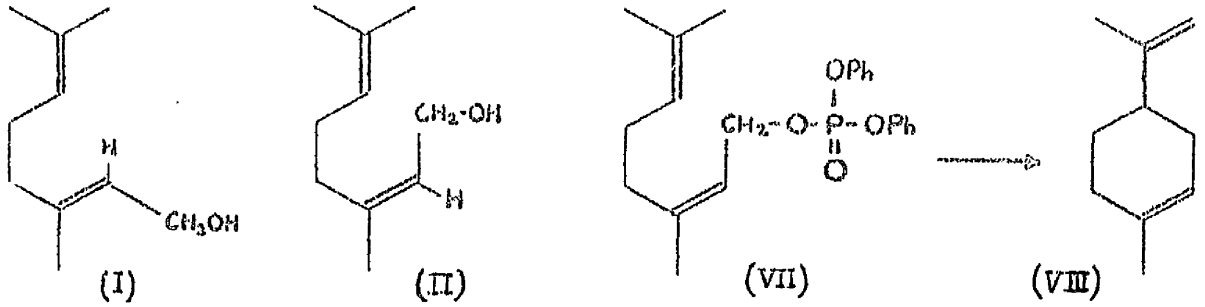
THESIS SUMMARY - J. A. Miller

MODEL EXPERIMENTS IN BIOSYNTHESIS USING PHOSPHATE ESTERS

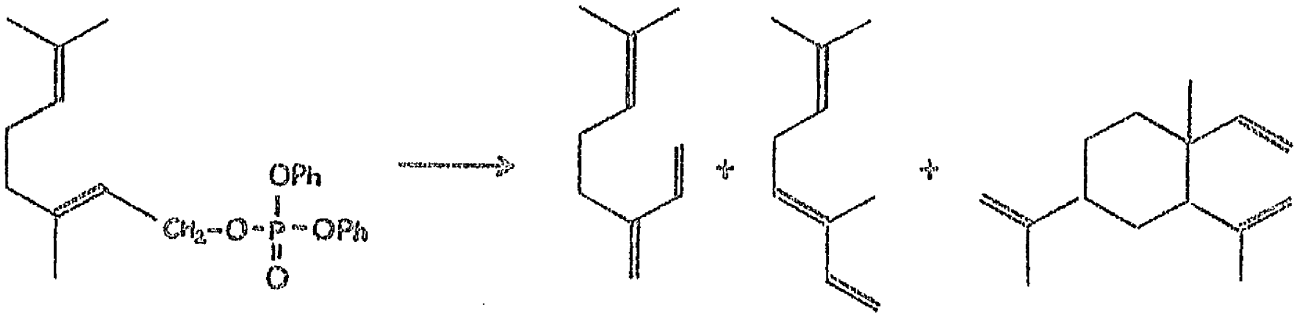
Interest in the chemistry of phosphate esters has been stimulated by recent advances in the knowledge of the role played by these compounds in the biosynthesis of many important molecules including terpenes, steroids, acetylene fatty acids, sugars, proteins and nucleic acids.

Phosphate esters often act as biological alkylating ag and the phosphate or pyrophosphate residue is therefore a leaving-group in these circumstances. The present chemical studies are concerned with the alkylating properties of all and substituted allyl, phosphates, when these are treated w substances containing nucleophilic atoms or groups such as those normally found in nature.

The diphenyl phosphates of the monoterpenoid alcohols, geraniol (I) and nerol (II), have been decomposed by allowi them to stand in an inert solvent. Geranyl diphenyl phosphate (III) has been found to decompose to the monoter- penoid hydrocarbons myrcene (IV) and ocimene (V), and the sesquiterpenoid hydrocarbon, β-elemene (VI). Neryl diphenyl phosphate (VII) decomposed mainly to limonene (VIII), a monocyclic, monoterpenoid hydrocarbon, and two other, unknown hydrocarbons.

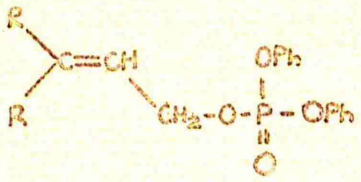


(I) (II) (VII) (VIII)



(III) (IV) (V) (VI)

Allyl diphenyl phosphate (IX, R = H) and 3,3-dialkylall
diphenyl phosphates (IX) have been found to alkylate phenols
Phenol and allyl diphenyl phosphate produced allyl phenyl et
o-allyl phenol, p-allyl phenol and diphenyl hydrogen phospha
when heated together, and the latter has been found to be
responsible for the subsequent rearrangement of each of the
initial products to 2-methylcoumaran (X). The 3,3-dialkyl
allyl diphenyl phosphates invariably produced 2,2-dialkyl-
chromans from phenols, and this general reaction was used to
synthesize several natural products, including α-tocopherol
and iso-grifolin (XII). Although a derivative of vitamin K_1
(XIII) was obtained by an analogous reaction, the vitamin
itself was not prepared because it was found impossible to
prevent the formation of a chroman structure.



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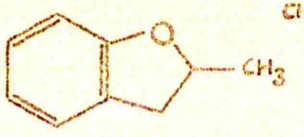

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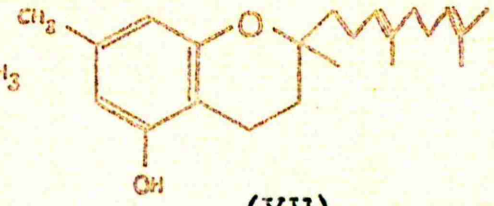

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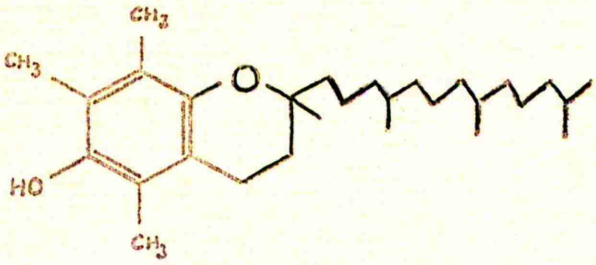

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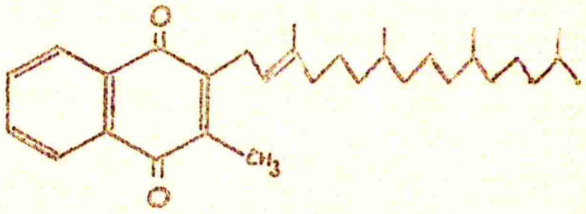

(XIII)

Further studies of the properties of allyl diphenyl phosphate (IX, R = H) have shown that thiols can be alkylated to produce allyl sulphides, and that dialkyl sulphides can be converted to allyl dialkyl sulphonium salts on treatment with the phosphate.

In each of the model systems described above, considerable attention has been paid to the mechanisms and the possible implications of the alkylation reactions.

These reactions, in which allyl diaryl phosphates, and 3,3-dialkylallyl diaryl phosphates act as alkylating agents, demonstrate conclusively that the diphenyl phosphate anion is a good leaving-group from carbon undergoing nucleophilic attack in in vitro systems. Furthermore, these model

experiments often result in products so similar to those found in biological systems, that they can be used to provide chemical evidence in support of postulated biosynthetic schemes.

MODEL EXPERIMENTS IN BIOSYNTHESIS

USING PHOSPHATE ESTERS

A T H E S I S

submitted to

THE UNIVERSITY OF GLASGOW

in fulfilment of the

requirements for the

DEGREE OF DOCTOR OF PHILOSOPHY

by

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UNIVERSITY OF STRATHCLYDE

Glasgow, C.1.

JULY, 1965.

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

The author would like to express his thanks to Dr. H. C. S. Wood for the encouragement and guidance which made this thesis possible. The author would also like to record his debt to Professor P. L. Pauson for laboratory facilities, to Dr. P. Bladon for aid in spectral and gas-liquid chromatographic studies, and to Dr. G. R. Proctor for micro-analyses.

The author would like to acknowledge the award of a Research Studentship from the Department of Scientific and Industrial Research.

OBJECTIVES

The aim of this Thesis was to synthesise and investigate the properties of allyl- and 3,3-dialkylallyl diaryl phosphates. In particular, a study was made of the alkylating properties of these phosphates, when attacked by different nucleophiles. The phosphates and nucleophiles used in these studies were chosen with a view to model experiments in biosynthesis.

S U M M A R Y

The synthesis of a range of allyl- and 3,3-dialkylallyl diaryl phosphates has been achieved. Some of these esters, notably the polyisoprenoid phosphates, have been found to be extremely unstable, and to decompose spontaneously.

All the allyl- and 3,3-dialkylallyl diaryl phosphates studied were found to eliminate diaryl phosphate readily, when attacked by different nucleophiles, and are therefore alkylating agents. The nucleophiles used included alkenes, the oxygen atom and anionoid ring-positions of phenols, and the sulphur atom of thiols and sulphides. The efficiency of these alkylations varied greatly from system to system, and was very sensitive to changes in solvent, and to changes in the stereochemistry of the reactants.

The experiments with terpenoid phosphates, and those concerned with alkylation of phenols, are believed to have some chemical significance, as models for the biosynthesis of terpenes and phenolic isoprenoids.

CONTENTS

INTRODUCTION

It is only within the last two decades that organic chemists have begun to take an interest in, and make systematic studies of, the properties of phosphate esters. Prior to this, the known chemistry of phosphate compounds had been mainly confined to that derived from the reactions of ortho- and pyrophosphoric acids. Due to the polybasic nature of these acids, much of these chemical studies had not been properly understood and some of the conclusions reached have since been found to be erroneous, often because of over-simplification.

Gradually, however, it was realized that phosphates play an unusually important role in biological systems, ranging from their structural function in the hereditary material, deoxyribonucleic acid (D.N.A), to their part as intermediates in biochemical syntheses. This realisation has quickly led to investigations of the properties of phosphate esters, especially of those which are analogous to phosphates of biological importance, and this thesis is primarily concerned with the chemistry of some of these esters.

There is a surprising variation in the detail known to chemists and biochemists, of the mechanisms of biological reactions involving phosphates. In some cases the individual stages of a complicated biosynthesis are known, while in others

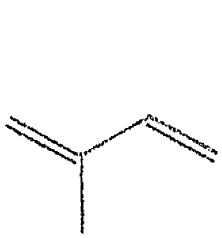
there is merely scant evidence for the participation of phosphate esters. Occasionally, paper schemes have been proposed for the biosynthesis of a class of naturally occurring compounds, which could arise from phosphate esters by an acceptable mechanism, long before there is any evidence that phosphates are in fact involved.

BIOSYNTHESIS OF POLYISOPRENOIDS:

One of the most exciting chapters in modern organic chemistry concerns the elucidation of the biosynthetic pathway of terpenoid, carotenoid and steroid compounds, a pathway in which phosphate esters are intimately concerned. Although it was known in 1937[1] that labelled acetate is incorporatedinto ergosterol, it is only within the past twelve years that rapid progress has been made in elucidating the intermediate steps between acetate and the sterols.

Terpenes have long attracted the attention of chemists, presumably because of their often attractive aromas and relative ease of isolation, and theories about a possible common method of biosynthesis have been made ever since the late nineteenth century,[2] by which time many terpenes had been isolated and purified, and some of their structures assigned. The theory which has best stood the test of time, is the isoprene rule, postulating that all terpenes are synthesised *in vivo* by a

mechanism which involves the 'head' to 'tail' linkage of two or more molecules of a C_5-hydrocarbon, isoprene (1). This theory arose, because, structurally, many terpenes could be derived from a branched C_5-unit possessing the same carbon skeleton as isoprene. Although many famous names, such as Tilden, Wallach, Tiemann and Willstätter, are associated with the first ideas leading to the rule, it is the name of Ruzicka, which one connects with its full enunciation and development.[2]



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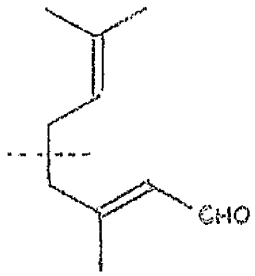
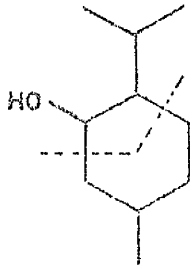
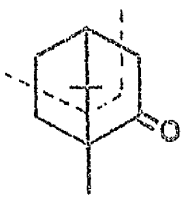


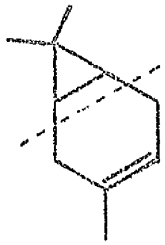
CITRAL



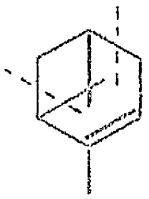
MENTHOL



CAMPHOR



Δ^3-CARENE



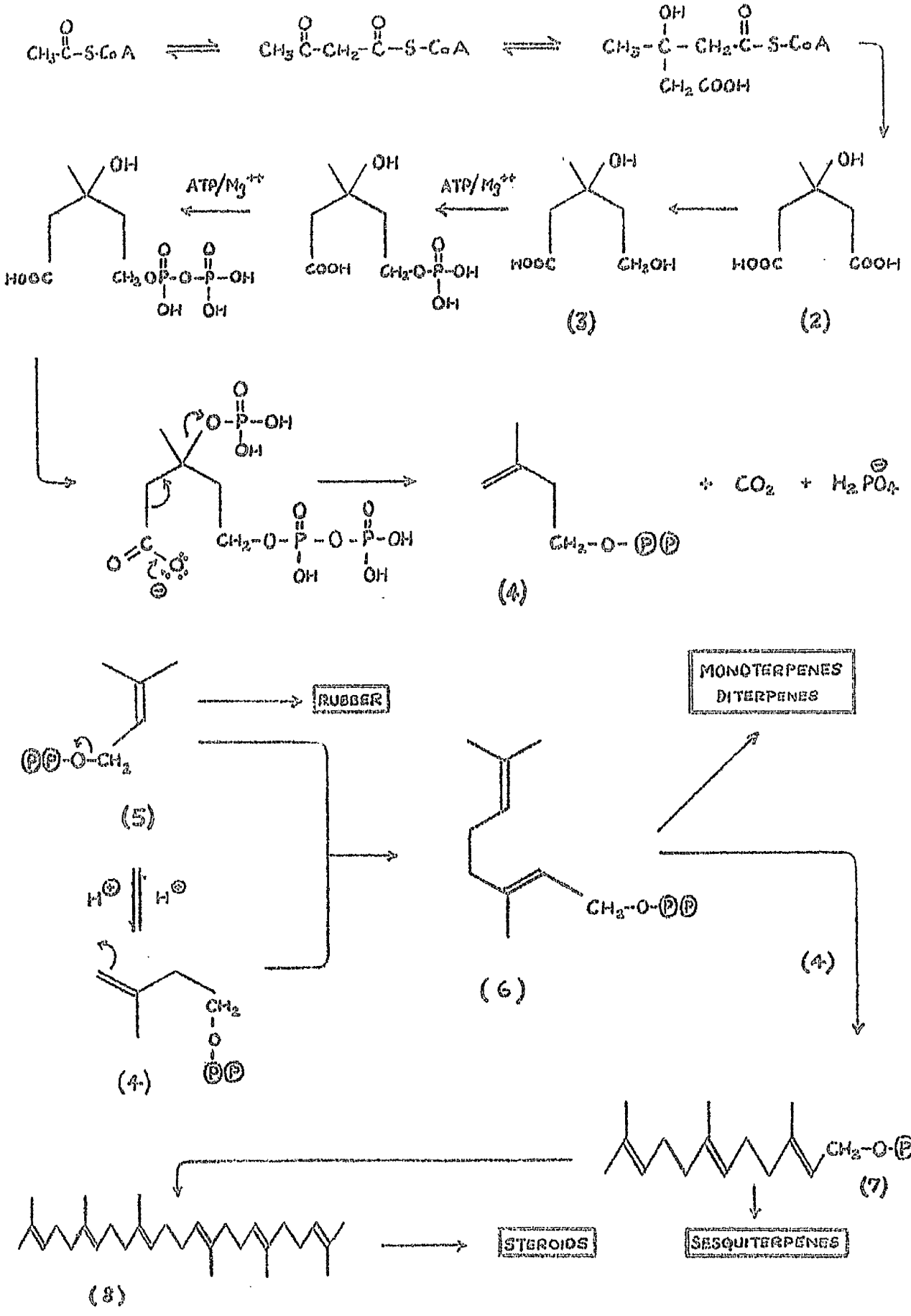
α-PINENE

The recent work of Bloch, Lynen, Folkers, Popjak and Cornforth, and others, has led to a brilliant explanation of why terpenes and other polyisoprenoids are built in multiples of 'isoprene' units. Perhaps the biggest single contribution to this biosynthetic work was the discovery, in 1956, by Folkers and co-workers,[3] of mevalonic acid (3), a substance which not only

had the basis of an isoprene unit in its structure, but which could also be formed by the condensation of three molecules of acetate, in the form of acetyl co-enzyme A, and reduction of the resultant 3-hydroxy-3-methyl glutaric acid (2), which had been recognised for some time[4,5] as a vital intermediate between acetate and the sterols. Since mevalonic acid (3) possesses six carbon atoms, experimental evidence was soon sought to demonstrate which carbon was lost during its conversion to a C_5 unit, and Folkers showed[6] that the carboxyl carbon was in fact eliminated. Although it was also known that phosphorylated intermediates were involved in the decomposition of mevalonic acid,[7] it was some time before the isolation and identification of isopentenyl pyrophosphate (4)[8,9] finally established the claim of a C_5 isoprene unit as the basic building block of terpenoid biosynthesis.

The evidence for the isomerisation of this pyrophosphate to 3,3-dimethylallyl pyrophosphate (5)[10] followed rapidly, and all the vital intermediates between acetate and squalene (8) had thus been identified, since the role of geranyl pyrophosphate (6)[10] and farnesyl pyrophosphate (7)[9] had previously been elucidated Apart from the exact mechanism of the tail-to-tail coupling of farnesyl pyrophosphate (7) to give squalene (8), the sequence from acetate to the sterols and other polyisoprenoids is now well authenticated, and appears on the following page.

BIOSYNTHESIS OF POLYISOPRENOIDS

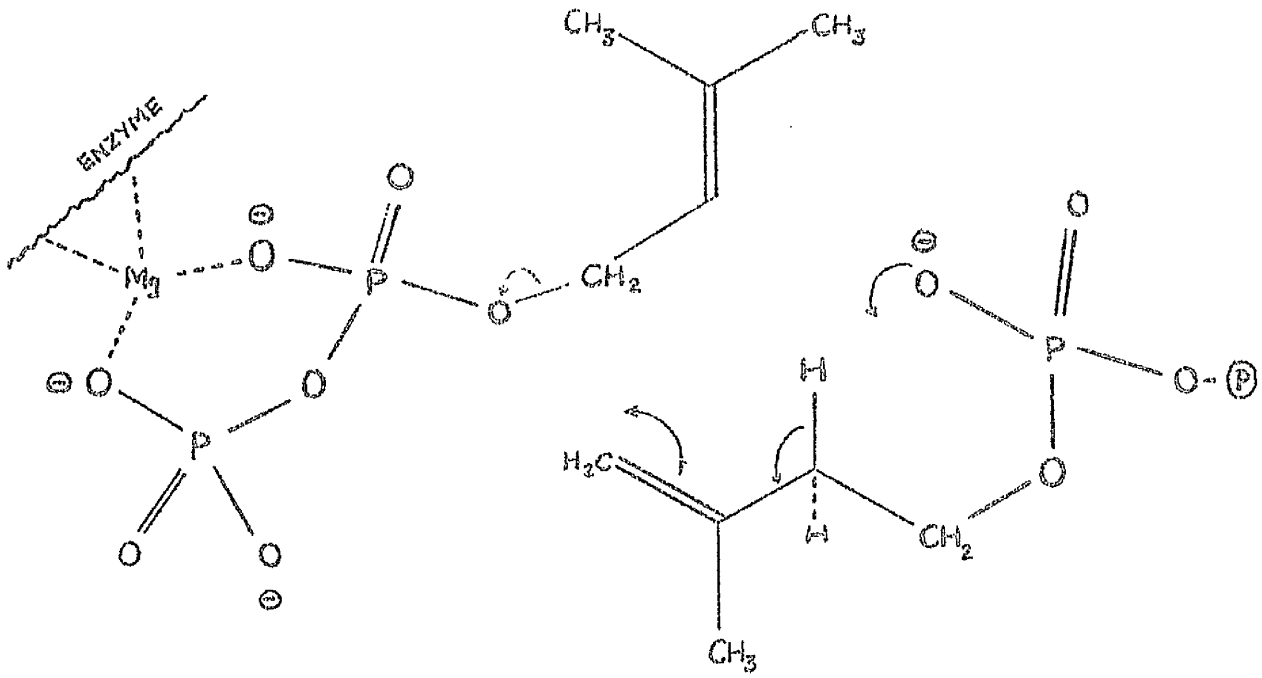


The new reactions in this sequence are the simultaneous decarboxylation and "dehydration" of mevalonic acid-5-pyrophosphate, and the C_5-coupling reaction involving olefinic attack at the allyl position of a pyrophosphate.[11] In each case the phosphorus moiety acts as a leaving-group, the result of intramolecular decarboxylation in mevalonate and of C-C bond formation in the coupling reaction.

It is worthy of note, that, while geranyl pyrophosphate has definitely been established as the immediate precursor of farnesyl pyrophosphate and squalene, there is no direct evidence that geranyl pyrophosphate is the precursor of all monoterpenoid compounds.[12] Because of the trans structure of geranyl pyrophosphate, it does indeed seem likely that it is the precursor of acyclic monoterpenes such as myrcene, but the mono- or bicyclic monoterpenes would appear to arise, structurally at least, from a cis-geranyl (or neryl) pyrophosphate. What little tracer study that has been made of the biosynthesis of cyclic monoterpenes, has shown merely that they are derived from mevalonate[13], or C_5 precursors.[14,15]

There is still disagreement as to the exact mechanism of the C_5-coupling reaction, notably over the question of its being a synchronised process,[16,17] or one involving generation of allyl carbonium ions.[18] Konowar[17] even regards the process

as being assisted by the pyrophosphate residue of the isopentenyl-pyrophosphate.

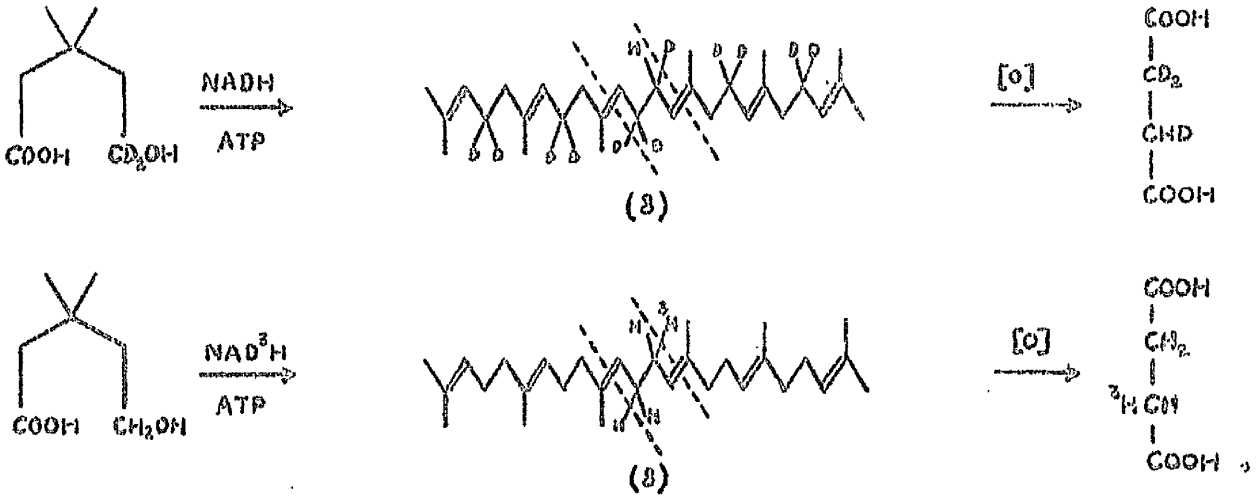


CONCERTED C_5-COUPLING

BIOSYNTHESIS OF SQUALENE FROM FARNESOL:

It has been noted previously that the details of the C_{30}-coupling reaction, converting farnesyl pyrophosphate to squalene, are still not known with certainty, and several schemes, such as those of Lynen,[9] Woodward,[19] and Cornforth[19,20] have had to be discarded because they did not fit the facts

gained from tracer studies and stereochemical considerations. Preliminary experiments showed that two molecules of farnesyl pyrophosphate (later shown to be trans-trans)[11] are required and that the coupling was reductive, requiring the presence of reduced tripyridinenucleotide (NADH).[21] Later work by Cornforth and Popjak[19] showed that squalene synthesised from 5-D_2-mevalonic acid contains only 11, and not 12, deutero atoms, and that the succinic acid produced by ozonolysis of the labelled squalene contained only 3 deutero atoms. This meant that one of the hydrogens on the carbons at the centre of the squalene had come from a source other than mevalonate, and further tracer work on NAD^{3}H showed that the nucleotide supplied this other hydrogen.



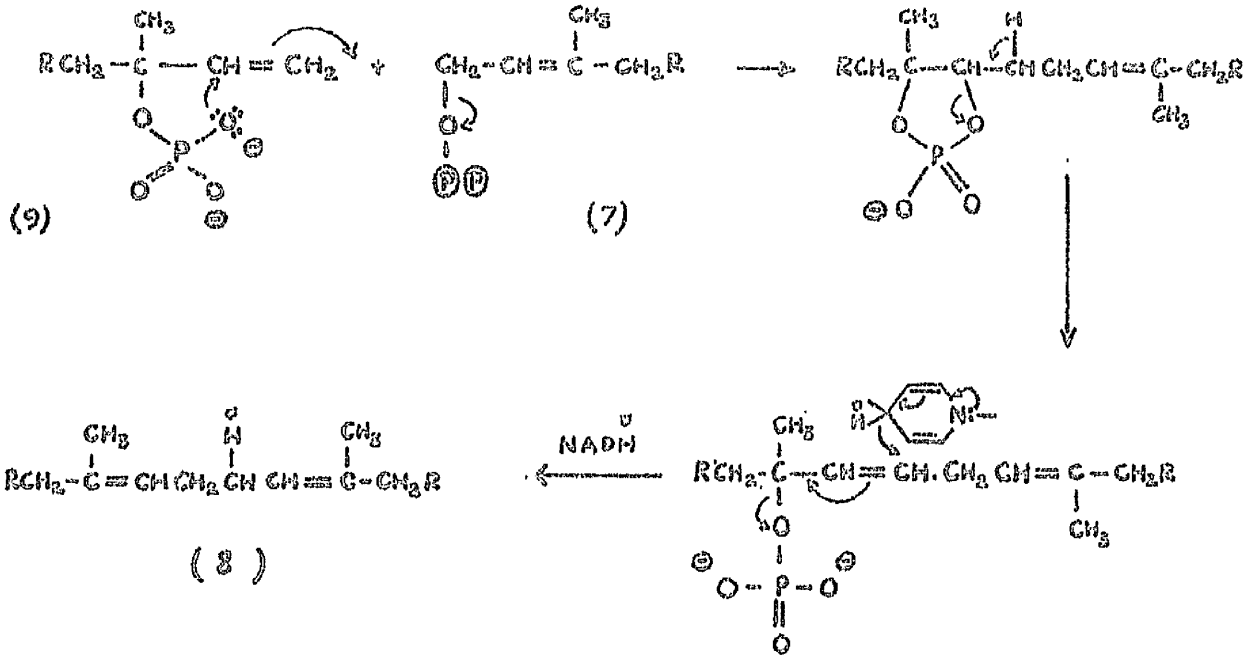
H = HYDROGEN ; D = DEUTERIUM ; ^{3}H = TRITIUM.

More recent experiments have shown that the hydrogen replacement is highly stereo-specific,[22,23] and is thus likely to have occurred on an intermediate more advanced in the biosynthetic pathway than farnesyl pyrophosphate. For several years, Popjak and Cornforth[19] held to a scheme involving preliminary isomerisation of one molecule of farnesyl pyrophosphate (7) to nerolidol pyrophosphate (9), with subsequent coupling by a mechanism similar to the C_5-coupling reactions discussed previously, but recently their group have considered another mechanism involving the rearrangement of a sulphonium salt.[24] They found that the nerolidol-mechanism did not fit all the required stereochemical facts, and was made less likely by the failure to isolate nerolidol-derivatives[19] from squalene-synthesising media, and by the fact that thiol intermediates were shown[19] to be vital.

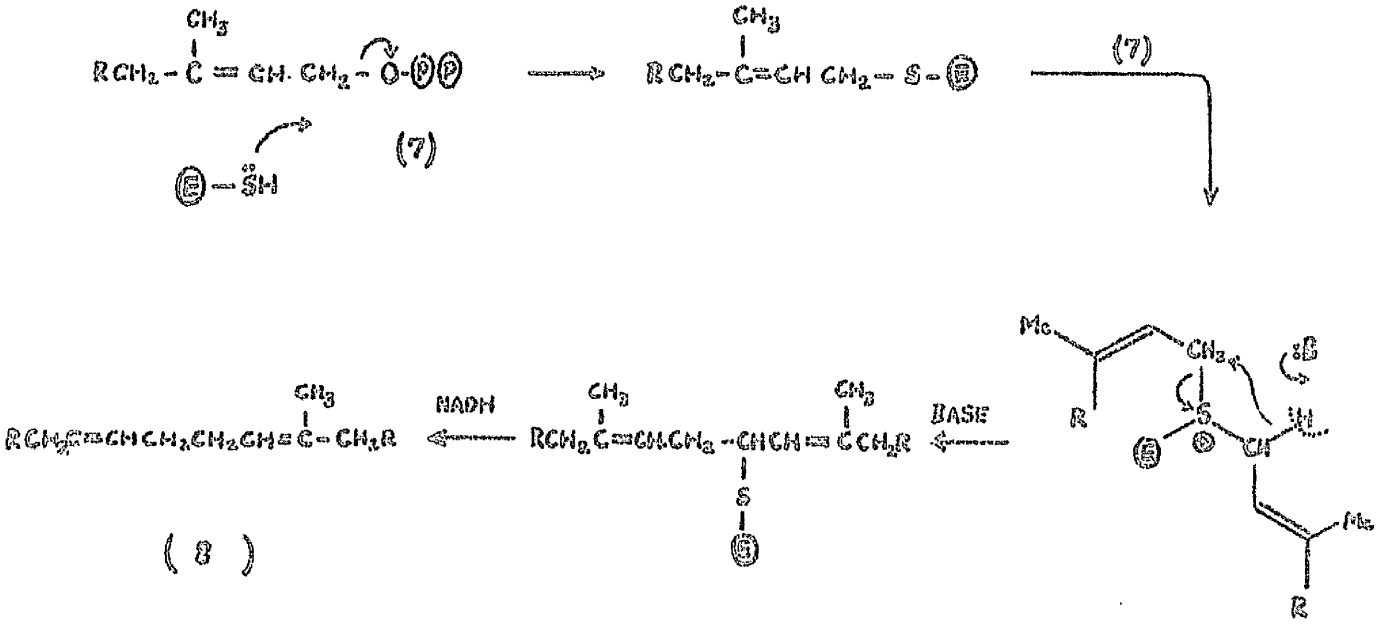
The current scheme of Cornforth and Popjak involves di-alkylation of an enzyme thiol by farnesyl pyrophosphate, in which the pyrophosphate again acts as a leaving group, and a Stevens-type Rearrangement[25] of the subsequent sulphonium salt. The introduction of the hydrogen from NADH comes in the last stage, during which the enzyme thiol is regenerated. Although there is no direct experimental evidence for this scheme, it is quite acceptable on chemical grounds, and above all is in agreement with all the tracer results and all the stereochemical requirements of the coupling. (see page 11).

THE BIOSYNTHESIS OF SQUALENE FROM FARNESOL PYROPHOSPHATE

1. NEROLIDOL MECHANISM :



2. SULPHUR MECHANISM :



R = 

Ⓔ = ENZYME

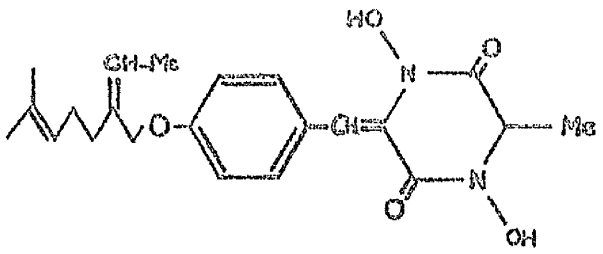
:B = BASE

The conversion of squalene to tetracyclic triterpene has been shown to be a concerted process possibly started by $\oplus_{OH}$[26] occurring from both ends of the squalene molecule,[28] but since this does not involve phosphate esters, the detailed mechanism is not relevant to the present discussion.

Considerable attention has been paid to the description of the experimental results leading to the elucidation of the biosynthesis of isoprenoid molecules, because of the recognition, that followed, of the importance of phosphate esters in biosynthesis. Furthermore, the mechanisms by which these esters have been found to react, in the formation of carbon-carbon bonds, have since been applied with confidence to the suggested biosynthesis of other important naturally occurring compounds, about which far less experimental detail has been available.

PHENOLIC ISOPRENOIDS:

A particularly striking example of this, has been the proposed biosynthesis[27] of a class of compounds, known as phenolic isoprenoids, which occur widely throughout nature, and which, as their name implies, can be derived structurally from a phenol and a C_5-fragment, of isoprene skeleton. Examples are given below of phenolic isoprenoids found in nature. It will be immediately obvious that the members of this short list of examples can be derived structurally by C_5-alkylation of different phenols, [page 13] including phenol itself, hydroquinone, resorcinol, acyl resorcinol and phloroglucinol, p-hydroxy benzoic acid and 1,4-dihydroxy-naphthalene. Furthermore it will be seen that alkylation is not confined to C_5-units, but can occur with longer, polyiso-prenoid groups, and, that once an isoprenoid residue is introduced, it is frequently altered by ring-closure, hydration, rearrangement, or even oxidation. The only tracer work that has been carried out on compounds of this class has been that of Birch[28,29] who studied the biosynthesis of mycolianamide (10) and mycophenol (11), metabolites of Penicillium Griseofulvum Dierckx and Penicillium Brevi-compactum, respectively, and of auroglaucin[30], another mould metabolite (12).



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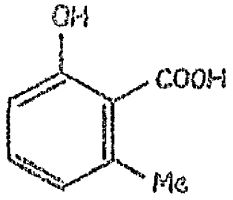

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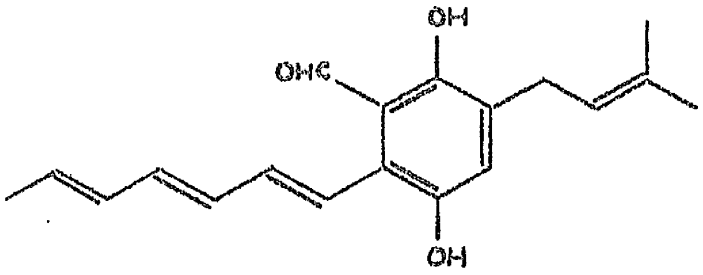

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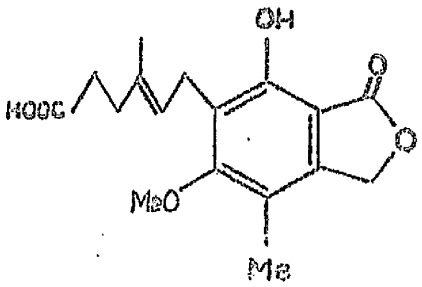


(11)

When ^{14}C-carboxyl-labelled acetic acid was fed to the fungus producing mycophenol, Birch found[30,29] that the label was incorporated equally into the phenolic part, and the isoprenoid part, which was considered to have arisen from oxidation of a geranyl residue. Previously,[31] Birch had shown that the 6-methyl salicylic acid skeleton (13) arises *in vivo* from four units of acetate, and the phthalide system of mycophenol is derived from this.

Later work by Birch[32] showed that ββ-dimethyl acrylic acid was not directly incorporated into mycophenol, but that it was

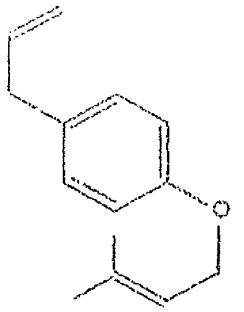
probably degraded to acetate before incorporation. Birch then proved[33,34] that mevalonic acid was incorporated directly into mycophenol, and that the labelling was confined to the side-chain. Although Birch was unable to show then a mechanism whereby mevalonate was converted into an isoprenoid chain, his problem was merely a parallel to that of chemists interested in terpene biosynthesis. Once the identity of 3,3-dimethylallyl pyrophosphate had been established,[10] it was merely a short step to suggest that the linkage of the isoprenoid chain to the phenol occurs by nucleophilic attack of the phenol at the allylic methylene, followed by expulsion of a pyrophosphate group.

It is clear, however, that if phenolic isoprenoids are initially formed by attack on the pyrophosphate of the phenols, either by the oxygen, or either of the ortho- and para- aminoid positions, then there is often a subsequent modification of the isoprenoid residue. This modification will often be seen to involve a ring-closure, followed by an oxidation which may introduce unsaturation or an oxygen function.

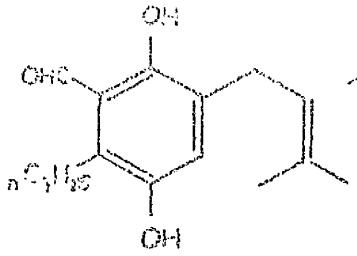
At present there is no experimental evidence[35] that these modifications do occur after the introduction of the isoprenoid side-chain, as shown below, but this does seem the most likely possibility, especially after experiments of Birch and his collaborators. Further support for the proposed scheme comes

PHENOLIC TERPENOIDS:

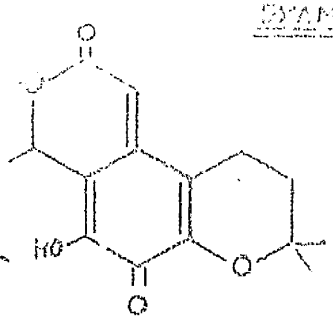
EXAMPLES:



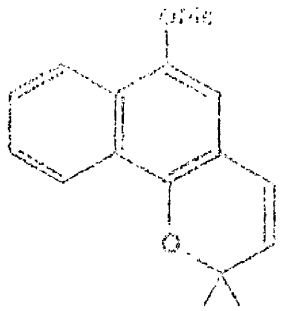
FOENICULIN



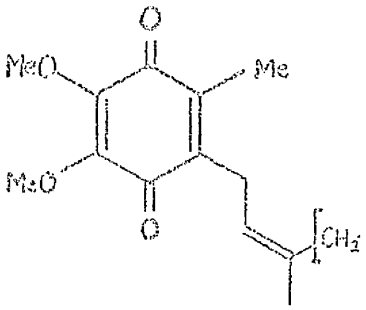
FLAVOGLAUCIN



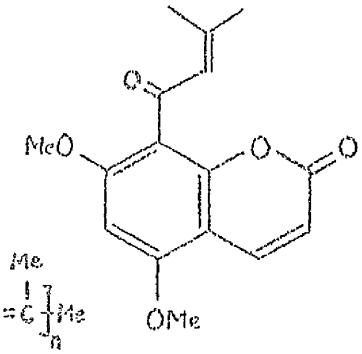
FUSCIN



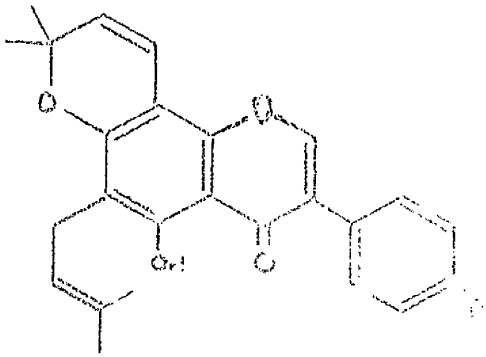
LAPACHOLENOLE



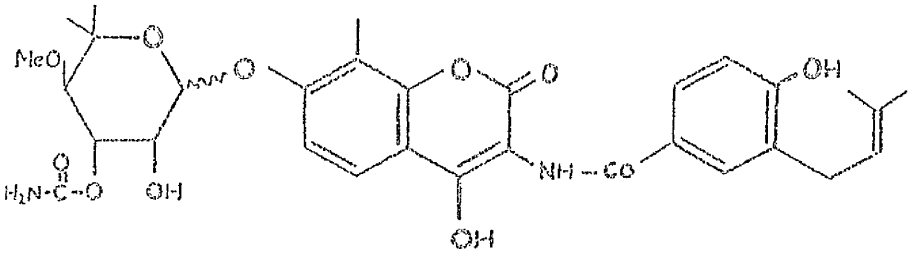
UBIQUINONE (20)



GLABRA LACTONE

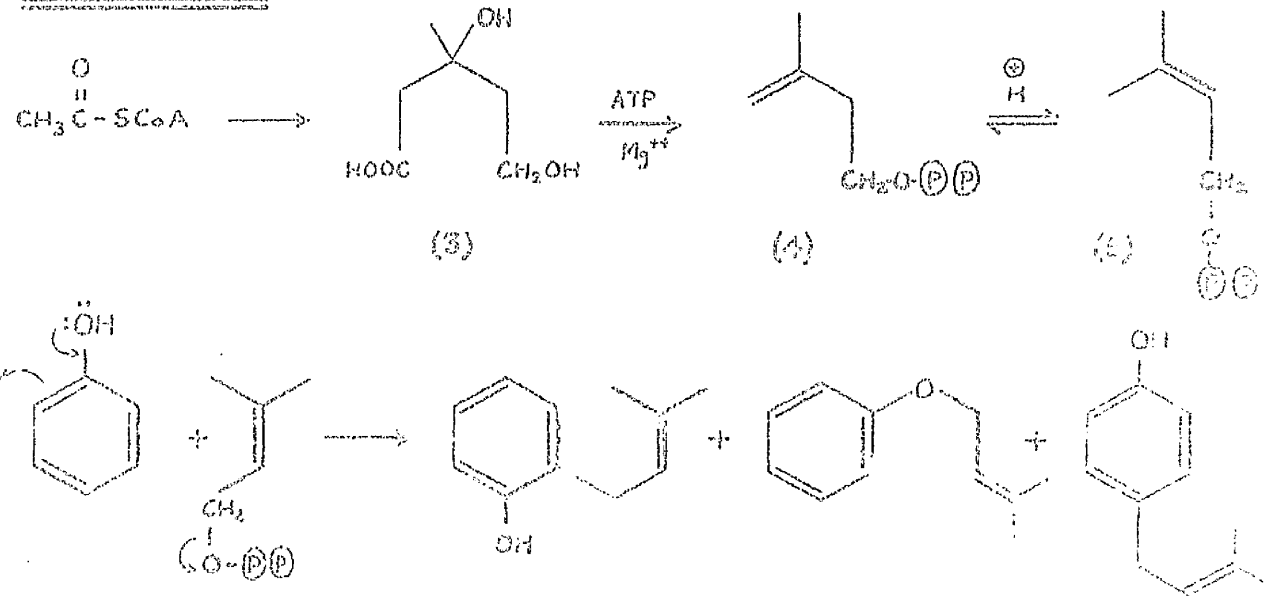


OSAJIN



NOVOBIOCIN (17)

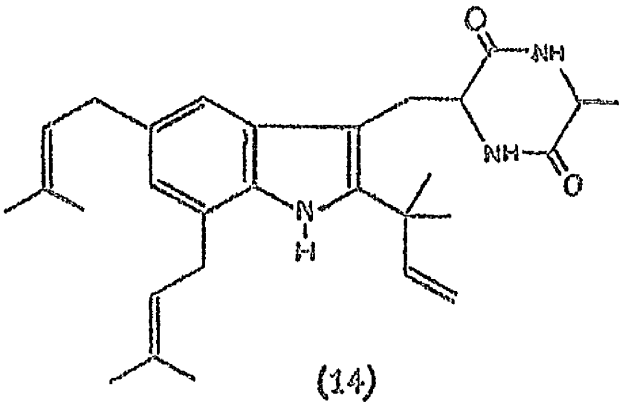
BIOSYNTHESIS:



(3) (4) (5)

from the readily-made observation that the isoprenoid residues are always introduced at anionoid positions in the aromatic rings, being found either ortho- or para- to phenolic, or phenolic derived, groups.

Dimethylallyl groups have recently been found occurring in the non-phenolic natural products, echinulin (14)[36] and triacanthine (15)[37,38] and the mechanism of introduction of the side-chain could well be analogous to that postulated for phenolic isoprenoids. Birch[36] has shown that the indole-nucleus of tryptophan (16) is incorporated into echinulin, and therefore the side-chains ortho- and para- to the nitrogen must be introduced by direct alkylation of the indole system. It has been suggested by Leonard and Deyrup,[38] that triacanthine is formed by reaction between adenosine and 3,3-dimethylallyl pyrophosphate, although they do not cite any experimental evidence in favour of their suggestions.



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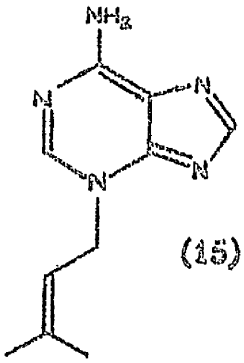

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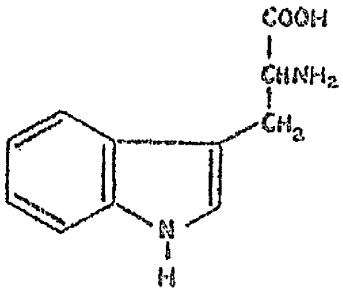
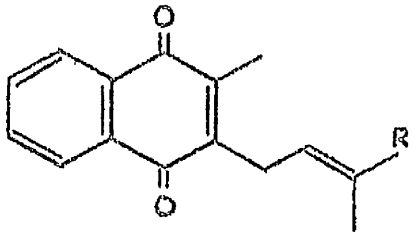
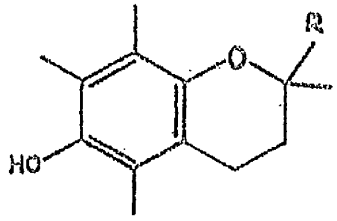


(16)

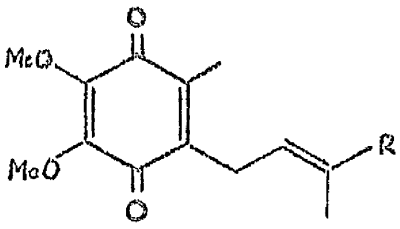
Although the C_5-isoprenoid phenols described above are of wide occurrence in nature, and some of them, such as novobiocin (17),[39] have important antibiotic properties, there is a group of structurally similar compounds, which has even more important and general biological functions, and which includes the vitamins E (18) and K (19) and the co-enzymes Q (ubiquinones) (20).



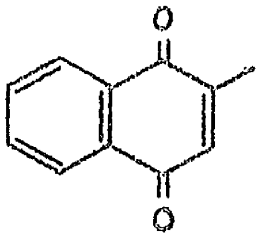
VITAMIN K (19)



VITAMIN E (18)



CO-ENZYME Q (20)



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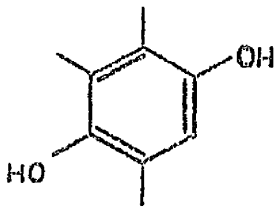

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The vitamins E[40] are a series of compounds possessing a 6-hydroxychroman system, the most important being α-tocopherol (18; R = $C_{16}H_{33}$), which has been found to have anti-sterility

properties in female rats, as well as the more general vitamin E property of being an anti-oxidant. The first syntheses of α-tocopherol carried out in 1938, involved the condensation of pseudocumenol (21) with various phytyl derivatives, such as phytol,[41] phytyl bromide[42] and phytadiene,[43] in the presence of acid catalysts.

