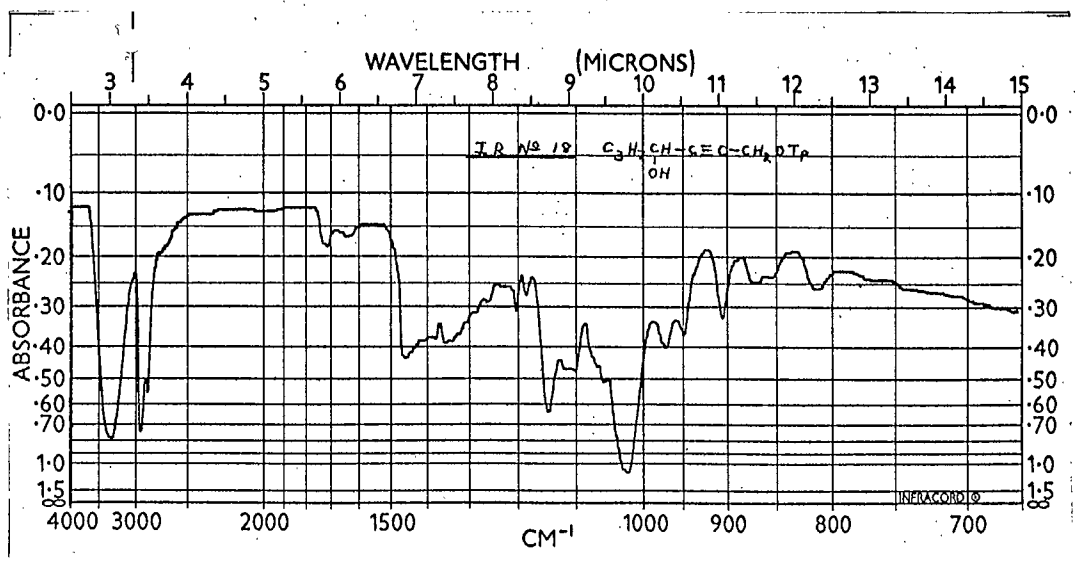

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
4000 3000 2000 1500 1000 900 800 700
CM⁻¹
I.R N° 13
in CHCl3 0·1 mm cell
INFRACORD

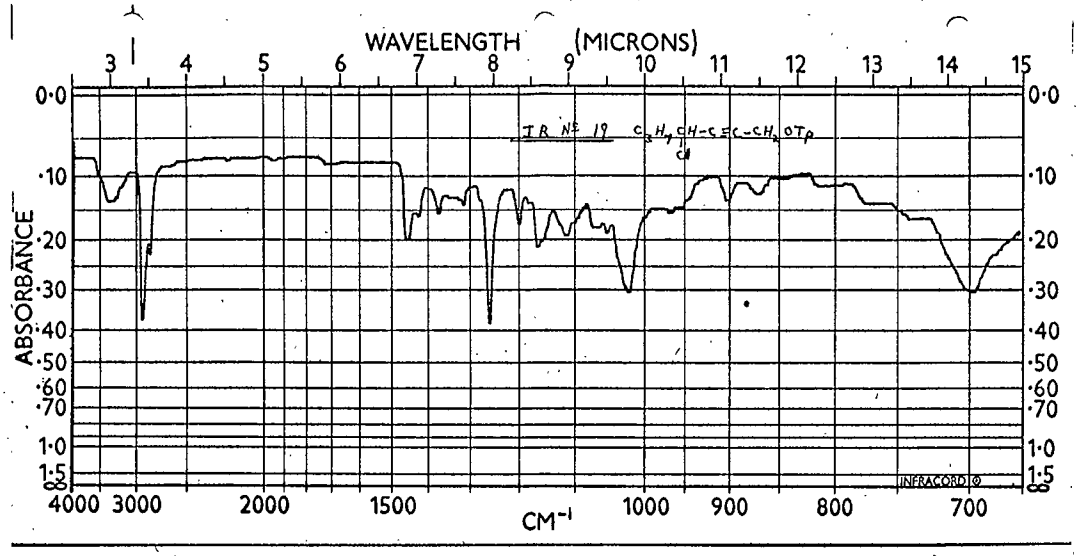

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
4000 3000 2000 1500 1000 900 800 700
CM⁻¹
I.R N° 14
Thin Film
INFRACORD

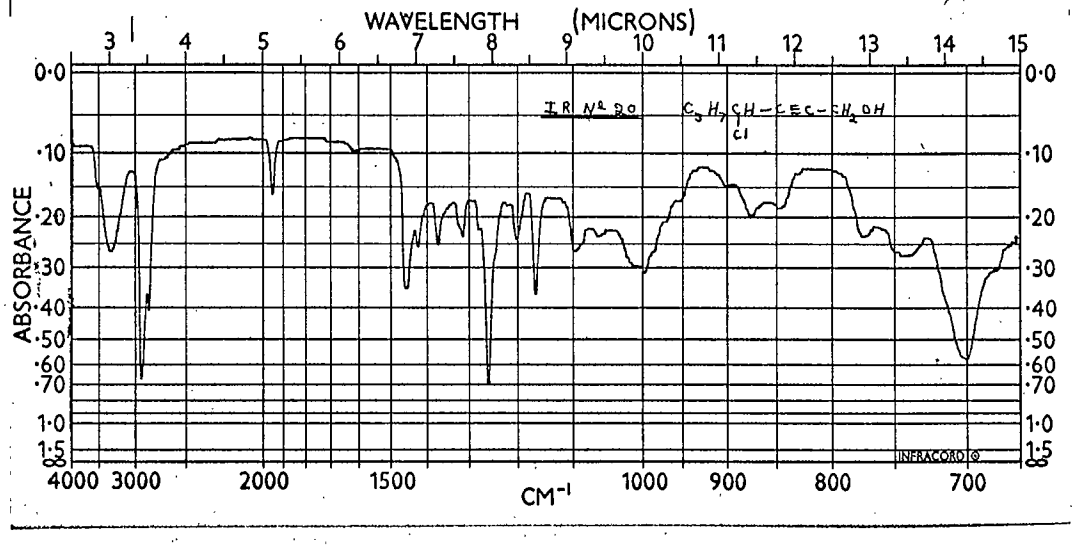

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
4000 3000 2000 1500 1000 900 800 700
CM⁻¹
I.R N° 15
INFRACORD

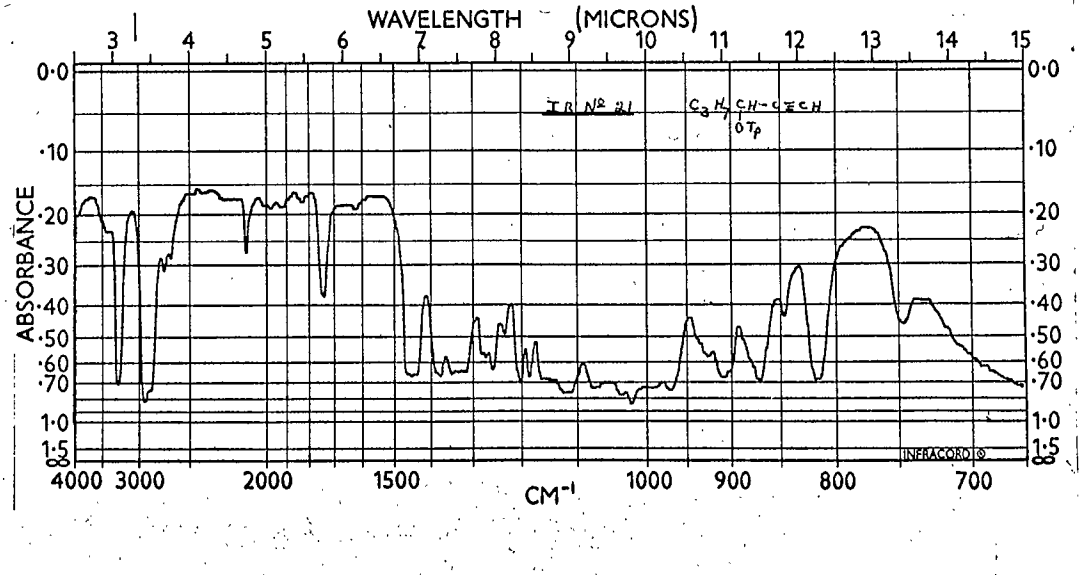

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
I R Nº 16. CH₃-CH=C=CH-CH₂CH₂OH
and
CH₃-CH=CH-CH=CH-CH₂OH
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 50 ·60 ·70 1·0 ∞
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
INFRACORD

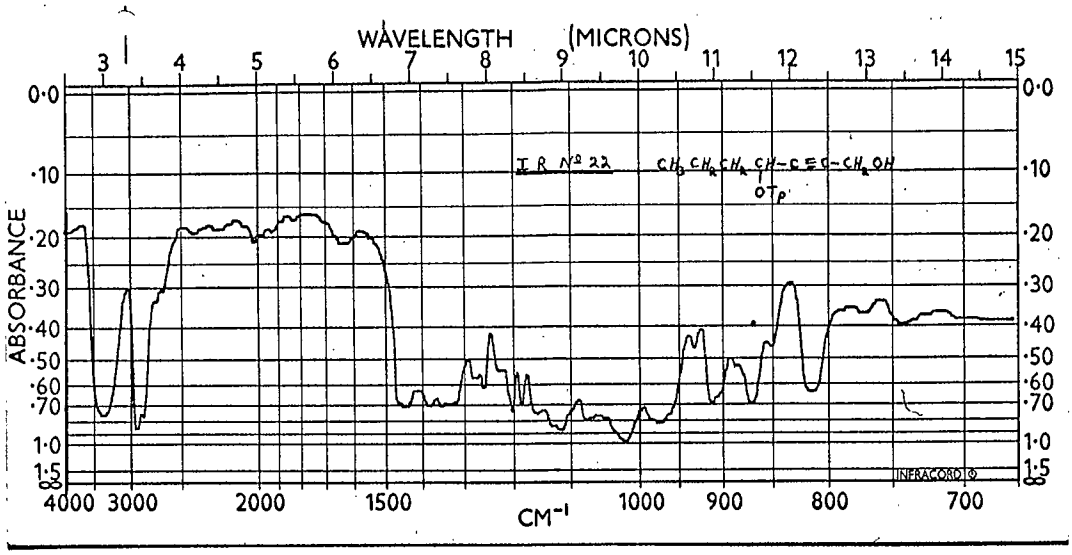

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
I R Nº 17 CH₃-CH=C=CH-CH₂CH₂OH
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5 ∞
4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
INFRACORD

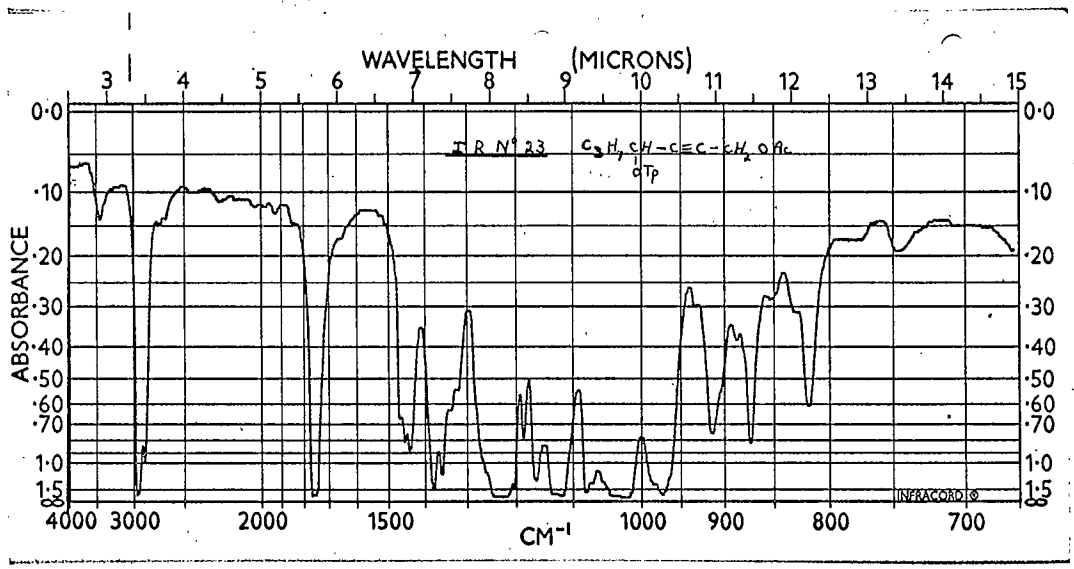

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
I R Nº 18 C₃H₇CH(OH)-C≡C-CH₂OTp
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5 ∞
4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
INFRACORD

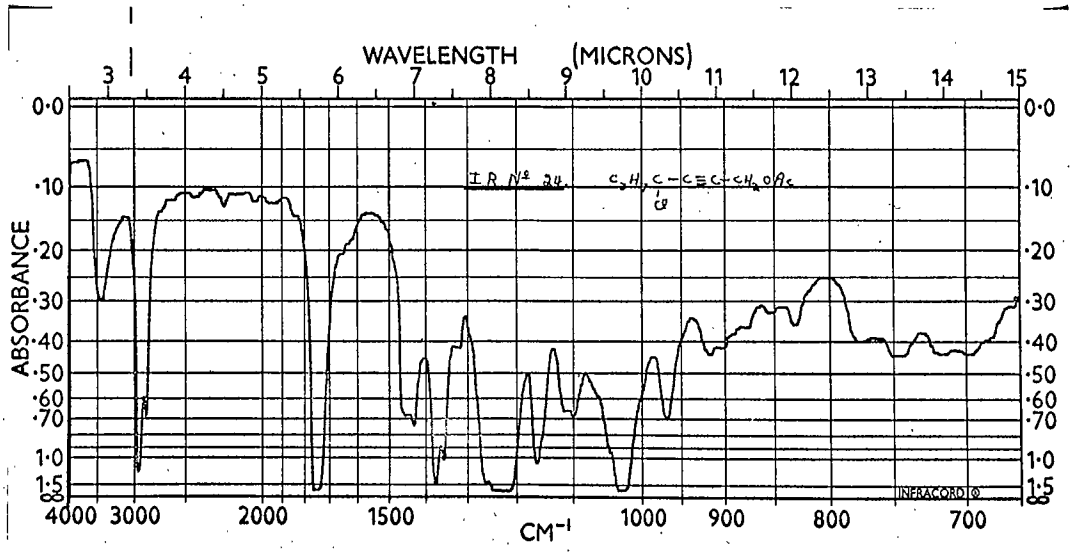

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
IR N° 19 C3H7CH(Cl)-C≡C-CH2OTp
4000 3000 2000 1500 1000 900 800 700
CM-1
INFRACORD