The vitamins K[44] have a parent 2-methyl-1,4-naphthoquinone (or menadione) system (22), but the nature of the side-chain varies, in size and in structure, although it is always a substituted allyl group, with an isoprenoid skeleton. The principal function of these vitamins is concerned with their blood-clotting properties, although their part in the process of respiration, by participation in coupled electron-transport and phosphorylation, is just beginning to be understood. Vitamin K was first isolated in 1939, and its synthesis the same year was achieved by condensing 2-methyl-1,4-naphthoquinol with phytyl derivatives.[45,46]

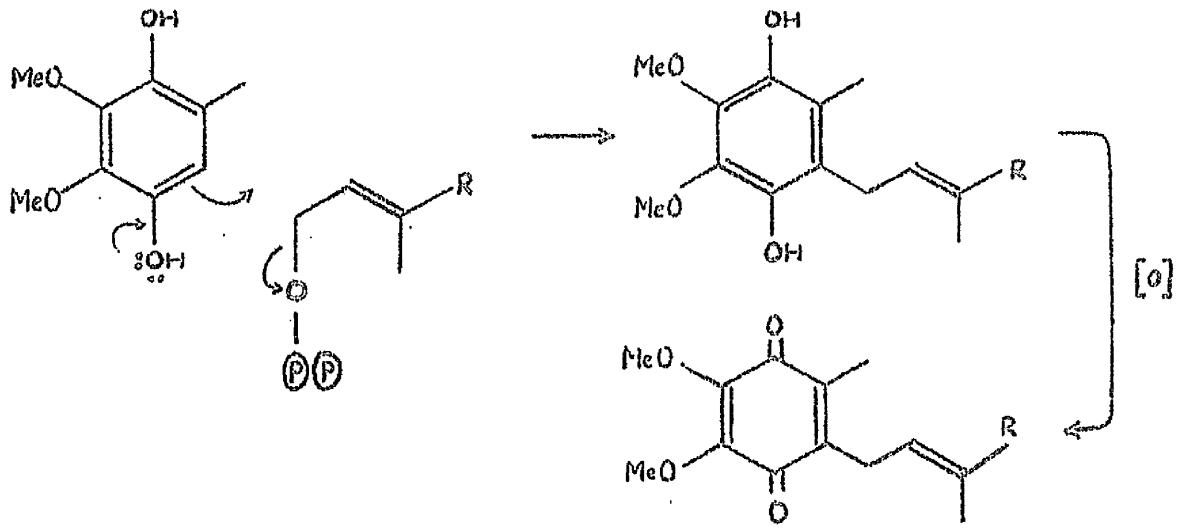
The co-enzymes Q, or ubiquinones, (20) are a recently discovered series of compounds whose biological function appears to be concerned with electron-transport and oxidative phosphorylation. The first known ubiquinone was isolated in 1955 by Festenstein,[47] and the isolation of other ubiquinones since then has shown them to be 2,3-dimethoxy-5-methyl-6-

alkenyl-1,4-benzoquinones, in which the 6-side-chain is a substituted 3',3'-dimethylallyl-group, with an isoprenoid skeleton. Side-chains with up to 50 carbon atoms have been shown to exist. Some of the ubiquinones have been synthesised.[48]

It is remarkable that very little experimental data is available about the biosynthesis of these vitamins and co-enzymes, in view of the fact that they are so important in biological systems. No work has been done on vitamin E,[49] and the only results on vitamin K show that all the vitamins K in mammalian systems are degraded to menadione (22) before conversion to vitamin $K_{2(30)}$ (19, R = $[-CH_2-CH_2-CH=C-Me]_3CH_3$), which is the active form.[50] This isolated set of experiments has shown that 2-^{14}C-menadione is incorporated into vitamin K_2 *in vivo*.[50]

The biosynthesis of the ubiquinones is better authenticated by experiment, and two groups have shown that labelled mevalonate,[51,52,53] and acetate,[54] are incorporated into the side chain of ubiquinone$_{(30)}$. Experiments have also been carried out showing that the methoxy groups come from the C_1-pool[55] and that phenylalanine probably is involved, directly or indirectly, in the formation of the aromatic ring system.[56]

Despite the lack of good experimental evidence as to the biosynthetic pathways of each of these vitamins and co-enzymes, suggestions have nevertheless been made,[87] that in the case of the ubiquinones at least, the isoprenoid side-chain is introduced by a mechanism similar to that for the C_5-isoprenoid-phenols. This would require that the isoprenoid pyrophosphate is attacked by the hydroquinone precursor, and that the quinone is formed by oxidation of the alkylated species i.e.



Although not directly within the scope of this thesis, it is worthwhile noting the latest ideas on the functions of Vitamin K and co-enzyme Q in the process of oxidative

phosphorylation, a term which refers to the coupling of citric acid oxidation to the synthesis of adenosine triphosphate (ATP), from adenosine diphosphate (ADP) and inorganic phosphate. The exact mechanism of this synthesis of ATP, which is the principal source of energy for cellular function, is not known and chemists have tried for several years to suggest plausible schemes.

The wide occurrence of co-enzyme Q and its property of restoring the capacity of mitochrondria to oxidise succinate in the presence of oxygen,[58] after extraction with acetone, have led biochemists to the belief that co-enzyme Q and the closely related vitamin K are intimately concerned with oxidative phosphorylation and electron-transport. Chemists and biochemists have been struck by the structural similarity between co-enzyme Q, vitamin K and oxidised vitamin E, and the more recent schemes of oxidative phosphorylation have given chemical significance to these similarities, especially the 2-methyl and 3-unsaturated alkyl groups in a 1,4-quinone.

Among those who have turned their attention to the problem are Clark and Todd,[59] Chmielewska,[60] and Lederer and Vilkas,[61] and the most recent attempt to clarify the chemistry of oxidative phosphorylation[62] is reproduced on page 23.

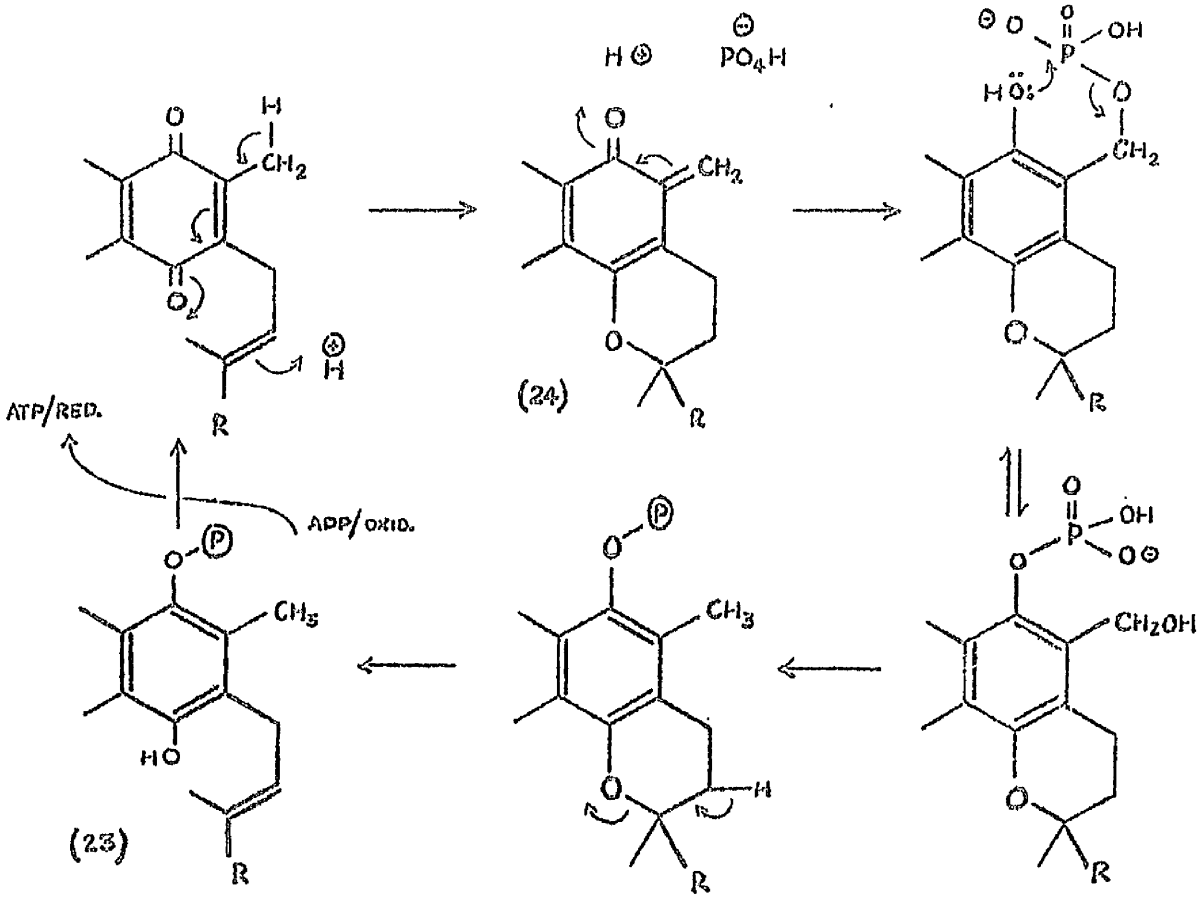
The proposed mechanism, which uses only reactions for which there is adequate precedent envisages an acid-catalysed rearrangement of the quinone system to a quinone-methide (24), which then adds inorganic phosphate, followed by a rearrangement of the phosphate to C_1 of the system. Reduction and further rearrangement produce the quinol-phosphate system (23), which readily undergoes oxidation to produce the parent quinone. It will be seen that phosphate is lost in this final step, during which ADP is converted to the more important ATP. The chemical analogy for this oxidative phosphorylation has been provided by Clark and Todd,[63,64] who have oxidised quinol monophosphates *in vitro* in the presence of orthophosphate and isolated quinone and pyrophosphate. Perhaps the best analogy to the 1,4 addition to the quinone methide (24) has been the experiment of Brodie and Russell,[65] who have obtained the acetate (25), from an experiment on vitamin K in the presence of acetyl chloride, and claim that this is evidence of the presence of the quinone methide form of the vitamin.

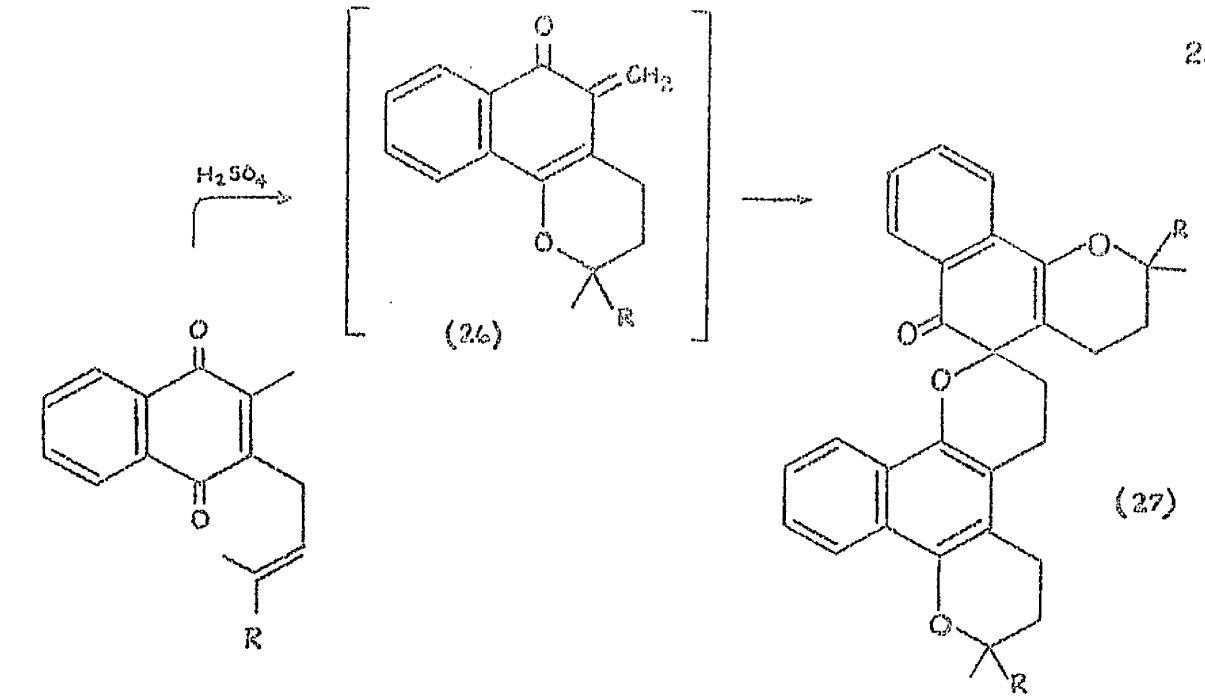
Further evidence for the existence of quinone methides in chemical systems has come from the identification of compounds which can be structurally derived from these unstable systems.[66] By treatment of vitamin $K_{2\,(20)}$ with sulphuric acid, Folkers has been able to isolate[67] a product

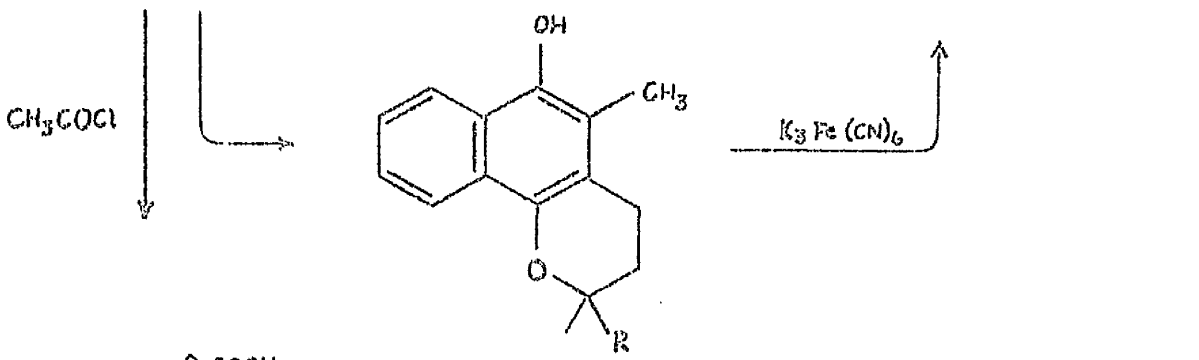
which has a dimeric structure (27), and which is claimed to have arisen by a Diels-Alder type of 1,4 addition between two molecules of the quinone methide (26). This substance has the same structure as the product obtained by potassium ferricyanide oxidation of the reduced chromanol form of the vitamin (28).

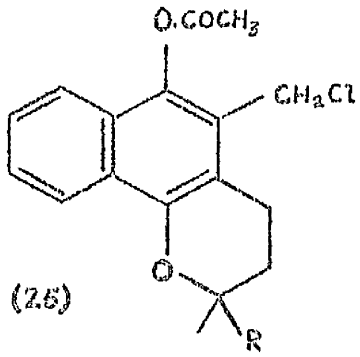
Analogous reactions have been tried by Isler and co-workers,[69] who oxidised an α-tocopherol derivative(29) to give the quinone methide (30), which dimerised to a product of structure (31).

PROPOSED MECHANISM OF OXIDATIVE PHOSPHORYLATION




H_2SO_4
(26)
(27)


CH_3COCl
$K_3Fe(CN)_6$
(28)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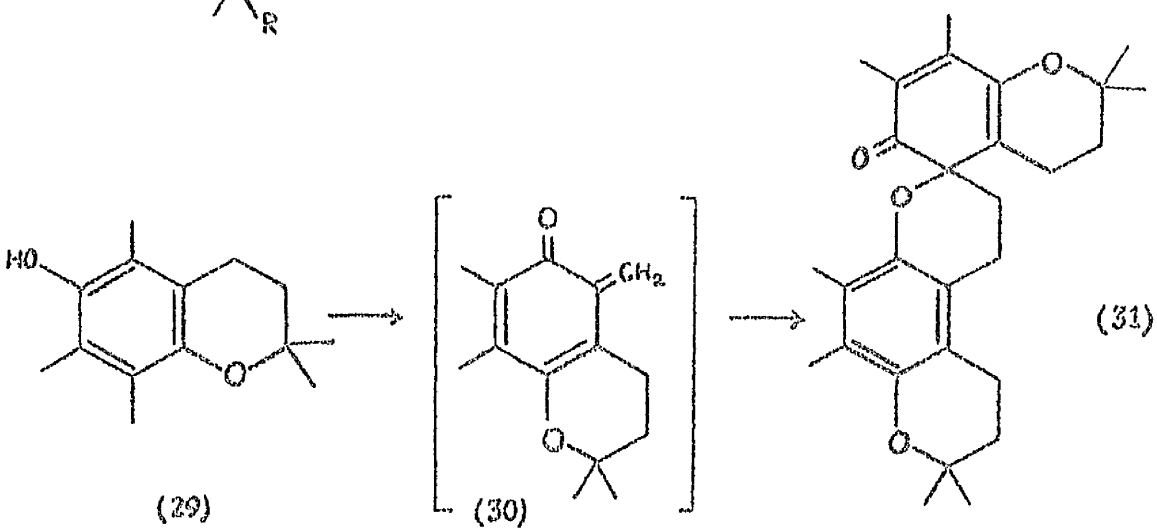
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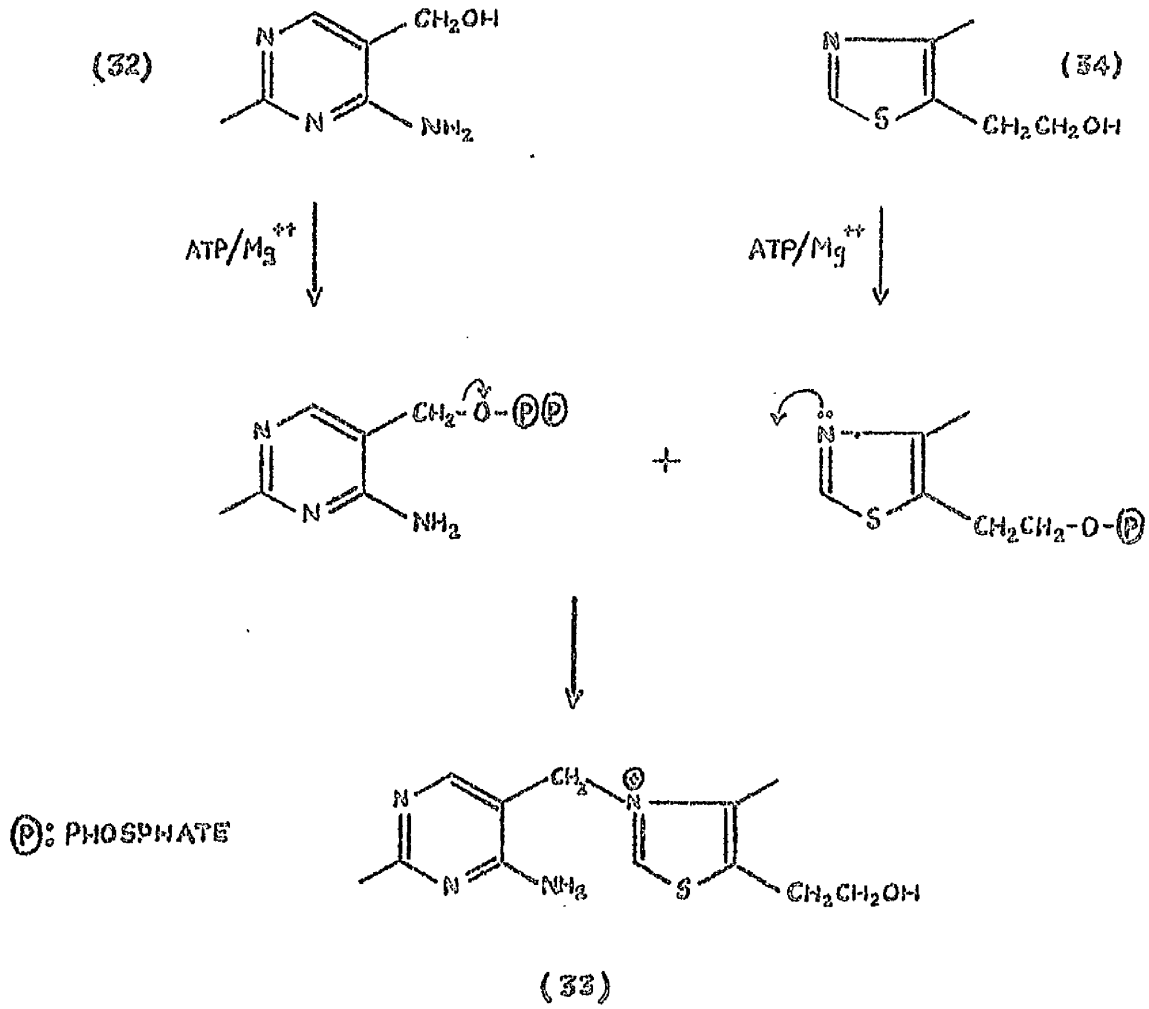
BIOSYNTHESIS OF THIAMINE (33) AND FOLIC ACID (36)

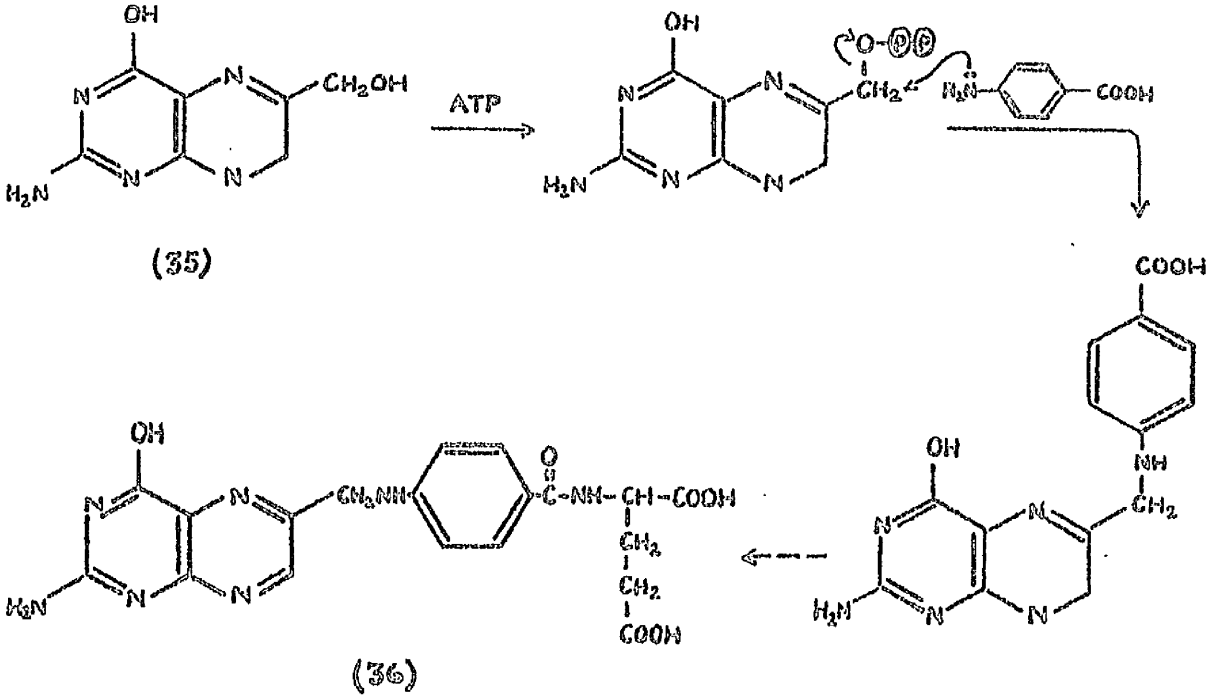
In 1960 Caminier and Brown[69] published the results of a series of investigations into the biosynthetic pathway by which the pyrimidine moiety (32) of thiamine (Vitamin B_1) (33) is joined to the thiazole (34). They found that phosphate and pyrophosphate esters are involved and that, in the coupling step, pyrophosphate is acting as a leaving-group as the C-N bond of the bridge is formed.



(33)

The pyrimidine moiety is phosphorylated on the 'benzyl-type' alcoholic group, and this is then attacked by the basic nitrogen of the thiazole moiety, the pyrophosphate being lost as its magnesium complex.

This biosynthetic scheme is the only one proven to date, in which a carbon-nitrogen bond is formed by attack of nitrogen on the electrophilic group, allylic or benzylic, of a pyrophosphate ester, although there is recent evidence[70,71,72] that the condensation between p-aminobenzoic acid and 2-amino-4-hydroxy-6-hydroxymethyldihydropteridine (35), which requires ATP, has a similar mechanism and ultimately leads to folic acid (36), the pteridine growth-factor.



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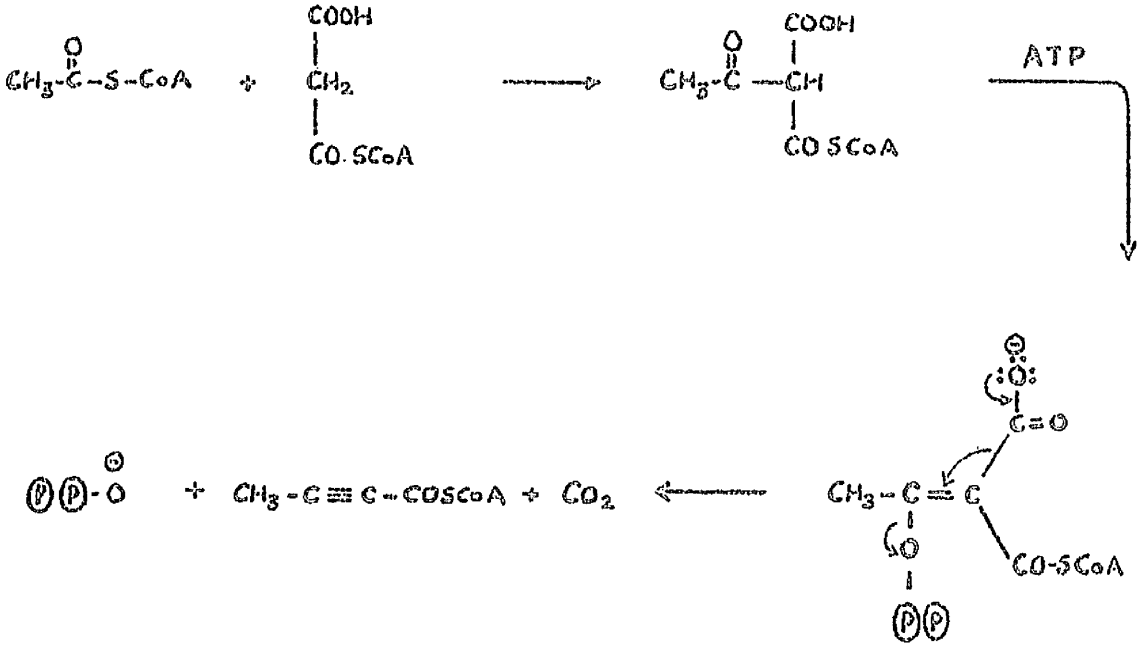
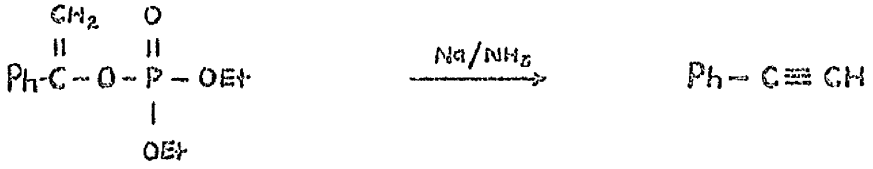
BIOSYNTHESIS OF ACETYLENES AND ALLENES

Suggestions have been made recently about the biosynthesis of acetylenes, polyacetylenes and allenes, and that the final stage in the formation of the acetylenic bond involves phosphate esters. In particular, Jones has published[72] ideas on a detailed mechanism starting from the polyketomethylene systems known to be produced from acetate precursors. There is some evidence[73,74] that acetate units are joined head to tail to form the biosynthetic precursors of acetylenes and allenes, and that the resultant polyketomethylene system produces the acetylene or allene bond; although the participation of pyrophosphate has not yet been demonstrated.



The above scheme is a simplified version, using only one molecule of acetate, but it nevertheless illustrates the mechanism whereby the enol-pyrophosphate decomposes in a concerted reaction, the driving force for which comes largely from the carbon-dioxide formation. In this respect, it is not unlike the concerted decarboxylation-dehydration of mevalonic acid in terpene biosynthesis. One interesting result of Jones' theory has been the efforts of two groups of chemists to experiment with chemical systems designed as models of the biosynthetic pathway to acetylenes and allenes.

Perhaps the closest analogy comes from the work of Craig and Moyle,[75,76,77] who have prepared the diethylphosphates of various activated enols and treated the phosphotriesters with base, causing decomposition and formation of acetylenes or allenes. For example, phenylacetylene has been prepared from the vinyl phosphate (37)[75], and phenylallene from phenyl acetone.[76] In a further series of experiments,[77] an acetylene and an allene have been prepared simultaneously, by decomposing with caustic alkali, the diethylphosphate of the doubly-activated acetone (38).



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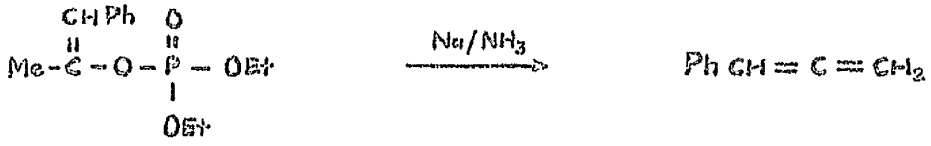
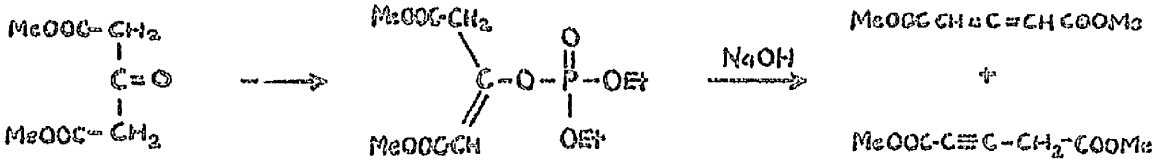




(38)

Fleming and Harley-Mason have also prepared acetylenes[78,79] by concerted reactions, analogous to the suggested biosynthesis, in which p-bromosulphonate is the leaving-group. It would appear that these model experiments require greater activation than the corresponding *in vivo* syntheses, and this has usually been obtained from phenyl or carbonyl groups.

The examples cited above from the biosynthesis of various types of compounds are quite sufficient to illustrate the importance of phosphates in biosynthesis. No mention has been made of the important

structural functions of phosphates in RNA and DNA, and of the parts played by phosphate esters in carbohydrate metabolism, peptide synthesis and biotin chemistry, because they are not relevant to this thesis, although this does not imply a failure to recognise their part in these processes.

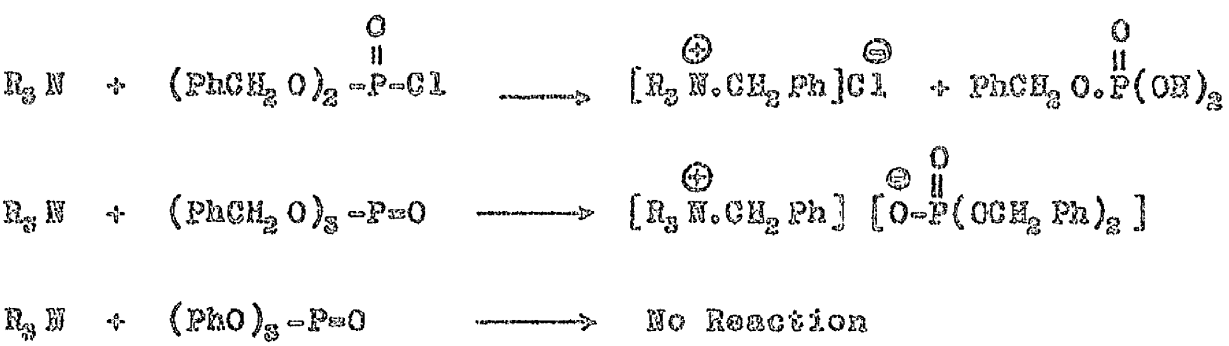
In the final section, on acetylene biosynthesis, attention has been paid to the value of model, in vitro, experiments in obtaining chemical support for postulated biosynthetic schemes, and the principal aim of this thesis is to describe and assess the value of similar experiments designed as models for some of the systems described earlier.

SYNTHESIS AND PROPERTIES OF TRIESTERS OF PHOSPHORIC ACID

Although it is probably a fair claim, that the systematic study of phosphate esters began with the experiments of Todd and his school at Cambridge in 1945, there are, nevertheless, isolated cases in the literature of the preparation of triesters of phosphoric acid and subsequent examination of a few of their properties. For example, Evans[80] prepared the trialkyl phosphates of aliphatic alcohols by treatment of the alcohol in pyridine with phosphorus oxychloride. Later workers showed that trialkyl phosphates could be de-alkylated by phenols,[81] giving low yields of alkyl phenols, and that

ethers could be produced[62] by treatment of trialkylphosphates with high-boiling aliphatic alcohols. These early experiments however were rather crude, especially because of the limited types of triester known before 1945, resulting in the use of extremely high temperatures to obtain low yields of products which can now be synthesised by more refined methods.

In 1945, Todd began to study organic phosphate esters in order to simplify and understand the chemistry of polynucleotides, and he was especially interested in chemical methods of removal of benzyl esterifying groups from benzyl phosphates used in nucleotide synthesis. Benzyl groups were frequently used as protecting groups and the known methods of removal, hydrogenolysis or mild hydrolysis, were sometimes not delicate enough. Using the reagents diphenylphosphorochloridate,[63] and dibenzylphosphorochloridate,[64] Todd and his collaborators synthesised mixed phosphate esters, in which the esterifying groups benzyl, phenyl,or alkyl could be varied, almost at will. During experiments[65] on the phosphorylation of alcohols with dibenzylphosphorochloridate, it was observed that the phosphorylating reagent was decomposed by tertiary amines, which attacked one of the benzyl groups, causing a de-benzylation of the phosphorochloridate.



$R_3N + (PhCH_2O)_2\text{-}P(=O)\text{-}Cl \longrightarrow [R_3N.CH_2Ph]Cl + PhCH_2O.P(=O)(OH)_2$

$R_3N + (PhCH_2O)_3\text{-}P=O \longrightarrow [R_3N.CH_2Ph]\,[O\text{-}P(=O)(OCH_2Ph)_2]$

$R_3N + (PhO)_3\text{-}P=O \longrightarrow$ No Reaction

In the same paper it was demonstrated that tribenzyl-phosphate underwent a similar decomposition, but that triphenyl-phosphate was quite stable to tertiary amine. Later work[86] by Clark and Todd extended this study, showing that other bases, primary and secondary, had similar de-benzylating properties.

It was then discovered[87] that anions, such as chloride derived from lithium chloride in ethoxyethanol, could bring about analogous de-benzylations, such as the decomposition of tribenzylphosphate to benzyl chloride and dibenzylphosphate, shown below.

$(PhCH_2O)_3\text{-}P(=O)\text{-}O\text{-}CH_2\text{-}Ph + Cl^{\ominus} \longrightarrow (PhCH_2O)_2\text{-}P(=O)\text{-}O^{\ominus} + PhCH_2Cl$

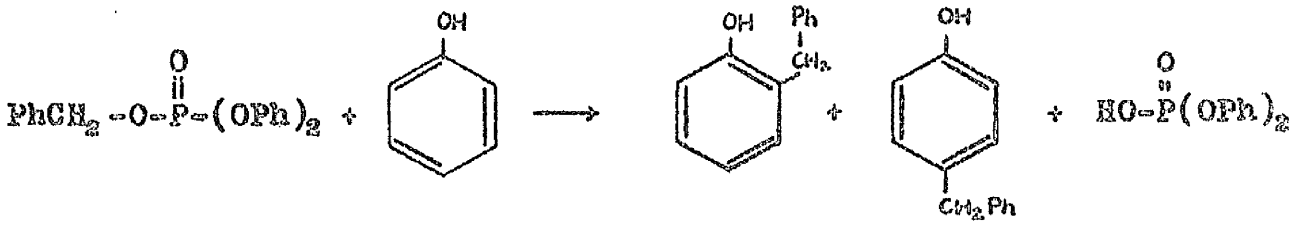
In 1954, it was shown by Todd,[88] that anionic de-alkylation of alkyl-phosphates could occur, and that this depended upon the nature of the other esterifying groups. When a series of n-propyl phenyl phosphates were treated with chloride, it was found that de-alkylation occurred successfully if there were two phenyl groups present, but only slightly when there were none.

$(CH_3CH_2CH_2O)_3\text{-}P{=}O + Cl^- \longrightarrow CH_3CH_2CH_2Cl$ (traces)

$CH_3CH_2CH_2O\text{-}P(OPh)_2 + Cl^- \longrightarrow CH_3CH_2CH_2Cl$ (good yield)

$PhO\text{-}P(OPh)_2 + Cl^- \longrightarrow$ no reaction

Two of Todd's collaborators, Kenner and Mather, later brought about debenzylation of benzyl phosphates with phenol.[89] They found that treatment of benzyl diphenyl phosphate with excess phenol produced a mixture of o- and p-benzyl phenols but that similar treatment of dibenzyl phenyl phosphate and tribenzylphosphate produced poorer results.



It will be noted that almost all these reactions produce a partially esterified phosphate, such as diphenyl phosphate, and Todd perfected[85] a method of isolation and identification of these, which depended upon their property of forming salts with cyclohexylamine.

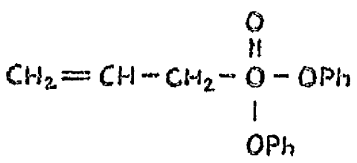
This account illustrates adequately the progress made by Todd's group in the elucidation of the chemistry of phosphate esters, although

it is far from being an exhaustive survey of all that they have accomplished since 1945. No reference has been made to their work on sugar phosphates and on the hydrolytic properties of mono, di- and tri-esters of phosphoric acid, which have more bearing on the problems of nucleotide and polynucleotide synthesis. In essence, the work described above is a summary of the properties of phosphate esters, and in particular, of how they react towards nucelophilic attack by the nitrogen of amines, by anions such as halides, and by phenolic systems. The conclusions of these experiments are extremely important to this thesis, because they form the theoretical background, upon which are based the model experiments about to be described.

Above all, Todd's experiments have shown that triesters of phosphoric acid, which often undergo nucleophilic attack at the phosphorus atom and are therefore phosphorylating agents, can be made to undergo nucleophilic attack at the α-carbon of one of the esterifying groups and therefore act as alkylating agents. The latter circumstance is favoured by phosphate esters which possess one electrophilic α-carbon, such as the methylene of benzyl or allyl phosphates, or alternatively two esterifying groups, such as phenyl, which tend to stabilise the

phosphoric acid anion generated from triesters acting as alkylating agents.

It would thus seem highly likely, that triesters of phosphoric acid, in which both of these factors are favourable, would be extremely efficient alkylating agents. For example the triesters, benzyldiphenylphosphate (39) and allyldiphenyl-phosphate (40), would be expected to fulfil this function, and it is with the properties of similar esters that this thesis is concerned.



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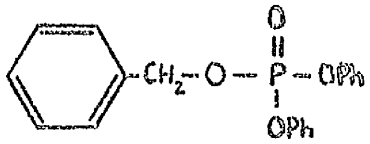


(39)

The contribution made to the understanding of phosphate ester chemistry by Todd's groups may be gauged by the light it has thrown on the biosynthetic schemes described previously since it would scarcely have been possible to postulate the mechanisms of biosynthesis of terpenes, phenolic isoprenoids, or vitamin B_1 without the knowledge gained from their experiments.

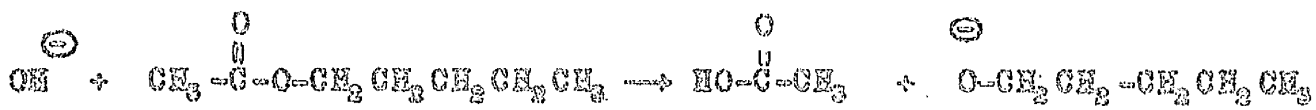
DISCUSSION

(1) THEORETICAL:

In the introductory section, it was noted that the experiments of Todd and his collaborators have clearly demonstrated that phosphate esters, such as propyl diphenyl phosphate and benzyl diphenyl phosphate, can act as alkylating agents, and were therefore similar in properties to the alkyl esters of aryl sulphonic acids. Before describing the results of the various experiments using phosphate esters, which form the main part of this thesis, it is intended to discuss the factors which enable these esters to act as good alkylating agents, and then to outline some of the mechanisms by which the alkylation process may occur.

Hydrolysis of Carboxylic Acid Esters:

It has long been recognised that the hydrolysis of aliphatic carboxylic acid esters may proceed either by alkyl-oxygen fission or by acyl-oxygen fission and standard textbooks on organic reaction mechanisms almost always discuss these two possibilities. The more common process, acyl-oxygen fission, occurs in the basic hydrolysis of most esters of primary and secondary alcohols, and is a bimolecular reaction, as illustrated for amyl acetate (41).



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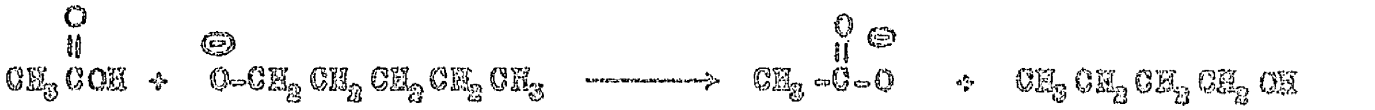
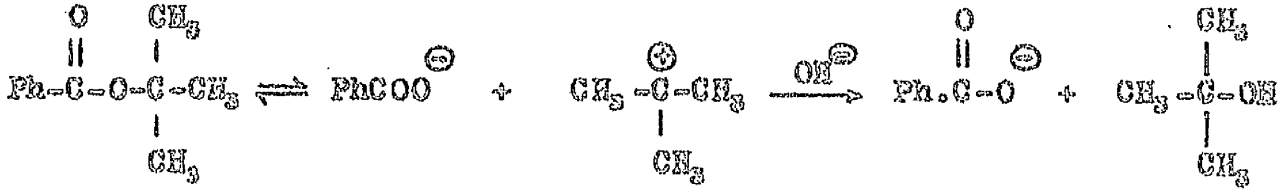


In the basic hydrolysis of esters of tertiary alcohols, and of certain secondary alcohols, the alkyl-oxygen bond is broken, and the reaction is unimolecular. The rate-determining step is the preliminary ionisation of the ester, as illustrated below for t-butyl benzoate (42).



(42)

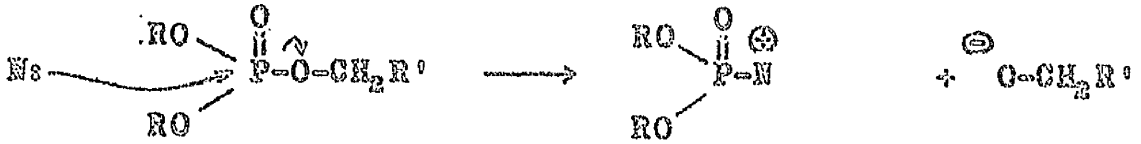
The carboxylate ion is thus a leaving-group in an S_N1 reaction, and the reaction will take this course when the esterifying-group is capable of forming a stable carbonium ion. The unimolecular mechanism will thus be favoured by tertiary esters, and by secondary esters, such as benzhydryl or substituted allyl, and will be enhanced by using solvents of high dielectric constant, which aid charge separation during the preliminary ionisation. Other factors, such as relief of steric hindrance, and favourable inductive and electromeric effects of any substituents in the

esterifying group will also aid the unimolecular mechanism.

Phosphoric Acid Esters:

The basic hydrolysis of carboxylic acid esters is a particular case of nucleophilic attack on esters which have two or more possible sites of attack, and the same principles may be applied to nucleophilic attack on esters of phosphoric acid, in which either the phosphorus or the α-carbon of one of the esterifying groups may be attacked. In the former case, the ester will act as a phosphorylating agent, resulting from oxygen-phosphorus bond cleavage, and in the second case the ester will be an alkylating agent, resulting from oxygen-carbon bond cleavage, although, as with carboxylic acid esters, there will only be a distinguishable product difference in non-hydrolytic reactions (unless tracers are used).

Phosphorylation:

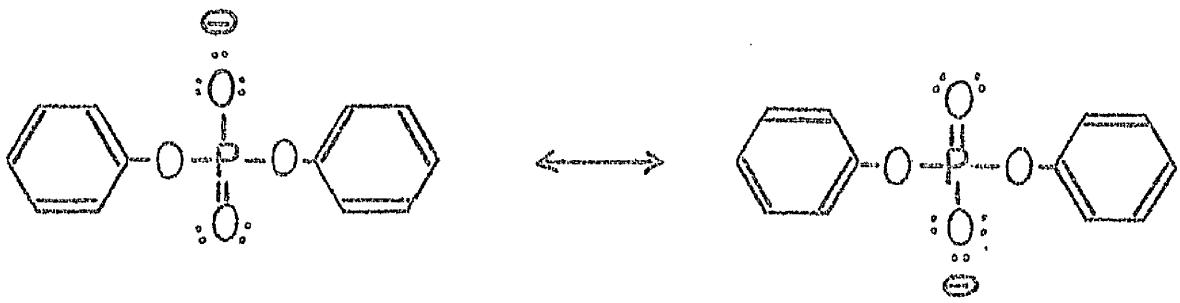


Alkylation:

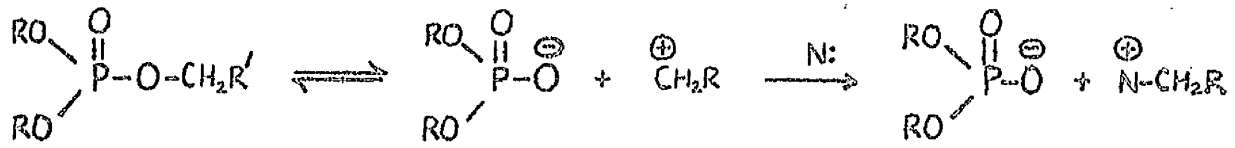
The general reactions of phosphorylation and alkylation are shown above, but the nucleophile may be an anion, or a multiple bond, rather than any specific, electron-rich atom, and the final products will often result from proton-transfer between the initial fragments.

Mechanism of Alkylation Reaction:

The alkylation reaction will clearly be preferred, when the α-carbon of one of the esterifying groups is electron deficient, and this is the case with benzyl phosphates, as shown in practice by Todd's work. Another important factor will be the stability of the anionic fragment produced, and when the two remaining esterifying groups are both electron-withdrawing, as with phenyl, the anion will be considerably stabilised. Once again, Todd has demonstrated this effect, by comparing the properties of trialkyl phosphates with those of alkyl diphenyl phosphates; the diphenyl phosphate anion, which can be formed by the latter, has each main canonical structure stabilised by electron-withdrawal from the oxygen-phosphorus system.



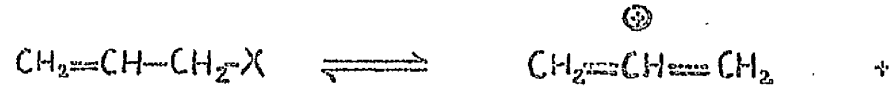
Although such considerations show why the alkylation reaction can occur under favourable circumstances, they do not give any indication as to the mechanism of the nucleophilic attack, which was illustrated above as occurring by a concerted process, but which could well have been a stepwise reaction.



The chemistry of phosphate esters, such as allyl diphenyl phosphate, thus becomes similar to that of allyl halides, the nucleophilic decomposition of which has been the subject of much mechanistic work carried out in the last thirty years. The literature shows abundantly that allylic compounds may react with nucleophiles either by a unimolecular or by a bimolecular mechanism, depending upon the solvent, the substitution of the allyl system, the leaving group, and the nucleophile being used. Although the diphenyl phosphate anion is a different leaving group from the more common halide ion, it is nevertheless worthwhile studying the factors which normally govern these alternative mechanisms.

Unimolecular Reaction:

The unimolecular reaction of allyl compounds under nucleophilic attack requires a preliminary ionisation to a mesomeric carbonium intermediate, and subsequent reaction may proceed with either retention or rearrangement in the allyl system.



Because of the delocalisation of the positive charge over 3 carbon centres, the cation is extremely stable, and this explains the increase in rate of 25-fold on comparing allyl chloride with propyl chloride in hydrolysis reactions.[90]

If the allyl compound is unsubstituted, any rearrangement will normally remain undetected, but when it is substituted asymmetrically, rearrangement will result in two products, e.g.

$$RCH{=}CH{-}CH_2X \rightleftharpoons RCH{=}\overset{\oplus}{C}H{-}CH_2 + X^{\ominus} \xrightarrow{Y^{\ominus}} RCH(Y){-}CH{=}CH_2 + RCH{=}CHCH_2Y$$

Furthermore, the substitution will affect the rate of reaction, either by electronic or steric effects, as is readily shown by the fact that 3,3-dimethylallyl chloride undergoes ethanolysis 2200 times more rapidly than allyl chloride.[91] The enhanced rate is due to the electron-releasing effect of the methyl groups aiding the initial ionisation, and also stabilising the resultant carbonium ion. Streitweiser[90] considers that the 3,3-dimethylallyl cation is more stable than the t-butyl cation, which in turn is more stable than the 3-methylallyl ion.

The effect of solvent polarity upon the S_N1 reaction of allyl compounds is also quite striking, and Young[91] has provided much evidence, that the higher the dielectric constant of the solvent, the faster the rate of reaction. This is hardly surprising, since a polar solvent will considerably aid the separation of the halide and carbonium ions, and hydroxylic solvents show particularly strong effects, because of their ability to solvate the anionic leaving-group.

The nature of the leaving-group may also be important in unimolecular reactions, and some guidance may be gained from studies of the stabilities of leaving-groups[91] (as estimated by the strengths of the conjugate acids). The pK_a of diphenyl phosphate is about 1.0 indicating that the anion will be a leaving group, comparable with the aryl sulphonates which have been used widely in mechanistic studies and in synthesis.

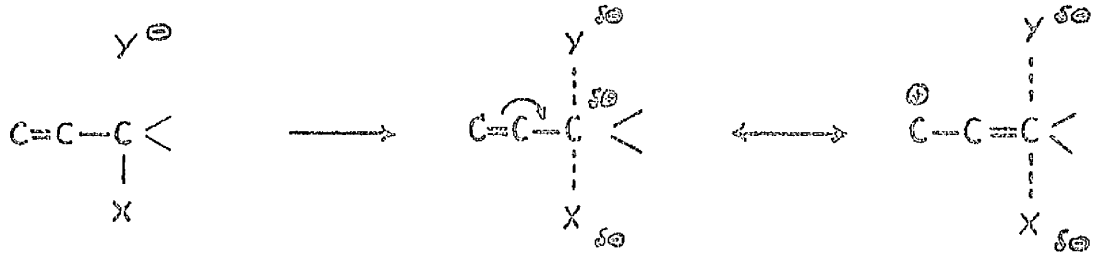
Thus, although substitution at primary carbon atoms very often proceeds by a bimolecular mechanism, if this carbon is part of an allyl system, especially one substituted by alkyl groups in the 1, or 3, positions, nucleophilic substitution may well proceed by a unimolecular mechanism. The unimolecular mechanism normally proceeds with some rearrangement in the allylic system, and two products are formed, although the proportion of rearranged product will depend upon individual reaction conditions.

Bimolecular Reaction:

As noted above, nucleophilic substitution at primary carbon proceeds usually by a bimolecular process, but once again allylic systems require special consideration. Although there is, in principle, the possibility of formation of a rearranged product by an S_N2' process, no experimental evidence has been obtained to show that rearrangement occurs, except in

3-unsubstituted tertiary or secondary allyl compounds.[91,92,93]

Allyl halides have been found always to undergo bimolecular nucleophilic substitution at a faster rate than the corresponding saturated compounds. The reasons for this are not really understood, although several attempts[90,91,93] have been made to explain the trend. One of the principal difficulties has been to decide if the allylic carbon undergoing substitution becomes more positive in the transition state, because if this is the case then the transition-state, during anionic nucleophilic attack, will be stabilised by olefin participation.



Furthermore, this participation will be enhanced by electron-releasing groups on the 3-position of the allyl system, and when these are methyl, hyperconjugative effects are believed to be important.[91] Gould has also discussed the difficulty of estimating the relative electron-density at the allylic carbon in the transition-state of any S_N2 substitution, and ascribes the increased rate as being due

to the ability of the double-bond either to withdraw electrons from, or to donate electrons to, the allylic carbon, and hence stabilise the transition-state, according to the requirements at the substitution centre.

Solvolysis Reactions:

The difficulties of predicting the mechanism of nucleophilic substitution in allylic systems are thus considerable, and several workers, notably Winstein,[91] have expressed views, which picture any one allylic system to be substituted by a single mechanism, which will be intermediate between the S_N1 and S_N2 extremes, as proposed by Ingold and Hughes.[94] In particular Winstein regards solvolysis reactions (i.e. reactions in which the nucleophilic substitution is carried out by the solvent) as having a complete spectrum of mechanisms, but that the single mechanism in any one case will be dependent upon solvent, substitution, and leaving-group. For example, allyl chloride undergoes a solvolysis in ethanol by an bimolecular mechanism, but 3,3-dimethylallyl chloride solvolyses in ethanol by a unimolecular mechanism,[91] thus the effect of substitution has been not only to increase the rate, but also to change the mechanism.

In solvolysis reactions the kinetics will be first-order, because in a bimolecular reaction it is not normally

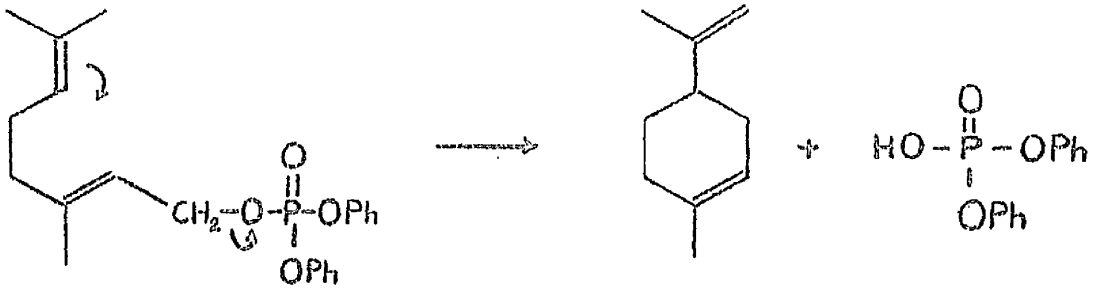
possible to detect changes in solvent concentration, and this means that S_N1 and S_N2 reactions will give kinetically indistinguishable results. Often, therefore, a decision between the alternative extreme solvolysis mechanisms has to be made on grounds of composition and nature of products, and the choice can be simplified because of two important facts about each type of mechanism. Firstly, in the unimolecular reaction of allyl compounds, every system, in which the kinetics have been clearly demonstrated, has resulted in the production of both the normal and the rearranged products. Secondly, allyl compounds undergoing reaction by a bimolecular process have never been known to rearrange when the 1-position is unsubstituted, i.e. when the allyl system is primary.

It is worthwhile noting, in view of the reactions to be discussed later in this thesis, that both the above conditions have been abundantly demonstrated in the case of 3,3-dimethylallyl halides undergoing nucleophilic substitution.

(2) TERPENOID PHOSPHATES.

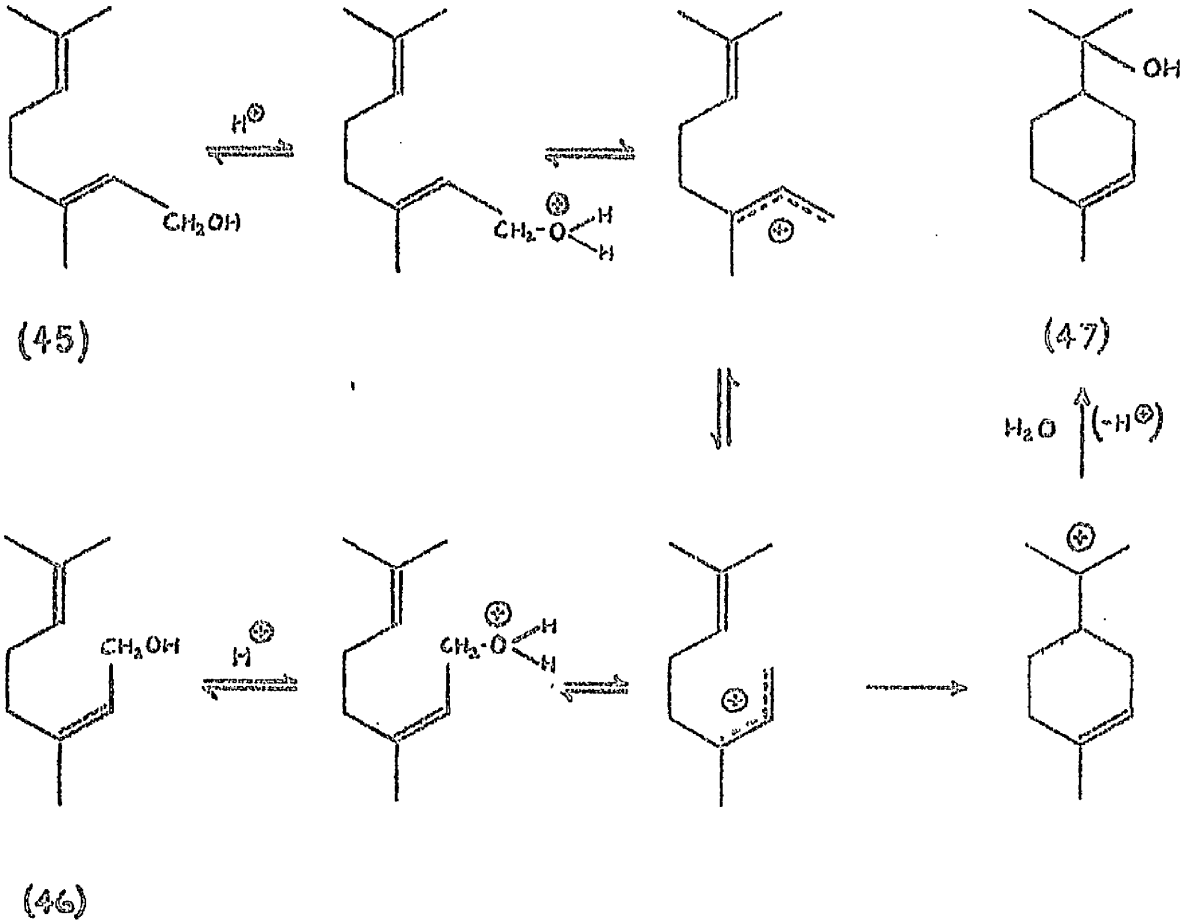
It will be recalled that in the Introduction to this thesis, it was noted that it has not been rigorously established that geranyl pyrophosphate (6) is the direct precursor of all monoterpenes. Furthermore, the exact mechanism of the *in vivo* formation of monoterpenes is still not clear, and some controversy still surrounds the question of whether geranyl pyrophosphate (6) produces monoterpenes by a concerted, or a stepwise process. The concept of intramolecular participation of the pyrophosphate leaving-group, as suggested by Kosower,[17] has given these mechanistic speculations a new dimension.

During the period 1956-1959, it first became clear that geranyl pyrophosphate (6) played a vital role in the biosynthesis of terpenes and steroids, and, shortly afterwards, Todd[95,96] speculated that an ester, such as geranyl diphenyl phosphate (43), might cyclise to give limonene (44) and diphenyl phosphate.



(43) (44)

The monoterpenoid alcohols, geraniol (45) and nerol (46), have long been recognised as cis- and trans- isomers of an acyclic primary alcohol. The stereochemistry of these alcohols was established after it was discovered[97] that each could be cyclised with mineral acid to α-terpineol (47). Since nerol (46)



cyclised much more quickly, and under less vigorous conditions, it was therefore likely to be the cis-isomer. The acid-catalysed cyclisation of both geraniol and nerol to α-terpineol is believed[98]

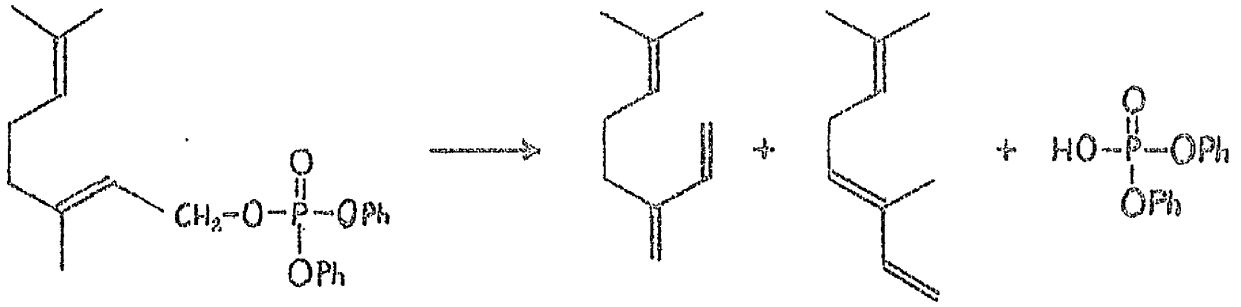
to be a process involving allyl carbonium ions generated by protonation of the primary allylic alcohols and subsequent dehydration.

Since there was no reason to believe that geranyl diphenyl phosphate (43) would necessarily decompose *via* a free carbonium ion, and hence readily cyclise by a mechanism similar to the above, it was decided to investigate the chemistry of geranyl and neryl diphenyl phosphates. It was hoped that the differing stereochemistry of each of these esters would cause them to decompose to different products, and perhaps at different rates.

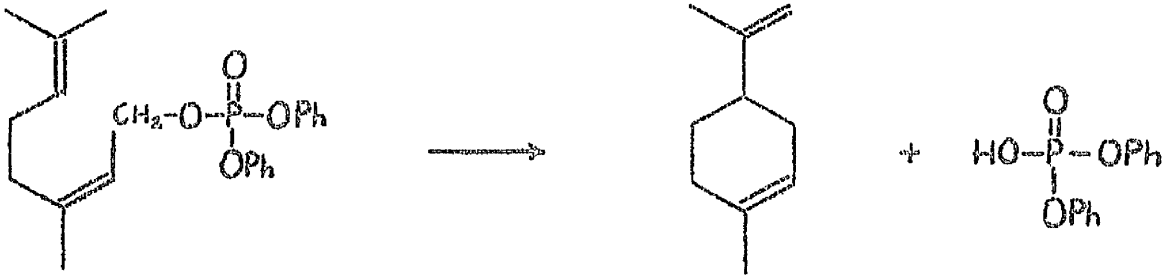
Decomposition of Geranyl and Neryl Diphenyl Phosphates in Ethers:

(i) Monoterpene Products:

It has been found that both these esters decompose readily when allowed to stand at 37°C in an inert solvent, such as anhydrous diethyl ether, and that geranyl diphenyl phosphate (43) decomposes slowly to give the acyclic trienes myrcene (48), and ocimene (49), whereas neryl diphenyl phosphate (50) decomposes very quickly to give mainly limonene (44), a cyclic monoterpene.



(43) (48) (49)



(50) (44)

Unfortunately, these decompositions are not so simple as the above equations imply, and considerable difficulty was experienced in separating the hydrocarbon products obtained from alumina column chromatography of the crude reaction products. The composition of the hydrocarbon products was determined by gas-liquid chromatography, and individual products were obtained pure by preparative gas-liquid chromatography, and, where possible, identified by spectroscopic methods.

The hydrocarbon products from geranyl diphenyl phosphate (43) were obtained in the proportions illustrated by a typical gas-liquid chromatogram (Figure A). Of the six products, the first two are myrcene(48) and ocimene (49), the next two trace products are probably monoterpenoid hydrocarbons, and the final two are sesquiterpene hydrocarbons. It is noteworthy that ocimene (49) was always obtained in greater amounts than myrcene (48), although the latter is by far the more common, and is believed to be more stable.[99] After three weeks at 37°C the total yield of hydrocarbons was about 40%, although this figure depended upon concentration, as did the proportion of monoterpenes in the hydrocarbon mixture, which contained 75% of myrcene and ocimene, when the phosphate concentration was low.

Infrared and nuclear magnetic resonance spectra provided the main evidence for the identification of myrcene and ocimene. The data of Kovats et al.,[100] who separated and studied the structures of all the possible ocimenes, was used to show that the ocimene obtained in this experiment was trans-β-ocimene (49). The α-ocimenes, which have a terminal

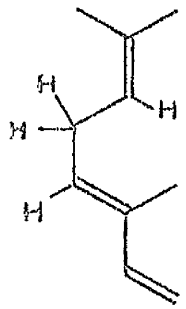


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FIGURE A: GERANYL DIPHENYL PHOSPHATE PRODUCTS AT 214°C

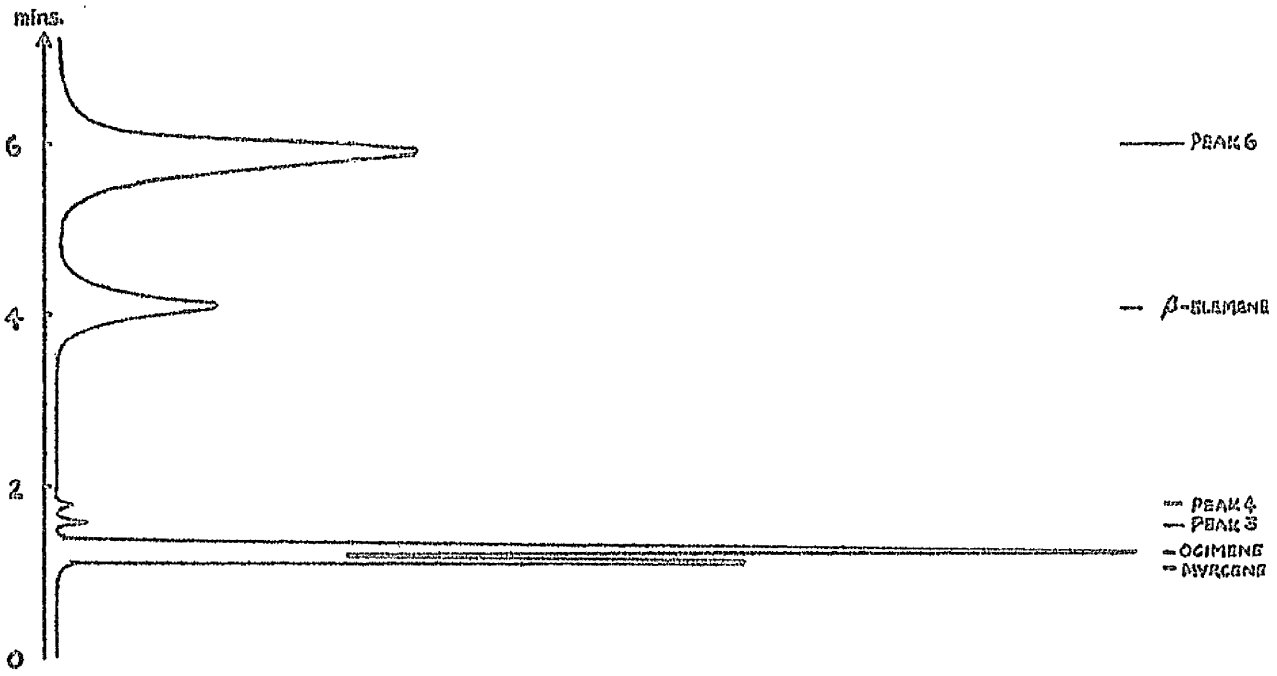
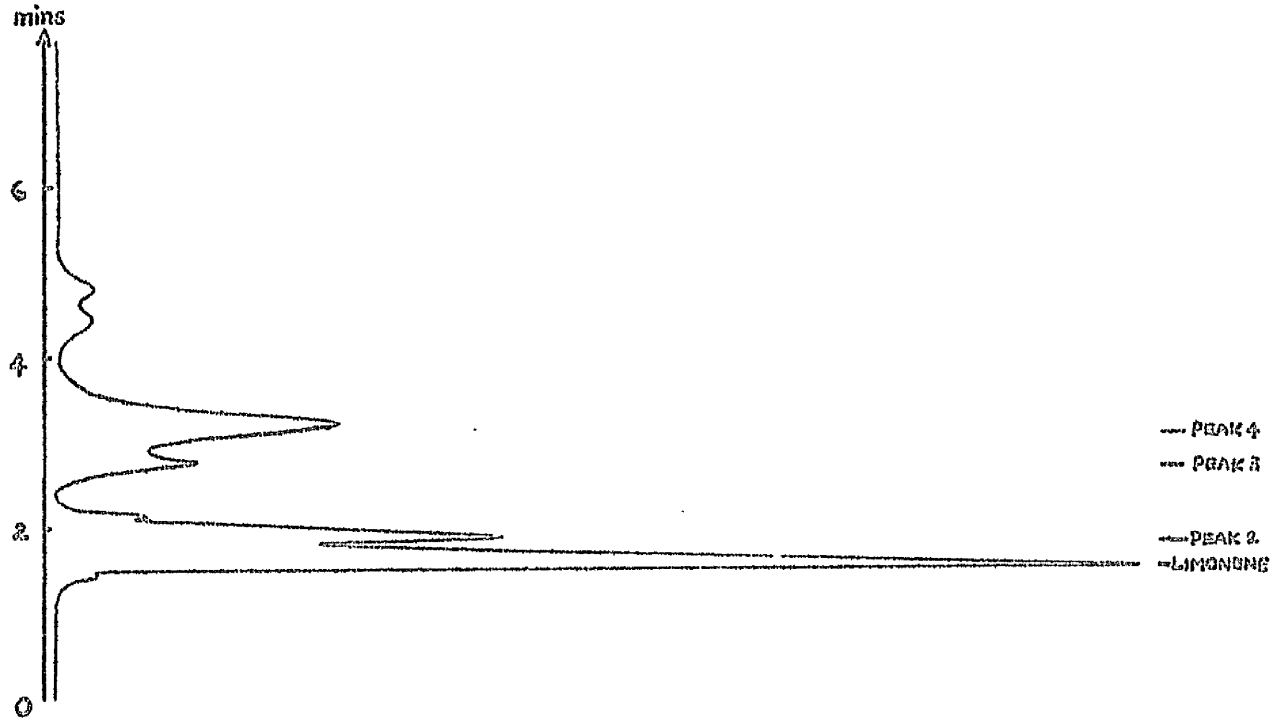


FIGURE B: NERYL DIPHENYL PHOSPHATE PRODUCTS AT 204.°C



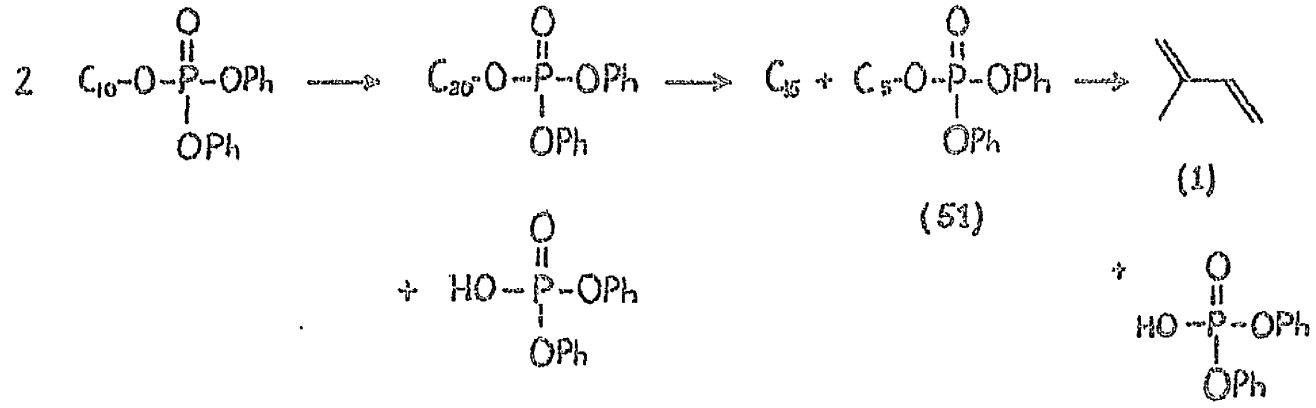
isopropenyl group, do not have a triplet at 7.2 τ in their nuclear magnetic resonance spectra, and the cis-isomers absorb at 1593 cm.$^{-1}$ in the infrared, whereas the trans-isomers absorb at 1609 cm.$^{-1}$ (cis- and trans- refer to the configuration about the central double-bond).

(ii) Sesquiterpene Products:

As has been noted above, the two less volatile hydrocarbon products from geranyl diphenyl phosphate have been characterised as sesquiterpenes, by microanalysis and molecular weight determinations. Although this may seem unlikely on theoretical grounds, since diterpene hydrocarbons would appear to be more probable products, the finding is quite compatible with the gas-chromatographic retention-times of the two compounds. The formation of a C_{15}-unit from two (or more) C_{10}-units is very likely to involve the simultaneous production of a C_5-unit, which would almost certainly be isoprene (1), and, if the mechanism of sesquiterpene formation involves fission of an intermediate C_{20}-unit, there will be one mole of isoprene per mole of sesquiterpene.

A sample of the ethereal vapour from the decomposition of geranyl diphenyl phosphate in ether was found to absorb at 232 mμ, as did a genuine sample of isoprene in ether. Attempted correlation of the isoprene formed, as measured from the intensity

of the 232 mμ absorption of the ethereal vapour, with the mechanism discussed above, was not too successful, since there was far less isoprene present than might have been expected - by a factor of 4. There are several factors which could explain the discrepancy without invalidating the suggested mechanism, and one which is quite plausible is that the C_5-unit being split off from the C_{20}-unit is not necessarily isoprene, but a C_5-phosphate, such as 3,3-dimethylallyl diphenyl phosphate (51) which is known to give isoprene on decomposition.



Evidence has been obtained, that each of these sesquiterpenes is being formed steadily as the reaction proceeds and, furthermore, that addition of sodium bicarbonate or hindered organic tertiary base to the reaction mixture does not inhibit the formation of either sesquiterpene. These facts indicate that the two products are being formed independently, and that one is

not being produced from the other by acid-catalysed rearrangement. The data obtained on each hydrocarbon will now be discussed.

The more volatile sesquiterpene showed only end-absorption ($\lambda_{max.}^{EtOH}$, 208 mμ) in the ultraviolet, and no band around 1600 cm.$^{-1}$ in the infrared, and therefore did not contain a conjugated diene system. The infrared spectrum showed all the bands associated with mono- (CH_2=CH-) and di-substituted (CH_2=$\overset{|}{C}$-) vinyl groups, but did not show any other form of unsaturation. The nuclear magnetic resonance spectrum confirmed this evidence, and, moreover, showed that there was one methyl in a saturated environment, and that there were probably two methyls attached to olefins, and probably three saturated, cyclic methylene groups. It is noteworthy that the evidence for the mono-substituted vinyl and saturated methyl groups is complementary, because one would expect <u>both</u> to be present on the same saturated carbon, as found in linalool (52), if <u>either</u> were found in a skeleton derived from geraniol.

A search of the literature on sesquiterpenes showed that only one skeleton has been discovered which possesses a

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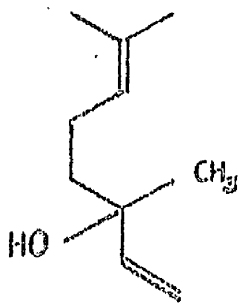


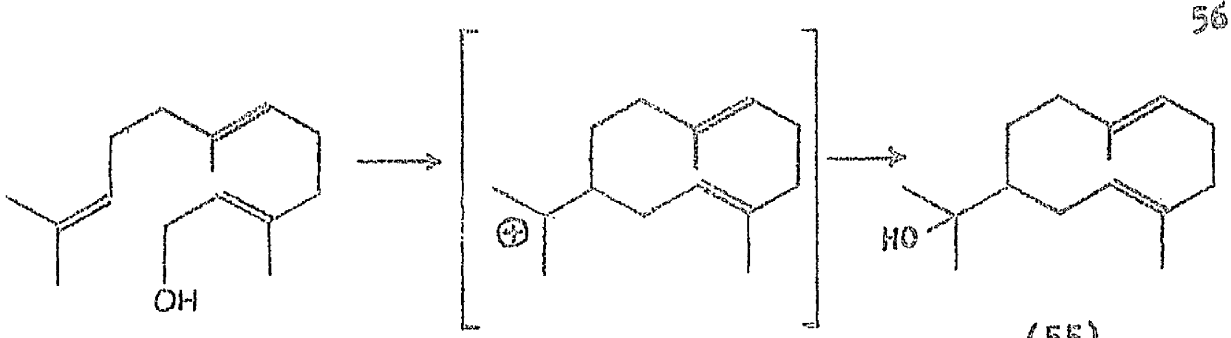
vinyl, or potential vinyl, group with one substituent. This is the skeleton of the hydrocarbon, elemane (53), which is found in the sesquiterpenoid alcohol, elemol (54), which Hendrickson[101] considers to arise *in vivo* by rearrangement of the germacrol system (55), produced by cyclisation of the cation derived from *trans*-farnesol (56).

There are three known sesquiterpene hydrocarbons of the elemane skeleton, namely α-elemene[102] (57), β-elemene[103] (58), and δ-elemene[104] (59), and, of these, only β-elemene is compatible with the infrared and nuclear magnetic resonance data for the unknown geranyl product. The published[105] infrared spectrum of β-elemene is identical with that of the unknown sesquiterpene, and the maxima of each are reproduced below.

β-elemene: 3096, band ~ 2900, 1825, 1783, 1642, 1441, 1414, 1370, 1244, 1176, 1151, 1136, 1089, 1056, 1007, 971, 907, 889, 793, 740 cm^{-1}.

Unknown $C_{15}H_{24}$: 3096, 2941, 2882, 1821, 1785, 1645, 1443, 1416, 1374, 1242, 1179, 1150, 1138, 1087, 1056, 1001, 963, 907, 888, 793, 738 $cm.^{-1}$

Although it is recognised that the identity of the infrared spectra of β-elemene (58) and the unknown does not prove beyond all doubt that the unknown is β-elemene, it is felt that



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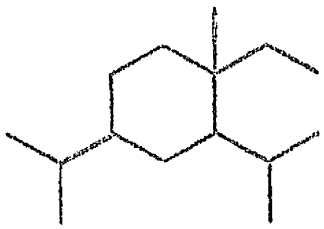

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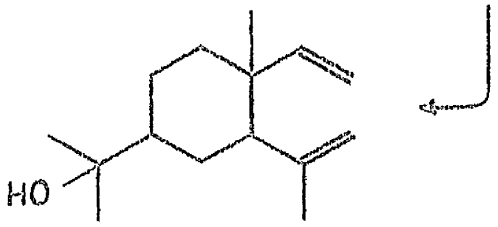

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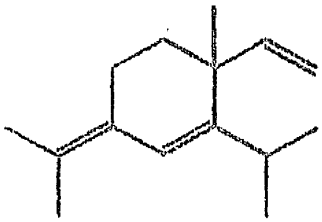

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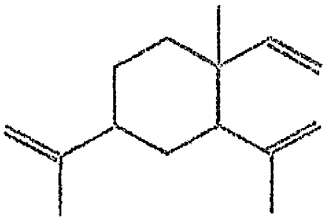

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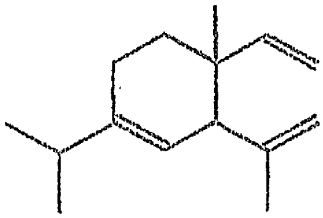

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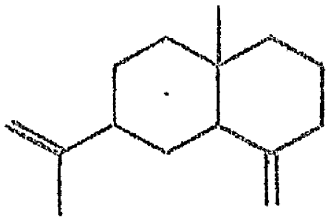

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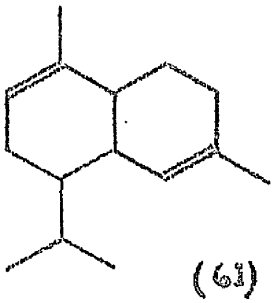

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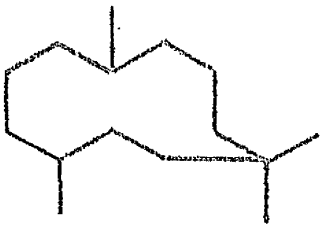

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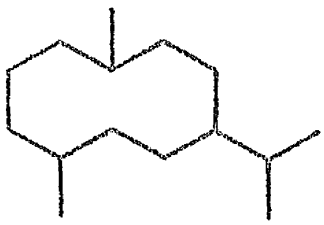


(63)

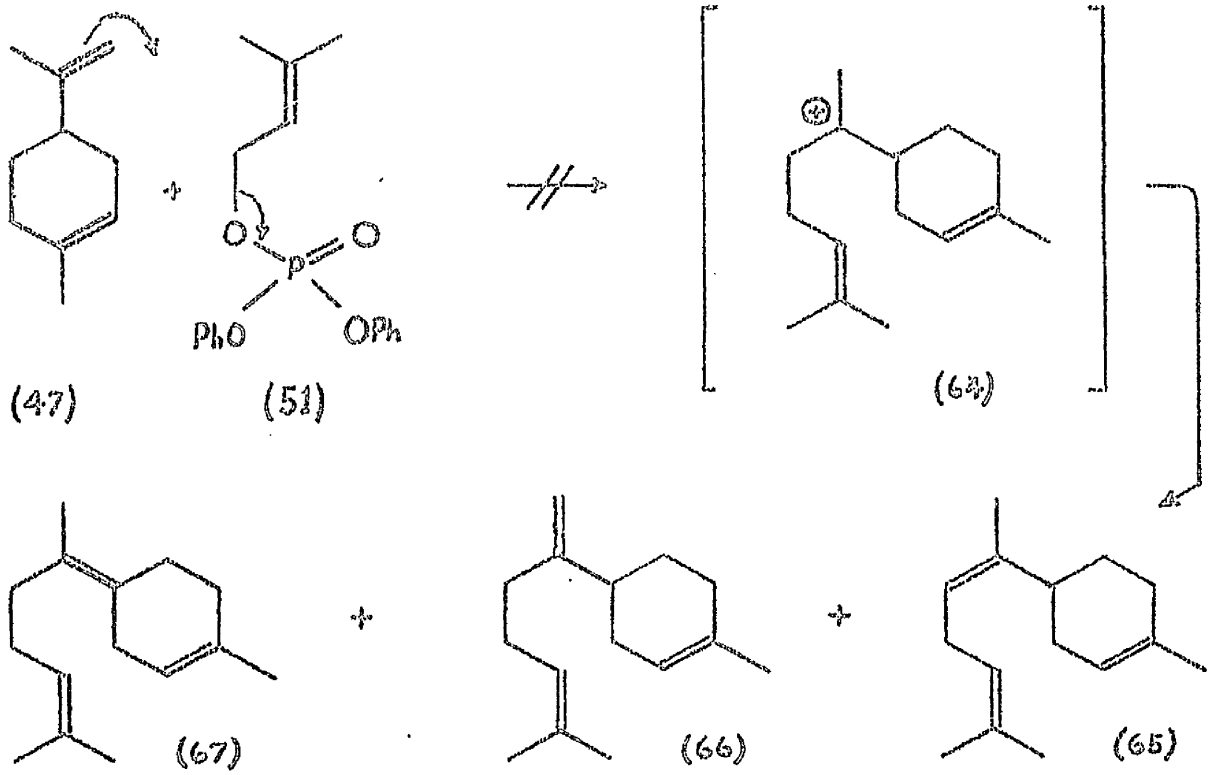
the nuclear magnetic resonance spectrum provides extremely good additional evidence in favour of the claim.

Unfortunately it has not been possible to solve the problem of the structure of the less volatile sesquiterpene without undertaking chemical study, principally because less information has been derived from the spectra of the hydrocarbon and because far more possibilities would need to be examined than for the more volatile isomer. The infrared spectrum showed the presence of a gem-dimethyl group, as well as absorptions for di-substituted vinyl (CH_2=$\dot{C}$-) and tri-substituted olefin (-CH=$\dot{C}$-). Both the infrared and ultraviolet spectra indicated that the double-bonds were not in conjugation. The nuclear magnetic resonance spectrum was disappointingly inconclusive, although it displayed typical absorptions for -CH-$\dot{C}$- (4.65 τ), -$\dot{C}$-CH_2 (5.35 τ), $-CH_2-\dot{C}-\dot{C}-$ (8.1 τ), $CH_3-\dot{C}-\dot{C}-$ (8.35 τ), $-CH_2-$satd.- (8.65 τ), and CH_3-satd. (9.15 τ). From the integral, it appeared that there were three olefinic groups, two of which were triply-substituted, three methyls in an unsaturated environment, and two methyls attached to a saturated carbon. The absorption for the saturated methyl groups was rather unusual, because it took the form of a triplet, such as an ethyl group would be expected to give, although it did

integrate for two methyls, as would be expected for a gem-dimethyl group.

It would appear that the less volatile sesquiterpene is a monocyclic, tri-unsubstituted hydrocarbon, perhaps with a gem-dimethyl group, and therefore could not be a selinene (60), or cadinene (61). The monocyclic structures, such as those derived from humulane (62) and germacrane (63) are, however, possibilities for the skeleton of the unknown hydrocarbon, although it is appreciated that there are many other skeletons which would fit the spectral evidence. Since the object of these experiments was primarily to establish the chemistry of the terpenoid phosphates, and not to spend time in detailed structural studies of complex products, it was decided not to embark upon a structural investigation of this sesquiterpene.

Among the most simple of the common sesquiterpenes are the three bisabolenes, α-bisabolene (65), β-bisabolene (66), and γ -bisabolene (67). Although it is clear that the unknown sesquiterpene is not a bisabolene, it was attempted to synthesise one or more of them by treating 3,3-dimethylallyl diphenyl phosphate (51) with limonene (44), but no sesquiterpene formation was observed, whether the reactants were heated alone, or in solution, over a period of several weeks at 37°C. In principle, the intermediate (64) could eliminate a proton to give α- (65) β- (66) or γ -bisabolene (67).



The isolation of limonene as the principal product from the decomposition of neryl diphenyl phosphate in ether has been discussed earlier, but one of the other products (peak 4 in the gas-liquid chromatogram - Figure B) was isolated and studied. The infrared spectrum showed gem-dimethyl absorptions, but the nuclear magnetic resonance spectrum did not confirm this evidence, despite the fact that the tendency of the neryl system to cyclise would lead one to anticipate that a gem-dimethyl group might be formed during decomposition. The nuclear magnetic resonance spectrum showed absorptions for triply-substituted olefin, at 4.7 τ; for methyl attached to olefin, at 8.3 τ ;

and for saturated methylene, at 8.5τ, but there were no bands above this position, which could be attributed to a gem-dimethyl group. In view of the uncertainty of the functional groups possessed by this compound, no further study was made of its structure.

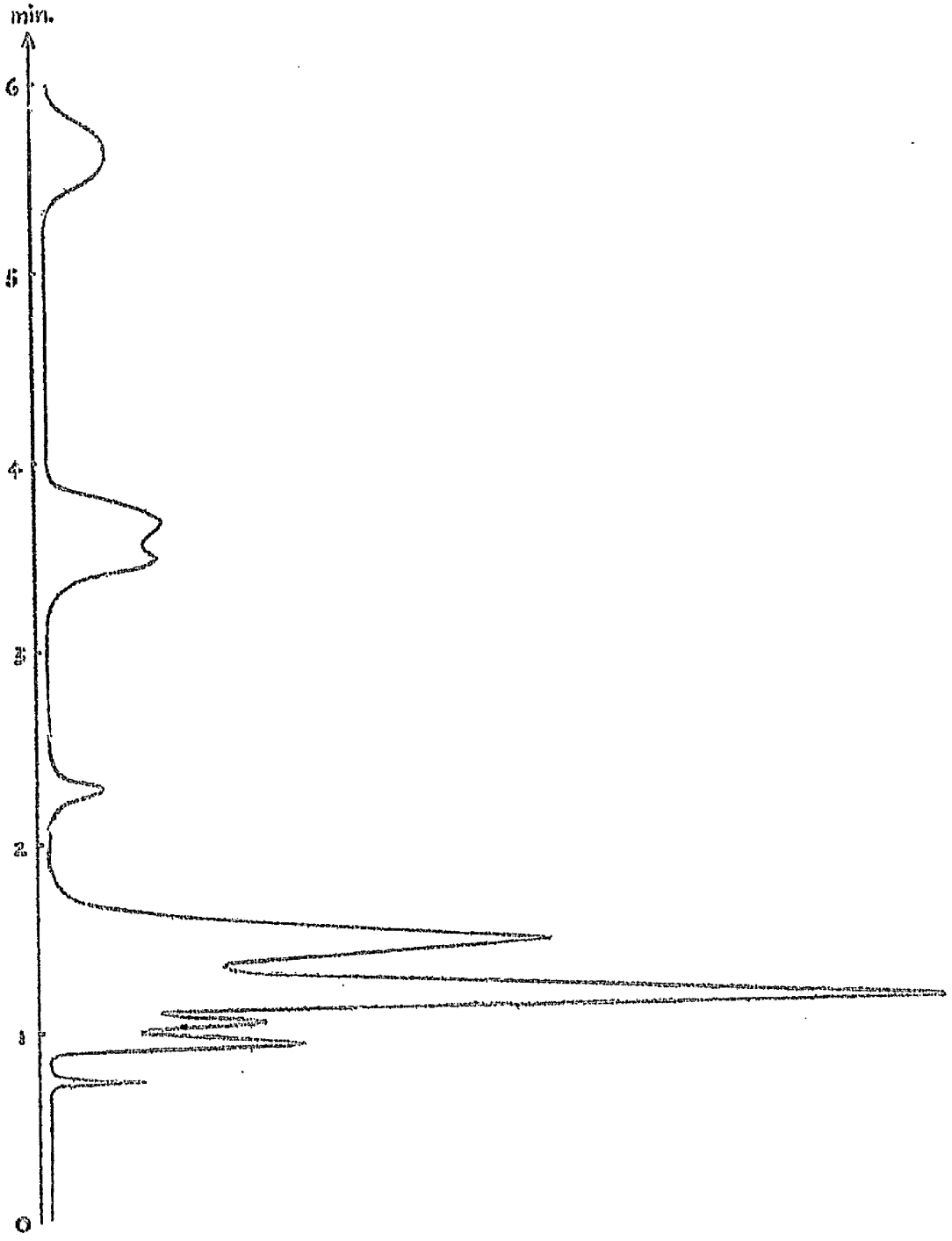
Decomposition of Geranyl Diphenyl Phosphate in Ethanol:

The phosphate was allowed to stand in ethanol at 37°C for 2 weeks and was found to give rise to an extremely complex mixture of products, seven of which, as indicated by the analytical gas-liquid chromatogram (see Figure C), were present in reasonable amounts, although the total yield was no greater than in the experiments in other solution. The change in solvent, to one of higher dielectric constant (ethanol = 24), and to one which could, in principle, participate in the reaction, produced some interesting results.

Although smaller amounts of hydrocarbons were produced the main products were two ethyl ethers, each of which was isolated as a pure liquid by preparative gas-liquid chromatography. The less abundant of these was not identified, although the presence of an ethyl ether was demonstrated by the infrared absorption at 1071 cm.$^{-1}$, and the nuclear magnetic resonance bands at 6.6τ (quartet) and 8.9τ (triplet).

The most interesting product, however, was the second

FIGURE C : GAS-LIQUID CHROMATOGRAM OF PRODUCTS FROM DECOMPOSITION OF GERANYL DIPHENYL PHOSPHATE IN ETHANOL AT 37°C.



(50) (47)

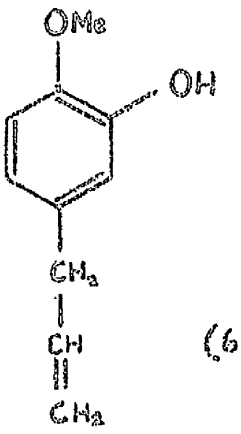
These base-catalysed decompositions are not surprising in view of the properties of the parent phosphates, and the fact that isomerisation accompanies each reaction is not a new observation in the chemistry of geranyl and neryl esters. One of the reactions discussed by Ingold[106] to illustrate the concept of anionotropic rearrangement is the basic hydrolysis of either linalyl or geranyl acetates, each of which gives a mixture of geraniol and linalool, the former, as in the case with the phosphate esters above, usually predominating.

Decomposition of Geranyl p-Toluene Sulphonate:

This ester was synthesised, in order to compare the p-toluene sulphonate anion with the diphenyl phosphate anion as a leaving-group. After treatment identical with that used for the decomposition of geranyl diphenyl phosphate, the sulphonate was found to give similar yields of hydrocarbon products, but the mixtures produced were much more complex.

The principal hydrocarbon product was not identified, although the less important ones were found to be the acyclic dienes, myrcene and ocimene.

When alumina chromatography of the crude geranyl products was continued beyond the hydrocarbon stage, two others were eluted, and one of these, the aromatic one, was found to be eugenol methyl ether (69). This apparent mystery was solved, when it was demonstrated that the original geraniol contained about 2% of eugenol (70) and its methyl ether (69).



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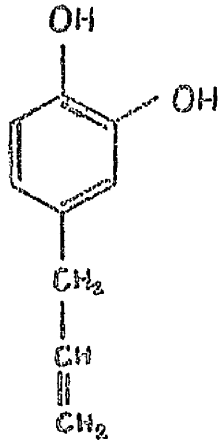


(70)

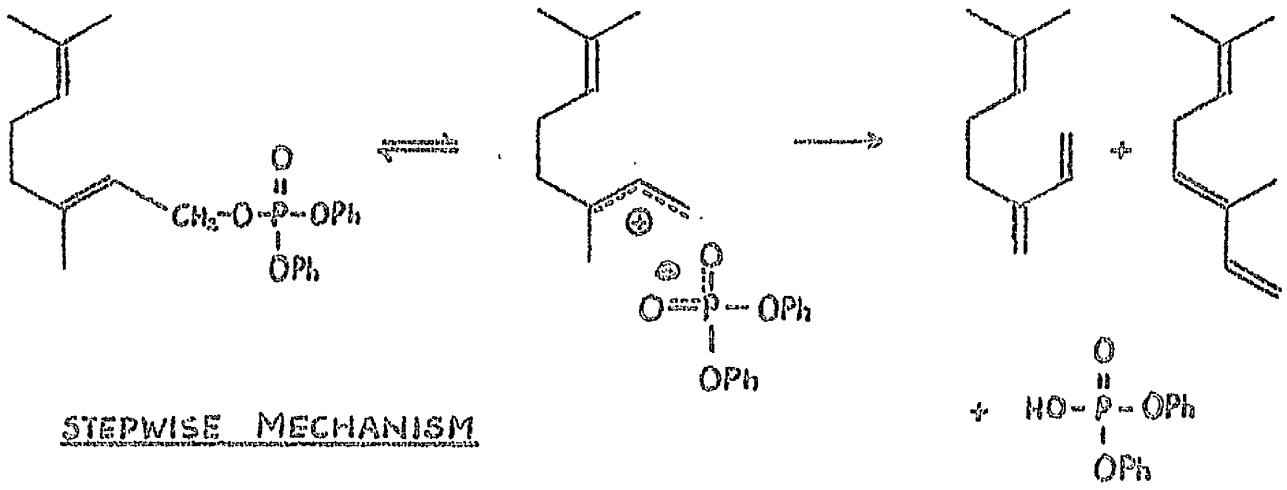
When the unreacted sulphonate was allowed to hydrolyse on the alumina column, it was found that three alcohols were produced. These were linalool, geraniol, and an unknown alcohol, which was not α-terpineol, and which was intermediate in volatility, and in polarity on an alumina column, between linalool and geraniol.

No attempt was made to identify the unknown hydrocarbon, ether, or alcohol obtained from this decomposition since the experiment was merely designed for comparative purposes.

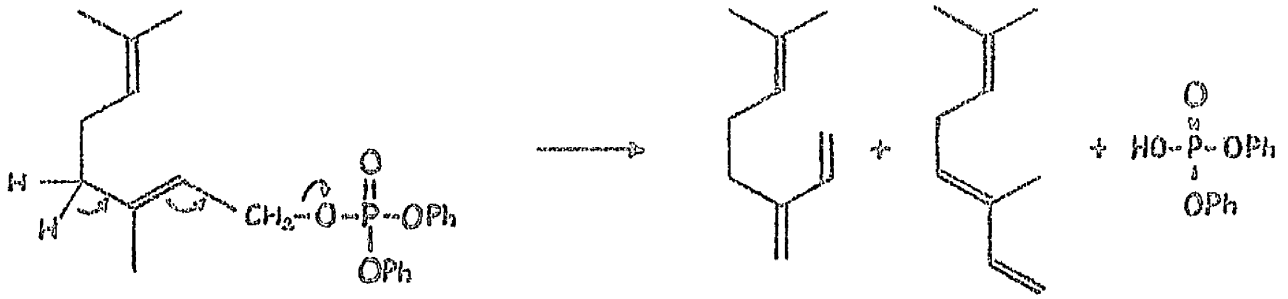
Mechanisms of Phosphate Decompositions:

Although these decompositions in organic solvents all produce mixtures, and all the products have not been identified, it is still possible to speculate on the possible mechanisms of decomposition, by considering the major products, their rates of formation, and the effect of changing the solvent.

There are two limiting mechanisms by which these phosphates could decompose, viz. the stepwise or ionic mechanism, and the concerted mechanism. Since the carbonium ions produced by a stepwise mechanism would be relatively stable, and comparable with 3,3-dimethylallyl ions, it is not possible to favour one mechanism on *a priori* grounds. The two available mechanisms are outlined below for the geranyl ester.