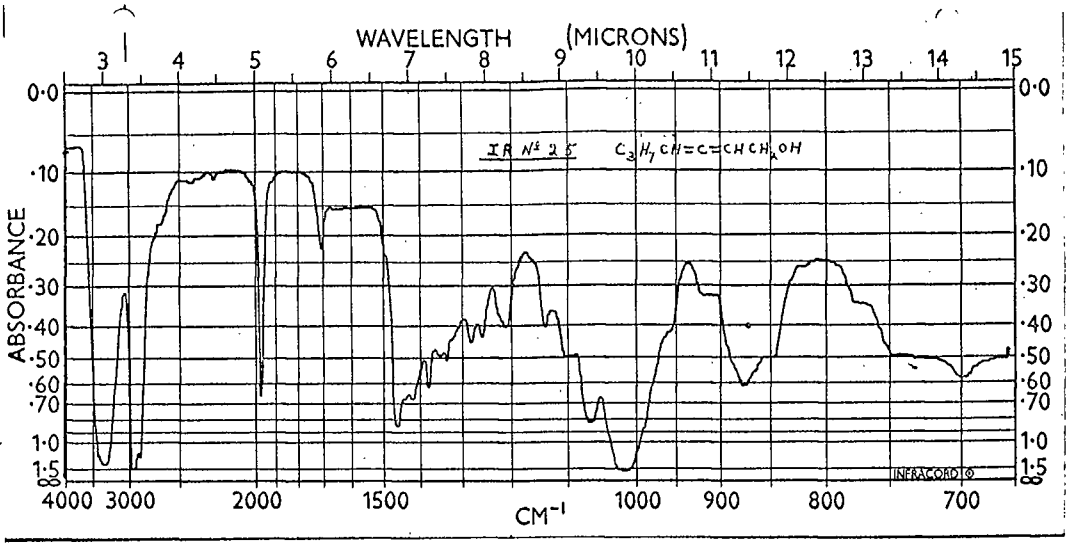

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
IR N° 20 C3H7CH(Cl)-C≡C-CH2OH
4000 3000 2000 1500 1000 900 800 700
CM-1
INFRACORD

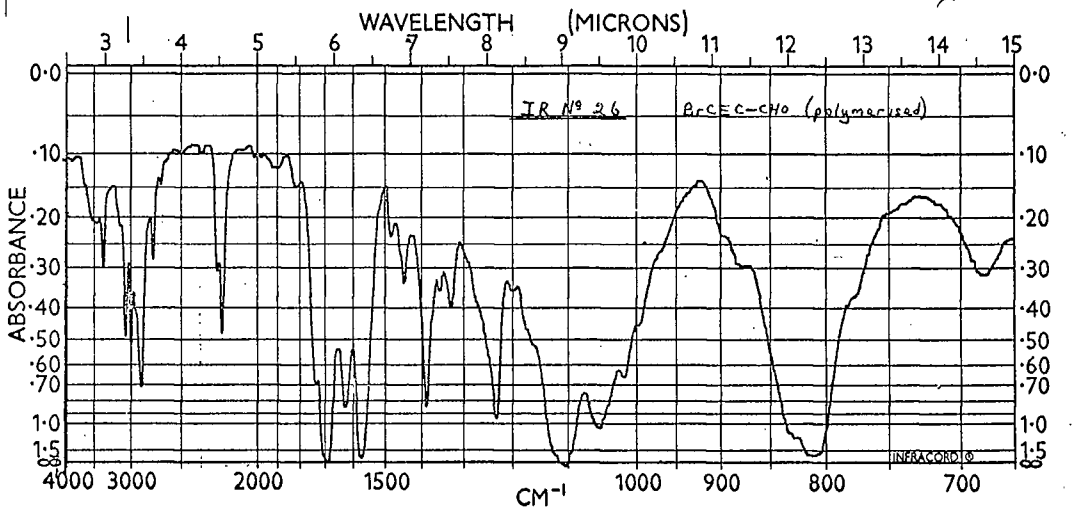

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
IR N° 21 C3H7CH(OTp)-C≡CH
4000 3000 2000 1500 1000 900 800 700
CM-1
INFRACORD

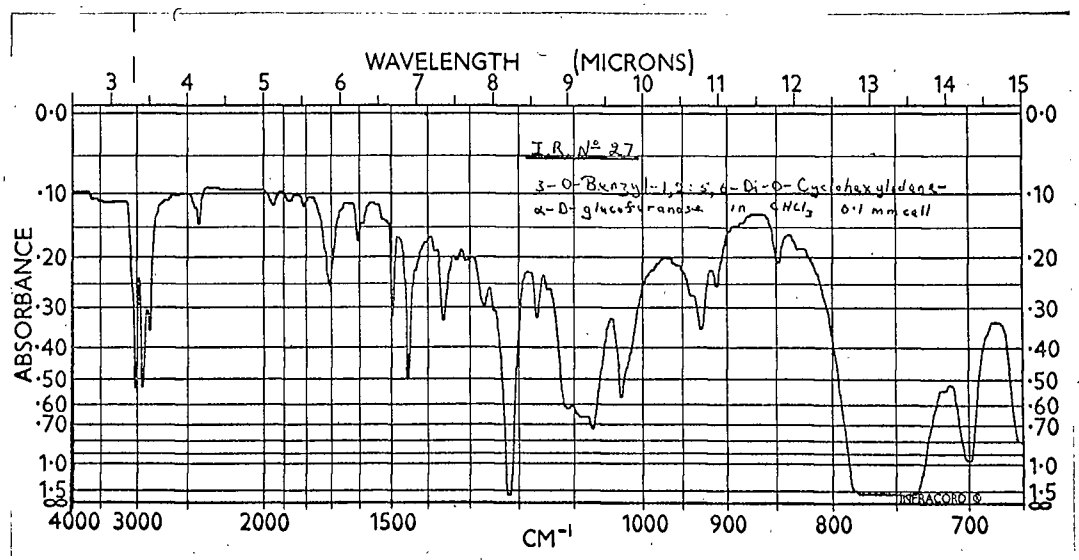

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
ABSORBANCE
IR N° 22 CH3CH2CH2CH(OTp)-C≡C-CH2OH
INFRACORD
4000 3000 2000 1500 1000 900 800 700
CM-1

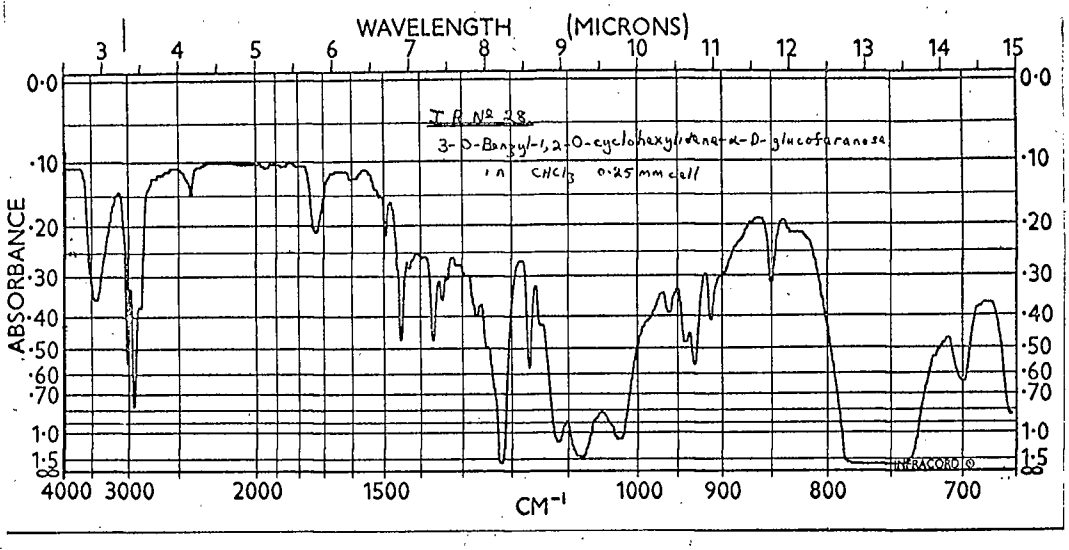

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
ABSORBANCE
IR N° 23 C3H7CH(OTp)-C≡C-CH2OAc
INFRACORD
4000 3000 2000 1500 1000 900 800 700
CM-1

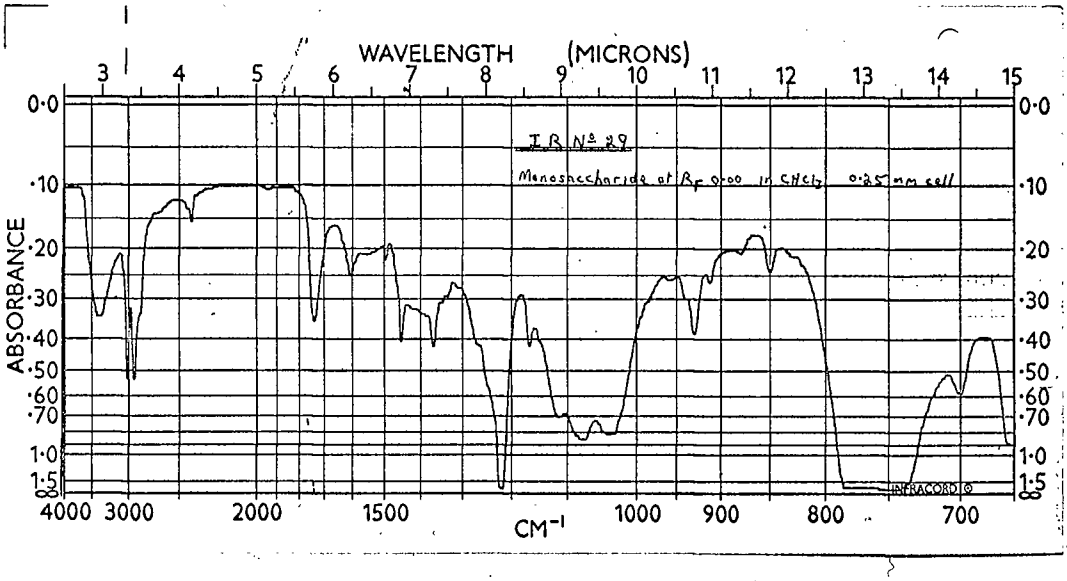

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
ABSORBANCE
IR N° 24 C3H7C(Cl)-C≡C-CH2OAc
INFRACORD
4000 3000 2000 1500 1000 900 800 700
CM-1

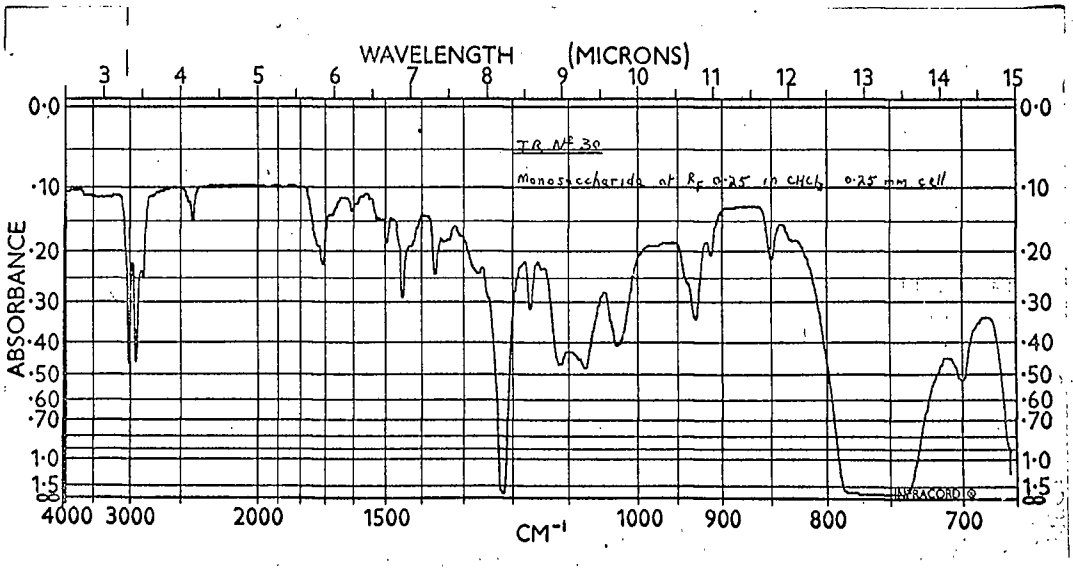

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
IR N° 25 $C_3H_7CH=C=CHCH_2OH$
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
4000 3000 2000 1500 1000 900 800 700
CM⁻¹
INFRACORD


WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
IR N° 26 $Pr C\equiv C-CHO$ (polymerised)
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
4000 3000 2000 1500 1000 900 800 700
CM⁻¹
INFRACORD


WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
IR N° 27
3-O-Benzyl-1,2:5,6-Di-O-Cyclohexylidene-
α-D-glucofuranose in $CHCl_3$ 0·1 mm cell
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
4000 3000 2000 1500 1000 900 800 700
CM⁻¹
INFRACORD

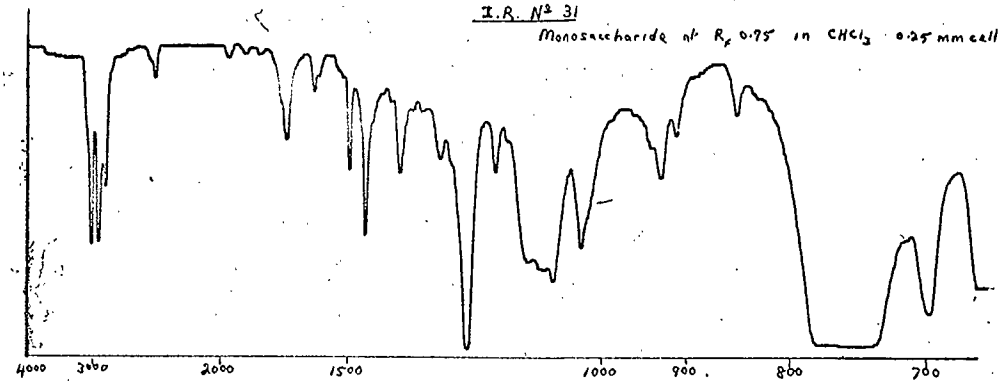

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
I.R Nº 28.
3-O-Benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose
in CHCl3 0.25 mm cell
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
4000 3000 2000 1500 1000 900 800 700
CM-1
INFRACORD


WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
I.R Nº 29.
Monosaccharide at Rf 0·00 in CHCl3 0·25 mm cell
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
4000 3000 2000 1500 1000 900 800 700
CM-1
INFRACORD

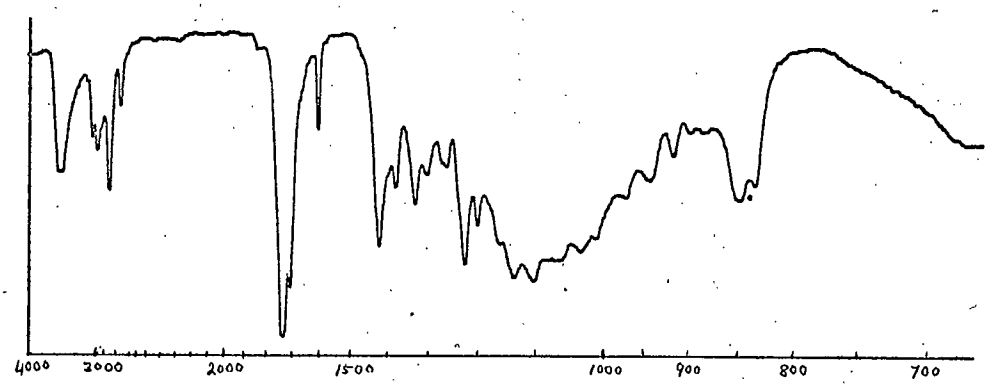

WAVELENGTH (MICRONS)
3 4 5 6 7 8 9 10 11 12 13 14 15
I.R Nº 30
Monosaccharide at Rf 0·25 in CHCl3 0·25 mm cell
ABSORBANCE
0·0 ·10 ·20 ·30 ·40 ·50 ·60 ·70 1·0 1·5
4000 3000 2000 1500 1000 900 800 700
CM-1
INFRACORD

I.R. N° 31

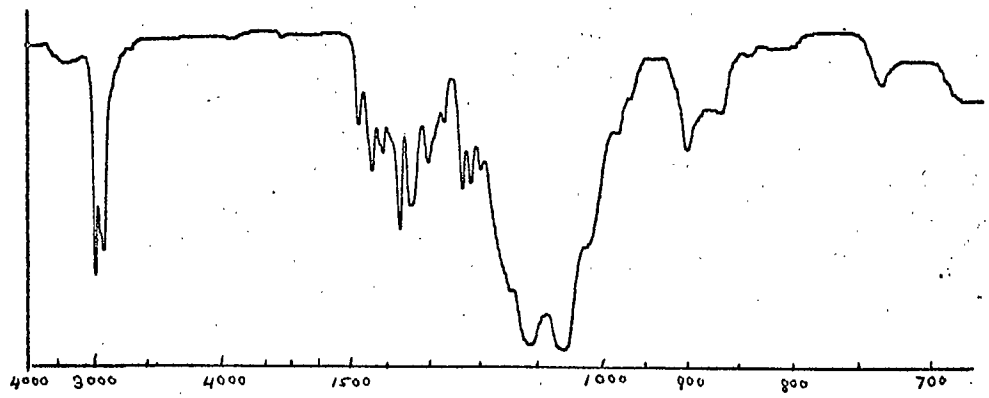
Monosaccharide at R_f 0.95 in $CHCl_3$ 0.25 mm cell



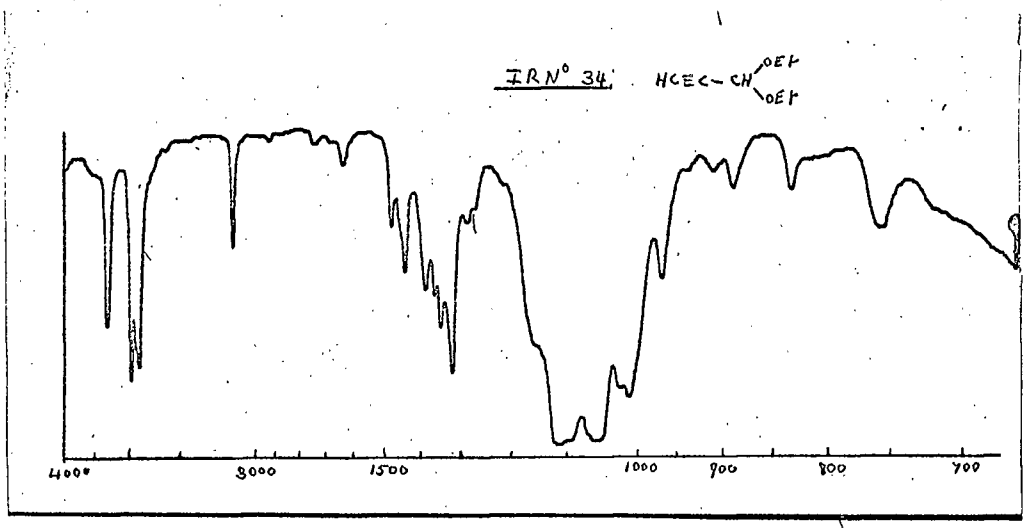
I.R. N° 32 $CH_2Br \cdot CH_2Br \cdot CHO$



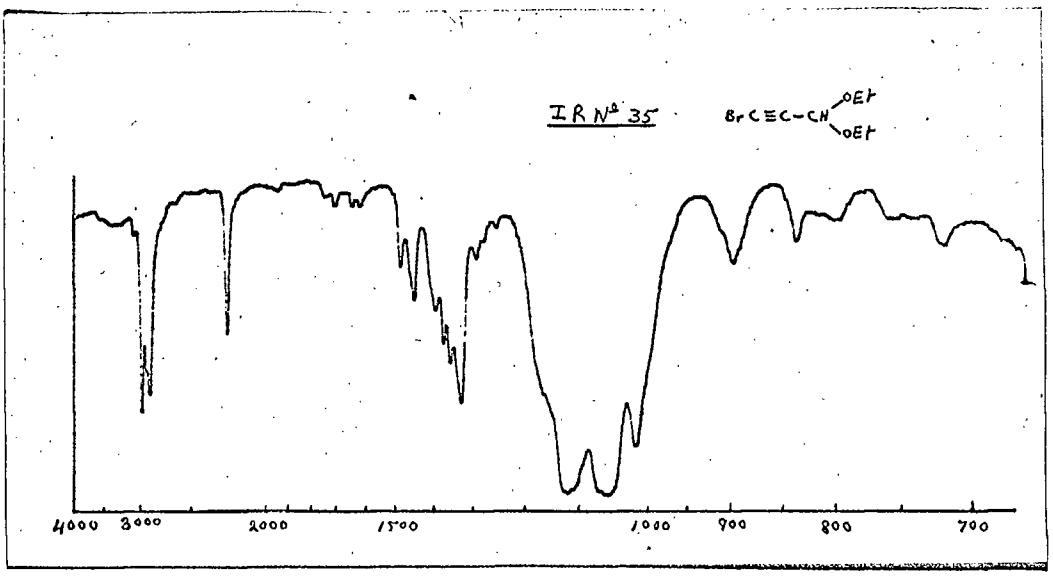
I R N° 33 $CH_2Br-CHBr-CH(OEt)_2$



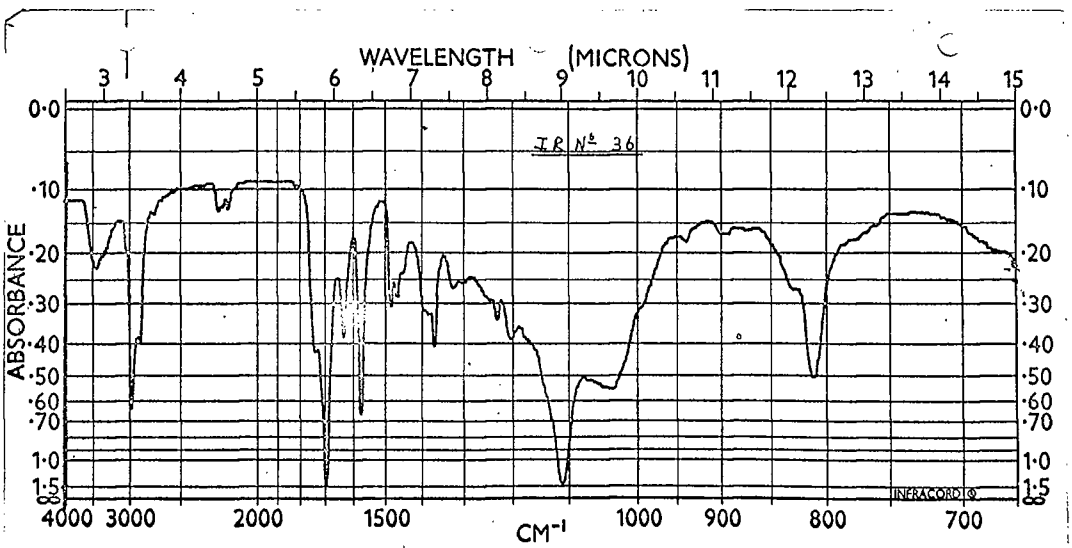
IR N° 34 HC≡C–CH(OEt)(OEt)



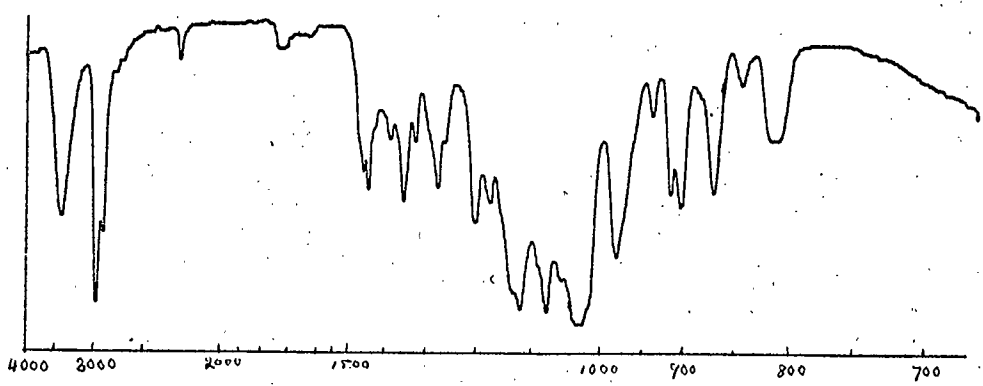
IR N° 35 BrC≡C–CH(OEt)(OEt)