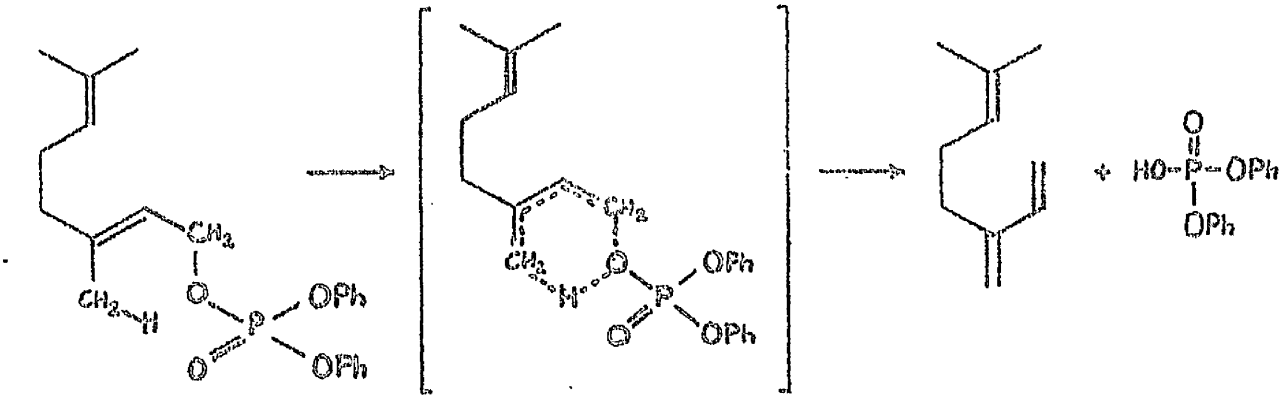


STEPWISE MECHANISM



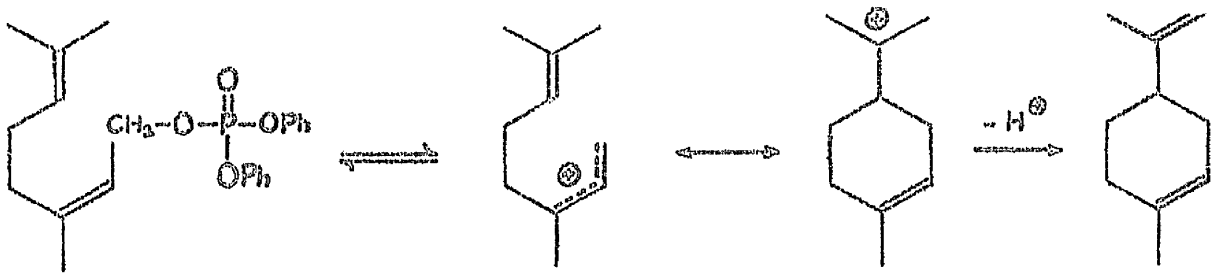
CONCERTED MECHANISM

Each of these mechanisms assume that the process is intramolecular and unimolecular, but there is the possibility that the phosphate assists the decomposition, by means of a cyclic process. This cyclic transition-state is readily envisaged in the formation of myrcene, but with ocimene, the

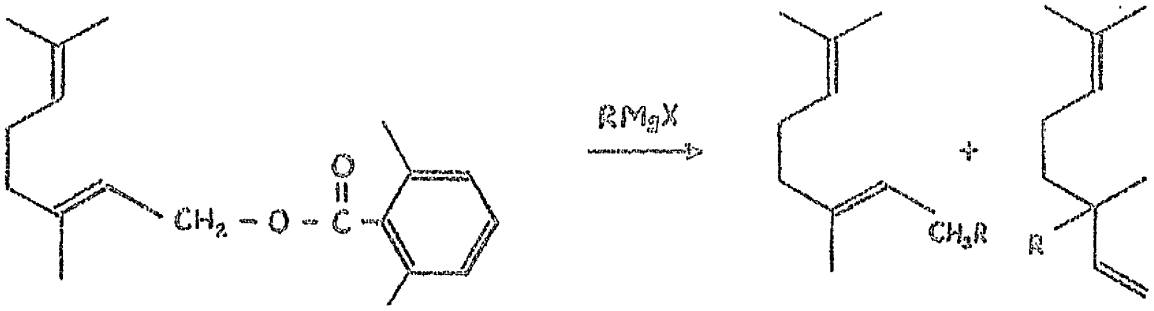


stereochemistry about the allylic double-bond does not permit this simple representation of a possible transition-state, and since ocimene is the major product, assistance by the phosphate would seem unlikely.

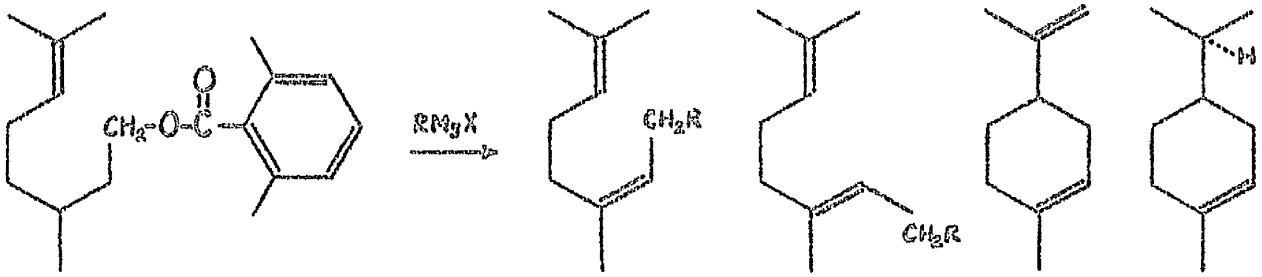
If the mechanism in the other decompositions is stepwise, then the rapid decomposition of the neryl ester can be attributed to participation of the isopropylidene double-bond, which is in a favourable position in certain conformations of the hydrocarbon chain. One is then faced with the fact, that since the geranyl ester decomposes slowly and does not produce any cyclic monoterpene, there can be no equilibrium between the geranyl and neryl cations. It has already been noted that this interconversion has been postulated[98] to explain the facile, acid-catalysed ring-closure of geraniol to α-terpineol in rather different circumstances.



Recently, some work appeared in the literature[107] describing the reactions of geranyl mesitoate (71) and neryl mesitoate (72) with simple, aliphatic, Grignard reagents, such as methylmagnesium bromide. Since these esters are hindered at the carbonyl carbon, normal Grignard addition is inhibited, and alkylation occurs at the electrophilic α-carbon of the geranyl or neryl esterifying group.



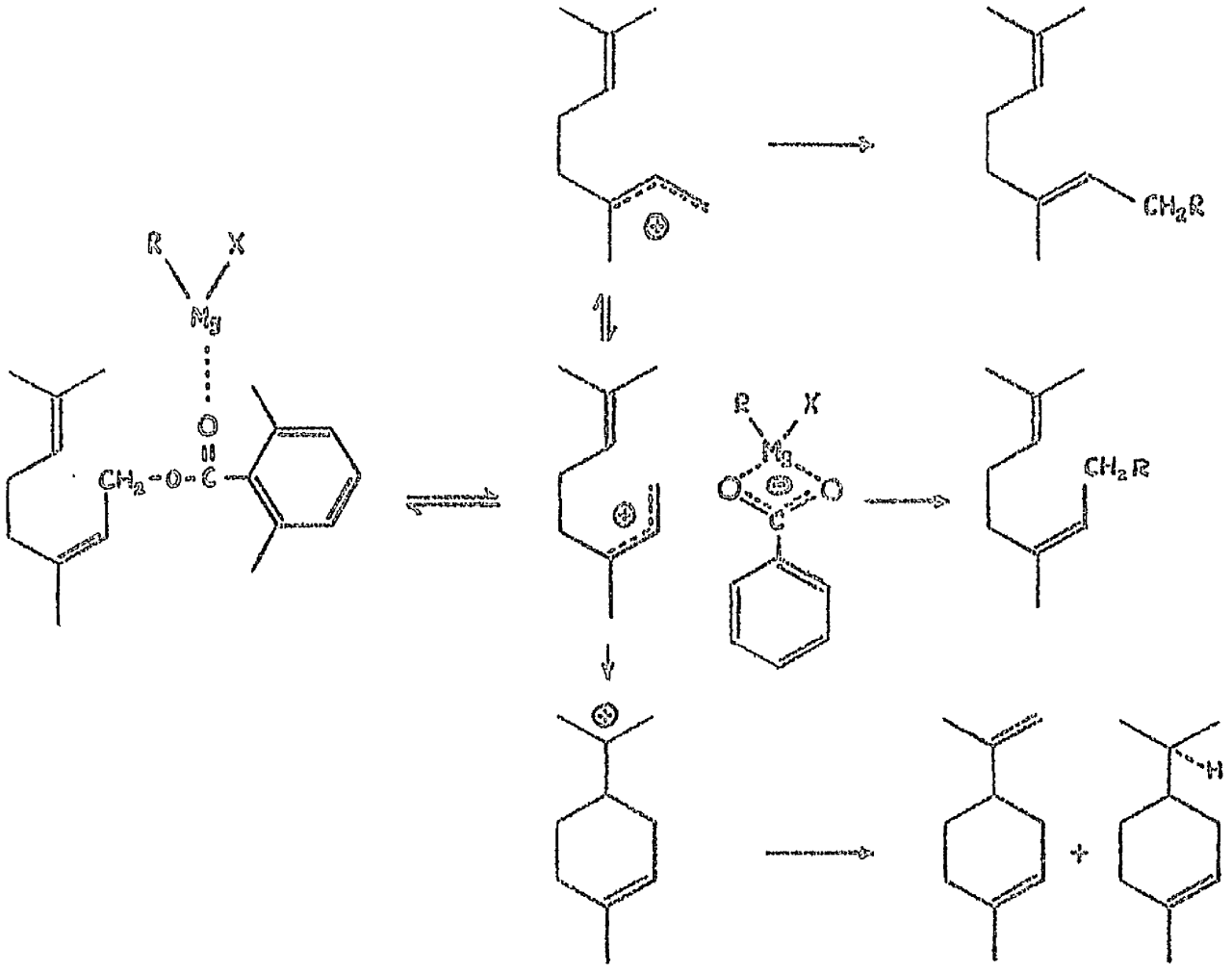
(71) [90%] [10%]



(72) [40%] [10%] [30%] [10%]

The authors claim that these reactions involve reversible dissociation to ion pairs, see below, and that the intermediate ions yield the products shown above. In these experiments, the rates for geranyl and neryl esters are almost the same, and the solvent is ether. The problem of deciding upon a mechanism is therefore similar to that occurring with phosphate-ester decomposition, but in this case the authors have chosen to ignore the fact that while the geranyl mesitoate gives no cyclic product, and therefore does not equilibrate with

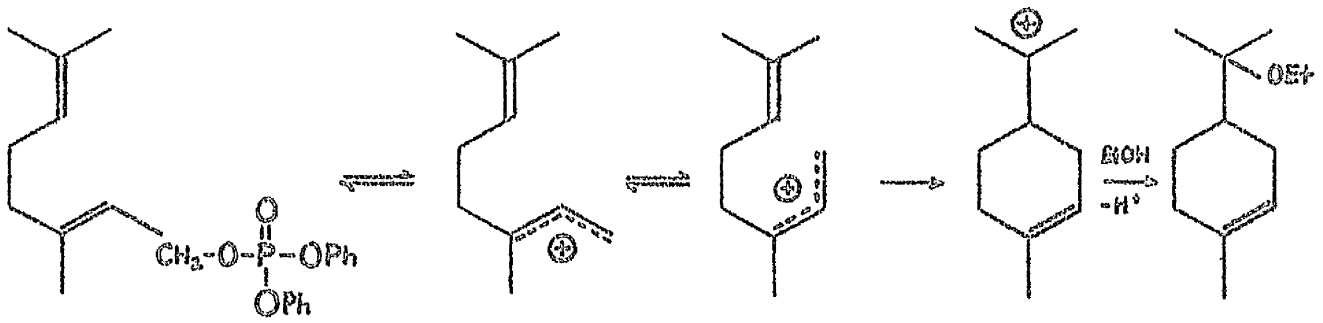
the neryl cation, the neryl mesitoate does give rise to cis- and trans- products, as well as cyclic hydrocarbon. Since the rates of each reaction are comparable, it follows that there must be some activation factor which prevents the equilibration of the geranyl cation, but which permits the equilibration of the less stable neryl cation. Although there is an apparent analogy in these mesitoate and phosphate decompositions, one must be very cautious, because of the uncertainty about the effect of the magnesium atom of the Grignard on the ionization of the mesitoates.



Perhaps the conclusions of these authors have been influenced by the findings of Arnold,[108,109] and of Young,[110] who have studied the reactions of crotyl- and 1-methylallyl mesitoates with aryl magnesium halides. These workers concluded that alkylation occurred when steric hindrance inhibited normal addition, and, more important, when the esterifying group of the mesitoate was capable of forming stable carbonium ions. The alkylation reaction was thus believed to be ionic, and was found to occur readily with 3,3-dimethylallyl mesitoate and t-butyl mesitoate, each of which could give rise to stable carbonium ions.

Returning to the discussion of the present studies on phosphate esters, there is at least a more clear-cut situation, in which, if an ionic mechanism is operative, both the geranyl and neryl ester give only products which do not necessarily require this interconversion from a geranyl to a neryl cation, or vice-versa. A concerted mechanism for the decomposition is however quite defensible, and the rate difference could certainly be explained by the favourable disposition of the nucleophilic isopropylidene olefin. There is no reason to assume, on precedent alone, that a geranyl or neryl phosphate ester would necessarily ionise sufficiently in ether to rule out a concerted process. Thus the problem is rather finely balanced.

The above considerations are somewhat altered by the cyclic nature of one of the main products from the decomposition in ethanol. Not only has the ethanol participated in the reaction, but it has also brought about an important structural alteration in the product. Clearly, the cyclisation is most likely to have been brought about by a carbonium-ion mechanism, in which the dielectric and solvating properties of the ethanol have permitted the barrier between the neryl and geranyl cations to be overcome, or, alternatively, have brought about a preliminary ionisation not possible in ether.



(43) (68)

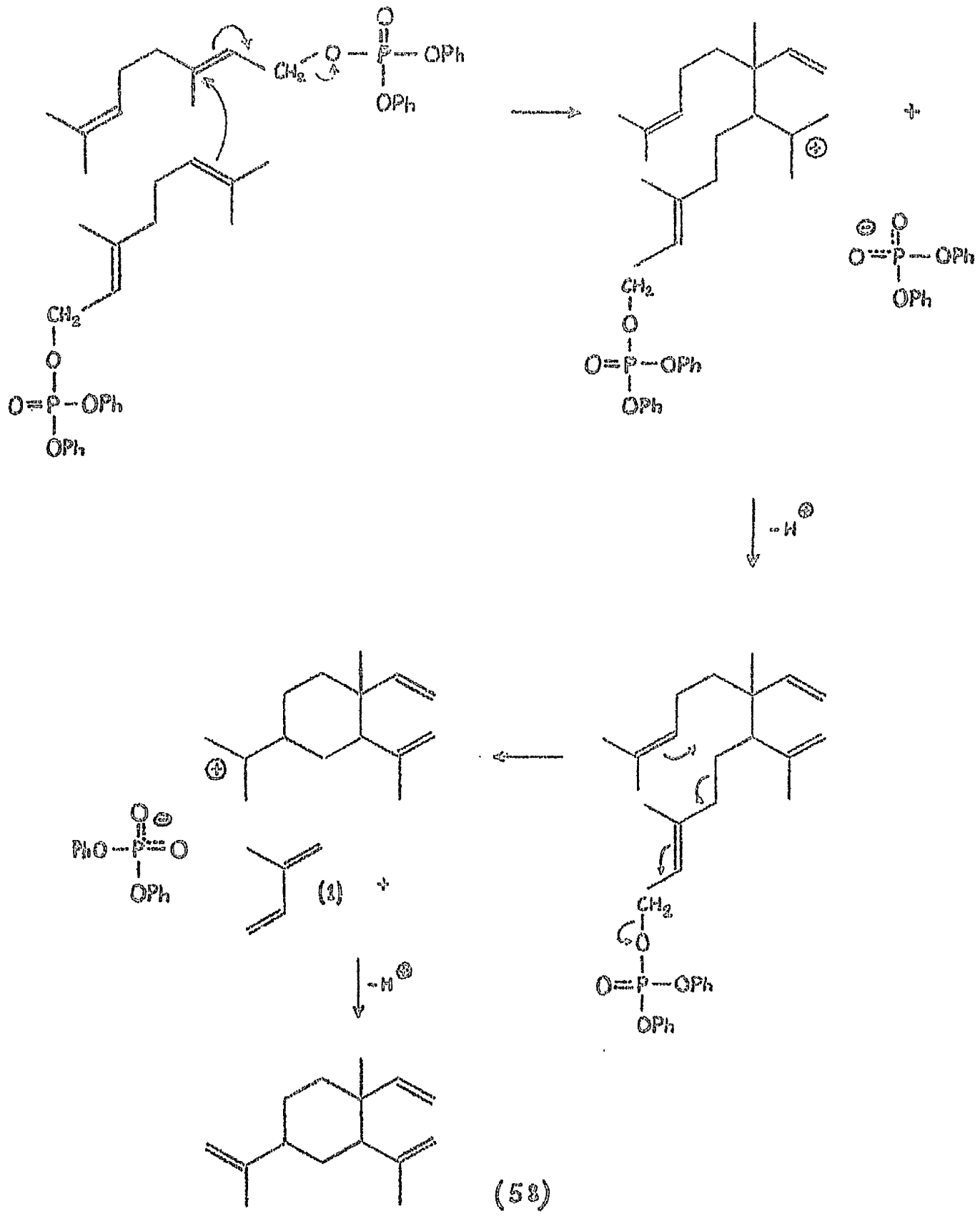
Since there was no further evidence of cyclised products from the ethanolic decomposition, it would appear that there is a dual mechanism operating in this case, and therefore it would be logical to assume that the decomposition in ether is wholly concerted. There is, however, the possibility that the

ethanol reacts with the acyclic ionic species present, before they can be irreversibly converted to the cyclic, tertiary carbonium ion. In view of the speed with which cyclisation of the neryl phosphate occurred in ether, this reaction would indeed need to be very fast, and, as there is no evidence of such a fast reaction, the concept of a dual mechanism in ethanol would appear to be sustained.

If the decomposition in ethanol is occurring by two different mechanisms, or, as Winstein would prefer, by one intermediate mechanism, it would seem likely that in a solvent of lower dielectric constant, such as ether, the decomposition would occur by a mechanism more closely analogous to the wholly concerted process. Although it is extremely hazardous to be dogmatic about such a matter, there is at least no evidence which makes the concerted process are unlikely one under the experimental conditions.

Sesquiterpene Formation:

The mechanism of sesquiterpene formation is even more uncertain, because of the unusual fission leading to C_5- and C_{15}-fragments, for which there does not appear to be any precedent. It has already been noted that the more volatile sesquiterpene hydrocarbon obtained from the ether decomposition of geranyl diphenyl phosphate was probably β-elemene (58), and this system can be obtained by the mechanism outlined below.

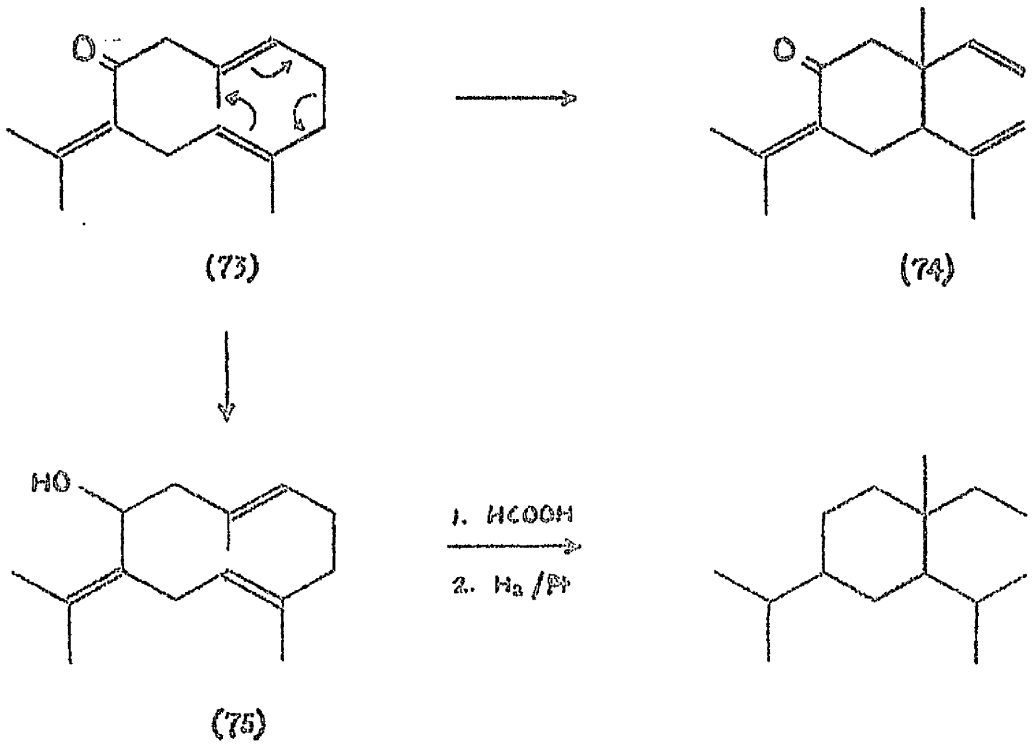


(58)

This mechanism, however, is unsatisfactory, because fission of a carbon-carbon bond in such circumstances is somewhat unusual, and because it violates the rule, explained in the theoretical section, that S_N2' attack does not occur when there is a primary allylic carbon available for nucleophilic attack. If the evidence gained from the monoterpenoid products had indicated that an ionic, stepwise decomposition was occurring in ether, then the second objection to the above mechanism would be removed.

One important point has been overlooked as yet, in this particular discussion; namely, it is not known at what stage in the decomposition the β-elemene skeleton is formed, although the above mechanism assumed it was formed in a direct attack on the phosphate. It has been demonstrated that the isoprene (I) is liberated during the decomposition in ether, and therefore that the C_{15}-fragment is formed in the initial reaction, but it has not been shown conclusively that the β-elemene system possesses the skeleton of the initial C_{15}-fragment. Considerable evidence[111] has been amassed by other workers to show that the elemane system can be formed from a pyrolytic rearrangement of a germacrane (63) skeleton. For example, two of the principal pieces of evidence leading to the structure of germacrone (73) were the observations[112] that

during distillation it produced elemenone (74), and that high-temperature dehydration of the alcohol (75) derived from germacrone produced elemene (53), after hydrogenation over an Adams Catalyst. These trans-formations are, of course, analogous to the biological formation of elemenes and elemol from germacrane systems, as suggested by Hendrickson.[201]



(73) (74)

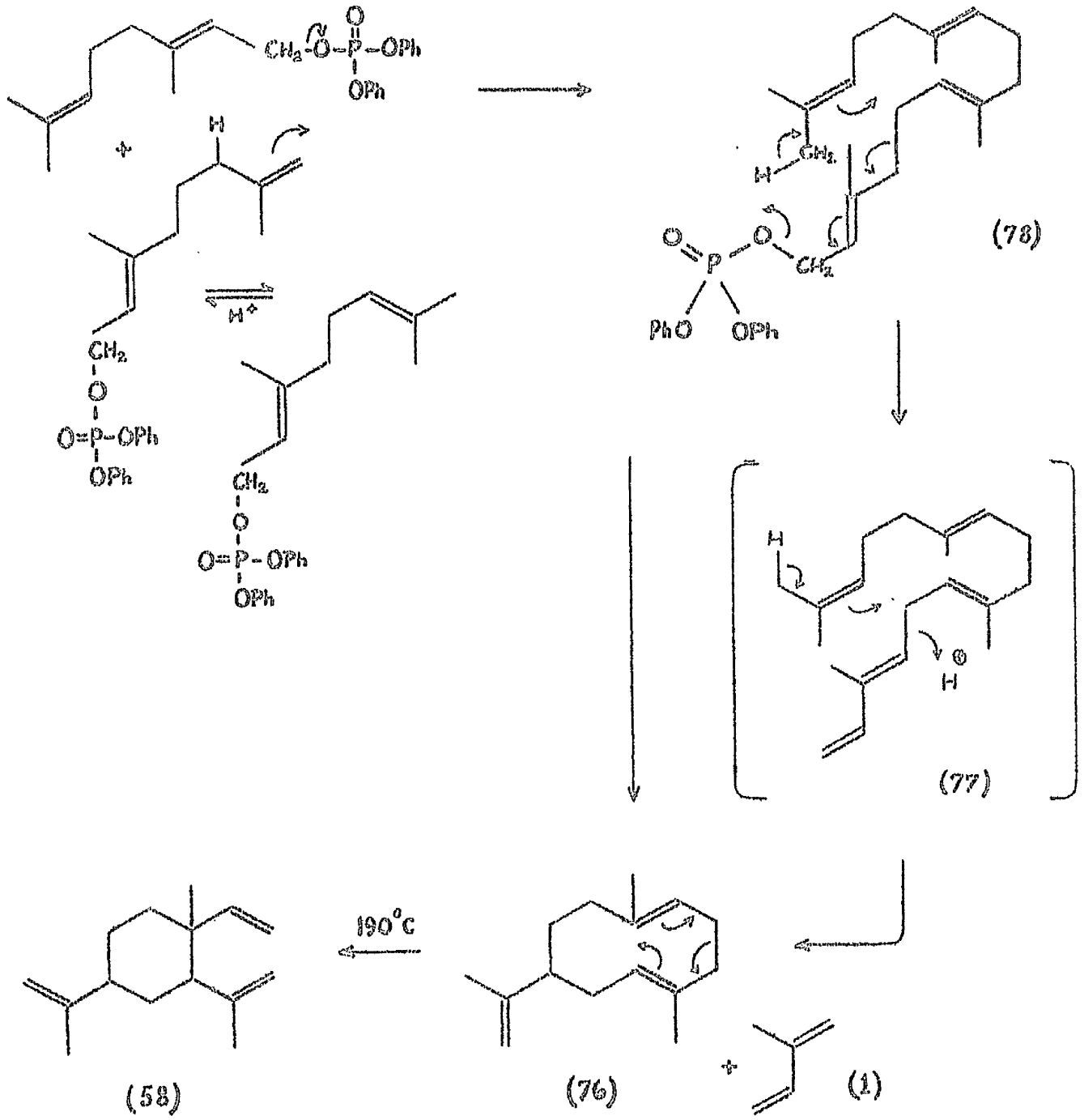
(75)

It is therefore quite possible that the β-elemene isolated by preparative gas-liquid chromatography at 190°C, was the result of an isomerisation of a germacrene (76) produced in

the original phosphate decomposition. The formation of a cyclodecene from the geranyl diphenyl phosphate is mechanistically more likely than direct formation of an elemene, although the fission reaction still remains an objection to the mechanism. Nevertheless, this fission does occur in solution and any mechanism suggested to explain it would seem unusual by normal standards. At least there is the favourable factor that two stable entities, isoprene and diphenyl phosphate, are being formed, although it must be admitted that the fission may be occurring on a conjugated diene (77), formed from the phosphate intermediate (78). Another possibility is that the fission of the C_{20}-phosphate (78) is aided by some form of participation by the phosphate leaving-group, as indicated in the mechanism shown below.

The conjecture surrounding the possible formation of a germacrene intermediate would, of course, be resolved if it could be demonstrated that the β-elemene (58) was not present before the gas-liquid chromatographic stages. This would only be possible if a separation of β-elemene, or its precursor, could be achieved by chromatography, or some other technique not requiring the use of heat, but the present indications are that this would be very difficult indeed. Despite the lack of conclusions about the details of the formation of β-elemene, it would have been rewarding to examine the differences in its formation, compared with the

other sesquiterpene obtained from geranyl diphenyl phosphate, but so little is known about the structure of the latter sesquiterpene that this comparison cannot be made.



Conclusions:

It can be claimed that the course of these *in vitro* decompositions of phosphate esters has shown that the stereochemistry of the allylic double-bond is of prime importance in determining the structures of the mono- and sesquiterpenoid products. The exact mechanisms of these reactions are not at all certain, since it is no more easy to demonstrate the presence or absence of carbonium intermediates in these experiments, than it has been in analogous biological systems. While the nature of the simple monoterpenoid products may have some biosynthetic significance, indicating that cyclic monoterpenes are more likely to be produced from a neryl ester, or a neryl cation, the same cannot be said of the sesquiterpene products, since the *in vivo* mechanism of sesquiterpene formation is not at all similar to that operating in these model experiments. The demonstration that cyclisation of a geranyl system can occur in ethanol, does show, however, that one cannot automatically extend to biological systems, conclusions which are solvent dependent in *in vitro* systems.

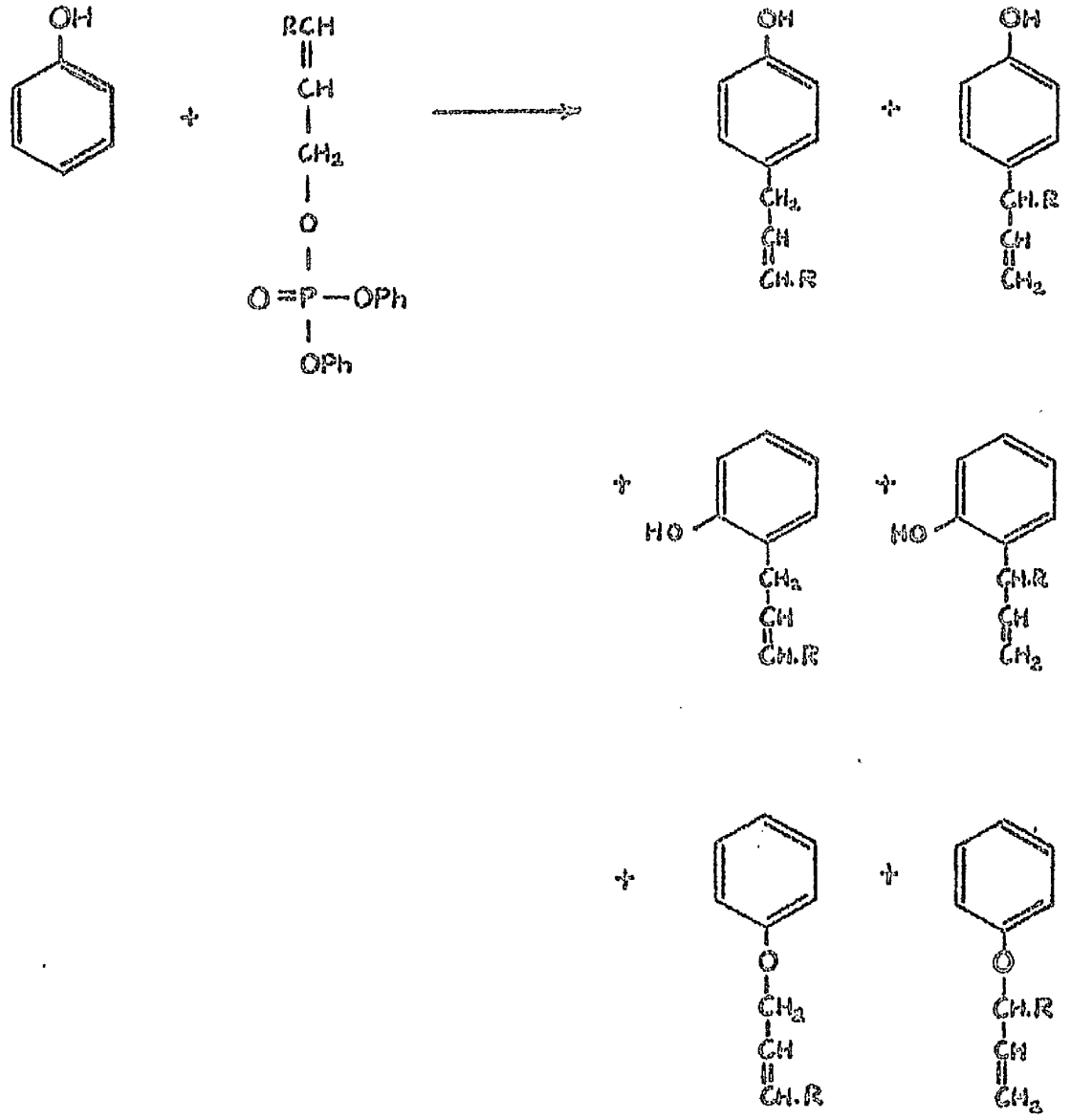
(3) ALKYLATION OF PHENOLS WITH PHOSPHATES:

In the Introduction to this Thesis, the current theory of the mode of biosynthesis of phenolic isoprenoids was outlined. It was also shown how this theory was originally suggested because of the structural similarities of these compounds, which appeared to have been produced by the alkylation of phenols with 3,3-dimethylallyl pyrophosphate.

By replacing the pyrophosphate residue, which is believed to act as a leaving-group *in vivo*, with diphenyl phosphate, it was hoped to construct model experiments which would lead to products analogous to those found in nature. These model experiments were begun with the reaction between phenol and allyl diphenyl phosphate (40), and then extended to other more complex systems containing polyhydroxy phenols and substituted allyl phosphates.

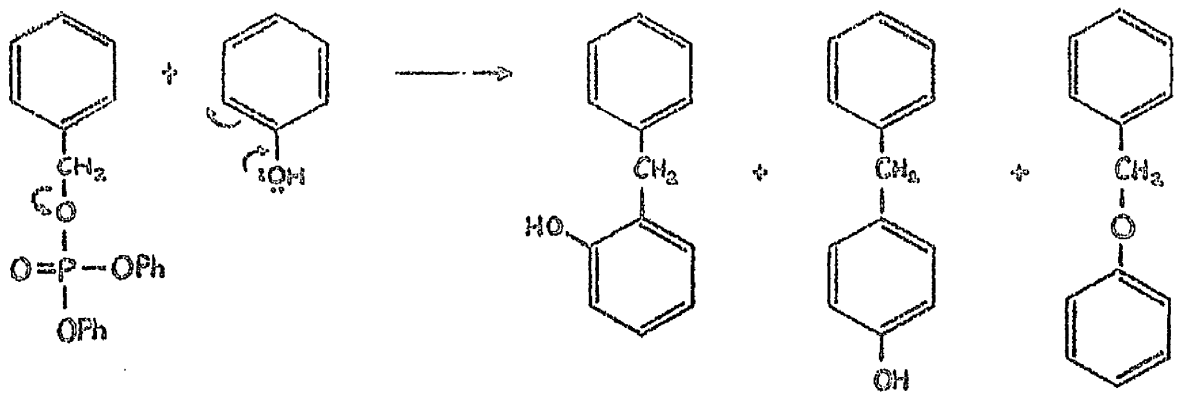
The reaction between a phenol and an allyl diphenyl phosphate is potentially very complex, because each of the reactants has more than one site of attack open to the other. For example, phenol can act as a nucleophile by virtue of electron-density on the oxygen, or on either the *ortho*- or *para*- ring carbons, and such molecules are known as ambident nucleophiles. Similarly an allyl ester, such as allyl diphenyl

phosphate, is an ambident electrophile, because it can undergo nucleophilic attack at either the 1- or 3-positions. When the allyl ester is asymmetrically substituted, the alternative sites of attack become chemically distinguishable, and, in a reaction with phenol, for example, there will be six possible products, as shown below.



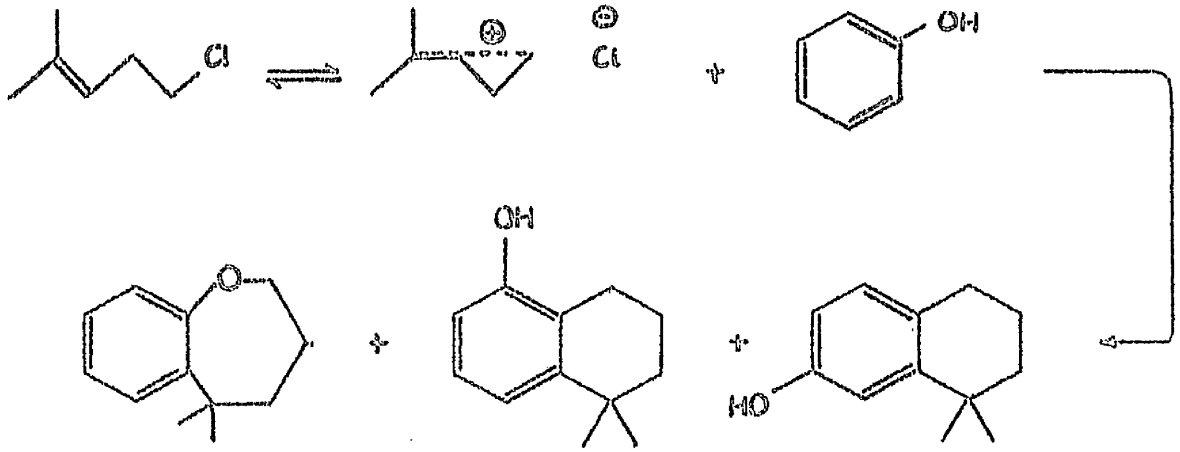
Fortunately, all these possible products are not normally produced, because electronic and/or steric factors inhibit the formation of certain structures. The phenol-phosphate systems studied in this thesis have been found to be relatively simple, in that they have given rise to fewer products than might have been expected.

There is little precedent in the literature for alkylation of phenol itself with allyl halides or esters, since most of the mechanistic studies of this type have been done with phenoxides.[113,114,115,116,117] Perhaps the best analogy to the present work is the solvolysis of benzyl diphenyl phosphate(39) in phenol, which was studied by Kenner and Mather,[89] because of an interest in mild methods of de-benzylation of nucleotides. They used a 50-fold excess of phenol at 50°C for 72 hr., and found that small amounts of benzyl phenyl ether (6%), and larger amounts of o-benzyl phenol (45%) and p-benzyl phenol (38%) were formed. The authors presented semi-quantitative kinetic evidence to show that the reaction was normally unimolecular, except in the presence of strong acids, when a bimolecular process was also believed to be important.



(39)

A more recent example of solvolysis[118] in phenol is the treatment of 2-methyl-5-chloro-2-pentene (79), a homo-allylic halide, with a 4-fold excess of phenol at 150°C for 11 hr., to produce the three alkylated products, shown below, in almost identical amounts. The authors gave tracer and kinetic evidence showing that the reaction involved a preliminary, rate-determining ionisation, and that there was double-bond participation.



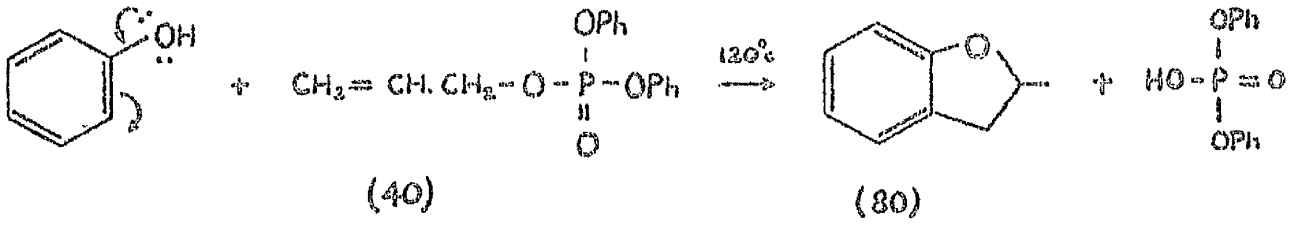
It will be noted that each of these solvolyses reactions in phenol gave three products, and as such are typical of alkylation by carbonium ions, which in general has been found to give substitution on oxygen, and at both the ortho- and para- ring positions.

Reaction of Phenols with Allyl Diphenyl Phosphate:

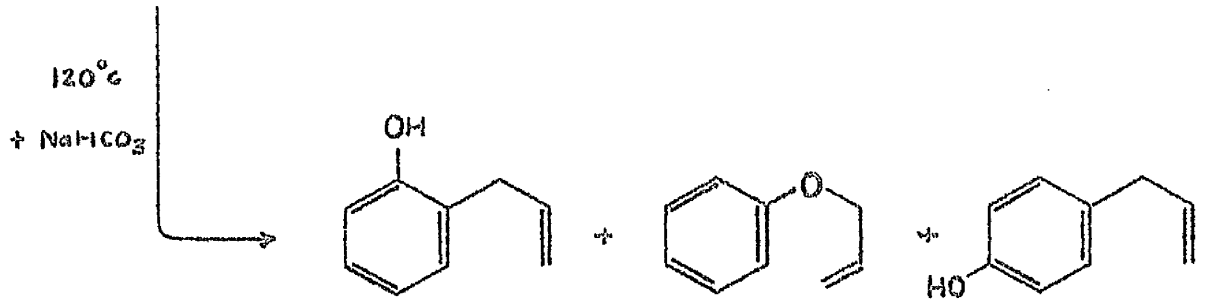
The above results have been described, because the conditions used, and the products obtained, are extremely similar to those obtained in the present studies of allyl diphenyl phosphate in phenol. It has been found that allyl diphenyl phosphate (40) alkylates phenol in about 50% yield after heating at 120°C for 6 hr. in an excess of phenol, and that the amounts of each preliminary product are of the same order.

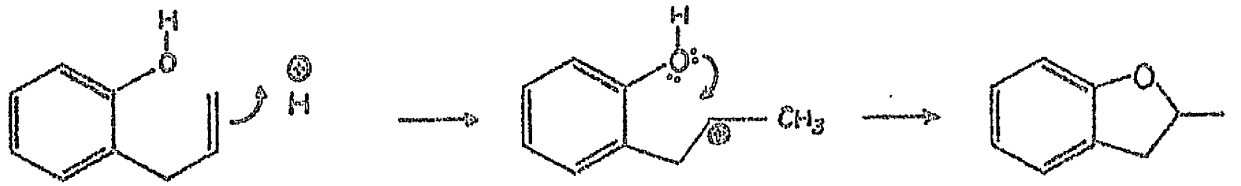
It was also found however, that the liberated diphenyl phosphate was sufficiently acidic to bring about rearrangement of each of these species to 2-methyl coumaran (80) on prolonged heating for 24 hr.

There is considerable precedent[119,120] for the ring-closure in acid conditions of o-allyl phenol to a coumaran, and this reaction is the basis of the conventional preparation of coumarans.[121] It was therefore no surprise to find that



(40) (80)



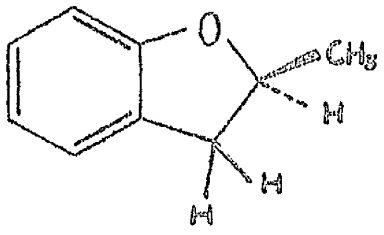


(80)

o-allyl phenol was converted quantitatively to 2-methyl coumaran on heating in phenol with diphenyl phosphate for 24 hr. at 120°C. Furthermore, when solid sodium bicarbonate was added to the allyl diphenyl phosphate in phenol before heating, it was found that there was no subsequent rearrangement of the initial alkylation products, each of which was obtained pure by preparative gas-liquid

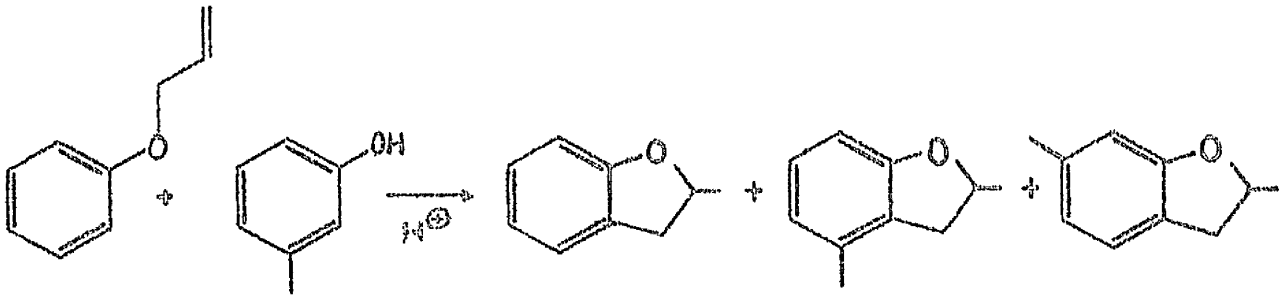
chromatography. Attempts to prevent the ring-closure by addition of a hindered organic base, tri-n-butylamine, were unsuccessful, since the only product in the mixed phenol-amine solvent was allyl phenyl ether. Further experiments showed that allyl phenyl ether was rearranged to 2-methyl coumaran by heating with diphenyl phosphate in phenol.

The end-product of these rearrangements was 2-methyl coumaran (80), which was identified very readily by nuclear magnetic resonance spectroscopy, by virtue of its quartet at 5.25τ (-O-C<u>H</u>-CH$_3$), triplet at 7.05τ (Ar.C<u>H$_2$</u>-), and doublet at 8.6τ (-O-CH.C<u>H$_3$</u>). The triplet at 7.05τ is not a genuine triplet, but is believed to arise from the fact that the ether ring is rigid, and therefore the methyne proton splits into doublets the non-equivalent methylene protons. Since the coupling constant is different for each of the methylene protons the band is not a true triplet, and is further distorted by long-range coupling with the aromatic protons.



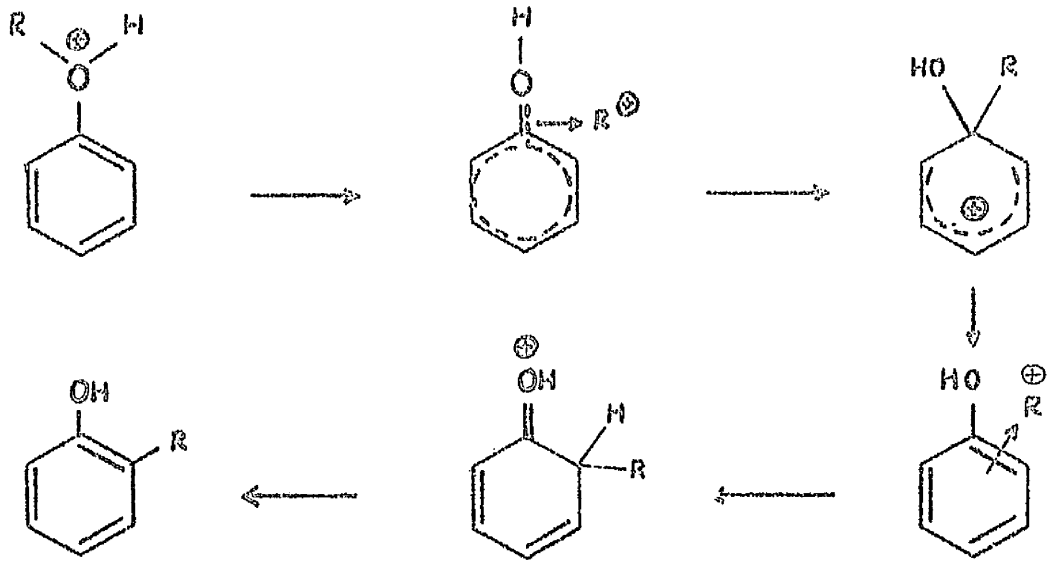
(80)

Although little trouble was experienced in isolating and identifying 2-methyl coumaran, the search for a mechanism to explain its formation from p-allyl phenol and allyl phenyl ether has not been too successful. Clearly, this rearrangement does not belong to the Claisen type of no-mechanism rearrangements, since the temperature is not high enough, and acid is required. A later experiment was designed to investigate if crossed-products would be obtained, when allyl phenyl ether was rearranged with diphenyl phosphate in m-cresol, but this only met with partial success, since products arising from both intra- and inter-molecular rearrangement were obtained.



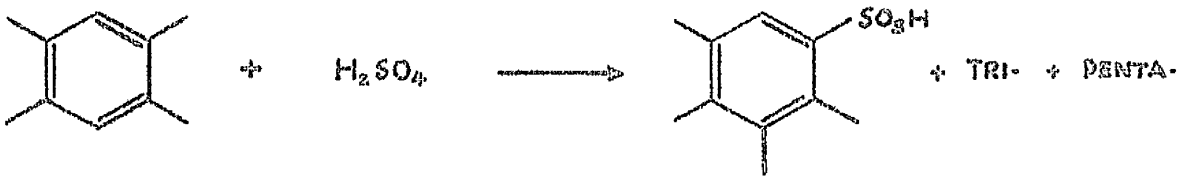
(80)

In a recent publication,[132] Dewar has pointed out that cross-migration during acid-catalysed aromatic rearrangements is not a good criterion of an intermolecular process, and the reasons for this become apparent on examining the mechanism of such rearrangements, outlined below.



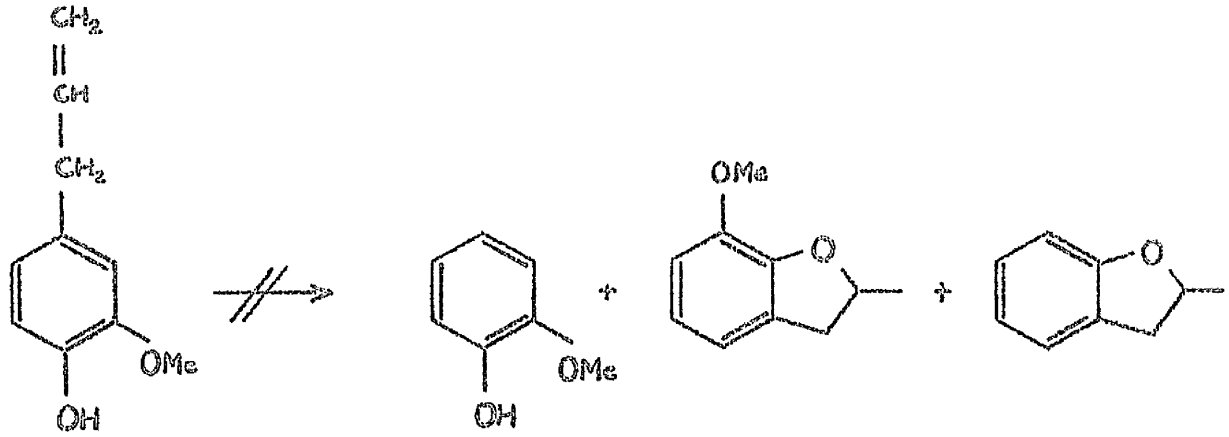
Thus the migrating-group, which is generally alkyl, may move round the aromatic system as a cation, using the π-electron-cloud as a 'rail-road', and there may well be intermediate states, which have higher energy than either the initial or final products, and which could therefore lose the migrating group to a reactive, foreign molecule, although neither the initial nor final products would necessarily do so. This mechanism would be expected to result in the retention of optical activity in saturated alkyl groups, since the alkyl-complex is pictured as being essentially π-bonded, and this phenomenon has in fact been observed with the rearrangement of sec-butyl phenyl ether in acid conditions.[128] Another example of an acid-catalysed process is the Jacobsen Rearrangement, in which a methyl group is found to migrate round a benzene ring during sulphonation, but cross-migration has

been found to occur, despite good evidence of a true intramolecular mechanism. The cross-migration was shown by isolation of small amounts of tri- and penta-methyl benzene derivatives, as well as the main rearranged tetra-methyl benzene sulphonate.