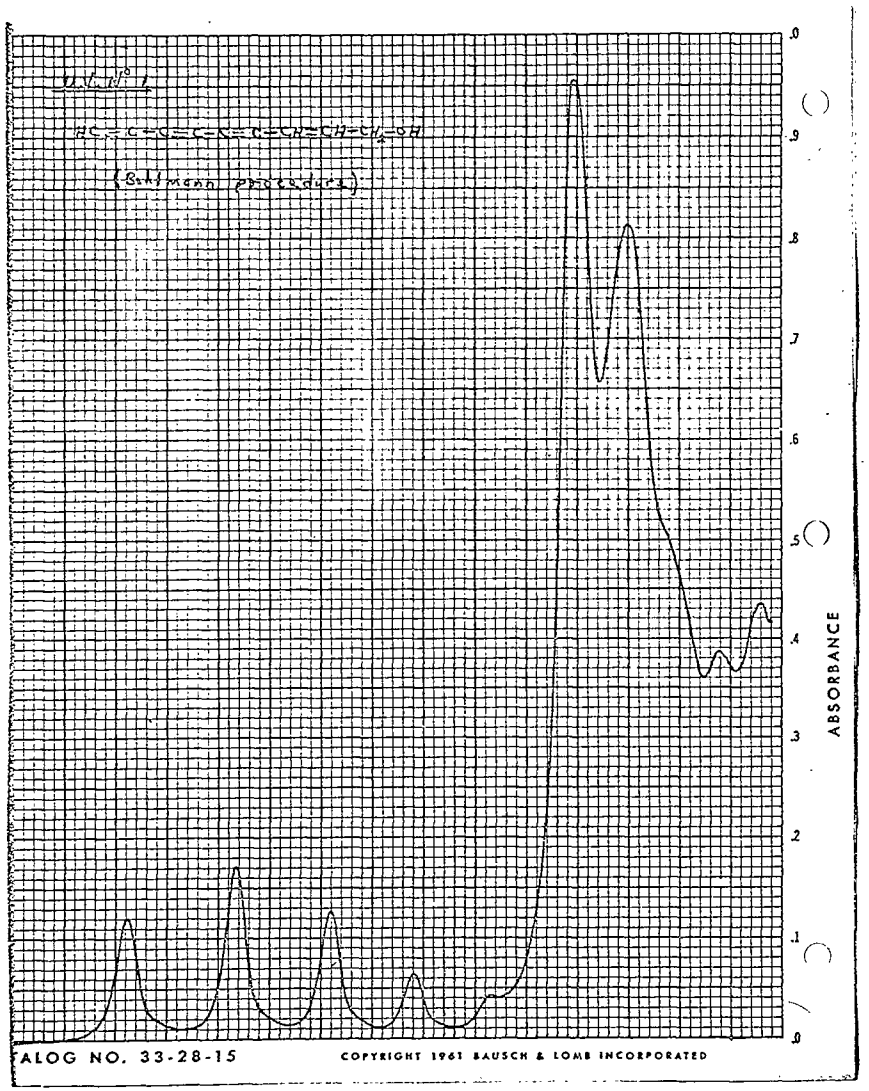


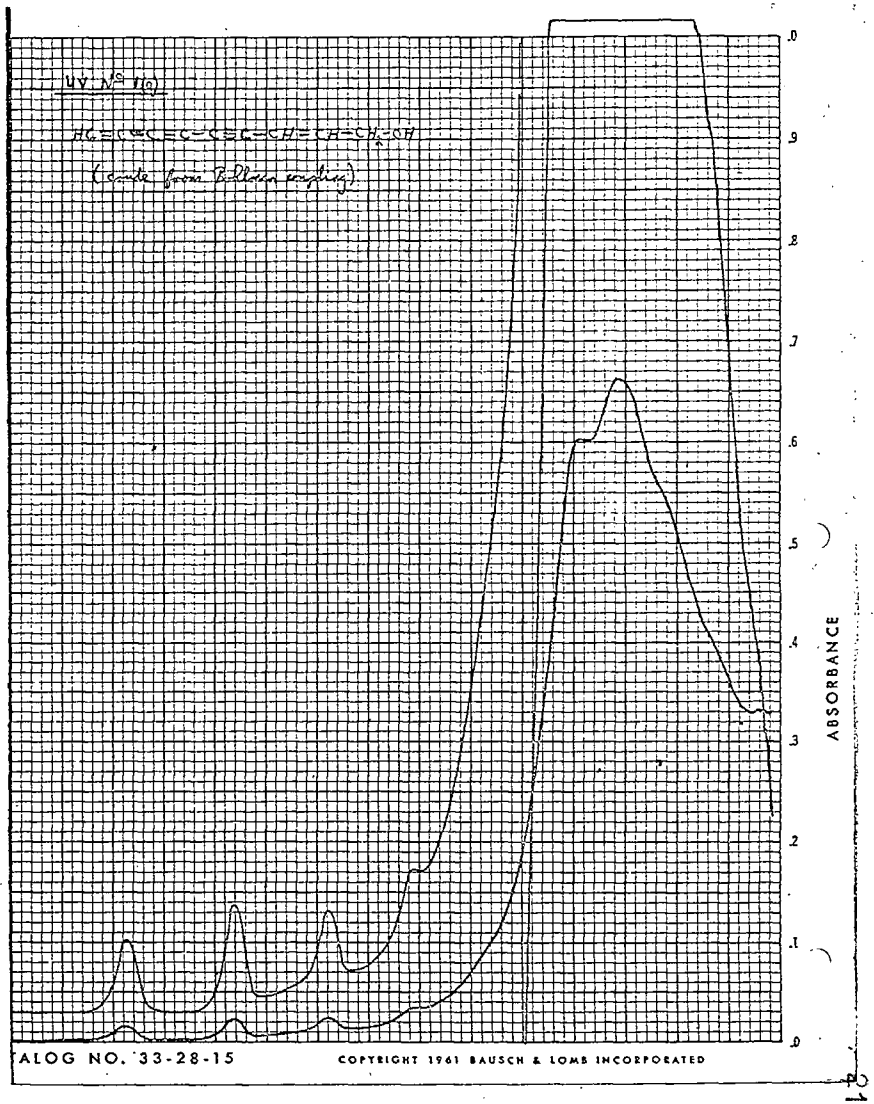
IR N° 36



IR N° 37




U.V. N° 1
HC≡C-C≡C-C≡C-CH=CH-CH₂-OH
(Bohlmann procedure)
.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
.0
ABSORBANCE
CATALOG NO. 33-28-15
COPYRIGHT 1961 BAUSCH & LOMB INCORPORATED


UV N° 10
HC≡C-C≡C-C≡C-CH=CH-CH₂-OH
(made from Bohlmann reaction)
.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
.0
ABSORBANCE
CATALOG NO. 33-28-15
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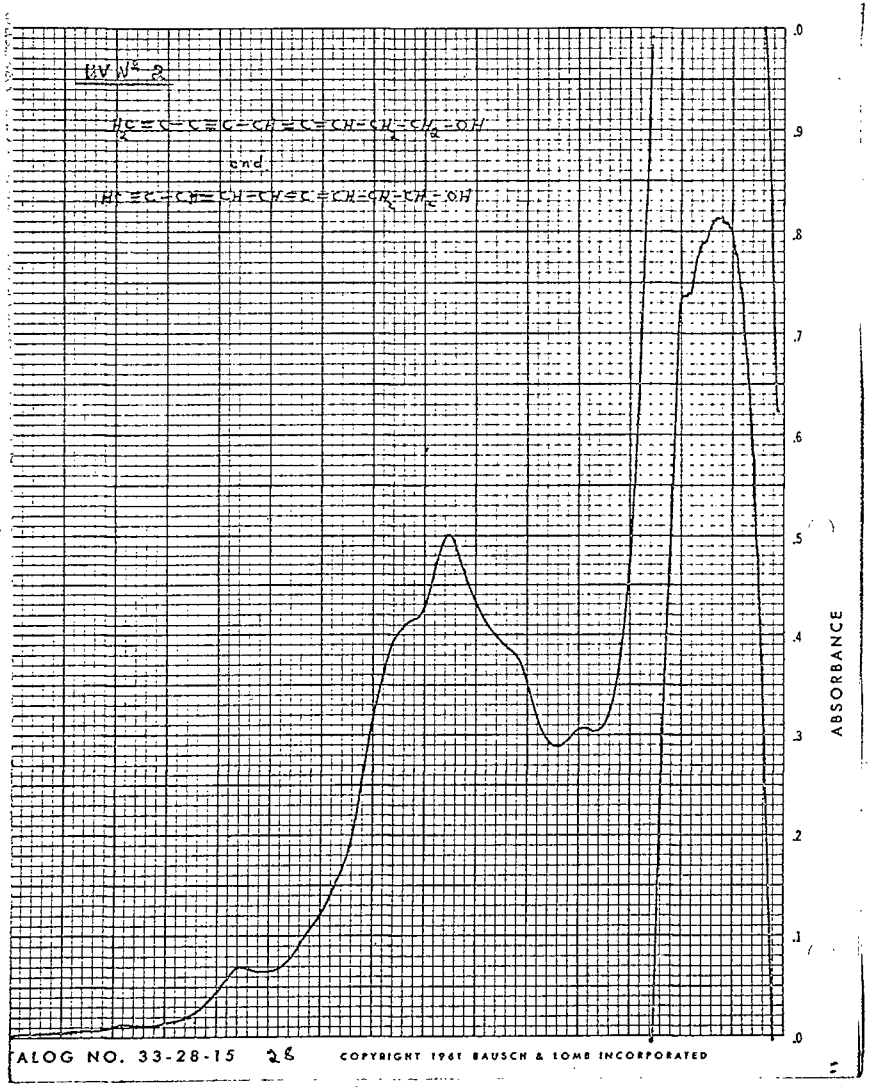
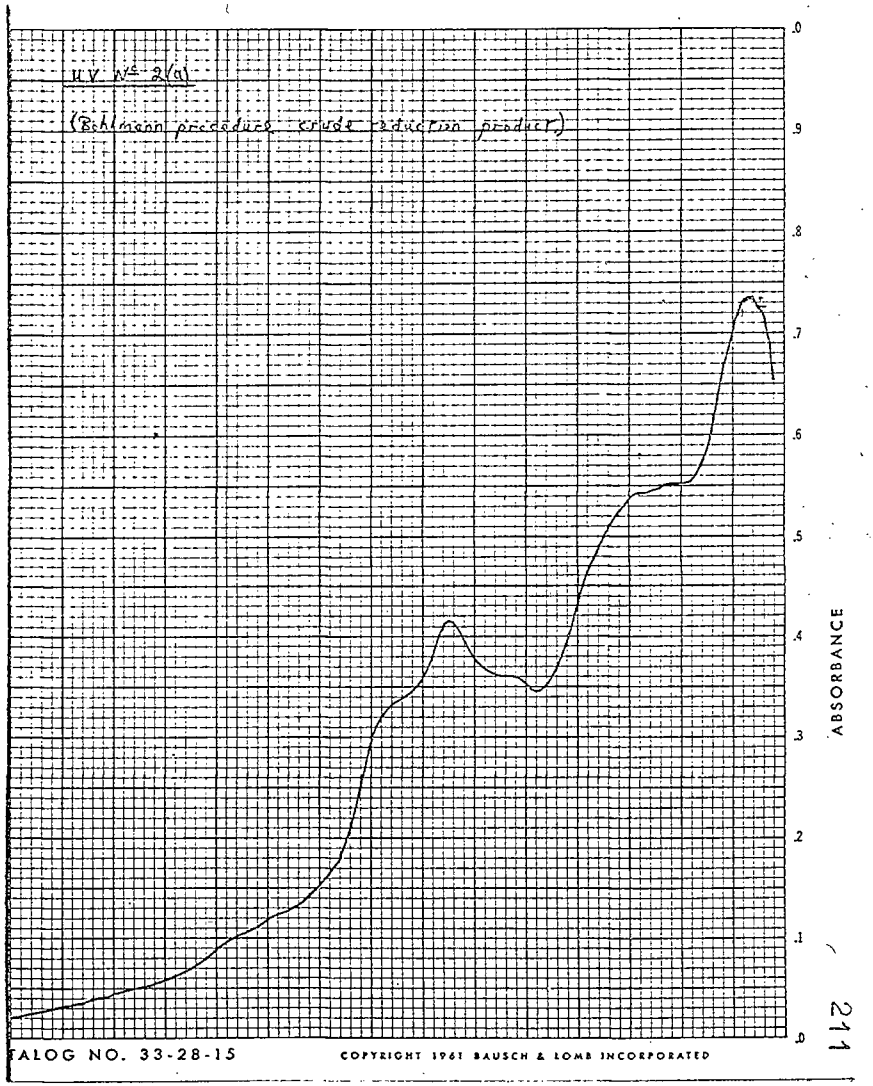

UV N° 2
and
.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
.0
ABSORBANCE
ALOG NO. 33-28-15 28
COPYRIGHT 1961 BAUSCH & LOMB INCORPORATED


UV N° 2(a)
(Bachmann procedure, crude reduction product)
.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
.0
ABSORBANCE
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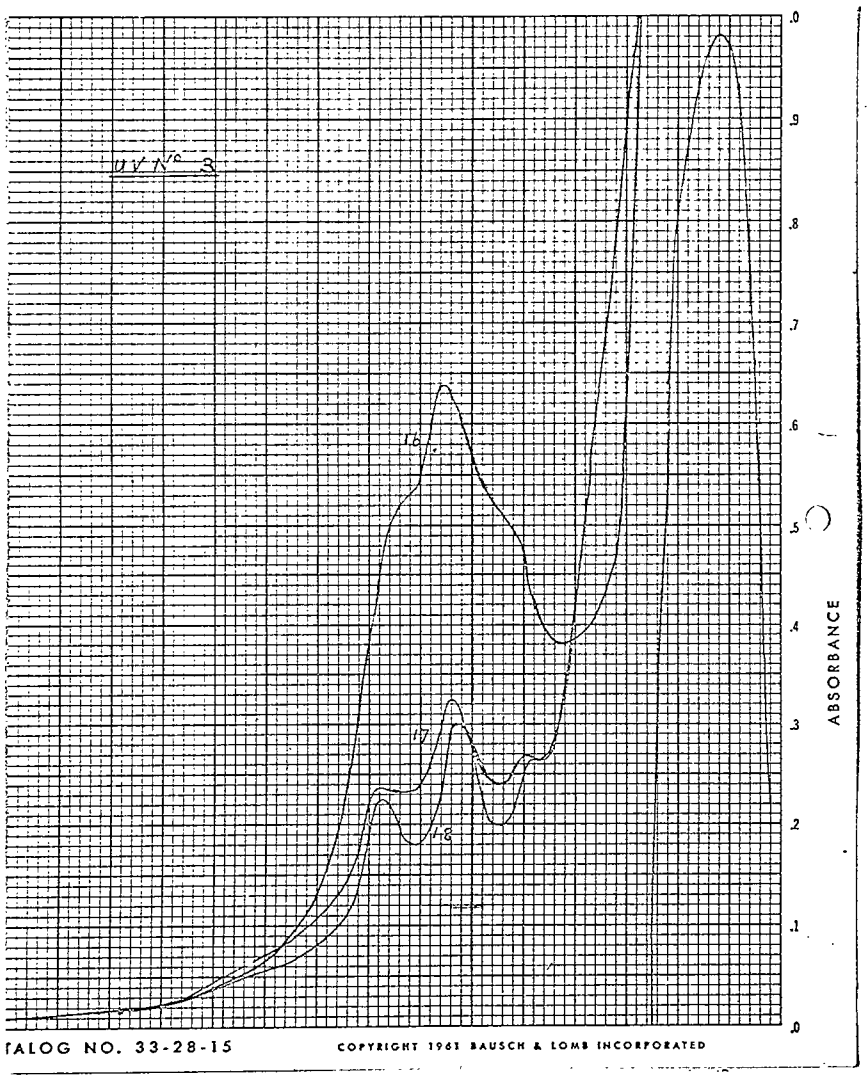
UV N° 3
16
17
18
.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
.0
ABSORBANCE
TALOG NO. 33-28-15
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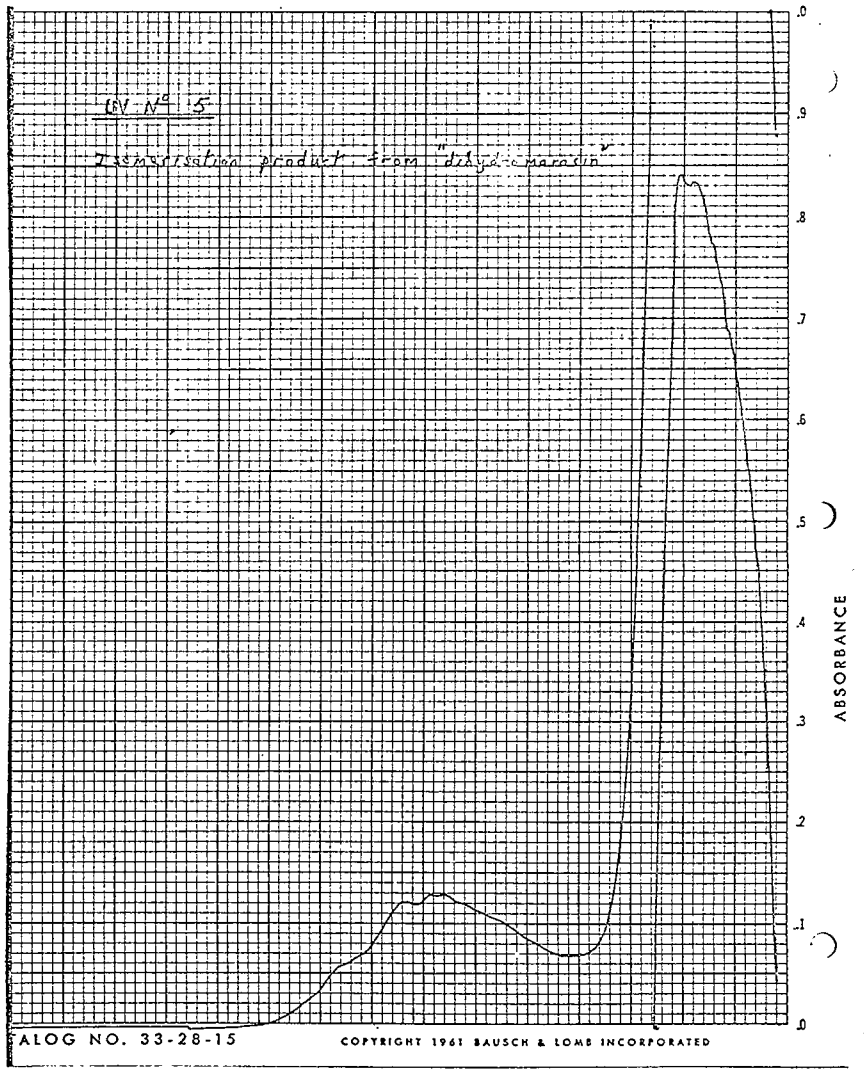
UV N° 5
Decomposition product from "dihydromaracin"
.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
.0
ABSORBANCE
ALOG NO. 33-28-15
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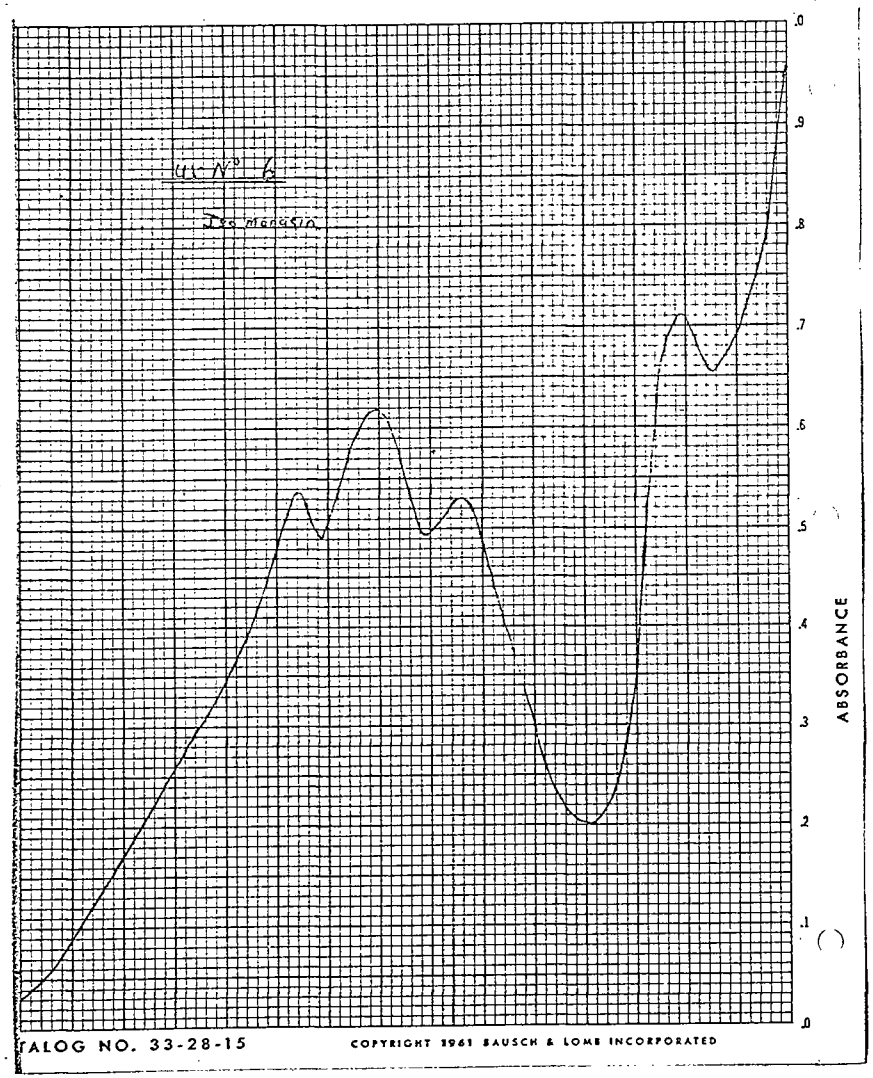
UV N° 6
Deo magasin
.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
.0
ABSORBANCE
TALOG NO. 33-28-15