There is no reason to believe that an allyl group could not migrate in a similar fashion, although it is obviously not possible to decide whether the cross-migration observed in m-cresol is the result of loss of an allyl group from an intermediate, or the result of a genuine intermolecular reaction.

An attempt to isomerise eugenol (70) with diphenyl phosphate in phenol failed, although gas-liquid chromatographic traces showed that the eugenol was decomposed during heating at 120°C. Despite this preliminary evidence of isomerisation, there were no detectable traces of possible products, as outlined below.

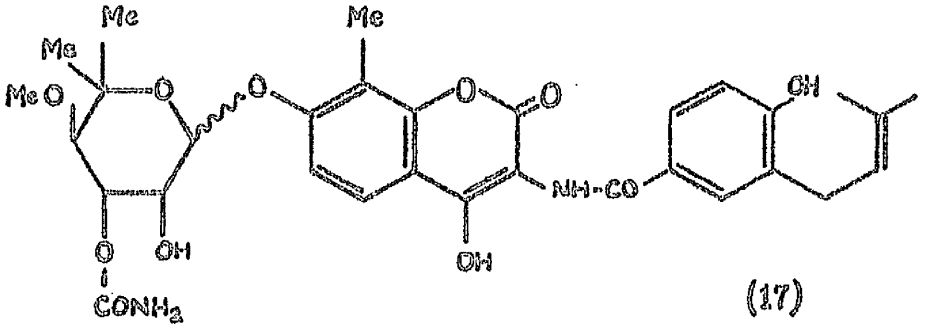


(70)

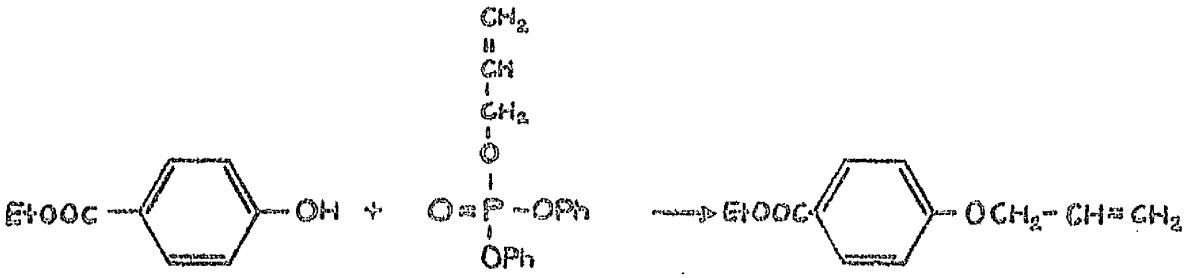
Having discussed the results of alkylation of phenol by allyl diphenyl phosphate in phenol, it is only correct to point out that, when the reaction was carried out at 100°, in ether, or without solvent, there was no detectable formation of alkylated products, and therefore it is concluded that the nature of the solvent is critical in this particular reaction.

The antibiotic, novobiocin (17), possesses an isoprenoid group attached to a p-hydroxy benzoic acid system, and, in an attempt to investigate possible alkylation of this system, allyl diphenyl phosphate was heated with ethyl p-hydroxy benzoate (81) in the presence of solid sodium bicarbonate in benzene-ether. The only product was the corresponding allyl ether, ethyl p-allyloxybenzoic (82) obtained in low yield, and no further experiments were tried with the benzoate, because it would appear

that the electron-withdrawing effect of the carbethoxy group results in deactivation of the ortho-(w.r.t. hydroxyl) positions of the ring, so that they are no longer capable of bringing about de-alkylation of the phosphate.



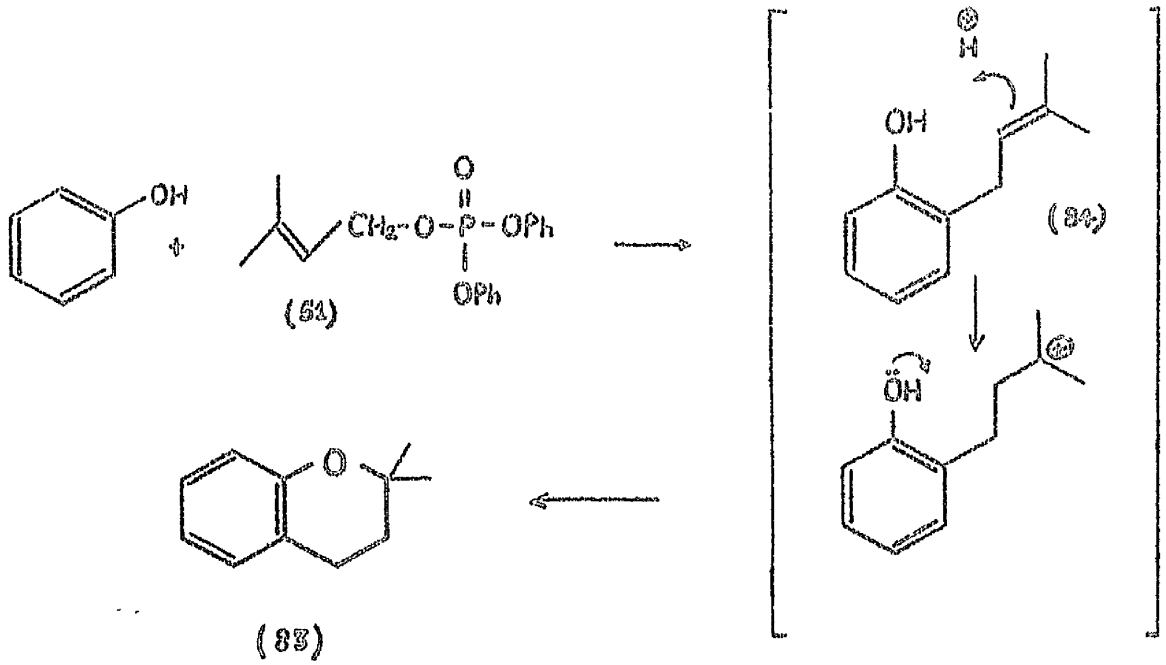
(17)



(31) (40) (32)

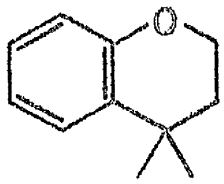
Reaction of Phenol with 3,3-Dimethylallyl Diphenyl Phosphate:

The reaction of 3,3-dimethylallyl diphenyl phosphate (51) with phenol is apparently a simple one, in which only one product is formed, but the implications behind this reaction are important, and more complicated than at first sight.

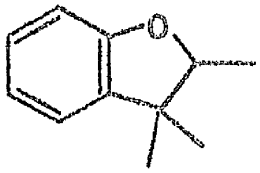


The 2,2-dimethylchroman (83) would appear to have been formed by acid-catalysed ring-closure of o-3',3'-dimethyl allyl phenol (84), but no evidence has been obtained for this phenolic or any other intermediate. The chroman is formed immediately in this reaction, whether the temperature is 120°C or 20°C, and its formation cannot be inhibited by the addition of solid sodium bicarbonate. The structure of 2,2-dimethylchroman (83) has been deduced mainly from the nuclear magnetic resonance spectrum, which showed a triplet at 7.4 τ ($ArC\underline{H}_2-$), a triplet at 8.3 τ ($Ar-\overset{|}{C}-C\underline{H}_2-$), and a singlet at 8.7 τ ($CH_3-\overset{|}{C}-O-$), and the infrared spectrum, which showed a gem-dimethyl group (1387, 1370 cm.$^{-1}$) and chroman group (1258 cm.$^{-1}$). There was no indication that either the

isomeric 4,4-dimethylchroman (85) or 2,3,3-trimethylcoumaran (86) had been formed in this reaction.



(85)

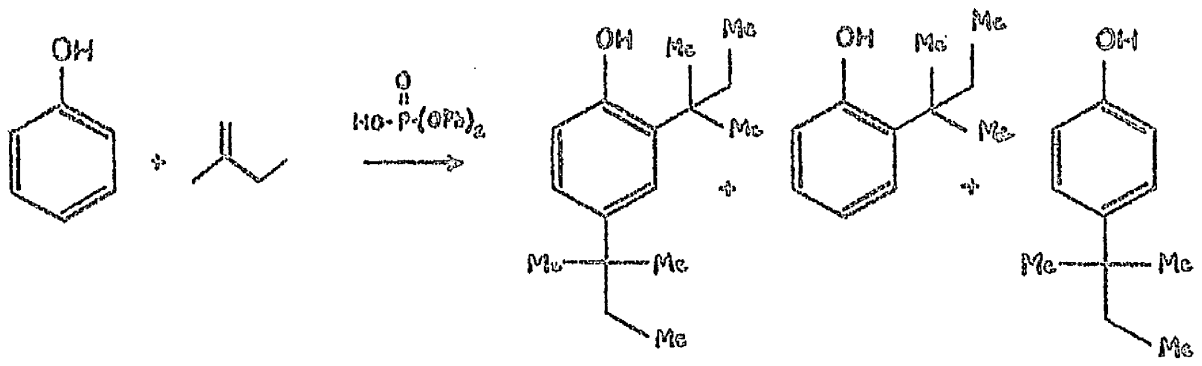


(86)

Addition of Phenol to Olefins:

It is evident that the ring-closure of allyl phenols giving either coumarans or chromans is controlled by the substitution of the double-bond in the allyl system, which determines which of the possible carbonium ions will be formed by protonation of the double-bond. This controlling factor has long been used in synthetic methods of obtaining cyclic ethers.[119]

In a series of experiments with diphenyl phosphate and phenol, it was found that different olefins can be made to condense with phenol at 100°C. and that the nature of the product was dependent upon the substitution of the olefin. Both cyclohexene and oct-2-ene gave ethers, in very low yields, but 2-methyl-but-1-ene gave a mixture of substituted phenols.



Although only traces of diphenyl phosphate were used in these experiments, the reactions did not proceed without the added acid, which presumably protonates the olefin to form a carbonium ion which then attacks the phenol. When the intermediate ion is secondary, others result, but when it is tertiary, alkylation occurs at the ortho- and para- ring positions.

These results show an interesting contrast to the observations of Kornblum,[118] who claims that for the reaction of phenoxides in solution with carbonium ions, the proportion of O-alkylation increases with increasing stability of the carbonium ion. Kornblum explains this by postulating that a less stable carbonium ion is not so selective as a stable one (such as trityl), which simply collapses onto the point of maximum

electron-density, which in the case of phenoxide is the oxygen atom. Extending Kornblum's argument to phenols in solution, it would appear from the olefin addition experiments that in phenols the oxygen is no longer the point of maximum electron-density, or, alternatively, that some other factor is governing the reactions.

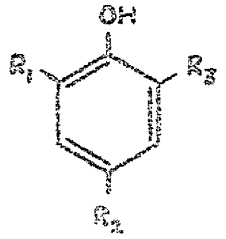
The spectroscopic properties of these alkylated phenols were rather interesting, and Table A (page 95) shows how the degree of hydrogen-bonding in each is dependent upon the degree of ortho-substitution. For example the -OH stretch in the infrared varies from 3690 cm.$^{-1}$ in the di-ortho alkyl phenol, to 3333 cm.$^{-1}$ in the p-alkyl phenol, and similar effects can be observed in the nuclear magnetic resonance spectra. It was found possible to separate the 2,6- and 2,4-dialkyl phenols, and the 2- and 4-monoalkyl phenols easily by alumina chromatography, the phenols being eluted in the above order.

Mechanism of Phenol-Phosphate Reactions:

In the theoretical section introducing these reactions it was shown that allyl phosphates could react with nucleophiles either by a unimolecular or a bimolecular pathway, and that product analysis could sometimes be used to determine, or at least to indicate, the mechanism in a particular case. It was

	Substituents			UV (mμ)	I.R. Spectrum ($cm.^{-1}$) υ_{max} (liquid film)			N.M.R. Spectrum (τ) (CCl_4)				
	R_1	R_2	R_3	λ_{max}	-OH	$(CH_3)_2$-C-	Aryl	Aryl-H	-OH	Ar-C-CH_2	Ar-C-CH_3	Ar-C-C-CH_3
I	R	H	R	271 278	3690, 1316 1238	1387, 1362 1163, 1142	862 692	2.8–3.2	5.0	8.1–8.4	8.5–8.8	9.0–9.25
II	R	R	H	279 285	3521 1177	1379 1359	815 785	3.0	5.5	7.8–8.5	8.5–8.8 (double)	9.0–9.25
III	H	H	H	274 281	3521, 1328 1183	1385, 1362 1166, 1159	749	2.65–3.65	5.4–5.5	7.9–8.5	8.5–8.7	9.0–9.25
IV	H	R	H	279	3333 1236	1383 1362	830	3.0 (quartet)	3.0	8.1 – 8.8 (inclusive)		9.05–9.25

TABLE A: SPECTRAL CHARACTERISTICS OF HINDERED PHENOLS



R = $-C(CH_3)_2-CH_2CH_3$

also noted that substitution of the allyl system with alkyl groups in the γ-position generally enhances the rate of nucleophilic substitution, whatever the mechanism of the reaction.

The solvolyses of benzyl diphenyl phosphate[89] (39) and 2-methyl-5-chloro-pent-2-one[116] (79) with phenol resulted in the productions of three alkylated products in each case, and these were considered to have arisen by an S_Ni mechanism. At one time Kornblum[113] considered that in the alkylation of phenoxides, the production of ethers together with o- and p-alkyl phenols was sufficient to indicate that an S_Ni mechanism was operating, but more recently[115] he has shown that alkylation of phenoxides with allyl bromide in very strongly bonding solvents such as phenol and water can give rise to all three possible mono-alkylated products by an S_N2 mechanism. Kornblum considers that the solvating powers of these solvents are so great that the negative charge on the oxygen is partially transferred to the solvent, and the ortho- and para- ring positions can then compete with oxygen in nucleophilic attack on the halide. Another important factor arising from the bonding properties of phenol and water is the ability of each to solvate the leaving-group and hence facilitate the nucleophilic displacement.

By analogy with the two solvolyses in phenol described earlier, it would appear that the allyl diphenyl phosphate

alkylation of phenol is a unimolecular reaction, since it produces allyl phenyl ether, and both o-allyl and p-allyl phenol, although all of these are subsequently converted to 2-methyl coumaran (60). The reaction of phenol with 3,3-dimethylallyl diphenyl phosphate (51) would therefore be expected to be a faster reaction, the products being formed by the same mechanism.

There is, however, very strong evidence that the substituted allyl phosphate is not reacting with phenol in a unimolecular process. It is clear from the experimental results that there is no rearrangement of the allyl system, as would be expected in a unimolecular reaction, and, furthermore, this lack of rearranged product is one of the criteria for bimolecular reactions. The fact that the reaction with 3,3-dimethylallyl diphenyl phosphate (51) is faster than that with allyl diphenyl phosphate (40) does not favour any one mechanism, because 3-alkyl substitution of allyl systems is known to increase the rate of both unimolecular and bimolecular nucleophilic substitution.

Perhaps the most surprising feature of the alkylation of phenol with 3,3-dimethylallyl diphenyl phosphate (51) is the complete preference for carbon o-alkylation. Many attempts were made to show that the production of the chroman system was analogous to that of the coumaran system from allyl phenols, but no evidence was ever obtained for the presence of any

intermediates between phenol and 2,2-dimethylchroman (63), whether the reaction was carried out at 20°C or 120°C, either in the presence or absence of bases. This preference is somewhat similar, in principle, to that demonstrated by Kornblum,[113] when phenoxides were alkylated with allyl bromide in non-polar solvents, such as ethers, but one cannot seriously claim analogy between these reactions and those between phosphates and phenol in phenol. Furthermore, one would need to explain why the reaction did not take this course with the unsubstituted allyl phosphate. It is therefore clear that there is a crucial difference between the mechanisms of each of these alkylation reactions, but the factor which controls the specificity of the alkylation by 3,3-dimethylallyl diphenyl phosphate (51) is not yet understood.

Among the possible explanations to the above problem which have been studied was one involving participation by the phosphate ester in an intramolecular removal of a proton from phenol, but this did not provide a satisfactory solution.

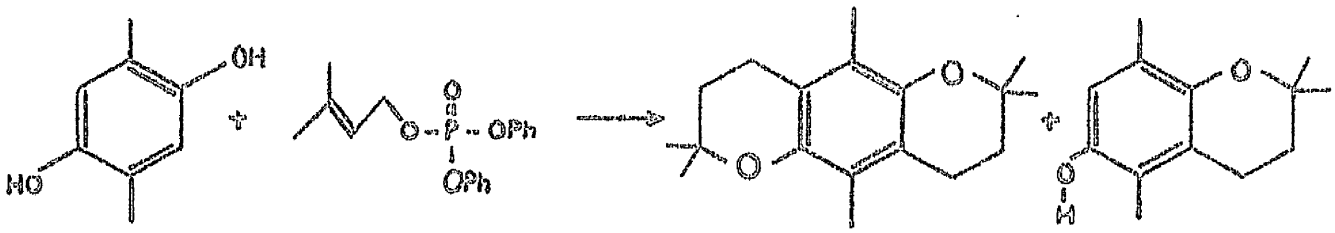
Another point of uncertainly is the question of the existence of open-chain intermediates before ring-closure to the chromen system. The experiments with diphenyl phosphate, olefins, and phenol showed that when a tertiary carbonium intermediate is involved, as would be the case with ring-closure of 3',3'-dimethylallyl phenol (64), alkylation occurs rapidly

and quantitatively. The subsequent observation that olefins capable of forming secondary carbonium ions alkylate phenol slowly, and in poor yield, may explain why o-allyl phenol could be isolated while the corresponding 3'-substituted allyl phenol could not.

More Complex Phenol-Phosphate Systems:

The preliminary experiments discussed above showed that allyl- and 3,3-dimethylallyl diphenyl phosphates were potentially good alkylating agents for phenols, whatever the mechanism involved, and subsequent experiments with hydroquinone, 2,5-dimethyl hydroquinone (87), 2,3,5-trimethyl hydroquinone (21), orcinol (88), and phloroglucinol showed that solid phenols gave moderate to good yields of alkylated products on heating with the 3,3-dimethylallyl diphenyl phosphate.

Where possible, polyalkylation was found to occur readily and sometimes this superceded the desired monoalkylation, as happened with 2,5-dimethylhydroquinone (87). Although the yield of the monochroman, 2,2,5,8-tetramethyl-6-hydroxychroman (89), was only 8%, this compared favourably with any previous synthesis,[183,184] and the yield of the dichroman was nearly 70%, also much better than that obtained by other methods.

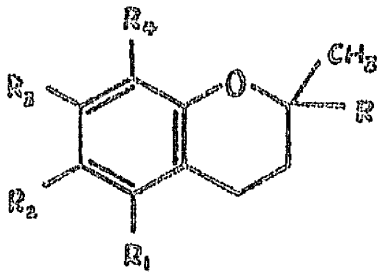


(87) (51) (89)

The 2,2-dimethylchroman system was formed in all the reactions of 3,3-dimethylallyl diphenyl phosphate with phenols, and its recognition was made particularly easy by the use of nuclear magnetic resonance spectroscopy, as indicated in Table B (page 101). In contrast to the coumaran ring, the chroman ring is quite flexible and there are no complications in the nuclear magnetic resonance spectra, which show each of the methylenes at the 3-and 4-positions as clear triplets. As with the phenol reaction there was never any product isolated which could have arisen from rearrangement of the allyl phosphate.

These alkylation reactions were then extended, in an attempt to synthesise, by new methods, several biologically

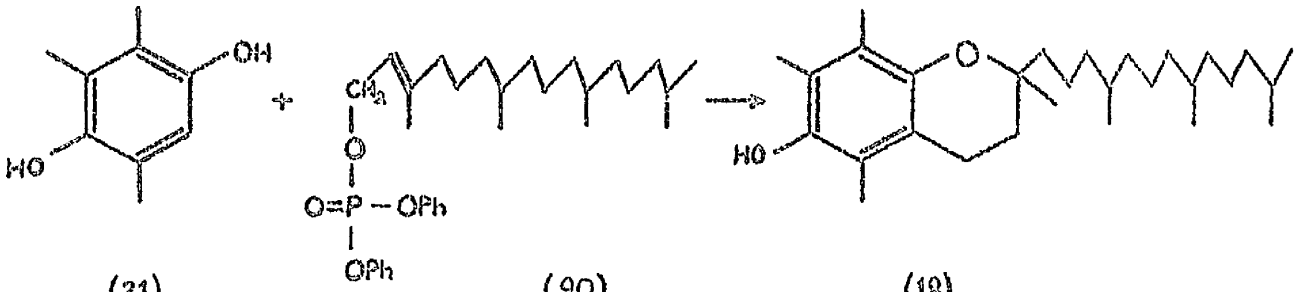
TABLE 8: N.M.R. SPECTRA OF 2,2-DIALKYLCHROMANS



(S) : SINGLET (T) : TRIPLET

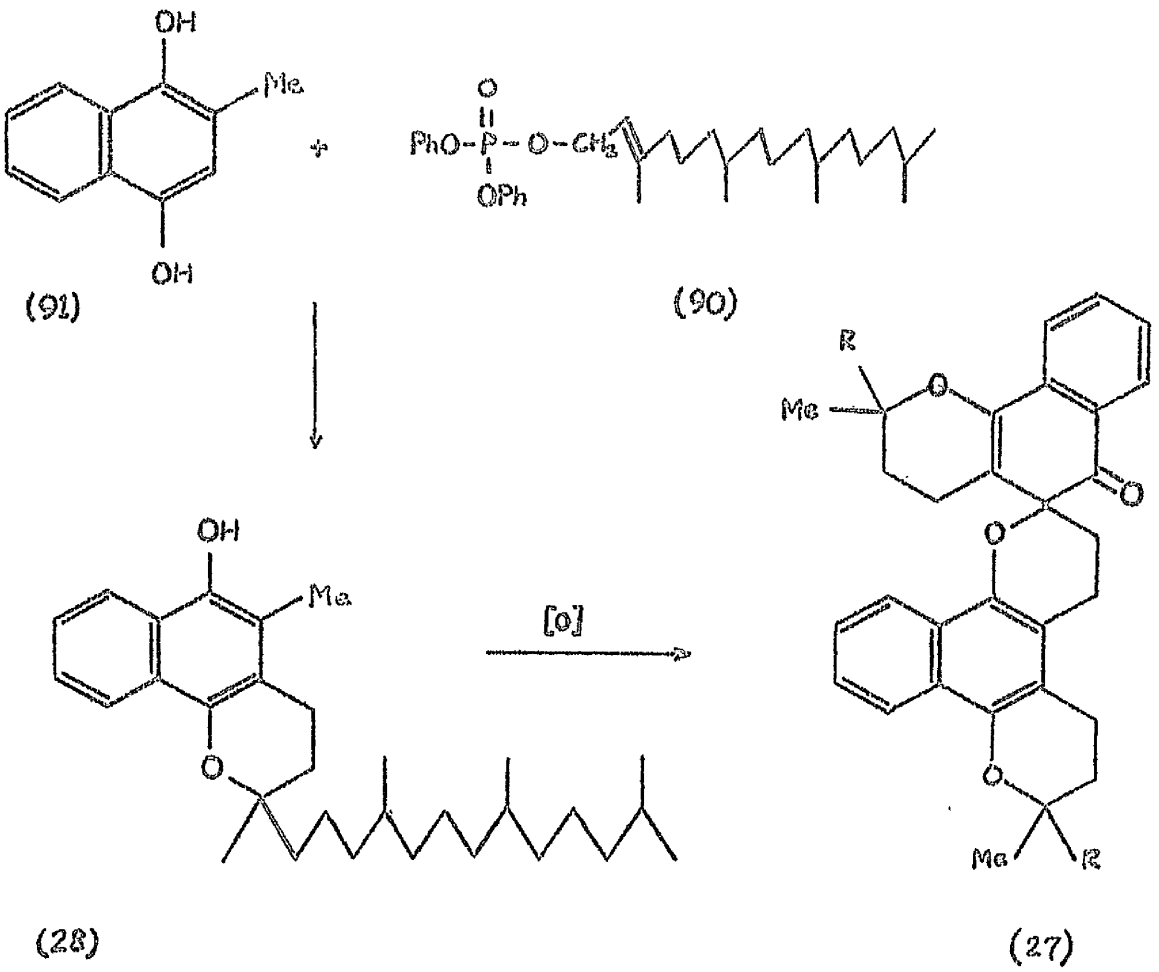
FORMULA NUMBER	NATURE OF SIDE GROUPS	CH_2-C-O(S)	Ar-CH_2 CH_2(T)		Phenol -OH
83	R=Me ; R_1=R_2=R_3=R_4=H	8.70	7.3	8.3	-
96	R=Me ; R_2=R_3=R_4=H ; R_1=OH	8.75	7.4	8.3	4.2
-	R=CH_3 ; R_1=R_3=R_4=H ; R_2=NHCOCH_3	8.70	7.3	8.25	-
89	R=R_2=R_4=CH_3 ; R_3=OH ; R_1=H	8.75	7.45	8.25	5.5
29	R=R_1=R_3=R_4=Me ; R_2=OH	8.75	7.6	8.3	5.95
104	R=R_1=R_3=R_4=Me ; R_2=OTs	8.62	7.4	8.25	-
-	R_1=R_3=R_4=CH_3 ; R_2=OH ; R=CH_3 . CH_2-CH=CMe_2	8.80	-		5.6
18	R_1=R_3=R_4=CH_3 ; R_2=OH ; R=-[CH_2 . CH_2 CH_2-C(Me)-CH_3]$_3$ CH_3	8.80	-		5.8
-	R=R_3=CH_3 ; R_1=OH ; R_2=R_4=H	8.75	7.4	8.3	3.95
-	R=R_1=CH_3 ; R_3=OH ; R_2=R_4=H	8.75	7.5	8.25	3.9
93	R_3=CH_3 ; R_1=OH ; R_2=R_4=H ; R=-[CH_2CH_2-CH=C(Me)-]$_3$ CH_3	8.80	-		4.05
95	R_1=CH_3 ; R_3=OH ; R_2=R_4=H ; R=-[CH_2CH_2 . CH=C(Me)-]$_3$ CH_3	8.80	7.5		3.9

important compounds. The most successful of these reactions was the synthesis of α-tocopherol (vitamin E) (19; R = $C_{16}H_{33}$) by heating 2,3,5-trimethylquinol (21) with phytyl diphenyl phosphate (90) at 100°C for 8 hr. The yield was almost quantitative, and this can partly be attributed to the fact that there is only one available site for ring-alkylation.



(21) (90) (19)

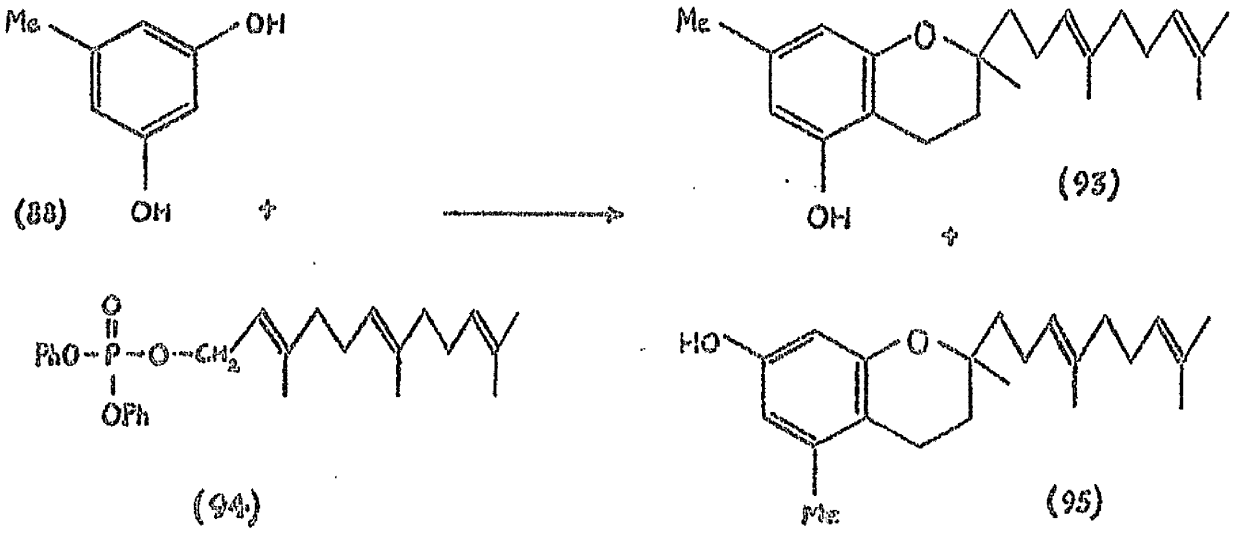
It was attempted to synthesise vitamin K_1 (80) (19; R = $C_{16}H_{33}$) by condensation of menadiol (91) with phytyl diphenyl phosphate at 100°C, but the reaction took the course outlined below.

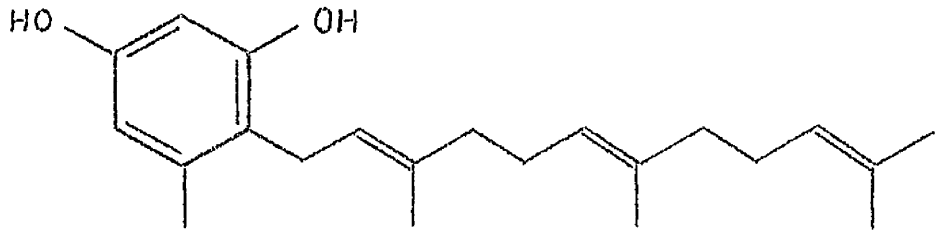


The product was found to be a dimer (27; R = $C_{16}H_{33}$) of vitamin K_1(30), and the structure appears to be the same as that obtained by Folkers[67] in 1965, although Folkers did not publish any spectral data which would enable a definite comparison to be made. The methods used by Folkers to prepare the dimer have been outlined in the Introduction to this thesis, and the data obtained on the yellow oil from the phosphate-menadiol reaction is not at variance with Folkers' structure. The dimer (27) showed no hydroxyl in the infrared

or nuclear magnetic resonance spectra, but displayed a strong carbonyl absorption in the infrared at 1695 cm.$^{-1}$, typical of aryl-alkyl ketones. The dimeric structure has clearly arisen from an oxidation of the 5-methyl-6-hydroxyl system of the chromanol (28), followed by a dimerisation of a Diels-Alder type.

A synthesis of the antibiotic *grifolin*[125] (92), or its isomer, isogrifolin (93), was also attempted, by heating orcinol (88) with farnesyl diphenyl phosphate (94). Since this system formed all four possible products by mono- and di-alkylation at the available ortho-positions (w.r.t. OH), followed by ring-closure, the main trouble was found to be one of separation.





(92)

The alkylation was found to be almost quantitative, and considerable heat was evolved in the initial stages of the reaction. The separation of the two mono-alkylated isomers, (93) and (95), was achieved by careful alumina chromatography, and it was believed that the less polar of these would be eluted more readily. Since the ease of elution from an alumina column would depend very largely upon the degree of bonding of the hydroxyl group in each molecule, it was felt that the two mono-chromans should also show differences in hydroxyl absorption in their infrared and nuclear magnetic resonance spectra. It was found that the less polar chroman absorbed at 3412 cm.$^{-1}$ in the infrared, and at 4.05 in the nuclear magnetic resonance spectrum, whereas the more polar chroman absorbed at 3400 cm.$^{-1}$, and 3.90 respectively. Although the differences

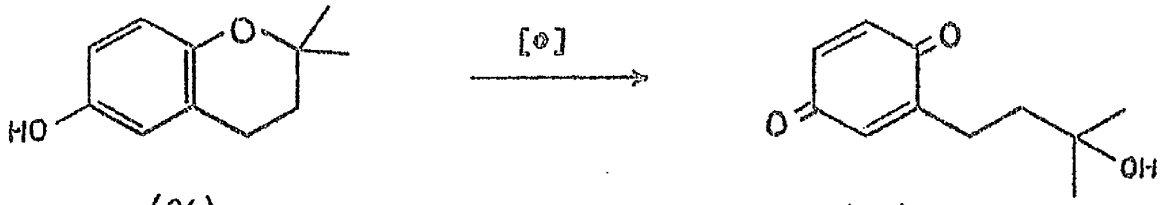
between these absorptions are small, they form a consistent pattern, and, when considered along with the chromatographic evidence, they are sufficient reason to claim that the less polar chroman is isogrifolin (93). This conclusion was later verified by comparison of infrared and nuclear magnetic resonance spectra of the less polar chromanol with those of a genuine sample of isogrifolin, obtained from the antibiotic.[126]

It will be noted that all the reactions of 3,3-dialkyl-allyl diphenyl phosphates described above have confirmed the observations, made in the phenol/3,3-dimethylallyl diphenyl phosphate system, that alkylation occurs only at the ortho-position, and never seems to involve rearrangement, and that ring-closure occurs automatically. The ring-closure reaction was, of course, advantageous in a synthesis of α-tocopherol, but was a serious disadvantage in the attempted synthesis of vitamin K_1 (αα), and grifolin, and the next two sub-sections of this discussion will be devoted to a description of attempts to prevent this ring-closure.

Oxidation Reactions of o-Methyl Phenols:

The dimerisation of the reduced chromanol form of vitamin K has been shown to be the result of the ease with which o-methyl phenols oxidise to quinone methides,[66] and then dimerise by a Diels-Alder addition. There are known reactions,[127]

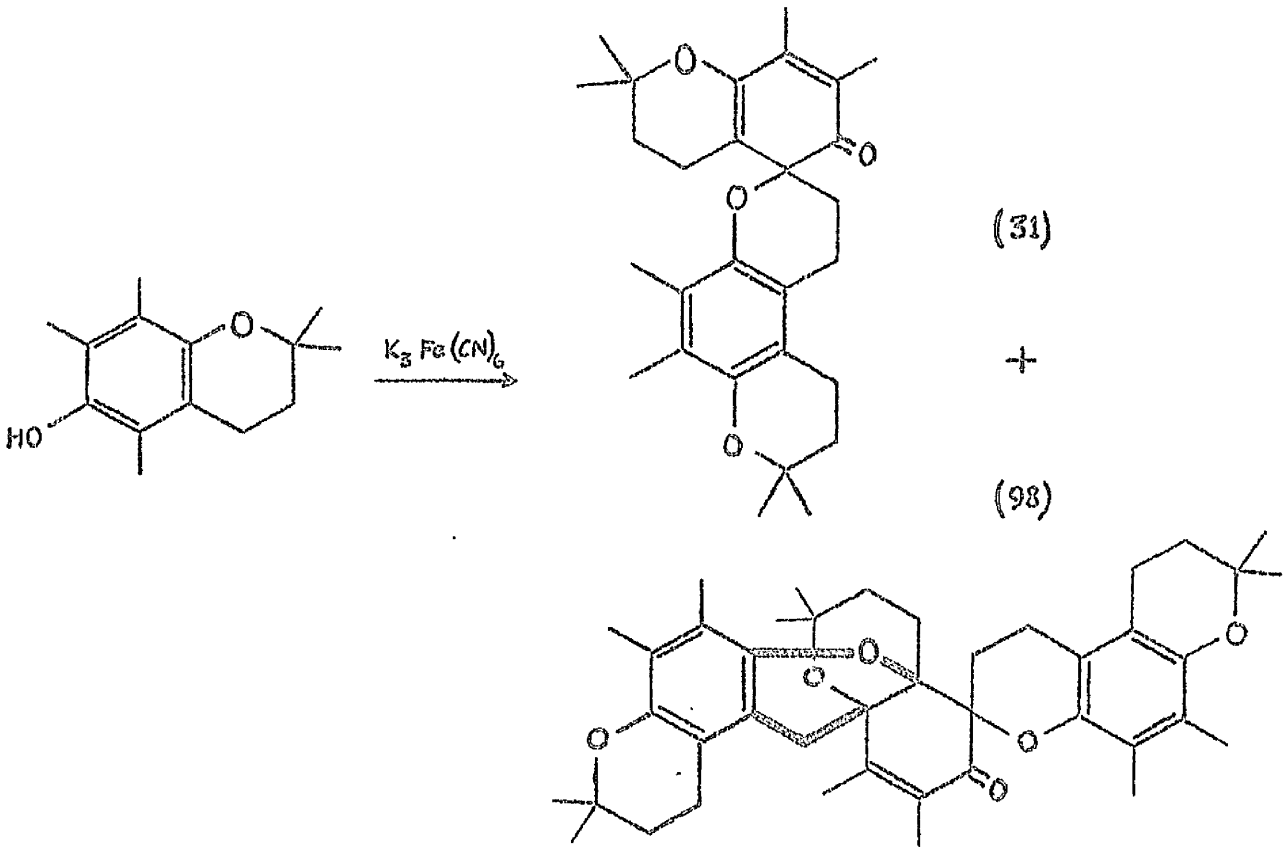
however, in which 6-hydroxychromans can be oxidised in aqueous solution to p-quinones, resulting from fission of the chroman ring. As an example of this, it was found that 2,2-dimethyl-6-hydroxychroman (96) oxidised readily to 3'-hydroxy-3'-methyl-butyl p-benzoquinone (97) on treatment with aqueous alcoholic ceric sulphate.



(96) (97)

It was therefore hoped that the 6-hydroxychroman form of vitamin K might be oxidised directly to the vitamin, despite the 5-methyl group, by a suitable, non-aqueous oxidation, and 2,2,5,7,8-pentamethyl-6-hydroxychroman (29) was regarded as a suitable model for the study of this oxidative ring-opening. Potassium ferricyanide oxidation of this latter compound has been widely studied within the last few years[as,128,129,130,131,132,133], because of its relevance to α-tocopherol oxidation reactions, which are so important biologically. It would appear that 2,2,5,7,8-pentamethyl-6-hydroxychroman (29) readily produces dimers and trimers in the ferricyanide oxidation, and the

structures of both the principal dimeric product[60] (31), and the principal trimeric product[151] (98) have been demonstrated recently, after some considerable difficulty.



It will be seen that the main structural difference between the dimer (31), and the trimer (98), is that the former has a diene-one chromophore, whereas the latter has only an αβ-unsaturated ketonic chromophore, and this difference is reflected in the infrared and ultraviolet absorptions of each molecule. Unfortunately, there is some disagreement between the various groups studying the properties of the dimer, and this seems to have arisen because of the great difficulty each

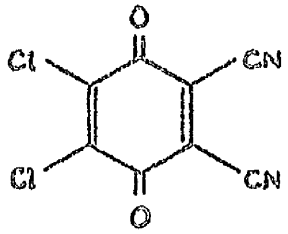
group has had in obtaining pure samples for analysis. Skinner[130,131] claims that the trimer has m.p. 227-228°C, and has absorption maxima at 220 (ε , 24,000) and 295 (ε , 5,600) mμ in the ultraviolet, and at 1689 cm.$^{-1}$ in the infrared.

Although the three groups working on the dimer agree on the structure, the melting-points, and the spectra data are amazingly inconsistent. For example, Nolan and Robeson[130] give m.p., 126-127°C; $\lambda_{max.}$ 300, 337 mμ; $\nu_{max.}$ 1675, 1650, and 1595 cm.$^{-1}$, but Schudel et al[68] give m.p. 120-122°C; $\lambda_{max.}$ 300, 345 mμ; $\nu_{max.}$ 1645, 1587 cm.$^{-1}$, and Skinner and Alaupovic give[130] m.p. 78-79°C; $\lambda_{max.}$ 300 mμ; $\nu_{max.}$ 1672, 1653, 1592 cm.$^{-1}$; each using alkaline potassium ferricyanide.

Three new oxidising agents were tried in the present study of the 2,2,5,7,8-pentamethyl-6-hydroxychroman (29); manganese dioxide, silver oxide and dichloro dicyano quinone (99). The first two gave extremely complex mixtures of products, although the silver oxide oxidation gave enough of one product to allow its isolation by alumina chromatography and recrystallisation from methanol. This product was a white crystalline solid, m.p. 216.5-217.5°C, which showed only one spot on a thin-layer chromatogram, and which had a molecular weight of 430. The ultraviolet spectrum showed absorptions at 215 and 294 mμ., as did the starting material, and the infrared spectrum showed bands at 1698 and 1650 cm.$^{-1}$. The nuclear magnetic resonance spectrum

was inconclusive, although it verified that no hydroxyl group was present. Although all the above data, except the molecular weight, is more compatible with a trimer than with a dimer, one cannot come to a decision on the structure of the product when the molecular weight is so near that of a dimer. Since the micro analysis agreed with that of the unoxidised starting material, it would appear that the sample may not be as pure as was indicated by the sharp melting-point and thin-layer chromatogram.

In contrast to the above reactions, the dichloro dicyano quinone (99) oxidation gave only one major product



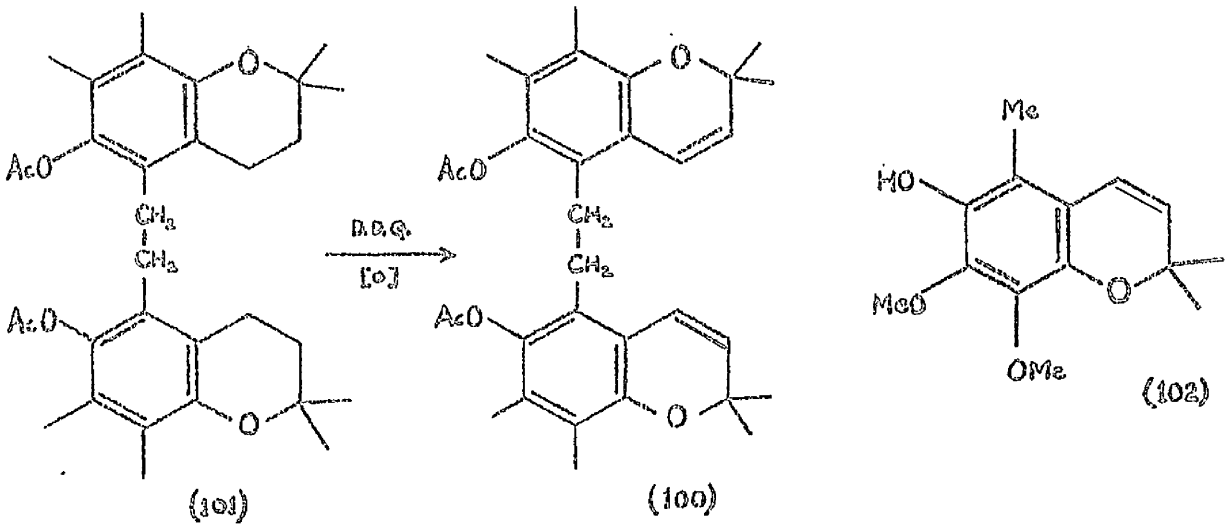
(99)

with 2,2,5,7,8-pentamethyl-6-hydroxychroman, and this was very different from any of those mentioned above. The product was a white powder, m.p. 167-169°C, with a molecular weight of 230, and did not show any hydroxyl absorptions in the infrared or nuclear magnetic resonance spectrum. The ultraviolet spectrum showed absorptions at 216, 226, and 297 mμ, and the infrared spectrum showed bands at 1712, 1639 and 1580 cm.$^{-1}$,

indicating that there was a new chromophore at 226 mμ, and that a cyclohexanone derivative had been formed. The nuclear magnetic resonance spectrum was extremely unusual, because of two identical doublets at 4.1 τ and 4.8 τ (J, 1.5 c/s), and because of the number of sharp bands at 7.95, 8.10, 8.55, and 8.70 τ. The integral showed that the ratio of the low-field protons to those at higher fields was about 1:25 or 2:50, and that the ratio of the 7.9 τ band ($ArCH_3$) to the 8.70 band ($CH_3-\overset{|}{\underset{|}{C}}-C-$) was 2:3, which is compatible with a trimer of the type discussed above. The 1712 cm.$^{-1}$ band indicates that, if a trimer has been formed, then the second addition has occurred across the olefin which is α-β to the carbonyl in the dimer. The absorptions at 4.1 and 4.8 τ in the nuclear magnetic resonance spectrum remain to be deciphered, and it is felt that they may hold the clue to the structure of this oxidation product.

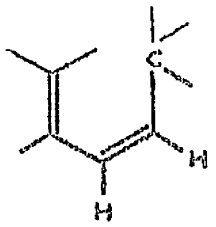
Dichloro dicyano quinone (99) has been used by Schudel et al[66] to oxidise 6-acetoxychromans to the corresponding chromenes, but these compounds have very different spectral features from the unknown oxidation product. For example, the chromene (100), prepared by dichloro dicyano quinone oxidation of the 6-acetoxychroman (101), showed absorptions at 3.44 τ and 4.38 τ in the nuclear magnetic resonance spectrum,

and at 270, 280 and 316 mμ in the ultraviolet, and these values compare well with those obtained by Morton[133] for ubichromenol (102) (3.42 τ and 4.38 τ; and 275, 283, and 332 mμ).

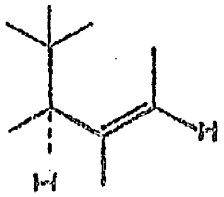


(101) (100) (102)

Clearly the unknown oxidation product is not a chromene, and furthermore, the small coupling constant is well below the normal associated with -CH=CH- systems, although the chemical shifts of the protons are compatible with a diene structure, such as the one shown belowin (A). The coupling constant is very small and is typical of that associated with an allyl system, as in (B), but it does not appear possible to obtain the latter skeleton from a 2,2,5,7,8-pentamethyl-6-hydroxychroman (29) structure, without some rearrangement.



(A)



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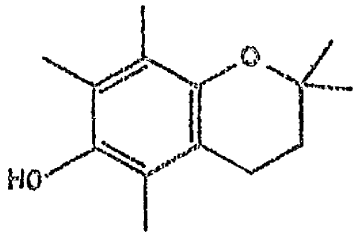


(29)

Although each of these three oxidising agents did react with the model compound, 2,2,5,7,8-pentamethyl-6-hydroxychroman (29), only the dichloro dicyano quinone (99) gave a reasonably homogeneous product. While the products of the oxidation reactions may have interesting structures, there was no evidence that the chroman system had been destroyed in any of the reactions, which therefore were not of use in solving the problem of the synthesis of vitamin K_1 (20).

Alkylation of Phenoxides:

Several groups have devoted considerable effort in recent years to a study of the factors influencing the reaction between alkali-metal phenoxides and alkyl halides, and one of the most frequently studied systems has been that containing an

allyl halide and sodium phenoxide. The work of the groups led by Kornblum,[113,114,115] and by Curtin[116] deserves particular mention, because their efforts have shown the influence of homogeneity solvent, concentration, and the nature of the halide employed, on the final product. In a brilliant paper, published in 1959, Kornblum[113] demonstrated that in bimolecular reactions, between allyl or benzyl halides and sodium phenoxides, the position of alkylation was almost wholly determined by the homogeneity or the heterogeneity of the reaction mixture, and devised a simple, yet ingeneous explanation of why o-carbon alkylation was the inevitable result of heterogeneous conditions. In this context, heterogeneity resulted from use of a solvent, such as anhydrous diethyl ether, in which the phenoxide was insoluble, and the product from reaction between sodium phenoxide and allyl bromide in this solvent was always o-allyl phenol.

It was thus hoped that the alkylation of sodium phenoxide under heterogeneous conditions with allyl diphenyl phosphate would give o-allyl phenol, which would not ring-close to 2-methyl coumaran (80). If this were the case, then the problem of preventing the undesirable ring-closure of reduced vitamin K_1 (80), and of grifolin (92), both described above, would perhaps have been nearer solution. Unfortunately the only product from this reaction was allyl phenyl ether, whether the

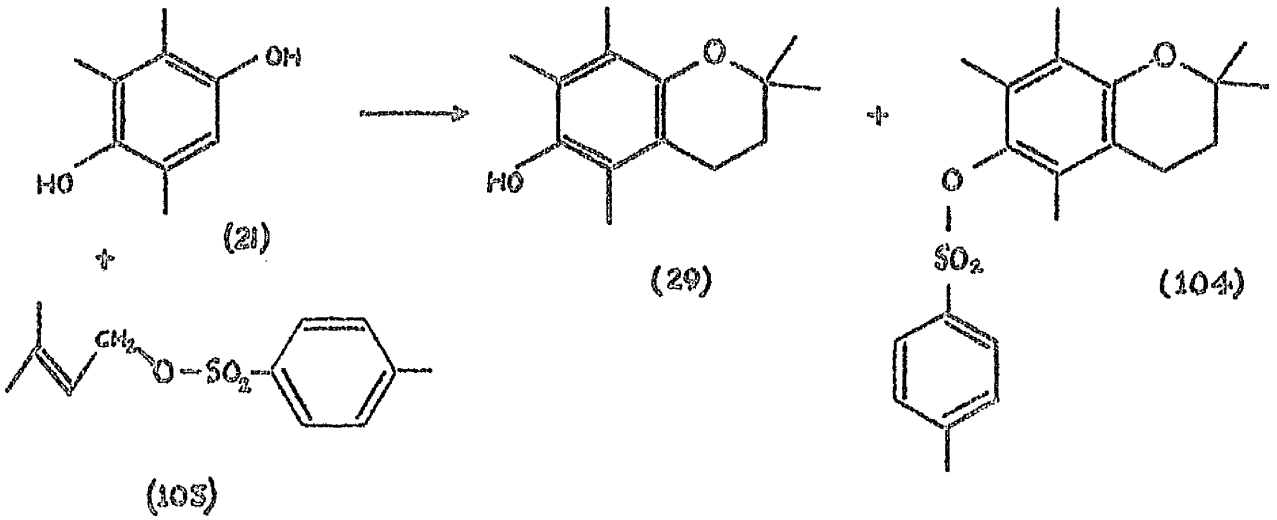
reaction was carried out at 18°C or at 100°C. When the same reaction conditions were applied to sodium phenoxide and 3,3-dimethylallyl diphenyl phosphate (51), a mixture of unknown products were produced in low yield, and these did not appear to include g-dimethylallyl phenol.

Since only a good yield of ortho-3',3'-dimethylallyl phenol (84) would have been of value in synthetic work under conditions similar to those used by Kornblum in his alkylations, the reactions of phenoxides were not further investigated.

Alkylation of Phenols with other 3,3-dimethylallyl Esters:

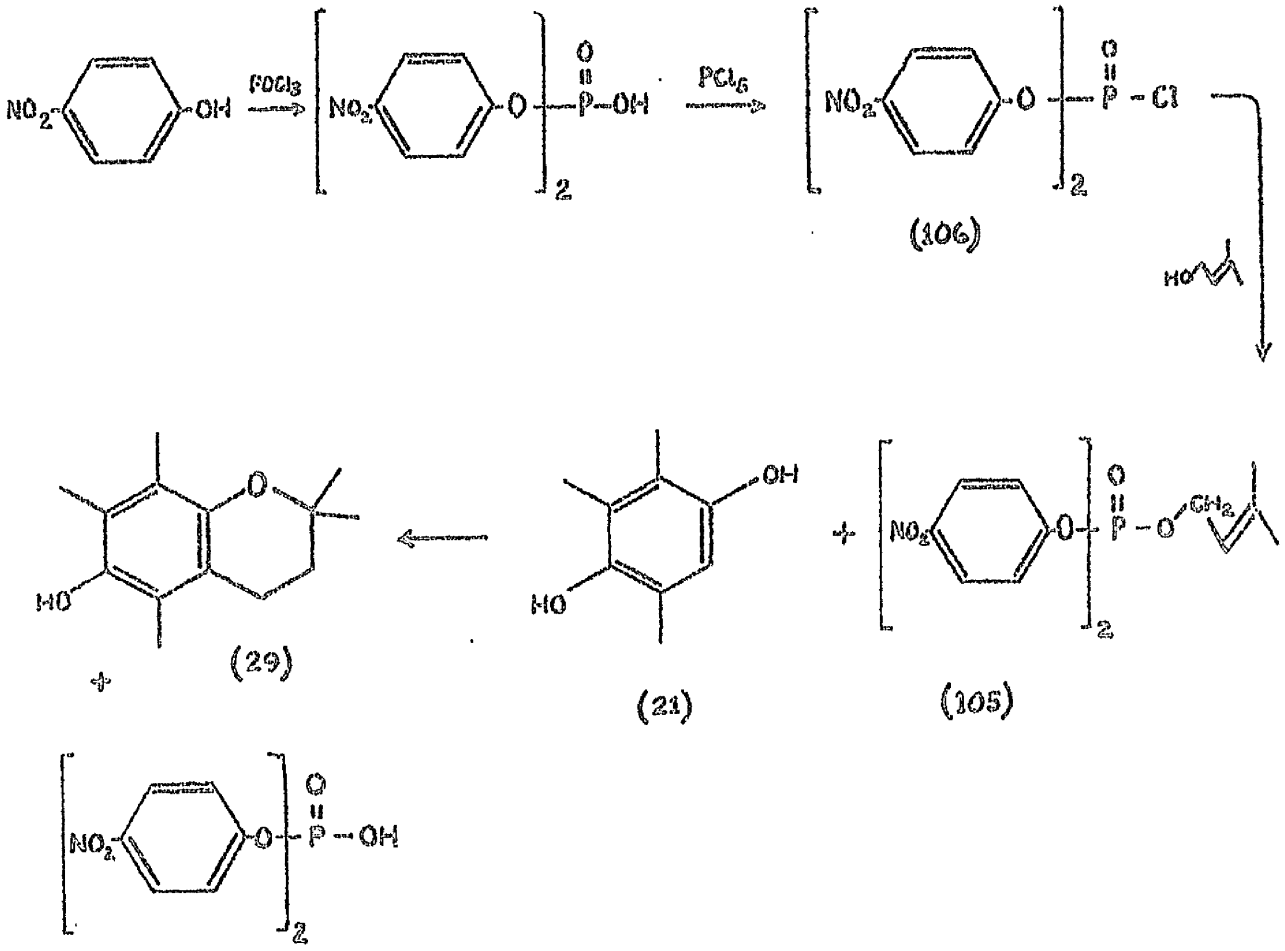
(i) p-Toluene Sulphonate:

Unlike phosphoric and carboxylic acid esters, sulphonat esters always undergo nucleophilic attack by oxygen-carbon fissio and are therefore alkylating agents.[134,135] When heated with 2,3,5-trimethylquinol (21), under the same conditions as the diphenyl phosphate, 3,3-dimethylallyl p-toluene sulphonate (103) gave almost the same yield of 2,2,5,7,8-pentamethyl-6-hydroxy-chroman (29) as the corresponding diphenyl phosphate, as well as very small amounts of the chromanyl-6-p-toluene sulphonate (104)



(ii) Di-p-nitrophenyl Phosphate:

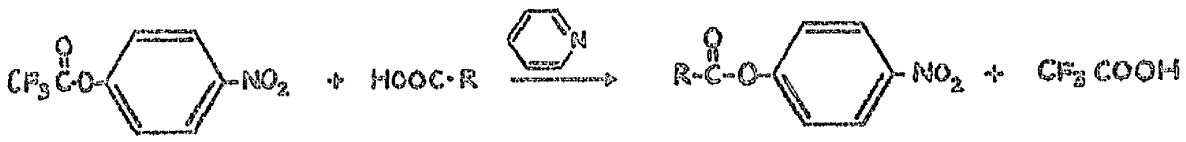
3,3-dimethylallyl di-p-nitrophenyl phosphate (105) was synthesised with some difficulty from di-p-nitrophenyl phosphorochloridate[136] (106) and was found to alkylate 2,3,5-trimethylquinol (21), almost quantitatively, in 6 hr. at 80°C. The crude reaction mixture yielded a yellow oil together with the expected 2,2,5,7,8-pentamethyl-6-hydroxychroman (29) when chromatographed on alumina, and the oil, after rechromatography was found to be the same as one of the small fractions obtained from manganese dioxide oxidation of the chroman (29). The yield of 2,2,5,7,8-pentamethyl-6-hydroxychroman was 50%, somewhat less than with the simple diphenyl phosphate.



The oxidation product showed very strong carbonyl absorption in the infrared, at 1639 cm.$^{-1}$, and another strong band at 716 cm.$^{-1}$, and the nuclear magnetic resonance spectrum showed a band at 5.3 τ, normally associated with non-conjugated vinyl groups, and had no bands above 8.35 τ. This latter observation means that the product does not possess a 2,2-dimethyl chroman system, and this was the only occasion on which the cyclic ether system was broken in non-aqueous conditions, despite all the oxidative reactions of the parent chroman (29)

which have been studied. Unfortunately, it was not possible to decide if the oxidation was the result of direct reaction of the parent chromen (29), or if it had occurred during the chromatographic isolation.

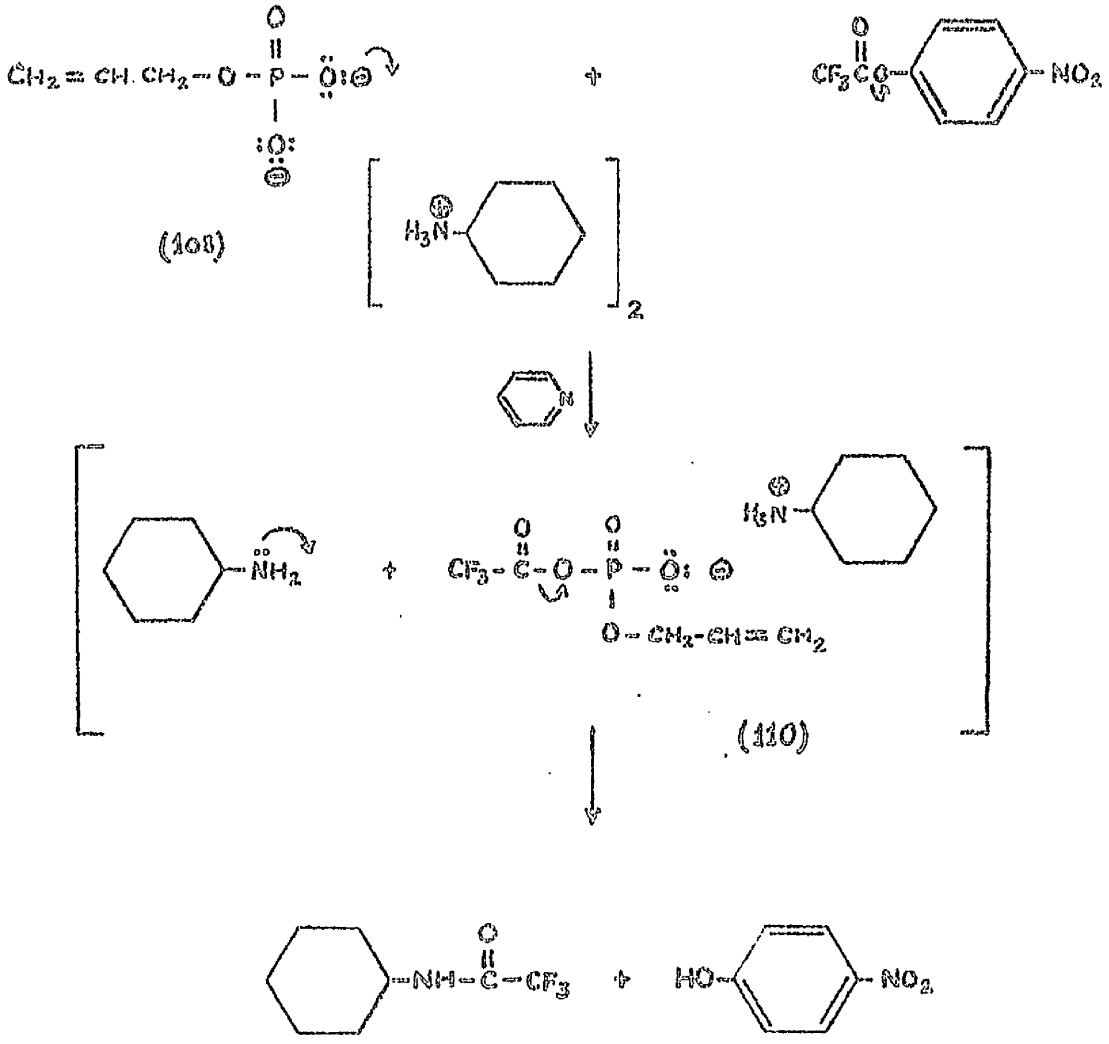
It has been noted above that the preparation of 3,3-dimethylallyl di-p-nitrophenyl phosphate (105) was very difficult and that the overall yield from p-nitrophenol was very low. An alternative synthesis of the phosphate was investigated for this reason, based upon the reaction of p-nitrophenyl trifluoroacetate (107) with acids. This reagent is known to react[137] with carboxylic acids in the presence of pyridine, producing the p-nitrophenyl ester of the added acid, presumably by an anhydride intermediate, and the reaction has been applied to peptide synthesis.



(107)

Two attempts were made to phosphorylate p-nitrophenol by this method, but with diphenyl phosphate, only p-nitrophenol was obtained, and with allyl biscyclohexylammonium phosphate (108)

both p-nitrophenol and N-cyclohexyl trifluoroacetamide (109) were obtained. A suggested mechanism is outlined below, although it does not explain why the anhydride intermediate (110) is decomposed by attack at carbon to produce the amide and a phosphate anion, instead of by attack at phosphorous, which would result in liberation of the more stable trifluoroacetate anion.



(108)

(110)

(109)

Conclusions on Alkylation of Phenols:

The experiments described in this section amply demonstrate the efficiency with which allyl diphenyl phosphates will alkylate phenols *in vitro*, thus verifying the soundness of the chemical principles upon which the reactions were based. It is especially noteworthy that the most successful alkylations undertaken were those applied to syntheses, or attempted syntheses of important, naturally occurring substances such as α-tocopherol (18; R = $C_{16}H_{33}$), vitamin K_1(20) (19; R = $C_{16}H_{33}$) and isogrifolin (93).

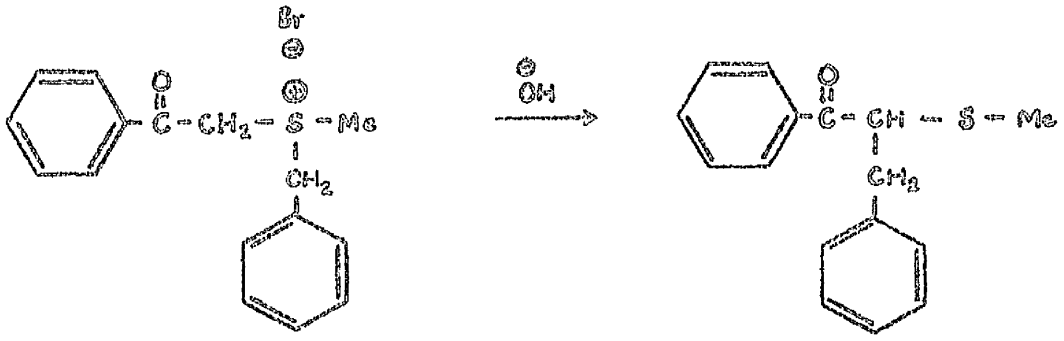
These model experiments are perhaps more significant when it is considered how closely similar they are to biological systems, in chemical terms at least. The results may therefore be claimed to be good chemical evidence for the proposed biosynthesis of phenolic isoprenoids.

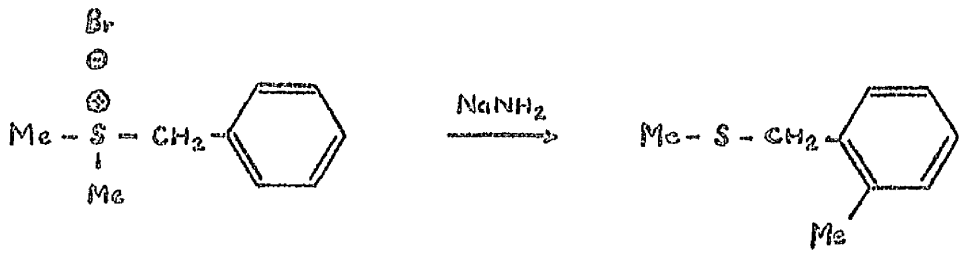
While the above experiments were designed as models in biosynthesis, they have also been of interest from a mechanistic point of view, largely because of the rearrangements found to occur during or after the alkylation step. Although the diphenyl phosphate anion has been found to be a good leaving-group from carbon undergoing nucleophilic attack, it has not been possible to obtain a clear mechanistic picture of all of these reactions.

4 REACTIONS BETWEEN ALLYL DIPHENYL PHOSPHATE AND SULPHUR COMPOUNDS

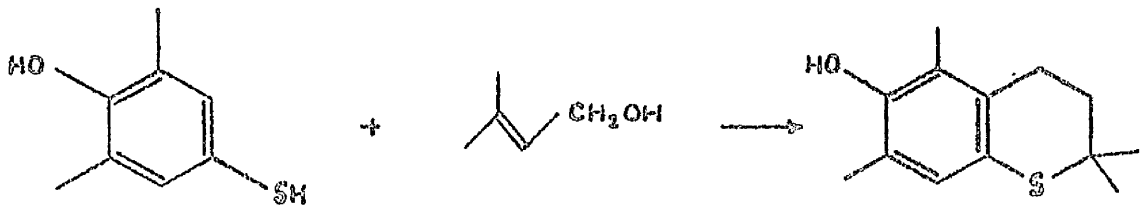
Interest in the reactions of allyl phosphates with thiols and sulphides was aroused by the recent theory[34] of the biosynthesis of squalene from farnesyl pyrophosphate, which was discussed in the main introduction to this thesis. Good chemical analogy is known for the postulated reactions leading to the formation of squalene, although the Stevens Rearrangement[150] has only been observed with sulphonium salts under vigorous conditions.

For example, it has been shown[25,150] that sulphonium halides, such as the two shown below can rearrange to give sulphide products on treatment with strong base. It will be seen that the benzoyl group is required to activate the α-methylene sufficiently for alkali to bring about rearrangement in the first example, and that without this activation, as in the second example, a much stronger base is required.



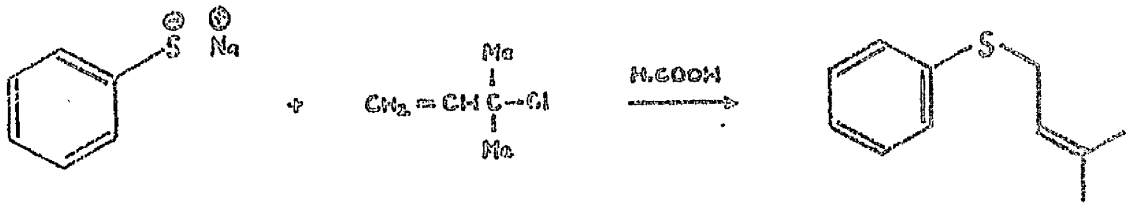


Another experiment, relevant to those about to be discussed, was that of Karrer,[140] who synthesised 5,7-dimethyl-6-hydroxy thiochroman (111), by treating 3,3-dimethyl-allyl alcohol with 2,6-dimethyl-4-mercaptophenol (112), and this appears to be the only example in the literature of alkylation of a thiol by a 3,3-dimethylallyl derivative.



(112) (111)

More recently, De la Mare and Vernon[101] treated 1,1-dimethylallyl chloride (113) with sodium thiophenoxide (114) in ethanol at 30°C for 12 hr., and showed that the production of 3',3'-dimethylallyl phenyl sulphide (115) was the result of the somewhat rare S_N2' mechanism. This experiment is analogous to the alkylation of phenoxide ions discussed earlier, although it is significant that the product is a sulphide, instead of a thiochroman as formed in the reaction with the free thiol.

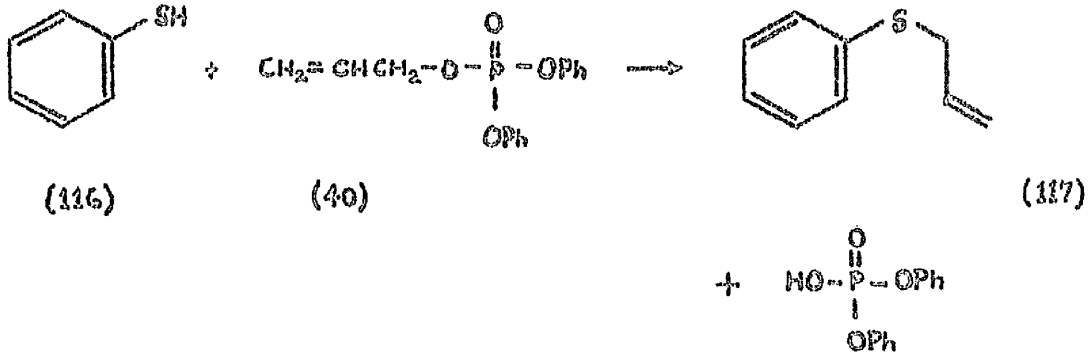


(114) (113) (115)

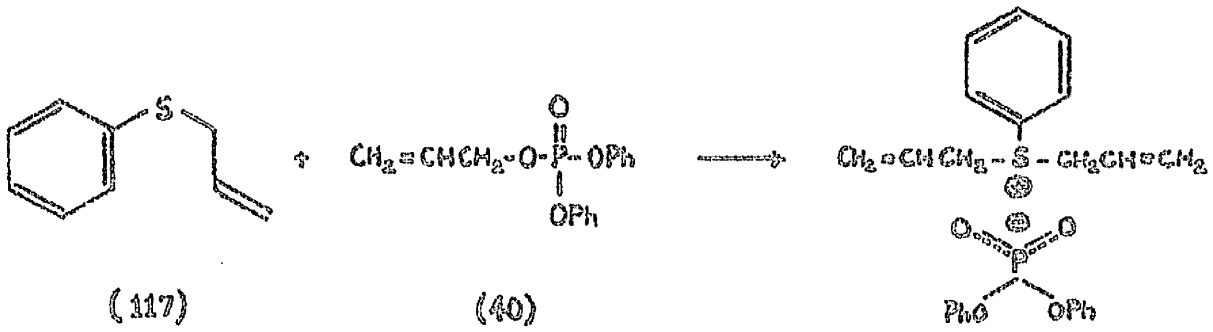
Alkylation of Phenyl Mercaptan (116):

As was found in the analogous reaction with phenol, an excess of phenyl mercaptan was found to be essential, before alkylation occurred on heating with allyl diphenyl phosphate (40). The only product formed in this system was allyl phenyl sulphide (117), and, after 12 hr., the amount of sulphide present reached a maximum, as measured by gas-liquid chromatography, before decreasing to about half this maximum value after 30 hr. In view of the fact that sulphides (see below)

have the property of de-alkylating allyl diphenyl phosphate, it would appear that the allyl phenyl sulphide is attacking the unreacted phosphate, probably with formation of a sulphonium salt, as illustrated in the equation below.



(116) (40) (117)



(117) (40)

It is noteworthy that no C-alkylation occurred initially, and that there was no evidence that rearrangement of the sulphide product had occurred. Both of these facts

represent important contrasts with the analogous phenol-phosphate system, although it is known that allyl phenyl sulphide is not so prone to rearrangement as the corresponding ether[148], and hence the latter observation is not unexpected.

Alkylation of Sulphides:

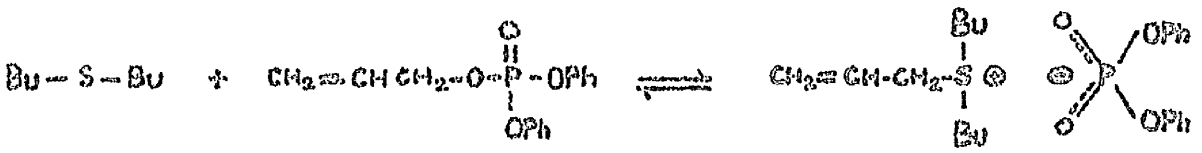
Three different symmetrical sulphides were heated with allyl diphenyl phosphate at 90°C, and there were interesting differences in their relative reactivities. Diphenyl sulphide (118) did not react at all with allyl diphenyl phosphate, but both dibutyl and diethyl sulphide did cause de-alkylation of the phosphate. These facts can readily be explained by the electron-withdrawing influence of the phenyl groups in the aryl sulphide, which reduce the electron-density on the sulphur atom, hence causing it to be a less potent nucleophile, when compared with the sulphur in a sulphide with two electron-releasing alkyl groups.

The reaction with ethyl sulphide (119) was comparatively simple and produced an allyl diethyl sulphonium salt (120) which was insoluble in ether but readily soluble in water. This salt proved to be extremely awkward to handle, since it was low-melting and hygroscopic, and the microanalysis was very unsatisfactory. This was believed to be due to decomposition

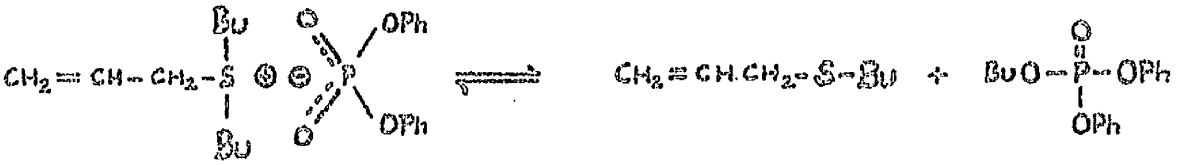
during the heating over phosphorus pentoxide at 0.01 mm., since the analysis corresponded to a mixture of allyl diphenyl phosphate and the sulphonium salt, the former probably being formed by loss of diethyl sulphide from the analytical sample. The belief that the structure of the salt has been correctly assigned, is based mainly on the nuclear magnetic resonance spectrum, which showed a multiplet at 4.3 τ (CH_2-CH-), a doublet at 6.15 τ (-$\overset{\oplus}{S}$-$\underline{\underline{CH_2}}$-CH=C-), a quartet at 6.90 τ (-$\overset{\oplus}{S}$-$\underline{\underline{CH_2}}$-$CH_3$) and a triplet at 8.65 τ ($\underline{\underline{CH_3}}$-$CH_2$-$\overset{\oplus}{S}$-). The lowering of chemical shift of the hydrogens of the methylene groups attached to the electron-deficient sulphur is extremely noticeable, and can be compared with the values obtained for allyl butyl sulphide (see below), which shows bands at 6.9 τ (-S-$\underline{\underline{CH_2}}$-CH=C-) and 7.5 τ (-S-$\underline{\underline{CH_2}}$-$CH_2$-).

(119) (40) (120)

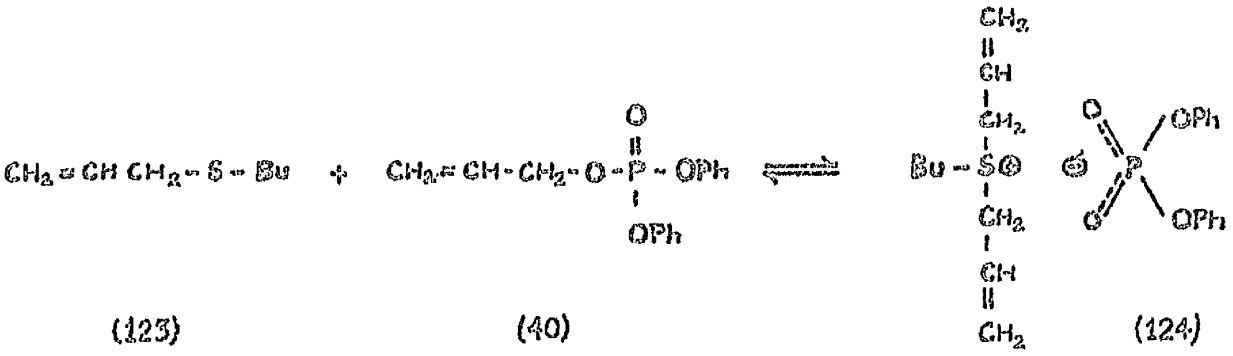
The third reaction with sulphides, that of dibutyl sulphide (121), was by far the most complex, since the initial alkylation products were decomposed slowly, to give simpler products, which were also capable of further reaction. The sequence of reactions is believed to be as illustrated below.



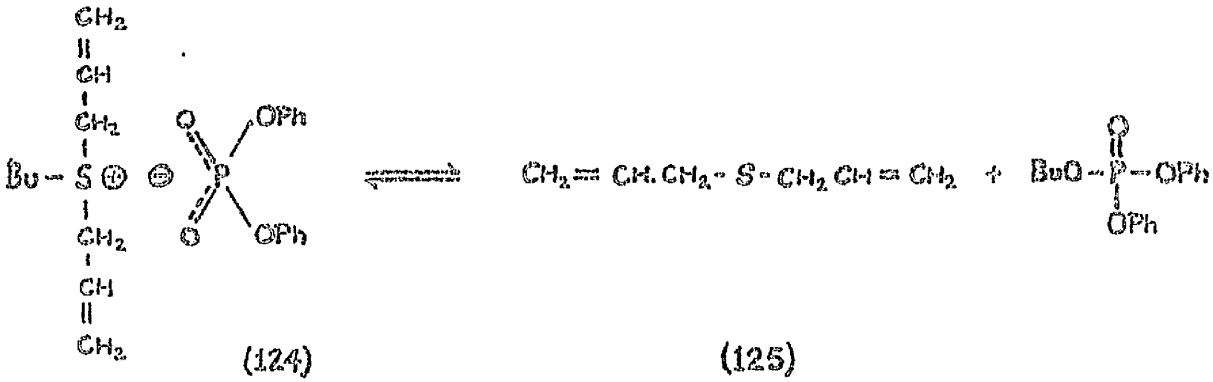
(121) (40) (122)



(122) (123)



(123) (40) (124)



(124) (125)

The principal evidence for the reactions outlined above was the rapid formation of allyl butyl sulphide (123), then traces of diallyl sulphide (125), when the butyl sulphide and allyl diphenyl phosphate were heated together at 100°C. The allyl butyl sulphide was isolated by fractional distillation and identified by spectroscopic methods, but the presence of diallyl sulphide (125) was not proven since it was formed in very small amounts as shown by gas-liquid chromatographic traces. There was no evidence of decomposition of the sulphonium salts to hydrocarbons and diphenyl phosphate.

In order to estimate the amounts of each product present after 200 hr., another run was studied in which a small amount of xylene was added as an internal chromatographic standard. Equilibrium was reached after 24 hr., when no xylene was present, but the same equilibrium was not quite reached after 200 hr. in the presence of xylene. At this stage some 31% of the dibutyl sulphide remained, and 22% of allyl butyl sulphide had been formed, but it was not possible to isolate, in a pure form, any of the relatively large amounts of sulphonium salts which should have been present. The sulphonium salts were found to be insoluble in water, and only partly insoluble in ether at certain, critical concentrations.

There are ample precedents for such equilibria in systems containing sulphonium salts, and it has been shown that sulphonium salts, in the presence of alkylating agents, will exchange alkyl groups, if, by this exchange, the size of the groups attached to the sulphur can be decreased. For example,[143] methyl iodide will de-allylate diallyl sulphide (125) and ultimately produce trimethyl sulphonium iodide (126), if sufficient excess of the iodide is present, by a series of equilibrium stages between sulphides and salts.

$$\left[CH_2{=}CHCH_2\right]_2S + MeI \rightleftharpoons \left[CH_2{=}CHCH_2\right]_2\overset{\oplus}{S}\text{-}Me\ \overset{\ominus}{I} \rightleftharpoons CH_2{=}CHCH_2\text{-}S\text{-}Me + CH_2{=}CHCH_2I$$

$$CH_2{=}CHCH_2\text{-}S\text{-}Me + MeI \rightleftharpoons Me_2\overset{\oplus}{S}\text{-}CH_2CH{=}CH_2\ \overset{\ominus}{I} \rightleftharpoons Me_2S + CH_2{=}CHCH_2I$$

$$Me_2S + MeI \rightleftharpoons Me_3\overset{\oplus}{S}\ \overset{\ominus}{I}$$

(126)

This exchange phenomenon can therefore be used to explain the rapid equilibrium, which is formed between the allyl dibutyl sulphonium salt (122) and allyl butyl sulphide (123), and to explain the relative stability of the analogous

allyl diethyl sulphonium salt (120) under the same conditions. Presumably the butyl-diallyl, and allyl-diethyl salts remain relatively unchanged in their respective systems because there is not sufficient excess of allyl diphenyl phosphate (40) in the former, and diethyl sulphide (119) in the latter reaction, to displace the equilibrium.

Conclusions on Alkylation of Sulphur Compounds:

Although only a few experiments have been tried, it is clear that both thiols and sulphides can be alkylated by allyl diphenyl phosphate in *in vitro* systems. It would therefore appear that the chemistry behind the suggested biosynthesis of squalene from farnesol is quite feasible.

The thiophenol-phosphate system was more simple than the corresponding phenol-phosphate system, discussed earlier, because of the complete preference for sulphide formation in the former, and because the sulphide did not show any tendency, to rearrange under acidic conditions. The dialkyl sulphide-phosphate systems were extremely complex due to the equilibria known to exist between sulphonium salts and alkylating agents.

PREPARATION AND PHYSICAL PROPERTIES OF ALLYL PHOSPHATES:

No mention has yet been made of the synthesis and stability of the various phosphate esters used in the experiments described in this thesis. All the alkyl diphenyl phosphates were synthesised by the conventional method,[89] by stirring the alcohol, in pyridine, with diphenyl phosphorochloridate (127) for several hours, and then extracting with ether.

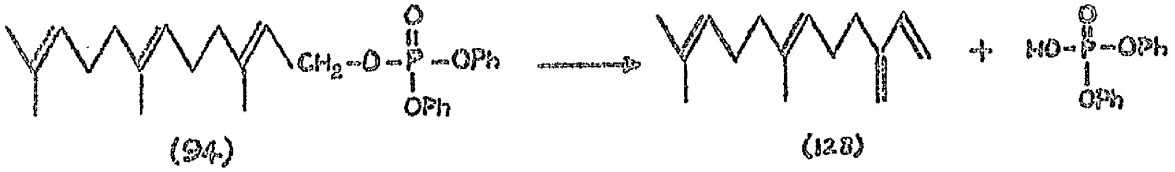
$$ROH + (PhO)_2\text{-}\overset{O}{\overset{\|}{P}}\text{-}Cl \longrightarrow (PhO)_2\text{-}\overset{O}{\overset{\|}{P}}\text{-}OR$$

(127)

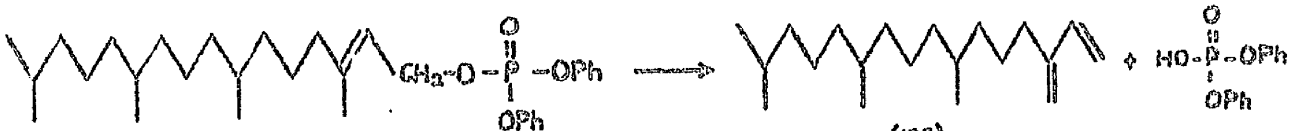
Without exception the phosphates were viscous, colourless, or almost colourless, oils with a characteristic smell, which was generally different from, although similar to, the parent allyl alcohol. The only one which was quite stable was allyl diphenyl phosphate (40), a sample of which was stored in a stoppered flask for two years without any apparent deterioration. A further distinguishing feature of allyl diphenyl phosphate (40) was that it could be distilled quite readily under vacuum, and the distillate analysed satisfactorily.

It was more common, however, for these esters to decompose on standing, or during vacuum distillation, although some were more unstable than others. For example, the 3,3-

dimethylallyl ester could not be distilled without decomposition to phenol and isoprene, and it became dark brown very quickly on standing, decomposing to isoprene and diphenyl phosphate. The farnesyl and phytyl esters were even more unstable and each had to be used immediately, since decomposition to farnesene (128) and phytadiene (129) occurred very rapidly at room temperature.



(94) (128)



(90) (129)

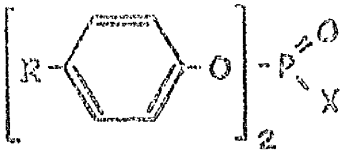
In the preparation of allyl diphenyl phosphate(40) and of benzyl diphenyl phosphate (39), it was found that the total stirring-time at 0°C in pyridine was not critical, but with 3,3-dimethylallyl diphenyl phosphate (51), and the higher terpenoid phosphates, the total time had to be reduced to 4 hr., from the more usual 6 hr., because pyridine attacked the base-sensitive phosphates, even at 0°c.

It is not surprising that the yields of these higher phosphates were extremely variable, even in preparations which were apparently identical in conditions and timing. For example 3,3-dimethylallyl diphenyl phosphate (51) was obtained in yields varying from 20-75%, and the geranyl,

neryl and farnesyl diphenyl phosphates showed a similar range of yield. The yields appeared to be dependent mainly upon a thorough drying of the apparatus, efficient cooling during stirring, a very fast extraction procedure, and, above all, the maintenance of a low temperature, around 40°C, during the solvent evaporation, after extraction and drying.

Although none of the isoprenoid diphenyl phosphates were analysed satisfactorily, it was ultimately found that the lack of a hydroxyl-stretch absorption in the infrared was sufficient criterion of a successful preparation. The infrared bands of all the phosphate compounds prepared for this thesis are tabulated in Table C (page 134), and these show a remarkable degree of consistency. The bands associated with the $-\underset{|}{\overset{|}{P}}=O$ and Ph-O-P- groups were extremely reliable, as well as being strong, and their position confirms the assignments made by other workers [144,145] for these absorptions. For example, the $-\underset{|}{\overset{|}{P}}=O$ absorption in fully esterified phosphates always appeared in the range 1282-1290 cm.$^{-1}$, although the presence of hydrogen-bonding in diesters resulted in a lowering of the absorption to 1250 cm.$^{-1}$ The characteristic doublet for the Ph-O-P- group always appeared at 1189 $\pm$ 1 cm.$^{-1}$ and 1162 $\pm$ 2 cm.$^{-1}$ in allyl diphenyl phosphates, although the former band was not so reliable in

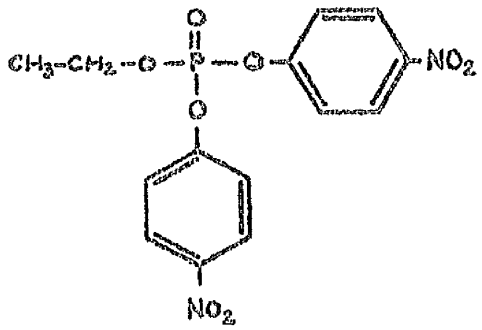
TABLE C: INFRARED SPECTRA OF PHOSPHATES



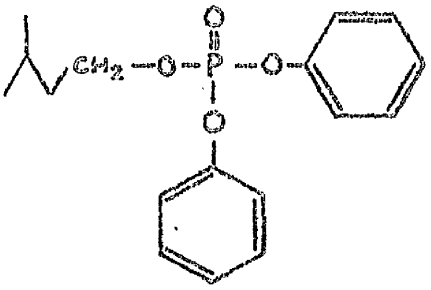
NO.	X	R	P=O	P-O-C(aryl)	P-O-C(alk)	OTHER BANDS
127	-Cl	H	1299	1203, 1181 1159, 966	-	-
-	-OH	H	1250	1189, 1163 969	-	2604
-	-OPh	H	1290	1176, 1157 948	-	-
40	-O-CH_2-$CH{=}CH_2$	H	1288	1217, 1190 1161, 952	1032	-
51	-O-CH_2 $CH{=}CMe_2$	H	1290	1220, 1190 1164, 953	1054	-
39	-O-CH_2 Ph	H	1289	1214, 1190 1162, 949	-	-
43	-O-Geranyl	H	1289	1217, 1190 1162, 956	1052	1662 832
50	-O-Neryl	H	1282	1218, 1190 1162, 956	1051	1663 835
94	-O-Farnesyl	H	1286	1218, 1190 1164, 953	-	1667 841
90	-O-Phytyl	H	1282	1189, 1163 945	-	-
-	-OH	NO_2	1244	1208, 1192 1161, 928	-	1515 1344
131	-OEt	NO_2	1274	1235, 1198 1163, 949	1026	1522 1344
105	-O-CH_2 $CH{=}CMe_2$	NO_2	1299	1203, 1161 942	1047	1527 1348
-	-OH	Br	-	1218, 1193 1161, 920	-	828
120	-O $\overset{\ominus}{O}$ $\overset{\oplus}{S}(Et)_2$ $CH_2CH{=}CH_2$	H	1282 1264	1211, 1098 890 876		1098 778
-	-O $\overset{\oplus}{N}H_3$ C_6H_{11}	H	1233	1214, 1083 925, 901	-	1083 774

di-p-nitrophenyl phosphates, or in the free acids.

The nuclear magnetic resonance spectra of only a few phosphates was obtained, because of the instability of most of those used in the experiments discussed above. The spectra of diphenyl phosphate and di-p-bromophenyl phosphate showed the acidic -P-OH protons at -3.1 τ and -0.90 τ respectively. The spectra of esters such as allyl diphenyl phosphate (40), isoamyl diphenyl phosphate (130) and ethyl di-p-nitrophenyl phosphate (131) showed that the coupling between the phosphorus and the α-hydrogens of the alkyl group was of the same order as that between the α-hydrogen and the β-hydrogen of the alkyl group. This phenomenon is, of course, quite common in esters of phosphoric acid which possess both α- and β- hydrogens. The principal effect



(131)



(130)

of this coupling between the phosphorus and the α-hydrogens is to make the anticipated triplet in the isoamyl ester (130) into a quartet, and the anticipated quartet in the ethyl ester (131) into a quintet.

EXPERIMENTAL

Abbreviations:

The following abbreviations have been used in this section:

conc.	concentration	g.l.c.	gas-liquid chromatography
mole	gram.molecule	t	g.l.c. retention-time
b.p.	boiling point	T.L.C.	thin-layer chromatography
m.p.	melting point	L.F.	liquid film
m.m.	millimetre	υ	wave-number
m.l.	millilitre	λ	wavelength
g.	grams	mμ	millimicrons
M	molecular weight	U.V.	ultraviolet
n	refractive index	n.m.r.	nuclear magnetic resonance
d	optical density	J	coupling constant in cycles/second
ε	extinction coefficient	τ	tau units.

Instruments and Techniques:

The following have been used in experimental work:

(i) Infrared Spectra: These were all run on a Grubb Parsons D.P.-1/54, either as liquid films (L.F.) or pressed discs in potassium chloride (KCl). Absorption maxima are recorded in cm.$^{-1}$, and, where possible, the vibration responsible for the absorption is indicated.

(ii) Ultraviolet Spectra: These were run on a Perkin-Elmer 137 U.V. The maxima are recorded in millimicrons (mμ) and the corresponding extinction coefficient (ε) indicated in parenthesis.

(iii) Nuclear Magnetic Resonance Spectra: These were run on a Perkin-Elmer R10 spectrometer (40 megacycles per second) with tetramethyl silane as internal standard. Chemical shifts are expressed in τ units (tetramethyl silane = 10). The solvent used for each compound is denoted by a superscript. The chemical group responsible for each absorption is given in parenthesis (where possible), and, if splitting is observed, this group is underlined, while the proton(s) responsible for the splitting is (are) not. Where appropriate, the integrated value of an absorption is given.

(iv) Gas-Liquid Chromatography: Analytical and preparative traces were run on a Griffin and George Mk.IIB instrument The carrier gas was nitrogen. The following columns were used:

Column (A): 1 part silicone gum E.301 on 4 parts celite 545. Used in all preparative separations.

Column (B): 1 part polyethylene glycol on 9 parts celite 545.

(v) Thin-Layer Chromatography: Ascending solvent technique on microscope slides (2.5 cm. x 7.5 cm.). The two stationary

phases used, in films about 0.2 m.m. thick. These were Kieselgel G (Merck), using iodine vapour detection,[146] and Kieselgel D.F-5 (Camag), using ultraviolet light detection (where appropriate).

(vi) Column Chromatography: The stationary phase used was either silica (B.D.H.) or alumina (Spences, Grade H).

(vii) Molecular Weights: These were normally determined by the cryoscopic method (in benzene). One molecular weight was determined by the osmometric method, using a Mechrolab Vapour Pressure Osmometer (Model 301A).

(viii) Melting Points: These were determined on an Electrothermal Melting Point Apparatus (IA 6301).

PART 1: PREPARATION AND DECOMPOSITION OF TERPENOID PHOSPHATES AND SULPHONATES:

Diphenyl Phosphorochloridate (127).[147] - Phenol (376 g., 40 mole) and phosphorus oxychloride (336 g., 2.2 mole) were heated under reflux in a 1 litre round bottomed flask, until the temperature reached 260°C (about 4 hr.), and maintained at that temperature under reflux for 30 min. The reflux condenser was fitted with an HCl trap. The mixture was then fractionally distilled, and the fraction distilling at 164-165°C/2.5 mm Hg. was found to be diphenyl phosphorochloridate (360 g., 61.0%) [Found: C,53.6; H,3.7; Cl,12.6%. $C_{12}H_{10}ClO_3P$ requires C,53.6; H,3.7; Cl,13.2%].

Geranyl Diphenyl Phosphate (43). - Diphenyl phosphorochloridate (56 g., 0.21 mole) was added over 1½ hr., dropwise, to a mixture of geraniol (30.8 g., 0.2 mole) and pyridine (32 ml., 0.4 mole), stirred at 0°C in a round-bottomed flask, kept in an ice-bath. The whole apparatus was dried before the experiment and during the experiment the apparatus was sealed with silica-gel tubes. Stirring was continued for 3 hr. further, before adding water (75 ml.) and extracting twice with ether (2 x 75 ml.). The combined ether extracts were washed successively with 2N sulphuric acid (100 ml.), dilute sodium bicarbonate (100 ml.),

and water (50 ml.)., before drying over anhydrous magnesium sulphate. After filtering, the ether was evaporated under vacuum at 40°C, leaving a slightly discoloured oil, which was identified as geranyl diphenyl phosphate (45-65%). The product had a smell similar to that of geraniol, although none of the parent alcohol was found to be present, since there was no hydroxyl stretch in the infrared spectrum (See Table C page 136).

Decomposition of Geranyl Diphenyl Phosphate:

(i) High Temperature: Geranyl diphenyl phosphate was heated at 100°C for 16 hr. and then it was attempted to fractionally distil the dark brown mixture. At 116-124°C 13 mm. a few drops of a colourless, sweet-smelling oil was obtained and this was found to be a mixture of hydrocarbons of polymeric nature.

(ii) Ether Solution at 37°C: The ethereal solution obtained from the synthesis of geranyl diphenyl phosphate was made up to 125 ml. with dry ether (0.1 molar) and then kept in a stoppered flask at 37°C, in the dark, for 3 weeks, before extracting with dilute sodium bicarbonate (75 ml.) and water (75 ml.). After drying over anhydrous magnesium sulphate, the ether was evaporated at 40°C under vacuum and the residual,

pleasant-smelling oil then placed on an alumina column (500 g.) and eluted with 40-60°C petrol. The total eluant with petrol was found to consist of six components, all hydrocarbons (6.0 g., 25% based on geraniol) and four major components were then obtained pure by preparative g.l.c. at 200°C. A typical g.l.c. trace is shown in Figure A (page 51), and the components are designated by a peak number, according to the order of elution.

Peak (1): This had a retention-time of 1.16 min., on column (A) run at 214°C. The infrared spectrum showed ν_{max}^{LF} 3106 (CH_2=C), 2985 and 2941 (CH_3, CH_2), 1815 (CH_2=CH-), 1802 (CH_2=C-) 1675 (-CH=$\dot{C}$-), 1637 (CH_2=$\dot{C}$-), 1597 (C=C-C=C), 1441 and 1377 (CH_3, CH_2), 1105, 989 and 902 (CH_2=CH-), 893 (CH_2=$\dot{C}$-), 826 (-CH=$\dot{C}$-) cm.$^{-1}$. The ultraviolet spectrum showed λ_{max}^{EtOH} 225 mμ (ε, 17,600), and $\lambda_{max}^{CHCl_3}$ 251.5 mμ (ε, 22,000). The n.m.r. spectrum showed τ^{CCl_4} 3.6 (C=$\dot{C}$(H)-C=C), 4.9-5.1 (CH_2=C-C=CH_2), 8.0 (-CH_2-$\dot{C}$=$\dot{C}$-), 8.35 (CH_3-$\dot{C}$=C-). This data was identical with that of a genuine sample of β-myrcene (48).

Peak (2): This had a retention-time of 1.32 min. on column (A) run at 214°C. The infrared spectrum showed ν_{max}^{LF} 3086 (CH_2=C 1795 (CH_2=C), 1675 (-CH=$\dot{C}$-), 1645 (CH_2=C-), 1610 (C=C-C=C), 1105, 986 and 912-890 (CH_2=$\dot{C}$H-), 829 (-CH=$\dot{C}$-) cm.$^{-1}$. The ultraviolet spectrum showed $\lambda_{max.}^{EtOH}$ 232 mμ (ε, 3,900), and

$\lambda_{max.}^{CHCl_3}$ 250.5 mμ (ε ,7,400). The n.m.r. spectrum showed τ^{CCl_4} 3.70 (C=C-$\overset{H}{\overset{|}{C}}$=C), 4.8-5.0 (C=C-C=$CH_2$), 5.3 ($CH_2$=C-), 7.2 (triplet, -C=CH-CH_2-CH=C-), 8.1 (-CH_2-$\overset{|}{C}$=$\overset{|}{C}$-), 8.3 (CH_3-$\overset{|}{C}$=$\overset{|}{C}$-). This data indicated that the unknown hydrocarbon was trans-β-cubmene (49).[100]

Peak (3): This had a retention time of 1.62 min. on column (A) at 214°C. The infrared spectrum showed $\upsilon_{max.}^{LF}$ 1680 (wk), 1647 (wk), 888, 823, 723 cm.$^{-1}$. The n.m.r. spectrum showed $\tau_{max}^{CCl_4}$ 4.7 (-CH=C-), 8.2, 8.35, 8.70.

Peak (4): This had a retention time of 1.85 min. on column (A) at 214°C. It was only obtained in amounts sufficient to determine the infrared spectrum, $\upsilon_{max.}^{LF}$ 1825, 1681, 1645, 1378, 1366, 1031, 983, 952, 837, 785 cm.$^{-1}$.