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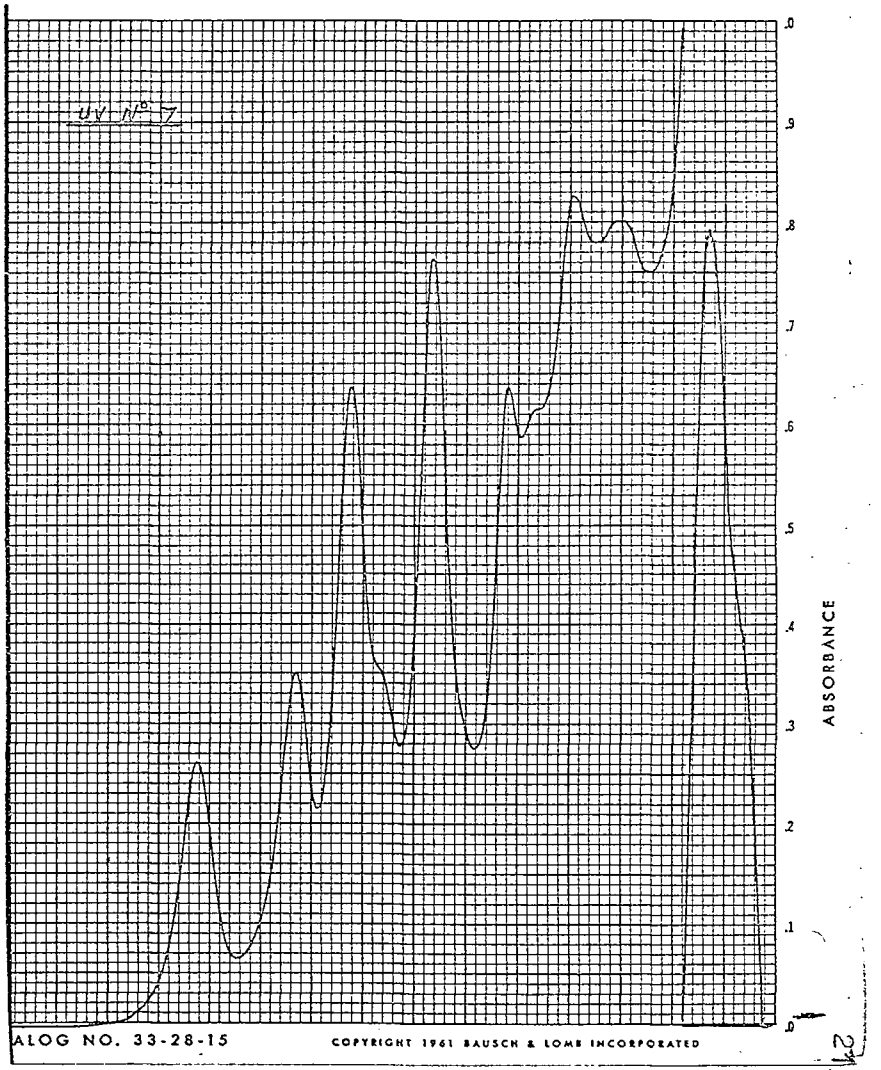
UV N° 7
.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
.0
ABSORBANCE
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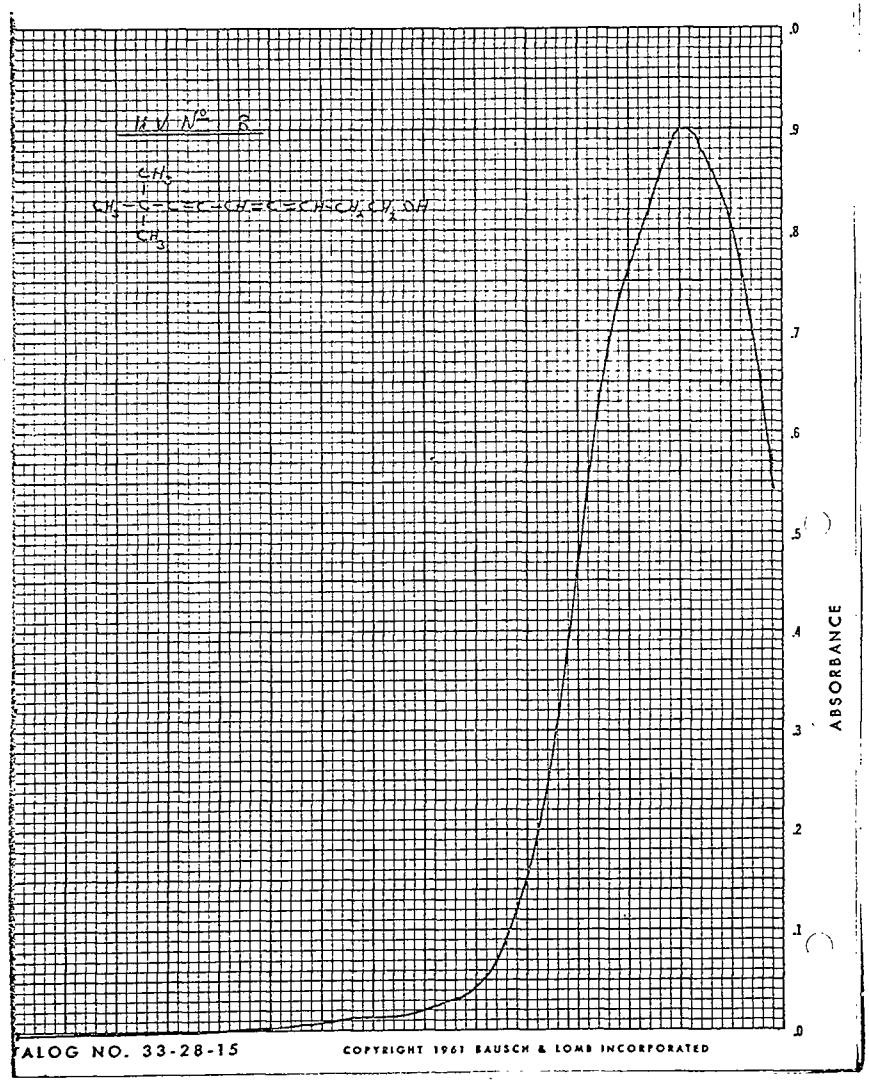
UV N° 8
CH3
CH3–C–C≡C–CH=C=CH–CH2CH2OH
CH3
ABSORBANCE
.0
.1
.2
.3
.4
.5
.6
.7
.8
.9
1.0
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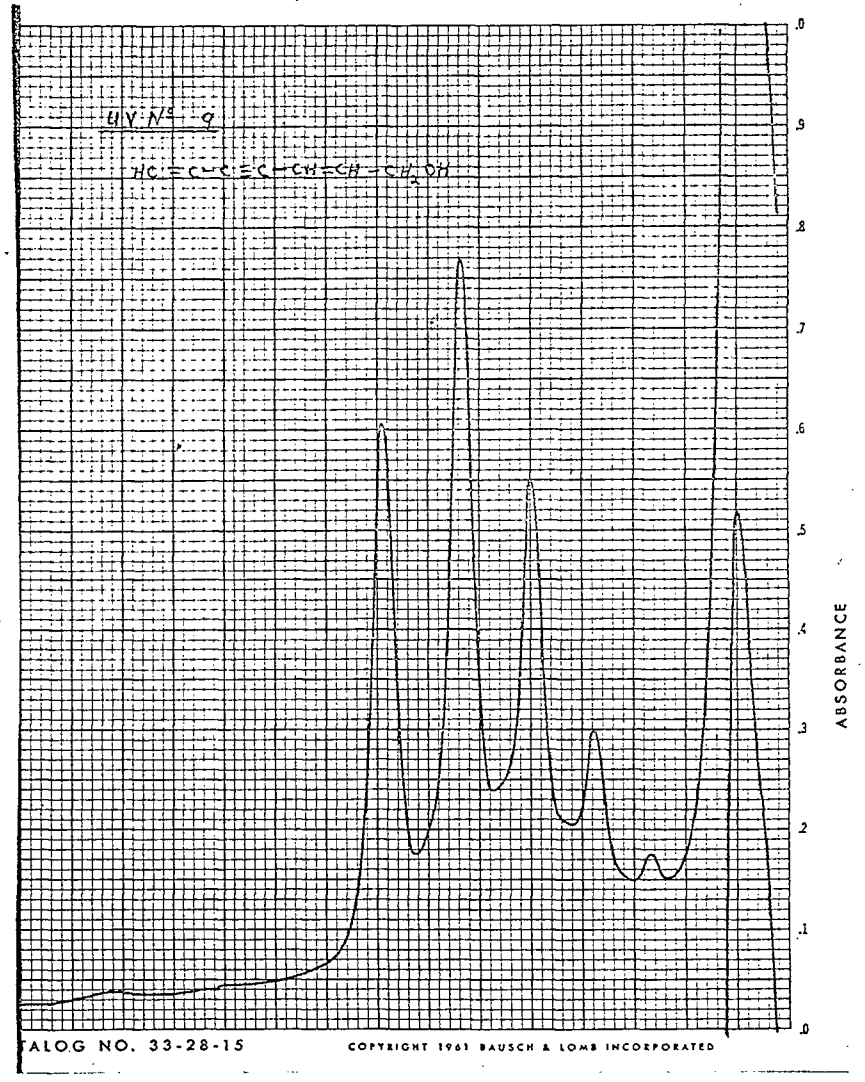
UV N° 9
HC≡C–C≡C–CH=CH–CH2OH
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.1
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1.0
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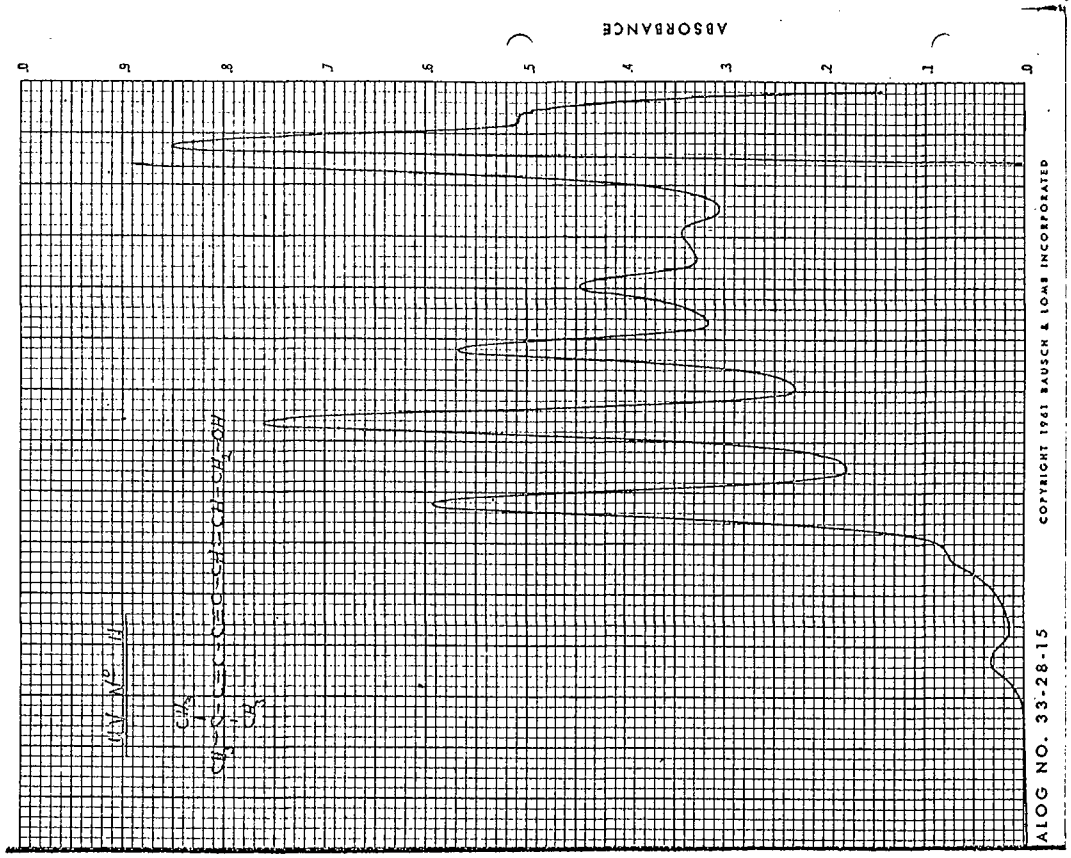
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UV N° 11
CH3
CH3-C≡C-C≡C-C≡C-CH=CH-CH2-CH2-OH
CH3