Peak (5): This had a retention time of 4.10 min. on column (A) at 214°C. The infrared spectrum showed $\upsilon_{max.}^{LF}$ 3096, 2941, 2882 1821 (CH_2=CH-), 1783 (CH_2=$\overset{|}{C}$-), 1645 (CH_2=C), 1443, 1416 (CH_2=C) 1374, 1242, 1179, 1150, 1138, 1087, 1056, 1001 (CH_2=CH-), 963, 907 (CH_2=CH-), 888 (CH_2=$\overset{|}{C}$-), 793 and 738 cm.$^{-1}$. The ultraviolet spectrum showed $\lambda_{max.}^{EtOH}$, 208 mμ. The n.m.r. spectrum showed τ^{CCl_4} 4.15, 5.0, 5.3 (CH_2=C), 7.9 (-$\overset{|}{C}$H-), 8.3 (CH_3-$\overset{|}{C}$=$\overset{|}{C}$-), 8.5 (cyclic -CH_2-), 9.02 (CH_3-$\overset{|}{\underset{|}{C}}$-). This data showed the hydrocarbon to be β-elemene (58).[105] [Found: C,87.9; H,11.9%; M,197. $C_{15}H_{24}$ requires C,88.2; H,11.8%; M,204].

Peak (6): This had a retention time of 5.9 min. on column (A) at 214°C. The infrared spectrum showed $\nu_{max.}^{LF}$ 2934, 1675 (-CH=C-), 1650 (CH_2=C-), 1445, 1389, 1377 and 1370 (CH_3-C(-)-CH_3), 1178 and 1156 (CH_3-C(-)-CH_3), 886 (CH_2=C-), 834 (-CH=C-) cm.$^{-1}$. The n.m.r. spectrum showed τ^{CCl_4} 4.90 (-CH=C-), 5.30 (CH_2=C-), 8.0 (-CH_2-C=C-), 8.40 (CH_3-C=C-), 8.70 (acyclic -CH_2-) and 9.10 (triplet, CH_3-C-). Five determinations gave M,205 (± 20), indicating that the unknown was a sesquiterpene hydrocarbon [Found: C,89.4; H,11.6%. $C_{15}H_{24}$ requires C,88.2; H,11.8%]

(iii) Decomposition in Ether at Varying Concentrations: Samples of geranyl diphenylphosphate (8 g.) were dissolved in 10 ml., 100 ml., and 1000ml. of anhydrous ether in different flasks before storing at 37°C for 4-5 weeks. The solutions were then worked up as above and the terpenes isolated from the alumina chromatography shown to be the same as the above.

Flask	Days at 37°C	Terpene Yield	Volume Ether (ml.)	Percentage Monoterpenes
(A)	33	29%	10	67%
(B)	24	39%	100	76%
(C)	35	44%	1000	70%

The terpene yield represents the yield of hydrocarbon obtained from the phosphate, and the percentage of mono-terpenes

is based upon the fraction of the g.l.c. trace (at 150°C) taken up by peaks (1), (2), (3) and (4). The estimation of the latter was done by tracing the chart onto paper with constant weight/unit area and weighing.

(iv) Variation in Products of Decomposition with Time: Geranyl diphenyl phosphate (14.0 g.) was kept in ether (100 ml.) at 37°C for 5 weeks and samples (20 ml.) were withdrawn from the reaction every 4 days. After extracting with dilute sodium bicarbonate, the samples were dried and the ether evaporated. The residual oils were examined analytically by g.l.c., but it was found that the number and relative proportions of the volatile terpenoid products did not vary with time.

(v) Effect of Addition of Sodium Bicarbonate: Geranyl diphenyl phosphate (14.0 g.) was kept in ether (100 ml.) at 37°C for 3 weeks in contact with solid sodium bicarbonate (4.0 g.). The terpenoid hydrocarbons, isolated as above, were found to be the same as in the original experiment, and their relative proportions not significantly different.

(vi) Detection and Estimation of Isoprene (1): Geranyl diphenyl phosphate (8.0 g.) was kept at 37°C in dry ether (100 ml.) for 3 weeks and then the solution was gently heated and the ethereal distillate collected. The distillate showed only one peak on an analytical g.l.c. trace at 30°C and its

ultraviolet spectrum showed $\lambda_{max.}$ 232 mμ, after dilution six times.

A sample of isopentane (b.p. 28°C), 2-methyl-but-1-ene (dihydroisoprene, b.p. 31°C) diethyl ether (b.p. 34°C) and n-pentane (b.p. 36°C) was resolved into four peaks on a g.l.c. run under identical conditions to the above. A mixture of isoprene (b.p. 34°C) and diethyl ether (b.p. 34°C) was found to give a single peak under the same conditions, Isoprene in ether showed $\lambda_{max.}$ 232 mμ in the ultraviolet.

The extinction coefficient (ε) of isoprene in ethanol is 22,000, and this can be used to find the amount of isoprene formed during the phosphate decomposition.

$$\varepsilon = \frac{M.d}{C} \qquad d = \text{optical density}; \quad c = \text{conc in g/litre}$$

$$\therefore \quad c = \frac{68 \times 1.42}{22000} = 4.4 \times 10^{-3} \text{ g litre}$$

Since the distillate had to be diluted by a factor of 6, the actual concentration is 2.64×10^{-2} g litre.

The theoretical amount of isoprene formed, assuming one mole of isoprene is formed per mole of sesquiterpene, can be calculated from the initial weight of phosphate decomposed in 100 ml. ether, since the total hydrocarbon yield was 30%, of which 20% was sesquiterpenoid.

Moles phosphate use $= \frac{8.0}{386}$ mole/100 ml. $\equiv \frac{80}{386}$ moles/litre

$\therefore$ Theoretical isoprene concentration $= \frac{80}{386} \times 68 \times \frac{3}{10} \times \frac{2}{10} \times \frac{1}{2}$

$= \underline{4.25 \times 10^{-3}}$ g/litre

There is therefore less isoprene than anticipated - by a factor of 16.

(vii) Decomposition in Ethanol at 37°C: Geranyl diphenyl phosphate (15.3 g., 0.04 mole) was kept at 37°C for 18 days in ethanol (125 ml.) and then chromatographed on alumina (350 g.), after removing the ethanol, and extracting with sodium bicarbonate from an ether solution. Analytical g.l.c. at 205°C showed the petrol (40-60°, dried) eluant to be more complex than before, and the principal components of the mixture (1.4 g., 25%) were purified by preparation g.l.c. (see Figure C, page 61).

The products from this ethanol decomposition were found to vary from run to run. The one consistent product was found to show ν_{max}^{LF} 1389 and 1368 (CH_3-$\overset{|}{C}$-CH_3), 1253, 1227, 1164 and 1142 (CH_3-$\overset{|}{C}$-CH_3), 1071 (-CH_2-O-C-), 959, 917 and 800 cm.$^{-1}$ in the infrared. The n.m.r. spectrum showed τ^{CCl_4} 4.7 (-CH=$\overset{|}{C}$-, [1]), 6.7 (-O-$\underline{CH_2}$-CH_3, quartet, [2]), 7.6-8.6 (broad band), 8.9 (CH_3-$\overset{|}{C}$-O-, and $\underline{CH_3}$-CH_2-O-, triplet [6]). This data was only compatible with ethyl α-terpinyl ether (68).

A major product isolated from a different run showed $\nu_{max.}^{LF}$ 1678 (-$\overset{|}{C}$H=C-), 1642 (CH_2=C), 1377, 1367, 1134, 1071 (-CH_2-O-C-), 963, 886 (CH_2=$\overset{|}{C}$-) cm.$^{-1}$ in the infrared. The n.m.r. spectrum showed τ^{CCl_4} 4.7 (-CH=$\overset{|}{C}$-), 5.3 (CH_2=$\overset{|}{C}$-), 6.65 (-O-$\underset{\text{quartet}}{CH_2}$-$CH_3$, quartet), 7.8 (-$CH_2$-$\overset{|}{C}$=$\overset{|}{C}$-), 8.3 ($CH_3$-$\overset{|}{C}$=$\overset{|}{C}$-), 8.9 ($\underset{\text{triplet}}{CH_3}$-$CH_2$-O, CH_3-$\overset{|}{C}$-O). This data was inconclusive, although similar to that expected from linalool ethyl ether.

The more volatile decomposition products were found to be hydrocarbons.

Stability of Myrcene to Acid: Myrcene (0.265 g. 0.002 mole) and diphenyl phosphate (0.2 g., 0.0008 mole) were dissolved in anhydrous ether (50 ml.) and left standing at 37°C for 1 week. After extraction with N.sodium bicarbonate (10 ml.) the ether was dried and evaporated. An analytical g.l.c. run showed that the myrcene remained unchanged by the acid treatment.

Preparation and Decomposition of Neryl Diphenyl Phosphate: Neryl diphenyl phosphate was prepared by a method identical to that used for geranyl diphenyl phosphate, but it was found to decompose too quickly to enable a yield to be estimated. The phosphate (obtained from 0.067 moles nerol) was kept at 37°C in 1000 ml. ether for 12 days before extracting with N.sodium bicarbonate (100 ml.), drying, evaporating the ether

and chromatographing on alumina (270 g.) with petrol (40-60°). Great heat was liberated as the products were applied to the alumina column, the top of which tended to break up. The first fraction from the column (50 ml.) contained a mobile colourless oil (4.34 g.), which gave 4 main peaks on a g.l.c. trace at 208°C, the first two predominating greatly. The second fraction (1.10 g.) showed the same four peaks, with the last two predominating. There were four trace peaks present, in addition to the main group. (see figure B, page 51), but no attempts were made to identify these minor components. The total yield of hydrocarbon was 60%, based on nerol.

Peak 1: This has a retention-time of 1.7 min. on column (A) at 208°C. The infrared spectrum showed $\nu_{max.}^{L.F.}$ 3106 ($CH_2=C-$), 1650 ($CH_2=C-$), 887 ($CH_2=C-$) and 825 ($-CH=C-$) $cm.^{-1}$. The n.m.r. spectrum showed τ^{CCl_4} 4.7 ($-CH=\overset{|}{C}-$), 5.3 ($CH_2=\overset{|}{C}-$), 7.9 ($-CH_2-\overset{|}{C}=\overset{|}{C}-$), 8.3 ($CH_3-\overset{|}{C}=\overset{|}{C}-$). This data was identical to that of a genuine sample of limonene (44) (Yield 25%, based on nerol).

Peak 2: This had a retention-tim of 2.0 min. on column (A) at 208°C. The infrared spectrum showed $\nu_{max.}^{L.F.}$ 1686 (v.wk; $-CH=\overset{|}{C}-$), 794 (med.; $-CH=C-$). The n.m.r. spectrum showed τ^{CCl_4} 4.7 ($-CH=\overset{|}{C}-$), 7.3 ($-C=C-CH_2-C=C-$), 7.8 ($-CH_2-C=C-$), 8.35 ($CH_3-C=C-$).

This data was similar to that expected from the monocyclic monoterpene, α-terpinolene.

Peak 4: This had a retention-time of 3.25 min. on column (A) at 208°C. The infrared spectrum showed $\upsilon_{max}^{L.F.}$ 1681 (-CH=$\overset{|}{C}$-), 1387 and 1370 (CH_3-$\overset{|}{C}$-CH_3), 1157 and 1149 (CH_3-$\overset{|}{C}$-CH_3), 1116, 916, 800, 736 cm.$^{-1}$ The n.m.r. spectrum showed τ^{CCl_4} 4.7 (-CH=C-), 8.1, 8.35, 8.45-8.50. This data was not enough to identify the unknown hydrocarbon.

Decomposition of Geranyl Diphenyl Phosphate (43) on Alumina: Geranyl diphenyl phosphate (8.0 g.) was stored in ether (100 ml.) at 37°C for 3 weeks and the resultant mixture worked up as in the original experiment. After elution of the terpenoid hydrocarbons with 40-60 petrol, the column was allowed to stand overnight and then eluted with ether. Evaporation of the ether yielded a colourless mobile liquid (1.6 g.) which gave 2 peaks on an analytical g.l.c. When separated by preparation g.l.c. the two products were found to be geraniol, and linalool (52), in an approximate (g.l.c) ratio of 4 to 1.

The linalool had a g.l.c. retention-time of 1.5 min. at 206°C on column (B), and the infrared spectrum showed $\upsilon_{max.}$ 3390 (-OH) 3077 (CH_2=C), 1648 (CH_2=CH-), 1666 (-CH=$\overset{|}{C}$-), 1634 (CH_2=C), 1408 (CH_2=CH-), 993 and 918 (CH_2=CH-), 833 (-CH=$\overset{|}{C}$-) cm.$^{-1}$ The absorption at 918 cm.$^{-1}$ is typical of the $-CH_2-$ deformation of vinyl groups attached to a tertiary carbon with one or more oxygen substituents.[140] A genuine sample of linalool gave identical data.

Decomposition of Neryl Diphenyl Phosphate (50) on Alumina:

Neryl diphenyl phosphate (6.0 g.) was kept in ether (100 ml.) for 12 days at 37°C, and the crude products chromatographed on alumina (200 g.) with petrol (40-60), to remove the hydrocarbons formed. Ether was then used to elute an oil which was found to be pure, (g.l.c. retention-time at 180°C on column (B), 5.1 min.), and which had an infrared spectrum identical with α-terpineol (45); $\nu_{max.}$ 3436 (-OH), 1678 (-CH=C) 1221, 1130 (-C-OH), 949, 912, 886, 837, 800 $cm.^{-1}$

Attempted Preparation of Sesquiterpenones from Limonene:

Limonene (2.05 g., 0.016 mole) and 3,3-dimethylallyl diphenyl phosphate (51) (5.25 g., 0.016 mole) were stored in a sealed flask at 18°C for 6 months, but analytical g.l.c. showed that the limonene was virtually unchanged after this period.

In a similar reaction using ether solvent (100 ml.) at 37°C over 6 weeks, no sesquiterpene was detected on g.l.c. traces at 180°C.

Preparation of Geranyl p-Toluene Sulphonate: Geraniol (7.7 g., 0.05 mole), p-toluene sulphonyl chloride (9.5 g., 0.05 mole) and pyridine (8 ml. 0.1 mole) were stirred at -5°C for 2hr. before adding ether (50 ml.) and extracting with 5N hydrochloric acid (50 ml.), 2N sodium hydroxide (50 ml.) and water (50 ml.).

The ether solution, after drying over anhydrous magnesium sulphate, yielded a very pale yellow oil (10.35 g.) which had the infrared characteristics of geranyl p-toluenesulphonate (67%); $\upsilon_{max.}$ 1669 (-CH=$\overset{|}{C}$-), 1368 (Ar-$\overset{O}{\overset{\|}{S}}$-OR$_{O}$), 1176 (Ar-$\overset{O}{\overset{\|}{S}}$-OR$_{O}$), 830 (-CH=$\overset{|}{C}$-), 814 (p-tolyl) cm.$^{-1}$.

Decomposition of Geranyl p-Toluene Sulphonate: Geranyl p-toluene sulphonate (10.3 g.) was allowed to stand at 37°C for 14 days in ether (103 ml.), in a stoppered flask. The solution darkened slowly on standing, ultimately turning a bright yellow colour, and a sediment was deposited after 3 days. After 10 days fine leaf-like crystals were deposited on the bottom of the flask, and they were removed by filtration, and found to be p-toluene sulphonic acid, m.p. 114-117°C [lit. 104-106°C]. Although the m.p. is high, the solid was hygroscopic, effervesced with sodium bicarbonate, and gave the same infrared spectrum as a sample of p-toluene sulphonic acid, recrystallised (m.p. 105-106°C) from ether.

Some of the ether filtrate was distilled at 45°C and the distillate examined by U.V., $\lambda_{max.}$ 234, 240, 245, 249, 255, 261, 277 mμ (all shoulders). The g.l.c. of the distillate (run at 40°C) showed that volatile product, other than ether, was present, although only in small amounts, and that it was less volatile than ether.

The residue from the distillation was combined with the remaining ether solution and then extracted with 2N sodium hydroxide (50 ml.) as quickly as possible, washed with water (50 ml.), and dried over anhydrous magnesium sulphate. The residual oil, (9.30 g.) after evaporating the ether, was divided into two, and the major part (5.54 g.) chromatographed on alumina (180 g.) with dried, redistilled petrol (40-60°C).

The products eluted with petrol, ten in all, were found to be hydrocarbons (0.756 g., 27%). The column was then stood overnight before eluting with ether. The first ether products were eluted as a pale yellow band, and were found to consist of two major and two minor products, the infrared spectrum indicating that they were ethers (0.72 g.). Later ether fractions yielded a series of colourless oils which were found to be alcohols, (1.50 g., 53%), three altogether.

Hydrocarbon Products: There were five volatile, probably monoterpenoid, hydrocarbons and five higher terpenoid hydrocarbons as shown by g.l.c. traces at 198°C. The most volatile was identified as myrcene (retention-time 1.24 minutes; myrcene 1.24 min.) (1% yield) and the next most volatile as ocimene (1.45 min.) (3% yield), identified by infrared spectroscopy.

The third and fourth hydrocarbons were trace products. The fifth hydrocarbon was the most polar (2.34 min.) (15%), and was purified by rechromatography on alumina. It was not identified, although spectral data was obtained; $\nu_{max.}^{L.F.}$ 3077 (CH_2=C), 1672 (-CH=$\dot{C}$-), 1642 (CH_2=C), 886 (CH_2=$\dot{C}$-), 829 (-CH=$\dot{C}$-) $cm.^{-1}$; τ^{CCl_4} 4.7-5.0 (-CH=$\dot{C}$-), 8.3 (CH_3-$\dot{C}$=$\dot{C}$-). The higher hydrocarbons were not isolated.

Ether Products: The two ether products were separated readily by alumina chromatography with ether solvent. The less polar product (2.97 min.) (about 10%) was an aliphatic ether; $\nu_{max.}^{L.F.}$ 1678 (-CH=$\dot{C}$-), 1104, 1062, 830 (-CH=$\dot{C}$-) $cm.^{-1}$; τ^{CCl_4} 4.7-5.2 (-CH=$\dot{C}$- , [2]), 6.10 (doublet, R-O-$\underline{CH_2}$-CH=C-, [2]), 7.9-8.0 (-CH_2-$\dot{C}$=$\dot{C}$-, [4]), 8.2-8.5 (CH_3-$\dot{C}$=$\dot{C}$- [9]).

The more polar, and less volatile (4.27 min.) ether product was identified as eugenol methyl ether (69) (2%); $\lambda_{max.}^{EtOH}$ 233 mμ (ε ,6000), 282 mμ (ε , 2800); $\nu_{max.}^{L.F.}$ 3077 (aromatic CH), 2932 (-CH_2-), 2849 (CH_3-O-), 1832 (CH_2=CH-, wk), 1639 (CH_2=CH-), 1590 and 1515 (aromatic C=C), 1462 (-CH_2-), 1420 (CH_2=CH-), 1259, 1235, 1030 (all aryl methyl ether), 994 and 913 (CH_2=CH-), 851 and 806 (both 1,2,4-trisubstituted benzene) $cm.^{-1}$; τ^{CCl_4} 3.55 (aryl H, [3]), 4.8-5.2 (CH_2=CH-, [3]), 6.25 (CH_3-O-Ar, [6]), 6.70 (Ar-$\underline{CH_2}$-CH=C-, doublet, [2]). The ether was shown to have the same g.l.c. retention-time as a small

(< 3%) impurity in the original geraniol.

Alcoholic Products: These were readily separated by alumina chromatography with ether, the order of elution being the same as that of volatility. The most volatile alcohol was identified as linaloöl (1.68 min.) (7.5%) and the least volatile as geraniol (2.56 min.) (19%), by comparison of g.l.c. retention-times, on column (B), and infrared spectra with genuine samples of each alcohol.

The intermediate alcohol was not identified (2.43 min.) (26%), despite the large amount in which it was obtained in a pure form. The spectra data showed $\nu_{max.}^{L.F.}$ 3378 (-OH stretch), 1681 (-CH=$\overset{|}{C}$-), 1653 (CH_2=C), 1059 (primary or secondary alcohol), 889 (CH_2=$\overset{|}{C}$-), 835 (-CH=$\overset{|}{C}$-) cm.$^{-1}$; τ^{CCl_4} 4.9-5.1 (olefinic), 6.4-6.5 (triplet with superimposed singlet at 6.5, $-CH_2-\underset{\text{ca.}}{CH_2}-OH$, or $-CH_2-\underset{\text{ca.}}{CH}-\underset{\text{ca.}}{OH}$). The g.l.c. retention-time is almost the same as α-terpineol (2.40 min., b.p. 220°C), but the infrared spectrum is very different from that of α-terpineol or menthol, the unknown being more simple, and apparently primary or secondary.

PART 2: REACTION OF PHENOLS WITH ALLYL PHOSPHATES AND SULPHONATES

Allyl Diphenyl Phosphate (40): This was prepared by the same method as for geranyl diphenyl phosphate except that the diphenyl phosphorochloridate (127) was added over 2 hr., and the mixture stirred a further 4 hr.. The crude product was obtained as a colourless, viscous oil in yields of 70-90%, and was sufficiently pure for most experiments. An analytically pure sample was obtained by distillation, b.p. 154-155°C/0.3 mm.; n_D^{21}, 1.5388; g.l.c. retention-time at 226°C, 29.6 min. [Found: C,61.9; H,5.6; P,10.8%. $C_{18}H_{15}O_4P$ requires C,62.1; H,5.6; P,10.7%].

Reaction between Phenol and Allyl Diphenyl Phosphate:

(a) Ether solvent: Phenol (0.94 g., 0.01 mole), recrystallised from 40-60° petrol, and allyl diphenyl phosphate (2.9 g., 0.01 mole) were dissolved in dry ether (20 ml.) and the solution was heated at reflux on a steam-bath for 60 hr. The ether solution was then extracted with dilute sodium bicarbonate (20 ml.). Acidification of this extract did not cause the precipitation of any diphenyl phosphate. The ether solution was then extracted twice with 2N sodium hydroxide (2 x 20 ml.), before washing with water (20 ml.) and drying over anhydrous magnesium sulphate. Evaporation of the ether yielded a colourless oil (2.5 g.) which proved to be allyl diphenyl phosphate (g.l.c. evidence).

(b) No Solvent: Phenol (0.94 g., 0.01 mole) and allyl diphenyl phosphate (2.9 g., 0.01 mole) were heated together in a sealed flask for 8 hr. at 100°C. By an extraction procedure similar to the above, it was found that no diphenyl phosphate had been produced and that unreacted allyl diphenyl phosphate remained (2.2 g.) after alkaline extraction.

(c) Phenol as Solvent: Phenol (0.94 g., 0.01 mole) and allyl diphenyl phosphate (0.58 g., 0.002 mole) were heated at 120°C in a sealed flask for 50 hr., and the course of reaction was followed by g.l.c., on column (A) at 191°C. After 24 hr. the initial three volatile products had been converted into a fourth product and this remained stable during the remaining reaction-time. The reaction mixture, dark red in colour, was dissolved in 2N sodium hydroxide (20 ml.) and extracted with ether (25 ml.). The ether extract was then washed with water, dried over anhydrous magnesium sulphate, and fractionally distilled. The only product was found to be 2-methyl coumaran (80) (0.44 g., 33%) (47% from g.l.c. traces) b.p. 83-86°C/15 mm Hg. (lit. 82-83°/14), and was identified spectroscopically; $\nu_{max.}^{L.F.}$ 2985 (CH_3), 2941 ($-CH_2-$), 2882 (CH_3), 1464 ($CH_3-\overset{|}{C}-$), 1447 ($-CH_2-$), 1381 ($CH_3-\overset{|}{C}-$), 1232 (coumaran), 749 (ortho disubstituted benzene) cm.$^{-1}$; τ CCl_4 3.2 (aryl H), 5.25 ($-O-\underline{CH}-CH_3$, quartet [1]), 7.05 ($ArCH_2-$[2]) 8.6 ($\underline{CH_3}-\overset{|}{\underset{H}{C}}-O-$, doublet [3]).

(d) Phenol as Solvent, with Added Sodium Bicarbonate: Phenol (0.94 g., 0.01 mole), allyl diphenyl phosphate (0.58 g., 0.002 mole) and solid sodium bicarbonate (0.17 g., 0.002 mole) were heated together at 120°C in a flask sealed with drying-tube. The mixture was shaken gently every 30 min. and went completely solid after 90 min. Runs at 191°C on g.l.c. column (A) showed that three products were formed after 10 hr., and that after 30 hr., there was no change in their amounts relative to one another, or relative to phenol.

The reaction was repeated on a larger scale (0.02 molar) and the three products separated by preparative g.l.c. on column (A) at 190°C. The most volatile was found to be allyl phenyl ether (34%); retention-time at 191°C, 1.52 min; $\nu_{max.}^{L.F.}$ 3077, 1653, 1412 (all CH_2=CH-), 1242 (aryl-alkyl ether), 991 and 910 (both CH_2=CH-), 753 and 690 (mono-substituted benzene) $cm.^{-1}$; τ^{CCl_4} 3.08 (aryl H), 4.50 (CH_2=CH-), 5.50 (ArO-$\underline{CH_2}$-CH=C-; doublet).

The intermediate product was found to be o-allyl phenol (25%); retention-time at 191°C, 2.23 min.; $\nu_{max.}^{L.F.}$ 3521 (-OH), 2941 and 2865 ($-CH_2-$), 1845 and 1645 (CH_2=CH-), 1439 ($-CH_2-$), 1416 (CH_2=CH-), 1533 and 1220 (Phenol O-C str.), 997 and 917 (CH_2=CH-), 751 (ortho-di-substit.benzene) $cm.^{-1}$.

The third product was found to be p-allyl phenol (39%); retention-time at 191°C, 2.67 min.; $\nu_{max.}^{L.F.}$ 3390 (-OH stretch), 2933 and 2857 ($-CH_2-$), 1647 ($CH_2=CH-$), 1370 and 1235 (Phenol-OH), 994 and 916 (both $CH_2=CH-$), 824 (para-di-substit. benzene) $cm.^{-1}$

The yields of these three products were calculated from the g.l.c. traces used to follow the reaction, by reference to a calibration chart of each against phenol. By comparison of retention-time it was ascertained that the intermediate products in the reaction without bicarbonate were the same as the above products.

Preparation of p-Allyl Phenyl-p-nitrobenzoate:[149] p-Allyl phenol (0.097 g., 7.2×10^{-4} mole) from the above experiment was dissolved in pyridine (2 ml., dried and redistilled) and 3,5-dinitrobenzoyl chloride (0.165 g., 7.2×10^{-4} mole) added. The mixture was then refluxed for 1 hr. and after cooling, was added to 5% sulphuric acid (40 ml.). After solidification, the red solid product was washed with 2% sodium hydroxide (20 ml.). After three recrystallisations from aqueous ethanol, the white solid was identified as p-allyl phenyl p-nitrobenzoate, m.p. 100-102°C [Lit. 103°C].

(c) Phenol as Solvent, in Presence of Tri-n-Butylamine: Phenol (2.8 g., 0.03 mole), allyl diphenyl phosphate (5.8 g., 0.02 mole), and tri-n-butylamine (3.7 g., 0.02 mole) were heated at 100°C for 40 hr. The mixture was dissolved in 50 ml. ether, before extracting with N.sodium bicarbonate (50 ml.), 2N hydrochloric acid, 2N sodium hydroxide and water. The ether solution was then dried over anhydrous magnesium sulphate, and the ether evaporated to give a discoloured oil which was fractionally distilled under vacuum. The principal distillate was allyl phenyl ether (0.6 g., 22%). The alkaline extract yielded only phenol.

Reaction Between Sodium Phenoxide and Allyl Diphenyl Phosphate in Aqueous Solutions: To a solution of phenol (0.94 g., 0.01 mole) and sodium hydroxide (0.4 g., 0.01 mole) in water (2 ml.), allyl diphenyl phosphate (2.9 g., 0.01 mole) was added, and the mixture heated at 80°C for 15 min. The mixture had turned a green-yellow colour and the smell of allyl phenyl ether was detected. An ether (20 ml.) solution of the mixture was washed with 2N sodium hydroxide (20 ml.), and then water (20 ml.), and the ether solution dried over anhydrous magnesium sulphate, before evaporating the solvent. The residual, colourless oil was then distilled at 15 mm. Hg., and

the only distillate was allyl phenyl ether (0.34 g., 25%).

Reaction Between Solid Sodium Phenoxide and Allyl Diphenyl Phosphate in a Non-Polar Solvent: Allyl diphenyl phosphate (0.290 g., 0.001 mole) was dissolved in a solution of equal volumes of petrol (40-60°) and ether (both dry, 5.0 ml.) and solid sodium phenoxide (0.116 g., 0.001 mole) added. The mixture was then allowed to stand at 18°C for 40 hr., by which time most of the phenoxide had dissolved. The mixture was poured into water (10 ml.) and extracted with ether (10 ml.) and the dried ether extract yielded a colourless oil (0.246 g.), which was found to be a mixture of allyl phenyl ether and allyl diphenyl phosphate. The ether was identified by g.l.c. retention-time, and was obtained pure by distillation (28%). The alkaline layer yielded phenol.

Reaction Between m-cresol and Allyl Diphenyl Phosphate (40): Allyl diphenyl phosphate (3.90 g., 0.01 mole) and m-cresol (5.40 g., 0.05 mole) were heated at 110°C for 48 hr. in a sealed flask. The reaction mixture after 24 hr. showed peaks at 1.59 (m-cresol), 2.06 (shoulder), 2.50 and 4.0 (small, broad hump) minutes, and after 48 hr. the mixture had simplified to two peaks (1.59 and 2.38 min.) in gas-liquid chromatography runs at 190°C.

The crude mixture was poured into 5N-sodium hydroxide

(50 ml.) and extraction with ether yielded an oil, which was distilled from an oil bath at 120°C/15 mm. Hg. The volatile product was identified as a mixture of 2,4-dimethyl coumaran and 2,6-dimethylcoumaran (0.28 g., 19%). From a g.l.c. calibration the yield was 56%, and the n.m.r. indicated the ratio of isomers to be 2:1, although it was not possible to discriminate between them. The colourless oil gave the following spectral data; $\nu_{max}^{L.F.}$ 2985, 1579 (both CH_3), 1253 and 1235 (coumaran-doublet), 1020, 944, 909, 823 (1,2,4-tri-substit.benzene) 798.——769 and 706 (both 1,2,3-trisubstit. benzene) cm.$^{-1}$; τ^{CCl_4} 3.0-3.7 (aryl-H[3]), 5.27 (-O-C<u>H</u>-CH_3, [1]). 7.15 (Ar.CH_2-C-, [2]), 7.77 and 7.85 (ratio 1:2; aryl-CH_3 [3]), 8.62 (<u>CH_3</u>-CH-O-).

<u>Ring-Closure of σ-Allyl Phenol in Phenol:</u> <u>σ</u>-Allyl phenol (0.67 g., 0.005 mole) and diphenyl phosphate (1.25 g., 0.005 mole) were heated at 120°C in phenol (2.35 g., 0.025 mole) for 24 hr., and the reaction traced by g.l.c. at 190°C. After 5 hr. there were about equal amounts of <u>o</u>-allyl phenol (retention-time, 2.27 min.) and 2-methyl coumaran (3.78 min.), and after 24 hr. all the <u>o</u>-allyl phenol had been converted to 2-methyl coumaran (80).

<u>Isomerisation of Allyl Phenyl Ether in Phenol:</u> Allyl phenyl ether (0.4 g., 0.003 mole) and diphenyl phosphate (0.75 g., 0.003 mole) were heated for 75 hr. in phenol (1.4 g., 0.015 mole)

at 105°C, and the reaction followed by g.l.c. traces. After 1 hr. there was no detectable reaction, and after 5 hr. there was a shoulder present in the allyl phenyl ether peak. After heating for 75 hr., the allyl phenyl ether had disappeared and the only product was 2-methyl coumaran (80). At no time during the reaction was o-allyl phenol detected.

Isomerisation of Allyl Phenyl Ether in m-Cresol: Allyl phenyl ether (0.268 g., 0.002 mole) and diphenyl phosphate (0.50 g., 0.002 mole) were heated in m-cresol (1.08 g., 0.01 mole), at 120°C for 76 hr. in a sealed flask. The product mixture was examined by g.l.c. at 191°C and showed peaks at 1.21 min. (1.1 mole, phenol = 1.17 min.), 1.50 min., (broad, containing m-cresol and allyl phenyl ether), and 2.40 min., (1.0 mole).

The crude mixture was poured into 2N sodium hydroxide (25 ml.), and extracted with ether (25 ml.). This ether extract was found to contain three components. These were allyl phenyl ether (1.50 min.), 2-methyl coumaran (1.69 min.; standard = 1.70), and a third component (2.41 min.,), which was identified as a dimethylcoumaran. The relative amount of 2-methyl coumaran to the dimethylcourmaran was 3.1:1.0, and that of phenol to the dimethylcoumaran, 1.1:1.0.

Isomerisation of Eugenol in Phenol: Eugenol (70) (1.64 g., 0.01 mole) and diphenyl phosphate (2.50 g., 0.01 mole) were heated at 120°C in phenol (4.7 g., 0.05 mole) for 70 hr. in a sealed flask. The reaction was followed by g.l.c. at 190°C and the eugenol was seen to disappear gradually from the reaction mixture, and two small shoulders (1.45 and 1.62 min.) were seen to appear in the main phenol peak (1.16 min.)

The crude mixture was then diluted with 5N sodium hydroxide (50 ml.) and extracted with ether (50 ml.). The ether extract was washed and dried and yielded traces of an oil (90 mg.), which gave 4 peaks on the g.l.c.

The alkaline extract from above was acidified with 2N hydrochloric acid, and ether (100 ml.) added. The ether extract was washed with N sodium bicarbonate and water before drying, and evaporating the ether, to yield a dark, red, oil which did not appear to contain any component other than phenol.

Reactions of Phenol with Olefins in the Presence of Diphenyl Phosphate:

(a) Cyclohexene at 37°C: Phenol (0.94 g., 0.01 mole) and cyclohexene (0.82 g., 0.01 mole) were heated together at 37°C for 10 days in the presence of diphenyl phosphate (2.50 g., 0.01 mole). The mixture was then taken up in ether (25 ml.), before extracting with 2N NaOH (25 ml.), drying over anhydrous

magnesium sulphate, and removing the ether and unchanged cyclohexene on a steam-bath. The residual oil was distilled to give a colourless product, identified as cyclohexyl phenyl ether, (0.088 g., 5%); $\nu_{max.}^{L.F.}$ 2924, 2857, 1449 (all $-CH_2-$), 1236 (aryl-alkyl ether), 749, 691 (mono-substit. benzene).

(b) Oct-2-ene at 100°C: Phenol (0.94 g., 0.01 mole), oct-2-ene (1.12 g., 0.01 mole) and diphenyl phosphate (2.50 g., 0.01 mole) were heated together at 100°C for 60 hr., before taking up in ether (25 ml.) and extracting as above. The product from the ether solution was fractionally distilled to give a colourless oil, identified as an octyl phenyl ether, b.p. 114-116°C/11 mm. (0.084 g., 4%); g.l.c. retention-time at 232°C, 0.8 min; $\nu_{max.}^{L.F.}$: 2941, 2865, 1456 and 1372 (all CH_3- and $-CH_2-$ bands), 1241 (alkyl-aryl ether), 750 and 690 (mono-substit. benzene) $cm.^{-1}$; τ^{CCl_4} 2.9-3.1 (aryl H), 5.8 ($-\overset{|}{C}H-O-Ar$), 8.8 ($CH_3-\overset{|}{C}-O$). Phenol was the only phenolic product obtained from the alkaline extract.

(c) 2-Methyl-but-1-ene at 100°C: Phenol (0.94 g., 0.01 mole), diphenyl phosphate (0.1 g., 0.0004 mole) and 2-methyl-but-1-ene (1.40 g., 0.02 mole) were heated under reflux at 100°C for 60 hr. The crude mixture was then chromatographed on alumina (70 g.) with petrol (40-60°C). The first eluant (0.28 g.) consisted of

a low and a high-boiling product (2:1 by g.l.c.) and the former (g.l.c. retention-time on column (A) at 204°C, 14.2 min.) was identified as 2,6-di(1',1'-dimethylpropyl phenol (I, page 95) (0.18 g., 8%) by its spectral data (see Table A , page 95)

A second product was obtained with ether as solvent and this was identified as o-(1'1'-dimethylpropyl)phenol (III, page 95), 0.67 g., 40%) (g.l.c. retention-time on column (A) at 204°C, 5.1 min.) by its infrared and nuclear magnetic resonance characteristics (see Table A). A third product was eluted by ethyl acetate and this was found to consist of phenol (0.10 g., 11% return) and p-(1',1'-dimethylpropyl)phenol (IV, page 95), (0.067 g., 4%) (see Table A)(g.l.c. retention-time on column (A) at 204°C, 6.1 min.).

Reaction of Phenol with 2-Methyl-but-1-ene in the Presence of Sulphuric Acid: Phenol (4.7 g., 0.05 mole) and 2-methyl-but-1-ene (7.0 g., 0.1 mole) were heated under reflux at 100°C with 1 drop of concentrated sulphuric acid for 14 hr., The crude products were chromatographed on alumina (300 g.), and identified by spectral characteristics (see Table A, page.95) after a distillation.

The first product was 2,6-di(1',1'-dimethylpropyl) phenol (I, page 95) (3.3 g., 28%). b.p. 99-103°/0.01 mm. Hg.,

eluted with 40-60°C petrol. With petrol-benzene (1:1) the product was 2,4-di(1',1'-dimethylpropyl)phenol (II, page 95) (5.9 g., 34%), b.p. 109-110°C/0.02 mm. Hg. Mixtures of this phenol and 2-(1',1'-dimethylpropyl)phenol were obtained with benzene from the column, (g.l.c. evidence) and these are included in the total yields. With benzene-ether (1:1), pure 2-(1',1'-dimethylpropyl) phenol (III, page 95) (2.7 g., 34%) was obtained, b.p. 126-130°C/15 mm. Hg. With ethyl acetate, a small amount of phenol and 4-(1',1'-dimethylpropyl)phenol (IV, page 95) (160 mg. 2%) was eluted.

Reaction of Phenol and Diphenyl Phosphate: Phenol (0.94 g., 0.01 mole) and diphenyl phosphate (2.5 g., 0.01 mole) were heated at 100°C for 40 hr. Extraction with ether, from an alkaline solution of the reaction mixture, yielded a neutral (litmus), oily product, which solidified on cooling, m.p. 46.5-47.5°C [lit. 49°C]. The solid was identified as triphenyl phosphate (0.06 g., 2%) from its infrared spectrum see Table C, page 134).

Reaction of Phenol with Olefins: Phenol (0.94 g., 0.01 mole) and oct-2-ene (1.12 g., 0.01 mole) were heated at 37°C for 60 hr., before taking up in ether and extracting with alkali. The ether solution was found to consist of oct-2-ene only and the alkaline extract of phenol only.

Reaction Between Ethyl-p-hydroxy Benzoate (81) and Allyl Diphenyl Phosphate (40) in the Presence of Sodium Bicarbonate:

Ethyl-p-hydroxybenzoate (81) (1.68 g., 0.01 mole), allyl diphenyl phosphate (2.9 g., 0.01 mole) and sodium bicarbonate (0.84 g., 0.01 mole) were heated at 100°C for 45 hr., in a mixture of ether (10 ml.) and benzene (10 ml.). The mixture was then extracted with water (30 ml.), N. sodium bicarbonate (30 ml.), and 2N sodium hydroxide (20 ml.) before washing with water. The ether-benzene solution was then dried over anhydrous magnesium sulphate and evaporation of the solvents yielded a discoloured oil (2.5 g.) which showed both carbonyl and phosphate ester peaks in the infrared. The residue was then chromatographed on alumina (75 g.), and 40-60°C petrol solvent yielded a colourless liquid, ethyl p-allyloxy benzoate [82] (0.35 g., 16%); g.l.c. retention time at 227°C., 5.35 min.; $\nu_{max.}^{L.F.}$ 3086, 1650, 996 (all CH_2=CH-), 1712 (-$\overset{O}{\overset{\|}{C}}$-O), 1276, 1105 (-COOEt), 1253 (aryl ether), 847 (p-disubstit. benzene) cm.$^{-1}$; τ CCl_4 2.1 (doublet; aryl H o- to COOEt), 3.1 (doublet; aryl H o- to oxygen), 4.5 (allyl), 5.8-6.2 (ArO-CH_2-$\overset{H}{\overset{|}{C}}$=C-, and Ar$\overset{O}{\overset{\|}{C}}$-O-$CH_2$-$\overset{}{\overset{|}{C}}$-), 8.7 (triplet; $\underset{}{CH_3}CH_2$-O-).

The sodium hydroxide extract yielded ethyl-p-hydroxy benzoate, m.p. 102-105°C (1.05 g., 60% return). The sodium bicarbonate and initial water extracts yielded diphenyl phosphate

(0.41 g., 16%), identified as the cyclohexylammonium salt, m.p. 192-196°C [lit. 200°C][85].

Hydrolysis of Ethyl-p-allyloxy Benzoate [82]: Ethyl-p-allyloxy benzoate (0.69 g., 0.0035 mole) was treated at reflux with potassium hydroxide (0.2 g.) in methanol (5 ml.) for 2 hr. Extraction of the acidified methanolic solution with chloroform yielded p-allyloxy benzoic acid (0.037 g., 62%, m.p. 157-159°C [lit., 160°C].

Reaction Between 1,4-Dihydroxynaphthalene and Allyl Diphenyl Phosphate in Ethanol: 1,4-Dihydroxynaphthalene (3.16g., 0.02 mole) was prepared from 1,4-naphthaquinone (in the same fashion as menadiol from menadione, page 200), yield 95%, and added to a solution of allyl diphenyl phosphate (5.8 g., 0.02 mole) in ethanol (10 ml.). The solution was then refluxed for 65 hr. on a steam-bath, the ethanol removed and the purple residue dissolved in ether (50 ml.), before extracting with N-sodium bicarbonate (50 ml.) and washing with water. The ether solution was then dried, and the ether evaporated, yielding a purple oil (1.95 g.) which was chromatographed on alumina (60 g.) with ether as solvent. The first eluant was a reddish-brown solid which was found, after recrystallization from petrol (40-60°C), to be 1,4-diethoxynaphthalene (100 mg. 2%) m.p. 83-84°C. $\nu_{max.}^{KCl}$ 2981,

2941, 1381 (all CH_3-$\overset{|}{C}$-), 1241 (aryl-alkyl ether), 749 (naphthalene) cm.$^{-1}$; τ CCl_4 1.8 (α-H in naphthalene [2]) 2.6 (β-H in naphthalene, [2]), 3.5 (naphthalene H, α-to-OR [2]), 5.9 (Ar-O-$\underline{CH_2}$-CH_3, quartet [4]), 8.6 ($\underline{CH_3}$-CH_2-O-Ar, triplet [6]). The second fraction was a reddish-brown, viscous oil, which was found to consist mainly of 1,4-naphthaquinone. The third fraction with ether was a red-brown solid, which was sublimed from a water-bath at 70°C/0.1 mm., and found to be 1-ethoxy-4-hydroxynaphthalene (75 mg. 2%), m.p. 90-92°C [lit 104°C]; $\nu_{max.}^{KCl}$ 3260 (OH stretch), 1235 (aryl-alkyl ether), 803 (1,2,3,4-tetrasubstituted benzene), 760 (naphthalene) cm.$^{-1}$; τ CCl_4 1.8 (naphthalene α-H, [2]), 2.6 (naphthalene β-H, [2]), 3.5 (naphthalene, α-to-OR or-OH [2]), 4.8 (naphthol OH, [1]), 5.95 (Ar-O-$\underline{CH_2}$-CH_3, [2]), 8.5 (Ar-O-CH_2-$\underline{CH_3}$, triplet [3]). The only other product from the column was 1,4-dihydroxy naphthalene, obtained with ether-ethyl acetate (20:1).

<u>Preparation of Allyl-p-toluene Sulphonate</u>:[134] A mixture of allyl alcohol (38 g., 1 mole) and p-toluenesulphonyl chloride (190 g., 1 mole) were treated at 15°C with 25% sodium hydroxide (175 ml., 1 mole) over 2 hour, while the mixture was stirred. Stirring at 15°C was continued for a further 4 hr., then the mixture poured into cold water (2 litres), and the precipitated

clear oil extracted with ether. The extract was washed with 2N sodium hydroxide (200 ml.), and water, before drying and evaporating the ether. The resultant oil was distilled and the fraction, b.p. 136°C/0.6 mm. identified as allyl p-toluene sulphonate (125 g., 60%); $\nu_{max.}$ 1368 and 1178 (sulphonate), 995 and 918 (CH_2=CH-).

Reaction of Phenol with Allyl p-Toluene Sulphonate:

(i) Phenol solvent at 100°C: Allyl p-toluene sulphonate (4.2 g., 0.02 mole) and phenol (9.4 g., 0.10 mole) were heated at 100°C in a sealed flask for 24 hr., before dissolving the red mixture in ether (50 ml.) and extracting with N sodium bicarbonate (50 ml.), and then water (50 ml.). The dried ether solution was then examined by g.l.c at 176°C, but only phenol was detected.

(ii) No solvent at 20°C: Allyl p-toluene sulphonate (2.10 g., 0.01 mole) and phenol (0.94 g. 0.01 mole) were heated at 20°C for 5 days in a sealed flask. The mixture darkened, as in the previous experiment, and extraction with N-sodium bicarbonate from an ether solution produced much effervescence. The ether layer yielded a red oil (1.95 g.) which did not have any volatile component other than phenol.

PART 3: REACTION OF 3,3-DIALKYLALLYL PHOSPHATES AND SULPHONATES WITH PHENOLS:

Preparation of 3,3-Dimethylallyl Alcohol:[160]

(1) From 2,2-dimethylacrylic acid: A solution of 2,2-dimethyl acrylic acid (25 g., 0.25 mole) in sodium-dried, anhydrous ether (100 ml.) was placed in a 500 ml. 3-necked flask, fitted with a mercury sealed stirrer, a dropping funnel, and a thermometer. The side arm carrying the dropping funnel was open to the atmosphere through a drying-tube. The solution was cooled in an ice-salt bath to -10°C., and, from the dropping-funnel, a slurry of lithium aluminium hydride (11.9 g., 0.315 mole) in sodium-dried, anhydrous ether was added cautiously, over 45 min., to the stirred solution, so that the temperature in the flask never exceeded 5°C. Further 15 min., was allowed for completion of the reaction, before gradually adding enough water to remove any excess hydride. Sulphuric acid (80 ml. 10%) was then added cautiously, and the acidified solution was then extracted with ether (2 x 150 ml.). The combined ether extracts were then dried over anhydrous potassium carbonate, before filtering and evaporating the ether at atmospheric pressure. The product, which had a pale-yellow coloration was then distilled and the major fraction, 3,3-dimethylallyl alcohol, collected; b.p. 54-55°C/25 mm. (16.0 g., 75%). The alcohol showed $\nu^{LF}_{max.}$ 3365

(-OH), 1038. (broad, $-CH_2OH$), 1677 and 837 ($-\overset{|}{C}=CH-$) cm.$^{-1}$. A g.l.c. trace at 125°C showed the product to be pure, although in some experiments there were traces of isoamyl alcohol (b.p. 132°C) present with the 3,3-dimethylallyl alcohol (b.p. 140°C).

Preparation of 3,3-Dimethylallyl Diphenyl Phosphate (51). This was prepared in the same fashion as geranyl diphenyl phosphate, by adding diphenyl phosphorochloridate to 3,3-dimethylallyl alcohol in pyridine. The product obtained by evaporation of the ether in the final stage was an almost colourless oil, with rather a sweet smell, and the yields varied between 50% and 75%. The oily phosphate was deemed pure if there was no -OH stretch around 3300 cm.$^{-1}$ in the infrared.

Distillation of 3,3-Dimethylallyl Diphenyl Phosphate (51). The phosphate (3 g.) was distilled at 0.5 mm. and some of the phosphate was obtained, but this was found to be contaminated with phenol produced by decomposition of the phosphate.

In a further experiment, a small amount of the phosphate was distilled in a sausage flask using a mercury diffusion pump (5×10^{-3} mm.). The oily distillate was almost colourless, but darkened to yellow, then brown, on standing [Found: C, 63.1; H, 5.2; P, 10.3%. $C_{17}H_{19}O_3P$ requires C, 64.2; H, 6.0; P, 9.6%].

Reaction between Bromine and 3,3-Dimethylallyl Diphenyl Phosphate:

(i) In solvent: When the phosphate was treated with excess bromine in carbon tetrachloride, or in glacial acetic acid, there were no crystals formed on standing at room temperature.

(ii) No solvent: The phosphate (3.18 g., 0.01 mole) was treated with bromine (10 g., 0.06 mole) and the mixture stood at room temperature for 5 days, before diluting with chloroform (2 ml.) and filtering the white crystals which had formed (from which adsorbed bromine had to be drawn off). The product was recrystallized twice from chloroform (small volume), and was found to be acid to litmus, and to effervesce with N-sodium bicarbonate. It was then identified as di-p-bromophenyl phosphate (100 mg.), m.p. 163.5-165.5°C; $\lambda_{max.}^{EtOH}$ 223 (ε , 5610), 273 (ε ,765) mμ ; ($\nu_{max.}^{KCl}$ see Table C), τ TDF -0.9 (-$\overset{O}{\overset{\|}{P}}$-OH), + 2.65 (para di-substit.benzene, quartet). This substance was found to have the same infrared spectrum as a genuine sample of di-p-bromophenyl phosphate, m.p. 162-164°C, obtained by alkaline hydrolysis of di-p-bromophenyl phosphorochloridate.