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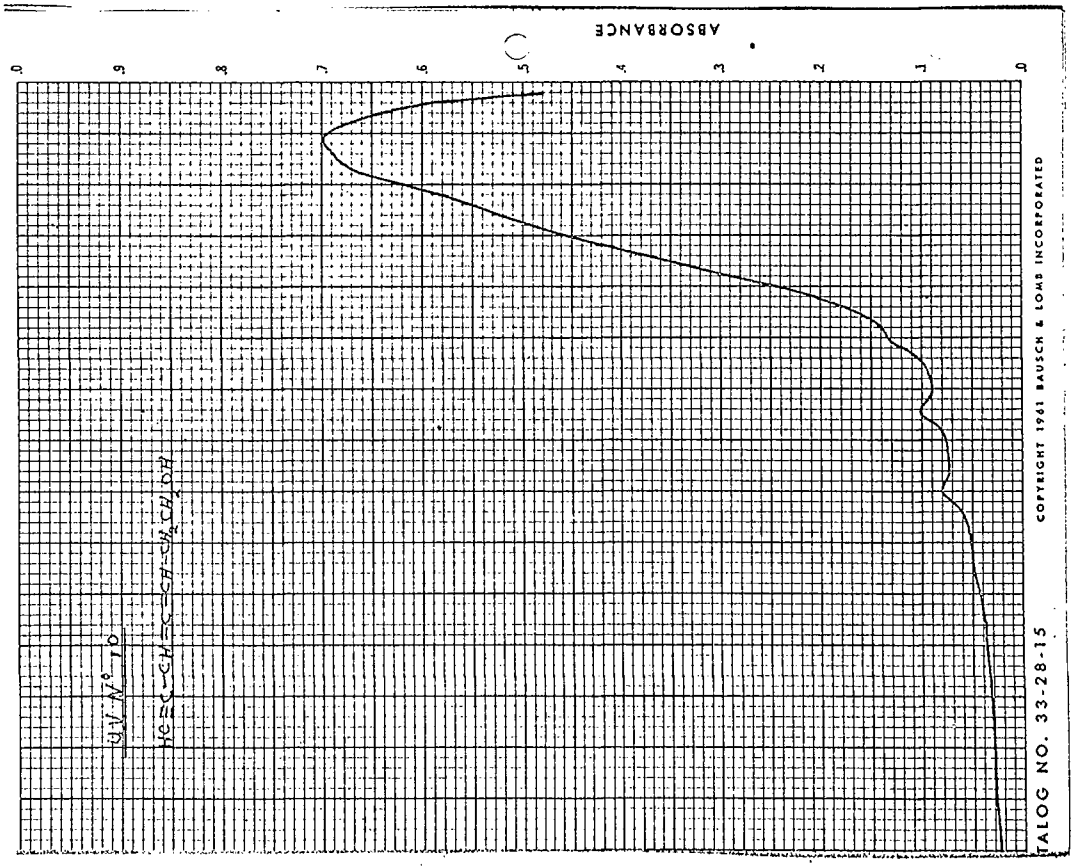
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UV N° 10
HC≡C-CH=C=CH-CH2-CH2OH
ALOG NO. 33-28-15
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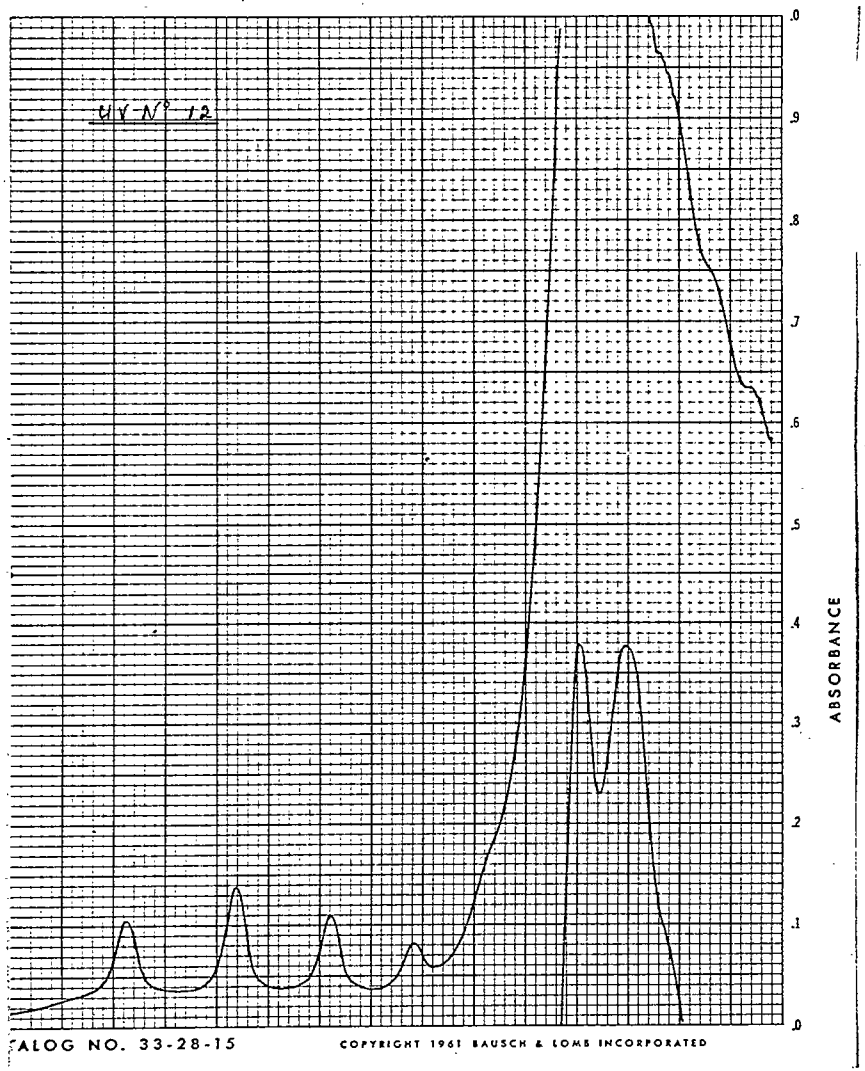
UV-N° 12
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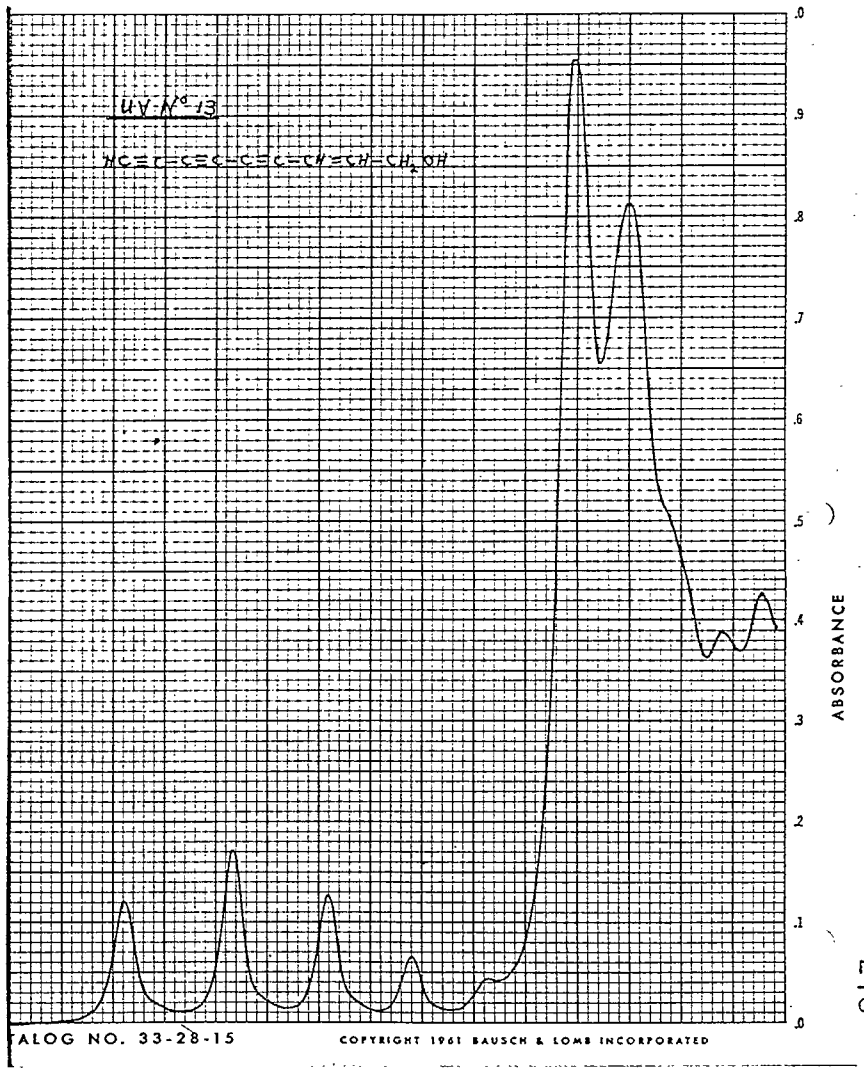
UV-N° 13
HC≡C-C≡C-C≡C-C≡CH-CH2OH
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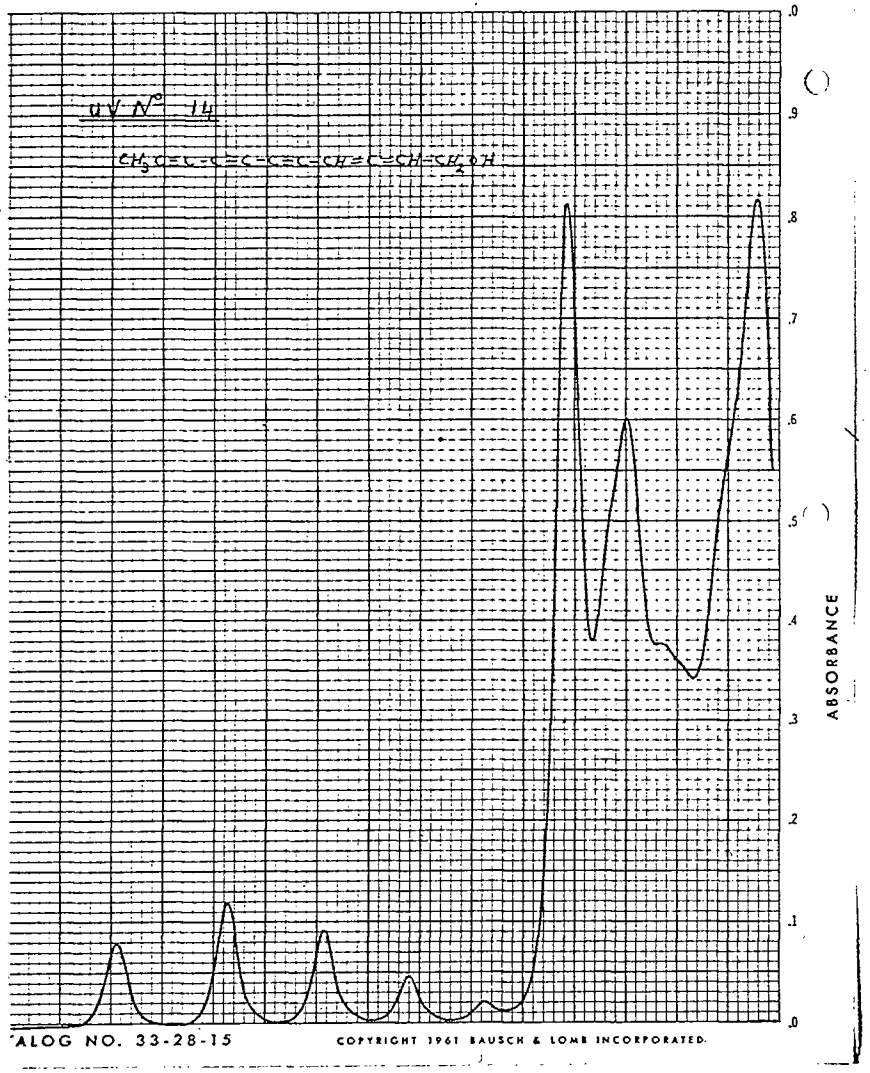
UV N° 14
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.9
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ABSORBANCE
CATALOG NO. 33-28-15
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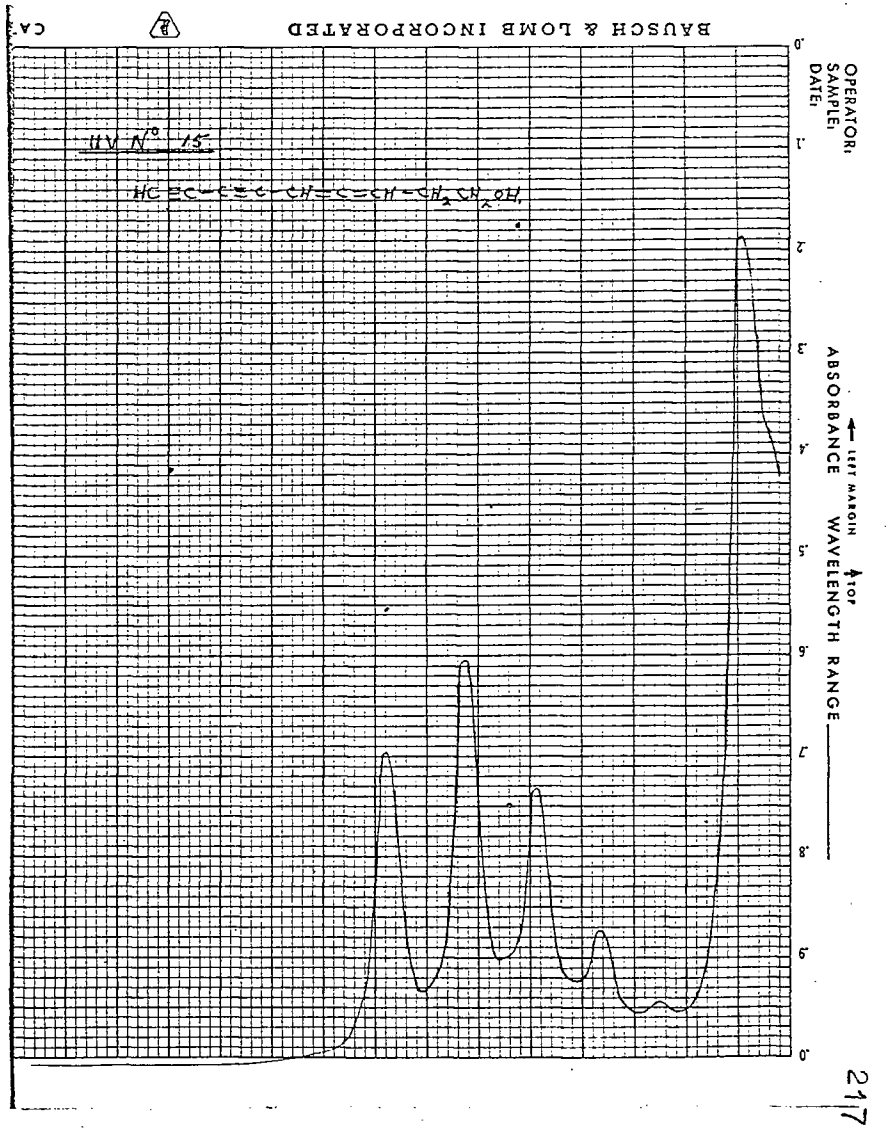
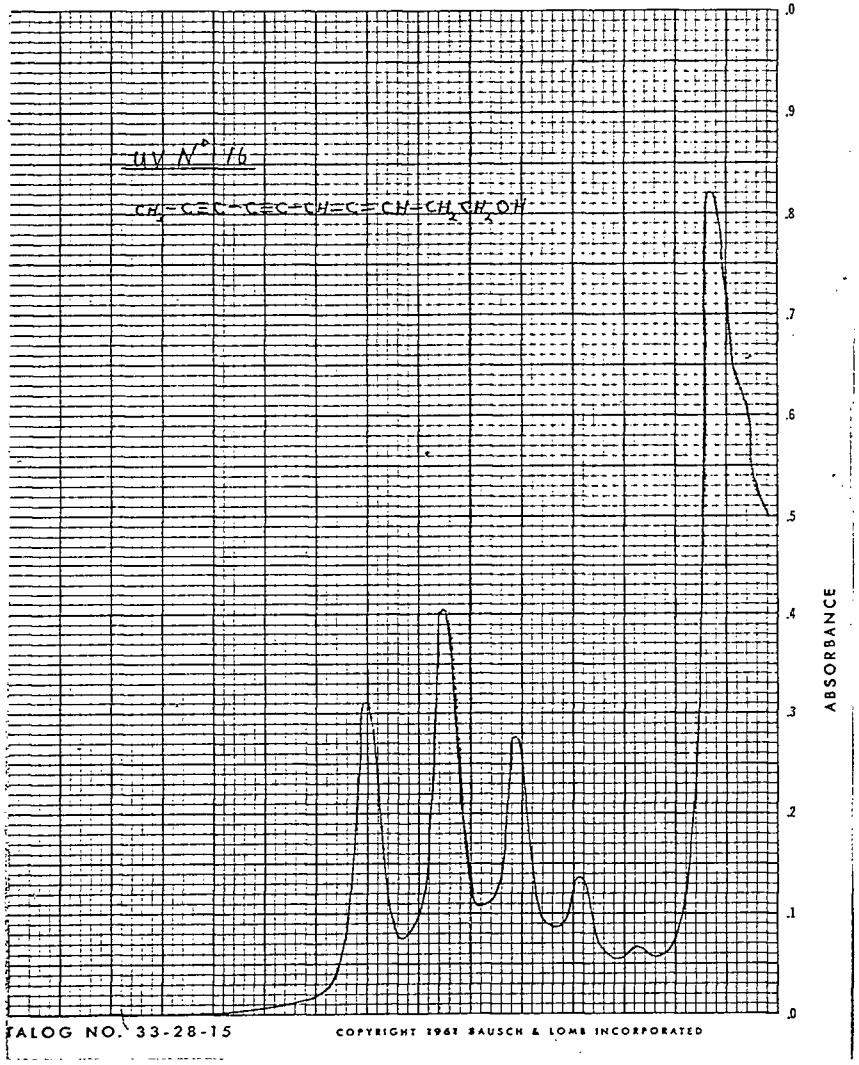

BAUSCH & LOMB INCORPORATED
UV N° 15
$HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH_2CH_2OH$
OPERATOR:
SAMPLE:
DATE:
ABSORBANCE
LEFT MARGIN
TOP
WAVELENGTH RANGE


UV N° 16
$CH_2-C\equiv C-C\equiv C-CH=C=CH-CH_2CH_2OH$
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ABSORBANCE
TALOG NO. 33-28-15
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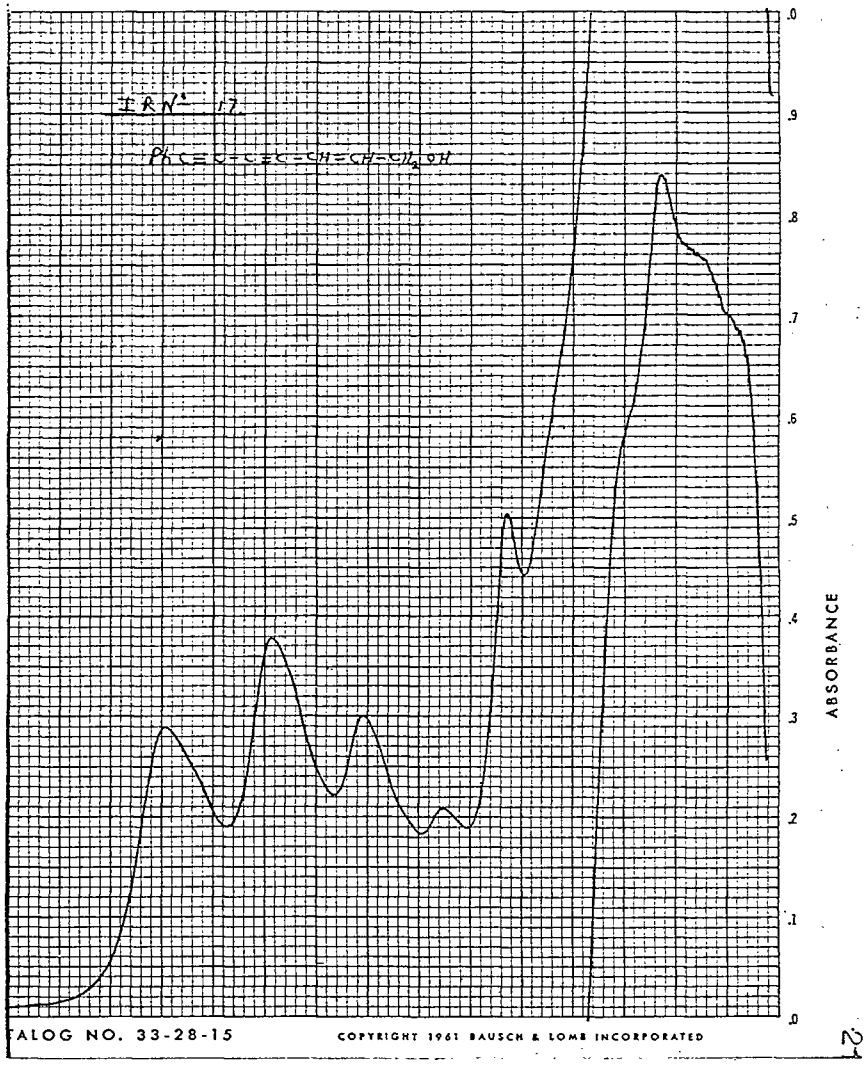
IR N° 17
$Ph-C\equiv C-C\equiv C-CH=CH-CH_2OH$
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.9
.8
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.0
ABSORBANCE
TALOG NO. 33-28-15
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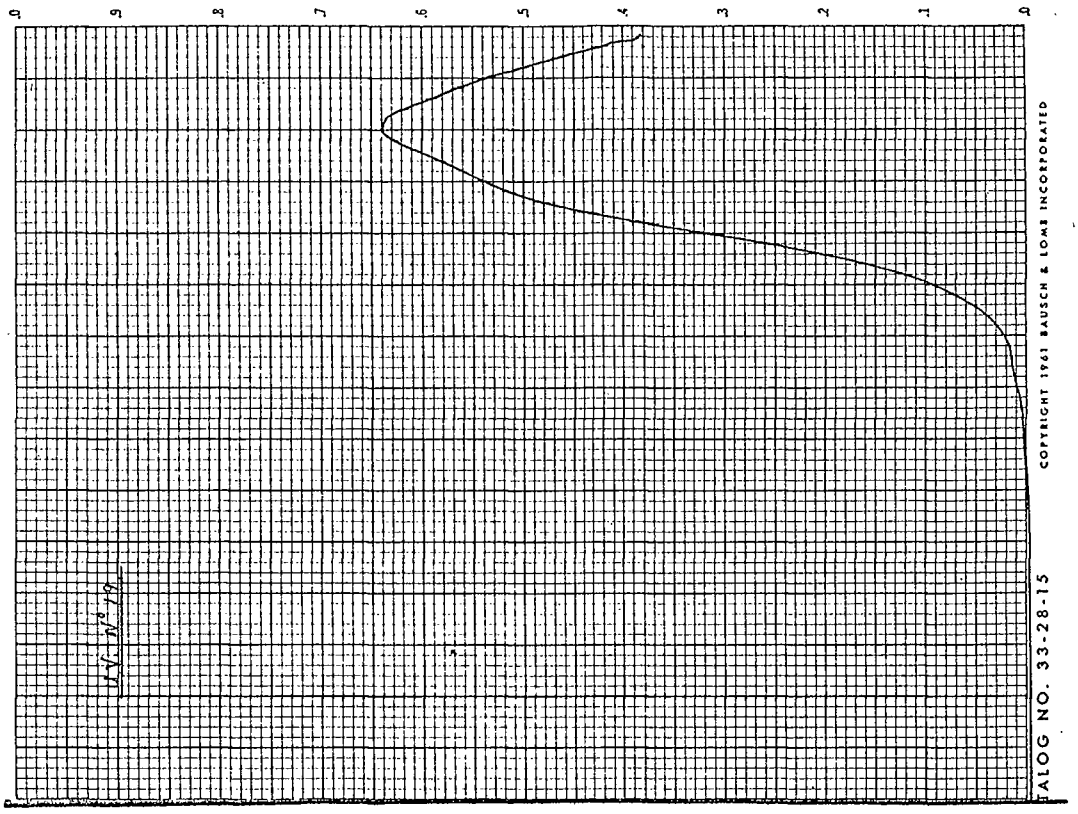
ABSORBANCE
UV. n° 19
CATALOG NO. 33-28-15
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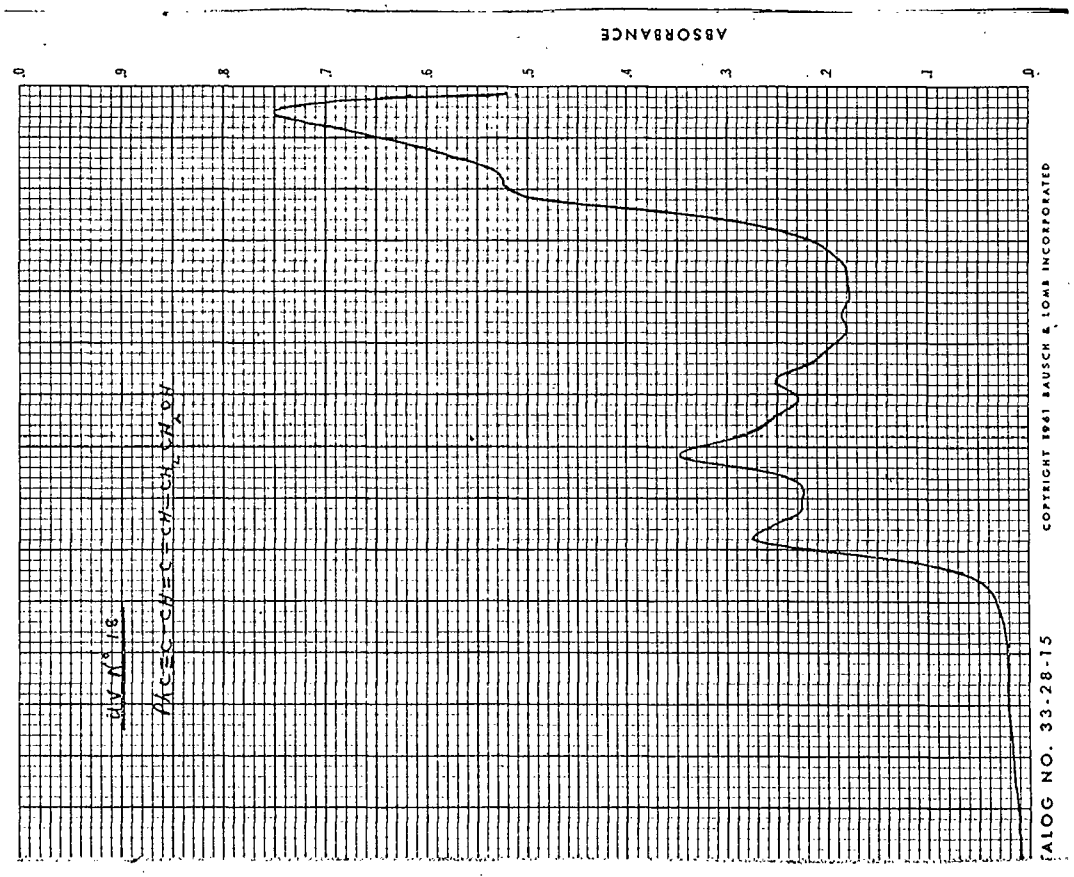
ABSORBANCE
UV. N° 18
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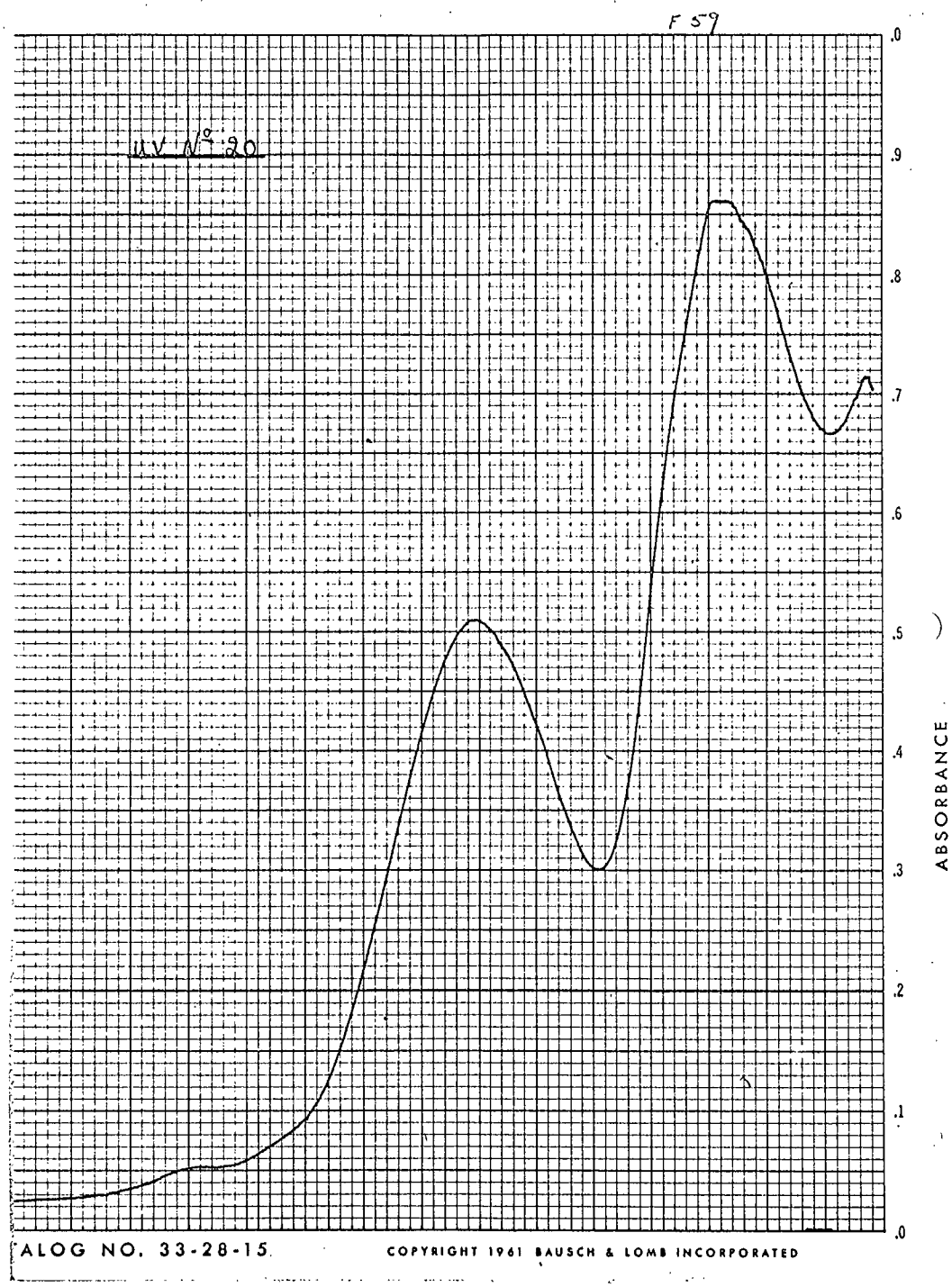
F 59
UV N° 20
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ABSORBANCE
ALOG NO. 33-28-15
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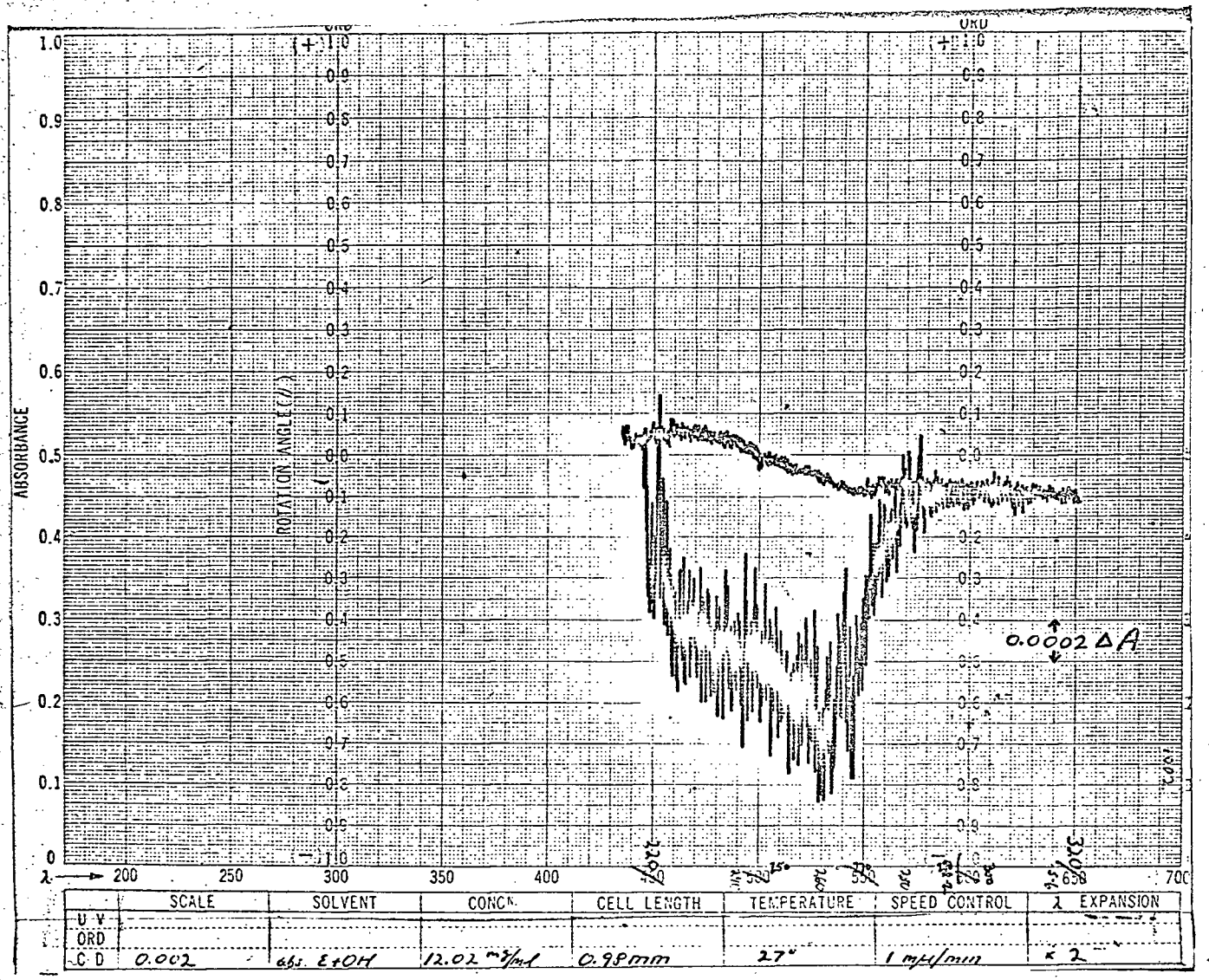

	SCALE	SOLVENT	CONCN.	CELL LENGTH	TEMPERATURE	SPEED CONTROL	λ EXPANSION
U V							
ORD							
C D	0.002	abs. EtOH	12.02 m^3/mol	0.98mm	27°	1 mμ/min	× 2

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