The chloroform filtrates from the initial recrystallisations were then chromatographed on alumina, with petrol (40-60°C), to produce a mixture of volatile liquids, which was found to consist of several volatile components (g.l.c) (approximate b.p. 120°C). These liquids gave only saturated hydrocarbon,

or halide, bands in the infrared, and did not possess bands due to hydroxyl, carbonyl, olefin or aryl groups. The nature of these products was not further investigated.

Reaction between Phenol and 3,3-Dimethylallyl Diphenyl Phosphate (51):

(i) Reaction in Phenol: The phosphate (1.6 g., 0.005 mole) was dissolved in phenol (2.35 g., 0.025 mole), and the mixture heated in a sealed flask for 24 hr. at 120°C. A g.l.c. trace showed that two peaks were present, and that the lesser of these was a volatile compound, less volatile than the other, which was unchanged phenol. The crude mixture was poured into 5N-sodium hydroxide (20 ml.) and extracted with ether (20 ml.). After washing, and drying, the ether extract yielded a pale yellow oil (1.05 g.), which was distilled from an oil bath (130°C) at 12 mm./Hg., to yield a colourless oil which was identified as 2,2-dimethylchroman (0.222 g., 27%); $\nu_{max.}^{I.R.}$ 2985, 2941, 2857 (all CH_3, CH_2 bands), 1387 and 1370 (gem $CH_3-\overset{|}{C}-CH_3$), 1258 (chromman), 1220, 1157, 1124, 949, 756 (ortho di-substituted benzene). The residue from the distillation was found to be unchanged phosphate (0.80 g., 50%).

The alkaline extract (above) was acidified with dilute hydrochloric acid, extracted with ether (50 ml.) and this ether

extract washed with N.sodium bicarbonate and water, before drying. The only product was phenol.

The dimethylchroman (t = 2.80 min.) was then calibrated at 190°C against phenol (t = 1.13 min.) and the amount present after 24 hours was found to be equivalent to a yield of 46%. At no stage during the reaction was there any evidence of intermediates between phenol and 2,2-dimethylchroman being present.

(ii) Reaction in Phenol in the Presence of Sodium Bicarbonate: The phosphate (1.6 g., 0.005 mole) was dissolved in phenol (2.35 g., 0.025 mole) and solid sodium bicarbonate (0.42 g., 0.005 mole) added. The mixture was then heated at 120°C in a loosely-sealed flask for 24 hr. The reaction followed the same path as in the system without the added bicarbonate. The neutral product was identified as 2,2-dimethylchroman, and g.l.c. traces showed the final yield to be 49%.

Reaction between Sodium Phenoxide and 3,3-Dimethylallyl Diphenyl Phosphate (51).

The phosphate (6.36 g., 0.02 mole) was dissolved in 80-100°C petrol (redistilled, 20 ml.) and then heated to 100°C under reflux after adding solid sodium phenoxide (2.32 g., 0.02 mole). Heating was continued for 6 hr. before pouring the yellow solution and white suspended solid into dilute hydrochloric acid,

and extracting with ether. The ether extract was washed with N. sodium bicarbonate (50 ml.), and then with 2N sodium hydroxide (2 x 50 ml.), and water before drying. The combined sodium hydroxide extracts were acidified and extracted with ether, and this ether extract washed and dried.

The 'neutral' ether extract yielded an oil (4.6 g.), which contained considerable amounts of unchanged phosphate (infrared), along with three volatile fractions with retention-times of 1.38, 1.90 and 3.37 min. at 188°C. The 'phenolic' ether extract contained only phenol (0.76 g.), retention-time 1.19 min., identified by comparison with a standard containing phenol (1.19 min.) and 2,2-dimethylchroman (2.97 min.) and run at the same temperature. The recovery of phenol represents a return of 81%.

Reaction between p-Hydroxyacetanilide and 3,3-Dimethylallyl Diphenyl Phosphate (51): p-Hydroxyacetanilide (5.1 g., 0.034 mole) and 3,3-dimethylallyl diphenyl phosphate (10.6 g., 0.033 mole) were heated together in a sealed flask at 85°C for 15 hr. The red-brown mixture was diluted with ether (75 ml.) and the resulting precipitate removed by filtration, and identified as unchanged p-hydroxyacetanilide (1.14 g., 26% return) m.p. 167-170°C (lit. 168°C). The ethereal solution was then extracted with N. sodium bicarbonate (2 x 50 ml.), 2N sodium hydroxide (75 ml.),

2N hydrochloric acid (50 ml.) and water, before drying over anhydrous magnesium sulphate. The residual red oil (10.9 g.) was chromatographed on alumina (300 g.) with petrol (40-60°) - ether (3:1) solvent.

Traces of hydrocarbon material (0.1 g.) were eluted with ether in petrol. The next eluant, with pure ethyl acetate as solvent, was a very viscous colourless oil, which solidified, m.p. 85-105°C on standing overnight. This solid was recrystallised twice from petrol-benzene solution and was then identified as 2,2-dimethyl 6-acetamidochroman, m.p. 113.5-114°C (2.63 g., 36%) [Found: C,71.3; H,7.8; N,6.5%. $C_{13}H_{17}NO_2$ requires C,71.2; H,7.8; N,6.4%].

The following spectra data was obtained: $\lambda_{max.}^{EtOH}$ 211 (ε, 12100), 255 (ε, 10400) mμ; ν_{max}^{KCl} 3322 (amide -NH-), 1664 (amide -$\overset{|}{C}$=O), 1558 (amide -NH-), 1387 and 1370 (gem. CH_3-$\overset{|}{C}$-CH_3), 1253 (chroman), 820 (1:2:4-trisubstituted benzene) cm.$^{-1}$ (see table (B), page 101, for the n.m.r. spectrum).

Reaction between 3,3-Dimethylallyl Diphenyl Phosphate and Hydroquinone:

(i) No solvent: Hydroquinone (2.2 g., 0.02 mole) and 3,3-dimethylallyl diphenyl phosphate (6.4 g. 0.02 mole) were heated for 30 hr. at 100°C in a sealed flask, the mixture changing from pale yellow to dark brown in colour. The mixture was diluted with ether (50 ml.) and extracted with N sodium bicarbonate (50 ml.)

2N sodium hydroxide (2 x 25 ml.) and water before drying over anhydrous magnesium sulphate. The residue of the ether solution was unchanged phosphate (2.75 g., 43% return). The sodium bicarbonate extract yielded diphenyl phosphate (2.0 g., 40%).

The alkaline extract was acidified and extracted with ether. The product from this extraction (2.04 g.) was a dark-red oil, which was chromatographed on alumina (60 g.). The first eluant, with ethyl acetate, was a discoloured solid, m.p.65-70°C., which was recrystallised from 40-60°C petrol (3 times), and which was found to be 2,2-dimethyl-6-hydroxychroman, m.p. 74-75°C, (0.6 g., 17%); $\lambda_{max.}$ 298 mμ (ε, 3500); $\nu_{max.}^{KCl}$ 3215, 1350, 1198 (all phenolic -OH), 1377, 1364 (both CH_3-$\overset{|}{C}$-CH_3), 1214 (chroman), 1025, 1012, 817 (all 1214 tri-substituted benzene). The n.m.r. spectrum is detailed in Table [B] (page 101).

A sample of the product was sublimed from a water-bath (50°C) at 1.0 mm., m.p. 74.5-75.0°C. [Found: C,74.1; H,8.2%. $C_{11}H_{14}O_2$ requires C,74.1: H,7.9%]

(ii) <u>Reaction in Presence of Sodium Bicarbonate:</u> Hydroquinone (1.1 g., 0.01 mole), 3,3-dimethylallyl diphenyl phosphate (3.18 g., 0.01 mole) and sodium bicarbonate (0.84 g., 0.01 mole) were heated together in a sealed flask at 100°C for 30 hr. before adding 50 ml. ether and extracting as above. The phenolic products were found to be 2,2-dimethyl-6-hydroxychroman (0.27 g., 15%), m.p. 73-75°C, and hydroquinone (0.5 g., 45% return), both isolated

from alumina chromatography of the sodium hydroxide extract.

The neutral products (2.0 g.) from the ether solution were separated by alumina chromatography (60 g.) and the first eluant with ether was a white solid, m.p. 155-157°C, which was found to be a di-(2,2-dimethyl)chroman of hydroquinone, (50 mg. 2%); $\lambda_{max.}^{EtOH}$ 299 mμ (ε, 2900); $\sigma_{max.}^{KCl}$ 1386, 1366 (gem- CH_3-$\overset{|}{C}$-CH_3); τ^{CCl_4} 3.6 (doublet, aryl H), 7.4 (triplet, $ArC\underline{H}_2$-CH_2-), 8.5 (triplet, Ar-CH_2-$C\underline{H}_2$-) and 8.75 (Ar-O-$\overset{|}{C}$-CH_3). The second eluant with ether was unchanged phosphate (30% return).

(iii) Reaction with Excess Phosphate: Hydroquinone (0.66 g., 6 x 10^{-3} mole) and 3,3-dimethylallyl diphenyl phosphate (3.84 g., 12 x 10^{-3} mole) were heated at 100°C for 13 hr. in a sealed flask. Soon after heating commenced the quinol dissolved and the mixture remained homogeneous. The product was dissolved in ether, extracted with N. sodium bicarbonate, and the ether residue (2.2 g.) chromatographed on alumina (65 g.). With petrol-benzene (4:1), a white solid was obtained which had the same spectral characteristics as the above dichroman. The dichroman was dublimed, m.p.157-158°C [Found: C,78.3; H,9.2%. $C_{16}H_{22}O_2$ requires C,78.0; H,8.9%].

Oxidation of 2,2-Dimethyl-6-hydroxychroman in Aqueous ethanol with Ceric Sulphate:[127]

2,2-Dimethyl-6-hydroxychroman (96) (72 mg., 4.05×10^{-4} mole) was dissolved in ethanol (3 ml.), and 0.1N ceric sulphate in sulphuric acid (4 ml.) was added. The mixture went cloudy instantly and then the colour changed from yellow to orange-yellow as the cloudiness cleared. The mixture was stood for five min. before extracting the product with ether, and washing the extract with sodium bicarbonate and water. Evaporation of ether from the dried extract yielded a red-orange oil (78 mg.), which was identified as 3'-hydroxy-3'-methyl-butyl p-benzoquinone (97) from its spectral data.

The infrared spectrum showed $\nu_{max.}^{L.F.}$ 3401 (-OH), 2976 (CH_3-), 2933 ($-CH_2-$), 1658 (p-quinone), 1383 and 1368 ($CH_3-\overset{|}{C}-CH_3$), 1242, 1198, 1157, 1124, 925, 893, 811, 793 cm.$^{-1}$ The n.m.r. spectrum showed τ^{CCl_4} 3.5 (aryl H [3]), 7.4 ($Ar-\underline{\underline{CH_2}}-CH_2-$, triplet [2]), 8.2-8.3 ($ArCH_2-\underline{\underline{CH_2}}$, triplet; and -C-OH, singlet; [3]) 8.75 ($CH_3-\overset{|}{C}-O-$, [6]).

Reaction between 2,5-Dimethylhydroquinone and 3,3-Dimethylallyl Diphenyl Phosphate:

2,5-Dimethylhydroquinone (0.69 g., 0.005 mole) and 3,3-dimethylallyl diphenyl phosphate (1.59 g., 0.005 mole) were heated in a sealed flask at 100°C for 44 hr. The semi-solid, black, tar was then taken up in ether (10 ml.) and the insoluble solid (0.42 g.) filtered off. The solid fraction showed one very

mobile and one fairly mobile spot on a T.L.C. plate (ether-benzene (1:1)on alumina), and the filtrate showed one mobile, three fairly mobile, and two very polar spots.

The solid fraction was then chromatographed on alumina (12 g.) with benzene and the first product was a white solid, which, after recrystallisation from methanol, was identified as the di (2,2-dimethyl)chromam of p-xyloquinone (0.24 g.), m.p. 192-194°C [lit. 193-196°C]; $\lambda_{max.}^{EtOH}$ 214 (ε, 32400), 302.5 (ε, 8210) mμ; $\nu_{max.}^{KCl}$ 1373, 1360, (both $CH_3-\overset{|}{C}-CH_3$), 1260, 1214, 1130, 1112, 1053, 1010, 953; τ^{CDCl_3} 7.2-7.8 ($ArCH_2-CH_2-$; triplet), 8.0 ($ArCH_3$), 8.1-8.7 ($ArCH_2-CH_2-$; triplet), 8.7 ($CH_3-\overset{|}{C}-O-$). A further small amount (0.167 g.) of the same dichromam was obtained from the filtrate, thus the total dichromam yield is 0.41 g. (59%). With benzene-ether (4:1) solvent 2,5-dimethylquinone was eluted from the column.

The filtrate was also chromatographed on alumina (50 g.) with benzene, to remove the dichromam (above), then with benzene-ether (9:1) to remove unchanged phosphate (32 mg., 2%), and with benzene-ether (4:1) to remove 2,5-dimethylquinone, m.p. 123-125°C [lit. 125°C] and an unknown red oil. This red oil was then rechromatographed on alumina with benzene, and separated into a yellow solid, 2,5-dimethylquinone, and a viscous oil, which solidified, m.p. 80-85° on standing. The solid was recrystallised

from petrol (40-60°C) and found to be 2,2,5,8-tetramethyl-6-hydroxychroman (89) (77 mg., 8%), m.p. 89-90°C [lit. 78°C][124] $\lambda_{max.}^{EtOH}$ 213 (ε, 11600), 297 (ε, 4200) mμ; $\nu_{max.}^{L.F.}$ 3333 (OH), 1377 and 1361 (CH_3-$\overset{|}{\underset{|}{C}}$-$CH_3$), 1230, 1212, 1157, 1116, 919, 893, 866 cm.$^{-1}$ The n.m.r. spectral data is recorded in Table [B], page 101.

Reaction between 2,3,5-Trimethylhydroquinone (21) and 3,3-Dimethylallyl Diphenyl Phosphate (51):

2,3,5-Trimethylhydroquinone (1.52 g., 0.01 mole) and 3,3-dimethylallyl diphenyl phosphate (3.18 g., 0.01 mole) were heated at 100°C in a sealed flask, until the mixture had become a uniform viscous, red oil (6 hr.). The mixture was dissolved in ether (20 ml.) and extracted with N-sodium bicarbonate (20 ml.), before chromatographing on alumina (100 g.). The first eluant, with ether solvent, was a reddish oil, which solidified on standing, m.p. 88-94°C., and this was recrystallised from petrol (40-60°C) and found to be 2:2:5:7:8-pentamethyl-6-hydroxychroman (29) (1.6 g., 74%), m.p. 93.5-94.5 [lit.94-95°C][43] as white needles; $\lambda_{max.}^{EtOH}$ 215 and 292 mμ; $\nu_{max.}^{KCl}$ 3322 (-OH), 1385 and 1370 (gem. CH_3-$\overset{|}{\underset{|}{C}}$-$CH_3$), 1261 (chroman), 1224 (phenolic OH) cm.$^{-1}$ (see Table [B] page 101 for the n.m.r.).

Reaction between 2,3,5-Trimethylhydroquinone (21) and Geranyl Diphenyl Phosphate (43):

2,3,5-Trimethylhydroquinone (3.04 g., 0.02 mole) and geranyl

diphenyl phosphate (7.72 g., 0.02 mole) were heated at 100°C in a sealed, silvered flask for 12 hr. The crude, red oil was then extracted from an ether (50 ml.) solution, with N-sodium bicarbonate (50 ml.) and water (50 ml.), before drying over anhydrous magnesium sulphate and evaporating the solvent. The red oil showed three major and three minor spots on a silica T.L.C. plate (petrol solvent, iodine detection), and the oil (7.4 g.) was chromatographed on alumina (23 g.) with petrol (40-60°C). The petrol eluants were all viscous, almost colourless oils which were found to be hydrocarbons (0.7 g., 26%), presumably formed by decomposition of the phosphate. The benzene eluant was principally unchanged phosphate (1.72 g., 23%). The ether eluant was a red oil which was rechromatographed on alumina. The first product of rechromatography was a yellow, low-melting solid, m.p. 30-32°C [lit. 32°C] found to be 2,3,5-trimethylquinone (0.12 g., 4%); $\lambda_{max.}^{EtOH}$ 210, 255, 338, 450 mμ; $\nu_{max.}^{L.F.}$ 1653 (quinone) cm.$^{-1}$; τ^{CCl_4} 3.6 (aryl), 7.95-8.00 (CH_3-Ar). The second product from the rechromatography was a pale red oil, which, after purification by short-path distillation (0.01 mm. Hg.), was found to be 6-hydroxy-2,5,7,8-tetramethyl-2-(4'-methyl-pent-3'-enyl)chroman (0.57 g., 20%); [Found: C,79.2; H,9.7%. $C_{19}H_{28}O_2$ requires C,79.1; H,10.0%]; $\lambda_{max.}^{EtOH}$ 213.5 mμ (ε, 20000), 293 mμ (ε,4000); $\nu_{max.}^{L.F.}$ 3497 (OH), 2941, 1449 and 1381 (all CH_3-$\overset{|}{\underset{|}{C}}$-), 1339 (phenolic-OH), 1256

(chroman), 1212 (phenolic-OH), 1168, 1087 cm.$^{-1}$ (see table [B], page 101, for n.m.r.). It is proposed to call the chroman product geropherol.

Preparation of Geropherol 3,5-Dinitrobenzoate: Geropherol (0.81 g., 2.8×10^{-3} mole) and excess 3,5-dinitrobenzoyl chloride (1.95 g., 8.4×10^{-3} mole) were refluxed for ½ hr. in pyridine (10 ml., dried), before taking up in ether (50 ml.) and washing with N-sodium bicarbonate (50 ml.), 5N sulphuric acid (25 ml.) and water. Evaporation of the ether from the dried solution (anhydrous magnesium sulphate) yield a red froth, m.p. 174-185°C, which showed 4 spots on a T.L.C. plate (benzene solvent, iodine detection). This solid was then recrystallised from petrol (40-60°C) before rechromatographing on silica with petrol. The first yellow band was identified as the 3,5-dinitrobenzoate of geropherol, m.p. 193-196°C; $\nu_{max.}^{KCl}$ 1742 (benzoate-$\overset{|}{C}$ = O), 1548 (aryl NO_2), 1344 (aryl NO_2), 1272 and 1164 (benzoate), 920, 730, 720 cm.$^{-1}$ [Found: C, 64.8; H, 6.5; N, 6.0 %. $C_{38}H_{50}N_2O_7$ requires C, 64.7; H, 6.2; N, 5.8%].

Preparation of α-Tocopherol (18): Phytyl diphenyl phosphate (90%) was prepared from phytol and diphenylphosphorochloridate in the same manner as 3,3-dimethylallyl- and geranyl diphenyl

phosphates. The product was extracted as quickly as possible and dried over magnesium sulphate in a refrigerator, and, after evaporating the ether at 35°C, the phosphate was used as quickly as possible. The phytyl diphenyl phosphate (2.64 g., 0.005 mole) was added to 2,3,5-trimethylhydroquinone (0.76 g., 0.005 mole), and the two heated at 100°C in a sealed, silvered, flask for 6 hr. The mixture was dissolved in ether (50 ml.) and extracted with N-sodium bicarbonate (50 ml.), and water, then dried over anhydrous magnesium sulphate, before evaporating the solvent to yield a red oil.

The oil (2.01 g.) was chromatographed on silica (60 g.) with petrol (40-60°C), which eluted traces of hydrocarbons (infrared evidence). Benzene as solvent eluted a pale-red oil (2.01 g.) which had an infrared spectrum almost identical to α-tocopherol. This fraction was then rechromatographed on alumina, and, with benzene-ether (9:1), the very pale yellow oil eluted was found to be α-tocopherol (18), (1.6 g., 70%); $\lambda_{max.}^{EtOH}$ 218, 294 (ε, 2500); $\nu_{max.}^{L.F.}$ 3509 (-OH), 2941 (CH_3-), 1460 and 1379 (CH_3-$\overset{|}{C}$-), 1258 (chroman), 1212, 1157, 1081 (chroman), 915, 862 $cm.^{-1}$ (see table B, page 101, for the n.m.r. spectrum). This data agrees with that available in the literature.[40]

Preparation of Di-p-Nitrophenyl Phosphate.[162] Phosphorus oxychloride (31.0 g., 0.2 mole) and p-nitrophenol (31.6 g., 0.4 mole) were dissolved in a mixture of dry acetonitrile (60 ml.) and dry benzene (480 ml.), and pyridine (24 ml., 0.3mole

was added dropwise over 20 min. to the stirred mixture. Stirring was continued for a further 5 hr. before filtering the pyridine hydrochloride precipitate, and concentrating the filtrate to dryness. The resulting solid was dissolved in chloroform (100 ml.), 5N sodium hydroxide added (160 ml.) and the mixture shaken until the sodium salt precipitated. The filtered, crude salt was dissolved in warm water and the insoluble tri-sodium salt filtered off. The filtrate was acidified with concentrated hydrochloric acid and the precipitated di-p-nitrophenyl phosphate collected, m.p. 176-178°C [lit.178°C].

Preparation of Di-p-Nitrophenyl Phosphorochloridate[136] (106): Di-p-nitrophenyl phosphate (4 g., 1.10×10^{-2} mole) was suspended at 0°C in dry chloroform (10 ml.), and the mixture stirred in a flask protected by a drying tube. Phosphorus pentachloride (2.8 g., 1.6×10^{-2} mole) was added in one batch and the mixture stirred until most of the solid had disappeared (2½ hr.). Petrol (30 ml., 60-80°C) was then added and the mixture scratched until crystals began to appear on the sides of the flask. The crystals were filtered, recrystallised by adding petrol (60-80°C) to a hot chloroform solution, and identified as di-p-nitrophenyl phosphorochloridate (106) (3.6 g. 85%), m.p. 96-97°C [lit. 97°C].

Preparation of 3,3-Dimethylallyl Di-p-Nitrophenyl Phosphate (105): Di-p-nitrophenyl phosphorochloridate (7.2 g., 0.02 mole) was ground thoroughly and added to a mixture of 3,3-dimethylallyl

alcohol (1.72 g., 0.02 mole) in anhydrous ether (10 ml.). Considerable heat was evolved and the mixture was cooled in an ice-bath to 0°C. Pyridine (dried and redistilled; 3.2 ml., 0.04 mole) was added dropwise at 0°C over ½ hr. while the solution was stirred, and stirring was continued for 1½ hr. The mixture was treated with ether (50 ml.) and washed with 2N sulphuric acid, N-sodium bicarbonate and water before drying and evaporating the ether. The product was a viscous, pale-yellow oil (1.3 g.; 16%) which was used immediately in any subsequent reaction.

Reaction between 2,3,5-trimethylquinol (21) and 3,3-Dimethylallyl Di-p-Nitrophenyl Phosphate (105): The phosphate (3.3 g., 0.008 mole) and the quinol (1.21 g., 0.008 mole) were heated together at 80°C for 6 hr. in a sealed flask, until the mixture had become a homogeneous red tar. The tar was then chromatographed directly on alumina (140 g.) with ether solvent. The first fractions were colourless hydrocarbons (traces), but the next fraction was a yellow oil (0.8 g.) which was found to be a complex mixture [T.L.C. in petrol-ether(1:1) solvent] and which had strong absorption in the carbonyl region of the infrared. This fraction (0.75 g.) was rechromatographed on alumina with petrol (40-60°C)-ether (20:1), and the first fraction gave 2 spots on T.L.C (as above). The spectral characteristics of this yellow oil were as follows; $\nu_{max.}^{L.F.}$ 3268 (very weak, sharp),

2967 (CH_3-), 2933 (-CH_2-), 1639 (-$\overset{|}{C}$=O), 1449 (CH_3-), 1375 (CH_3-C-), 1304, 827, 716 (cis-CH=CH-) cm.$^{-1}$; τ CCl_4 5.3 (CH_2=C-), 8.0 ($ArCH_3$), 8.2, 8.35 (CH_3-C=C-).

The original column gave 2,2,5,7,8-pentamethyl-6-hydroxychroman (29), (1.76 g., 50%), m.p. 90-93°C (recryst. from petrol) with ether-ethyl acetate (4:1) solvent.

Oxidation of 2,2,5,7,8-Pentamethyl-6-hydroxychroman (29).

(a) Manganese Dioxide in Benzene: The chromanol (0.44 g., 0.002 mole) was dissolved in benzene (25 ml. dry) and manganese dioxide (0.85 g., 0.01 mole) added. The stoppered flask was then shaken at room temperature (18°C) for 24 hr., and a T.L.C. (1,1-benzene-ether, ultraviolet detection) plate showed seven spots, three of which were strong (one of these being considerably less polar, and one more polar, than the starting material). The crude product, a yellow oil, was then chromatographed on alumina with benzene, and only two pure fractions (T.L.C.) were isolated.

The first was eluted with benzene-ether (20:1) as a yellow oil (15 mg.); $\lambda_{max.}^{EtOH}$ 215 (ε, 7300), 298 (ε, 900), 350 (ε, 300), 393 (ε, 105) mμ; $\nu_{max.}^{L.F.}$ 1678, 1661, 1600, 1418, 1379 and 1368 (CH_3-$\overset{|}{C}$-CH_3), 1261 (chroman), 1166, 1095 cm.$^{-1}$

The second product was eluted with benzene-ether (1:1) as another yellow oil (120 mg.); $\lambda_{max.}^{EtOH}$ 208 (ε, 140), 268 (ε, 4300) 343 (ε, 1500), 393 (ε, 50); $\nu_{max.}^{L.F.}$ 3584 (OH), 1645 (strong, $\overset{|}{C}$ = O),

1380 and 1370 ($CH_3-\overset{|}{C}-CH_3$), 725 cm.$^{-1}$; τ^{CCl_4} 8.0 ($Ar-CH_3$, [9]), 8.7 ($CH_3-\overset{|}{C}-O-$, [6]). There were no further pure eluants from the column.

(b) Silver Dioxide in Benzene: The chromanol (29) (2.20 g., 0.01 mole) was dissolved in dry benzene (15 ml.) and silver dioxide (2.4 g., 0.01 mole) added. The flask was stoppered and shaken for 1 hr (at room temperature) during which small samples were withdrawn for T.L.C. (benzene-ether, 50:1; U.V. detection). The T.L.C. showed that the starting material was consumed quickly, so that after 30 min. shaking only small traces were left. At the same stage, the solid had become predominantly grey, indicating that little silver dioxide remained. After 1 hr., a T.L.C run showed that the orange colour in solution was due to two spots, both orange-yellow in colour, and that there were seven products in all, two major spots (indicating a yellow one) being less polar than starting material, and one (the other yellow one) major one being the most polar product. The crude mixture was filtered, the benzene evaporated, and the residual red oil dissolved in 40-60 petrol (2 ml.) for chromatography on alumina (60 g.).

The first eluant, obtained with petrol-ether (10:1) solvent, was a yellow oil, which was found to contain only the two major, non-polar products, and this was rechromatographed

on alumina. With petrol-ether (50:1) the product was a white froth which recrystallised from methanol (3 times) as a white, crystalline solid (0.24 g., 11%), m.p. 216.5-217.5; $\lambda_{max.}^{EtOH}$ 215 mμ (ε ,2800; based on M,430)and 294 mμ (ε, 5370) mμ; $\nu_{max.}^{KCl}$ 2950 (CH_3), 1698 (strong,-C=O), 1650 (weak), 1381 and 1372 (CH_3-C-CH_3), 1267 (chroman), 1227, 1167, 1125, 1093, 1020, 976 cm.$^{-1}$; τ ^{CDCl_3} 7.7-7.9 (CH_3-Ar), 8.7 (CH_3-C-O-). [Found: C,76.12; H,9.12; M,430 (osmotic method), and M,238 (benzene). $C_{14}H_{20}O_2$ requires C,76.30; H,9.09; M,220. $(C_{14}H_{18}O_2)_n$ requires C,77.0; H,8.25; M, n = 218].

(c) Dichloro Dicyano Quinone (99) in Ether: The chromanol (29) (0.44 g., 0.002 mole) was dissolved in anhydrous ether (10 ml.) and dichloro dicyano quinone added (0.45 g., 0.002 mole). The mixture was shaken for 10 min. and T.L.C. [benzene-ether (50:1) solvent; U.V. detection] runs made to follow the progress of the reaction After 10 min. there were only traces of chromanol left and the main product was less polar than the chromanol. The precipitated dichloro dicyano quinol (0.31 g., 68%) was removed by filtration and the ether evaporated. The product was then chromatographed on alumina using benzene.

The first eluant was a pale cream solid (0.272 g.) which was recrystallised from methanol as a white powder (0.22 g., 50%), m.p. 167-169°C; $\lambda_{max.}^{EtOH}$ 216, 226 and 297 mμ

$\nu_{max.}^{KCl}$ 2970 (CH_3), 1712, 1639, 1580, 1431, 1418, 1387 and 1372 (CH_3-$\overset{|}{C}$-CH_3), 1261 (chroman), 1166, 1130, 1091 cm.$^{-1}$; τ $CDCl_3$ 4.1, 4.8 (doublets of equal intensity, J, 1.6 c/s, [2]) 7.1-7.7 (Ar$\underset{\text{max.}}{CH_2}$-$CH_3$-), 7.95 ($CH_3$-Ar, [12]), 8.10 8.2-8.5 ($\underset{\text{max.}}{CH_2}$-$\overset{|}{C}$-Ar) 8.55, 8.70 ($CH_3$-$\overset{|}{C}$-O-, [18]). The molecular weight (benzene) was found to be 230.

There was no further major product from the alumina column.

Reaction between Phloroglucinol and 3,3-Dimethylallyl Diphenyl Phosphate (51): Phloroglucinol dihydrate (1.26 g., 0.0078 mole) was heated with 3,3-dimethylallyl diphenyl phosphate (3.18 g., 0.01 mole) in a sealed flask at 100°C for 8 hr., after which the mixture was taken up in ether (50 ml.) and extracted with N-sodium hydroxide (25 ml.) and water (25 ml.), before drying over anhydrous magnesium sulphate. The red oil (2.4 g.) was then chromatographed on alumina (70 g.) using ether solvent.

The first eluant, with ether, was rechromatographed using petrol (40-60°C), producing a colourless viscous oil, which solidified on standing, and which, after recrystallisation from aqueous ethanol, was identified as the tri(2,2-dimethyl) chroman of phloroglucinol (0.29 g., 26%), m.p. 100-102°C [lit. 104°C]^{102} $\lambda_{max.}^{EtOH}$ 215 (ε, 20000), 296 (ε, 1250) mμ; $\nu_{max.}^{liq.}$ 2950, 2862 (CH_3- and -CH_2-), 1616 (aryl C=C), 1387 and 1370 (gem. CH_3-$\overset{|}{C}$-CH_3), 1159 and 1121 (both chroman, strong) cm.$^{-1}$;

τ^{CCl_4} 7.5 ($ArCH_2-\overset{|}{C}-$, [6]), 8.3 ($Ar-\overset{|}{C}-CH_2-$, [6]), 8.9 ($CH_3-\overset{|}{C}-O-$, [18]).

The second eluant, with ether, was rechromatographed with petrol (40-60°C) -benzene (1:1) to give traces of a phosphate (0.09 g., 3%). The third eluant, obtained with ether-ethyl acetate (4:1) solvent, was recrystallized from aqueous ethanol as white needles, or from petrol (40-60°C) as colourless, square prisms, and found to be a di-(2,2-dimethyl)chroman, m.p.157.5-158°C, (0.32 g., 25%); $\lambda_{max.}^{EtOH}$ 215 (ε, 20800), 275 (ε, 1310); $\nu_{max.}^{KCl}$ 3472 (OH stretch), 1629 and 1592 (aryl C-C), 1381 and 1360 (gem. $CH_3-\overset{|}{C}-CH_3$), 1156, 1119, 829, 806 cm.$^{-1}$ τ^{CCl_4} 4.1 (aryl H), 5.3 (aryl -OH), 7.4 ($ArCH_2-CH_2-$, triplet), 8.2 ($Ar-CH_2-CH_2-$, triplet), 8.7 ($CH_3-\overset{|}{C}-O-$). This dichroman did not give a pink colouration[162] when treated with ferric chloride.

The final products, using ethyl acetate solvent, were red oils or foams which could not be recrystallized. The solid foams could be ground, m.p. 125-128°C, and the infrared spectrum showed them to contain strong -OH absorption, but neither this, nor the n.m.r. spectrum permitted their structures to be assigned.

Reaction of Orcinol (5-Methyl Resorcinol)[88] with 3,3-Dimethylallyl Diphenyl Phosphate (51): Orcinol hydrate (2.84 g., 0.02 mole) and 3,3-dimethylallyl diphenyl phosphate (6.36 g., 0.02 mole) were heated in a sealed flask at 100°C for 16 hr. The crude red oil was taken up in ether (50 ml.) and extracted with N.sodium

bicarbonate (50 ml.), washed, and dried, before evaporating the ether. The resultant red oil (5.3 g.) was chromatographed on alumina (150 g.), after a preliminary T.L.C. run (benzene, silica) had shown three main spots to be present, and well separated.

With benzene-ether (1:1) solvent a colourless oil (1.14 g.) was eluted. This oil solidified, and was sublimed at 0.01 mm. to give a white solid, m.p. 118-119°C, identified as a di(2,2-dimethyl)chroman of orcinol (22%) [Found C,78.1; H,8.9. $C_{17}H_{24}O_3$ requires C,78.4; H,9.2%]. The U.V. spectrum showed $\lambda_{max.}^{EtOH}$ 213 mμ (ε, 9030) and 285 mμ (ε, 1530). The infrared spectrum showed $\nu_{max.}^{KCl}$ 1387, 1370 (both $CH_3-\overset{|}{C}-CH_3$), 1159, 1129 (chroman), 992, 886, 840 cm.$^{-1}$ The n.m.r. spectrum showed τ^{CCl_4} 4.05 (aryl H, [1]) 7.50 ($ArCH_2-CH_2-$, triplet [4]), 8.0 ($ArCH_3$, [3]), 8.30 ($Ar-\overset{|}{C}-CH_2$, [4]), 8.80 ($CH_3-\overset{|}{C}-O-$, [12]).

With ether as solvent, a pale red oil was eluted, which had similar infrared characteristics to a second oil, eluted with ether-ethyl acetate (9:1). The fractions containing these oils were rechromatographed on alumina, and a separation achieved with ether solvent. The first oil showed $\lambda_{max.}^{EtOH}$ 213 mμ (ε, 22,000) and 293 mμ (ε, 2400) in the ultraviolet. The infrared spectrum showed $\nu_{max.}^{L.F.}$ 3333 (-OH), 1618, 1575 (aryl C=C), 1379 and 1368 ($CH_3-\overset{|}{C}-CH_3$), 1230, 1160, 1119, 1058, 995, 873 and 821 cm.$^{-1}$

The n.m.r. spectrum is detailed in Table [B] (page 101). This data identified the oil as 2,2,7-trimethyl-5-hydroxychroman (0.37 g., 10%) [Found: C,74.3; H,8.7. $C_{12}H_{16}O_2$ requires C,75.0; H,8.3%].

The second oil was obtained in greater amounts, and was purified further by sublimation at 0.05 mm. The ultraviolet spectrum showed $\lambda_{max.}^{EtOH}$ 214 mμ, and 283 mμ. The infrared spectrum showed $\nu_{max.}^{L.F.}$ 3390 (-OH), 1616 and 1597 (aryl C = C), 1383 and 1368 (CH_3-ϕ-CH_3), 1318 (-OH), 1161, 1142, 1117, 1057, 990, 873, 838 and 755 cm.$^{-1}$. The n.m.r. spectrum is detailed in Table [B] (page 101). This data identified the oil as 2,2,5-trimethyl-7-hydroxychroman (0.72 g., 19%) [Found: C,74.8; H,8.5. $C_{12}H_{16}O_2$ requires C,75.0; H,8.3%]

Reaction between Orcinol (5-Methyl Resorcinol) (88) and Farnesyl Diphenyl Phosphate (94): Farnesyl diphenyl phosphate was prepared in the same way as geranyl diphenyl phosphate, and was isolated as a colourless, viscous oil (46% yield) and was used immediately in the reaction with orcinol.

Orcinol (1.31 g., 0.0092 mole, monohydrate) was mixed at room temperature with farnesyl diphenyl phosphate (4.18 g., 0.0092 mole) and a dark brown discolouration began to develop immediately. The reaction mixture began to heat until the orcinol monohydrate (m.p. 58°C) melted and the water of

crystallisation had been boiled off. At this stage three layers had formed, and, on shaking, these became miscible and the mixture was a dark red, viscous, homogeneous oil (time, 10 min.). The crude mixture was then sealed at 80°C and heated for 12 hr., before taking up in ether (50 ml.) and extracting with N.sodium bicarbonate (25 ml.). The ether solution was then washed with water, dried, and the solvent evaporated, leaving a red oil (4.84 g.).

The red oil was chromatographed on alumina (150 g.) with petrol (40-60°C), and the first fractions were eluted with petrol-benzene (20:1). The colourless oil (2.15 g.) appeared to consist principally of di-alkylated products, identified by the infrared spectrum which showed $\nu_{max.}^{L.F.}$ 1155, 1119, 836 cm.$^{-1}$.

The second fraction was obtained as a grey-green oil (0.696 g.) with varying proportions of benzene-ether mixtures (5:2 to 1:4), and this was rechromatographed on alumina with benzene. The bulk of this fraction was removed from the column with benzene-ether (4:1) and found to be pure on T.L.C. (benzene: ether, 5:1; silica plates). The crude, very pale-green, oil was distilled in a sublimation unit at 0.01 mm. Hg., from a bath at 70°C, and was identified as the 2-alkenyl-2,7-dimethyl-5-hydroxychroman (93). (crude yield, including that from next fraction, 0.78 g., 26%). [Found: C,80.6; H,10.5. $C_{22}H_{32}O_2$

requires C,80.5; H,9.8%]. The infrared spectrum showed $\nu_{max.}^{L.F.}$ 3412 (OH), 2923 (CH_3), 1620, 1586, 1449, 1373 (CH_3-C-), 1137, 1097, 1062, 1047, 993, 886, and 816 cm.$^{-1}$, and the U.V. spectrum $\lambda_{max.}^{EtOH}$ 213 mμ (ε, 6000) and 283 mμ (ε, 1200). The n.m.r. spectrum is detailed in Table [B], page 101. This data was comparable with that of a genuine sample of isogrifolin (95).[126]

The third original fraction was obtained as a pale red oil (1.20 g.) which contained (T.L.C. in 10% ether in benzene) a small fraction with R_f value the same as the above, and a main fraction, which was slightly more polar. The crude oil was rechromatographed on alumina (40 g.) with benzene and the initial fractions were found to be identical (I.R.) with the above 5-hydroxychroman. With benzene-ether (3:2) a main fraction was obtained as a very pale red oil and this was identified as the 2-alkenyl-2,5-dimethyl-7-hydroxychroman (95), (0.70 g., 23%). The infrared spectrum showed $\nu_{max.}^{L.F.}$ 3400 (-OH), 2940, 1600, 1462, 1380 (CH_3-$\overset{|}{C}$-), 1142, 1097, 1061, 992, 886, and 840 cm.$^{-1}$ The U.V. spectrum showed $\lambda_{max.}^{EtOH}$ 214 (ε,5600), 283 (ε,1080) mμ. The n.m.r. spectrum is detailed in Table [B] (on page 101).

The fourth and final fraction from the original column was found to be unchanged orcinol (100 mg. 10% return), eluted with ethyl acetate-methanol (20:1) solvent.

Preparation of 3,3-Dimethylallyl p-Toluene Sulphonate (103)

3,3-dimethylallyl alcohol (3.44 g., 0.04 mole) and p-toluene sulphonyl chloride (7.6 g., 0.04 mole) were cooled together to 0°C in a flask open to the air through a drying-tube. Pyridine (6.5 ml., 0.08 mole) was then added dropwise over 1½ hr. to the stirred, cooled mixture. After the pyridine was added, the mixture was stirred for a further 30 min. at 0°C, before adding ether (50 ml.) and water (50 ml.). The ether solution was then extracted successively with 2N hydrochloric acid (50 ml.), 2N sodium hydroxide (50 ml.) and water (50 ml.), before drying over anhydrous magnesium sulphate and evaporating the solvent The product was an almost colourless oil (3.11 g., 32%). The infrared spectrum showed $\nu^{Nujol}_{max.}$ 1669 (-CH=C(CH$_3$)-), 1366 and 1189 and 1176 (all sulphonate bands), 814 (p-tolyl)cm.$^{-1}$.

Reaction between 2,3,5-Trimethylquinol (21) and 3,3-Dimethylallyl p-Toluene Sulphonate (103): The sulphonate (3.1 g., 1.27 x 10^{-2} mole) were heated at 90°C in a sealed flask for 18 hr., to produce a dark red oil, which was chromatographed directly on alumina (150 g.) with ether. The first fraction yielded traces of hydrocarbons, and then a pale yellow oil with the infrared characteristics of a sulphonate was eluted (1.0 g.). Part of this oil solidified overnight, and addition of a small amount of petrol (40-60°C) caused further precipitation of the solid, which was filtered off. This solid was recrystallised from ether

and found to be 2,2,5,7,8-pentamethyl-6-p-toluenesulphonylchroman (104) (0.19 g., 4%), m.p. 157-158°C. [Found: C,67.5; H,7.2; S,8.3%. $C_{31}H_{36}O_4S$ requires C,67.4; H,7.0; S,8.5%]. $\lambda_{max.}^{EtOH}$ 230, 275 (shoulder), 288 (shoulder) mμ; $\nu_{max.}^{KCl}$ 1359 (sulphonate), 1265, 1250 (chroman), 1222, 1176 (sulphonate), 858 (p-disubstituted benzene); τ^{TDF} 2.4 (aryl H, quartet), 7.3-7.7 ($ArCH_2$- and p-tolyl CH_3), 7.9-8.1 (aryl CH_3), 8.25 ($ArCH_2$-$\underline{CH_2}$), 8.7 (CH_3-$\overset{|}{\underset{|}{C}}$-O-).

The final ether fractions yielded a red solid, which was recrystallized from petrol (40-60°C), and found to be 2,2,5,7,8-pentamethyl-6-hydroxychroman (29) (1.76 g. 62%). m.p. 91-94°C [lit. 95°C].[43]

Preparation of 2,2,5,7,8-Pentamethyl-6-p-Toluenesulphonylchroman (104): 2,2,5,7,8-Pentamethyl-6-hydroxychroman (0.22 g., 0.001 mole) was dissolved in dry pyridine (1 ml.) and added to a solution of p-toluene sulphonyl chloride (0.39 g. 0.002 mole) in pyridine (2 ml.) and the mixture heated at 80°C for 1 hr. The mixture was then poured into 2N hydrochloric acid (10 ml.) and stirred until the precipitated oil solidified. The solid was then filtered off and washed with a small volume of acetone (which removed much of the pale brown discolouration) before recrystallising from ether. The product was obtained as small white needles, m.p. 156-158°C.

Treatment of 3,3-Dimethylallyl p-Toluene Sulphonate with Alumina: 3,3-Dimethylallyl p-toluene sulphonate (80 mg.) was dissolved in (40-60°C) petrol (10 ml.) and alumina added. The mixture was stood for ten days before transferring to a column and eluting with petrol-ether (1:1) solvent. The only product identified was the unchanged sulphonate.

Stannous Chloride Reduction of 2-Methyl-1,4-naphthoquinone (22) (Menadione): 2-Methyl-1,4-naphthoquinone (17.2 g., 0.1 mole) was dissolved in hot ethanol (150 ml.) in a 600 ml. beaker, and a solution of stannous chloride (40 g., 0.18 mole, as dihydrate) in concentrated hydrochloric acid (40 ml.) added slowly, with stirring. The initial dark brown colour faded after heating for 5 min. at 60°C, leaving the solution a very pale green colour. Water (150 ml.) was then added and the mixture cooled to room temperature, and, if no crystals appeared, the solution was then evaporated on a rotatory evaporator at 60°C until crystals began to appear. After cooling, the crystals were removed by filtration, and the filtrate concentrated to produce more crystals. The crystals were then identified as 2-methyl-1,4-dihydroxy-naphthalene (91) (menadiol) (14 g., 80%), m.p. 154-157°C [lit. 159-160°C]; $\nu_{max.}^{KCl}$ 3268 (-OH), 1199 (-OH) and 757 (naphthalene).

The product was normally used directly, since it turned pink, and ultimately, a dark purple, on standing in the laboratory atmosphere. For this reason the product was never recrystallized.

and it was also deemed pure enough (no carbonyl in infrared) to use in any subsequent reaction. The yield was almost quantitative if the final filtrate was evaporated nearly to dryness.

Reaction of 2-Methyl-1,4-dihydroxynaphthalene (Menadiol) (91) with 3,3-Dimethylallyl Diphenyl Phosphate (51): The phosphate (0.954 g., 3.06×10^{-3} mole) and the diol (0.545 g., 3.16×10^{-3} mole) were sealed under nitrogen in a flask silvered with foil and heated at 100°C for 200 hr. The purple mixture showed 2 strong, non-polar, spots and 3 weak, more polar, spots on T.L.C. [benzene-methanol (50:1), iodine detection]. The infrared spectrum showed bands for OH, and two for -$\overset{\|}{C}$ =O. The crude purple mixture was the dissolved in benzene (not all of it did so) and chromatographed on alumina. The first products were menadione and traces of unchanged phosphate, but with benzene-ether (3:2) the product (0.237 g.) showed OH, and CH_3 bands, but no phosphate. An alkaline extract of this product was acidified with 2N hydrochloric acid and the precipitate taken up in ether. The resulting oil (14 mg.) showed -OH and two-$\overset{\|}{C}$=O bands in infrared. Later fractions from the column (ether solvent) were sublimed and found to be more menadione.

Reaction between of 2-Methyl-1,4dihydroxynaphalene(Menadiol) (91) and Phytyl Diphenyl Phosphate (90): Both reactants were prepared as required and used immediately. The phosphate

(2.8 g., 0.005 mole) and monadiol (0.87 g., 0.005 mole) were heated together in a sealed, silvered flask at 100°C for 5 hr. Within 15 min. of the commencement of heating, the mixture gave the appearance of viscous, but homogeneous red oil. The crude oil was taken up in ether (50 ml.) and extracted with N sodium bicarbonate (50 ml.), which caused fizzing, and water, before drying, evaporating solvent and applying the residual red oil (2.94 g.) to an alumina (100 g.) column. With petrol (40-60°C) benzene mixtures (9:1 to 3:2) the first three fractions appeared to be hydrocarbons, together with a carbonyl containing compound, which was present in the original crude phytol ($\nu^{L.F.}_{max.}$ 1742 cm.$^{-1}$). With petrol (40-60°C)-benzene mixtures (1:1 to 1:3), the eluant was a yellow-red oil, which showed a very strong band for carbonyl in the infrared ($\nu_{max.}$ 1698 cm.$^{-1}$). With ether solvent the same compound was being eluted but a hydroxyl-containing compound ($\nu_{max.}$ 3350 cm^{-1}) was also present. With ether ethyl acetate (3:1) as solvent two bands ($\nu_{max.}$ 1636, 1597 cm.$^{-1}$) appeared in the infrared of the product indicating the presence of monadione.

The yellow oil (0.80 g.) eluted with benzene was then rechromatographed on alumina (25 g.) and the middle fractions found to be (T.L.C. in benzene) a pure, yellow oil (0.37 g.); $\lambda^{EtOH}_{max.}$ 225 (ε, 53000), 251 (ε, 17000), mμ.; $\nu^{L.F.}_{max.}$ 3086 (naphthalene CH), 2941 (CH_2-, CH_3-), 1695 (carbonyl, strong),

1597 (naphthalene C = C), 1462 and 1381 (CH_3-$\overset{|}{C}$-), 1280 (naphthalene), 1258 (chroman), 1168 and 1159 (CH_3-$\overset{|}{C}$-CH_3), 753 (naphthalene) cm.$^{-1}$; τ CCl_4 1.9-2.9 (aryl H), 7.0-7.3 (ArCH_2-$\overset{|}{C}$-), 7.4-9.0 (Ar-$\overset{|}{C}$-CH_3-, -CH_2-satd., CH_3-$\overset{|}{C}$-O-) 9.0-9.3 (satd. CH_3). The molecular weight (benzene method) was found to be 442, 520 and 451, over three attempts.

Attempted Preparation of Diphenyl p-Nitrophenyl Phosphate:

Diphenyl phosphate (0.25 g., 0.001 mole) was dissolved in dried, redistilled pyridine (2 ml.) at 20°C. p-Nitrophenyl trifluoroacetate (107) (0.24 g., 0.001 mole) was added gradually over 5 min., and the mixture allowed to stand for 30 min., before adding water (5 ml.). This caused precipitation of an oil which was extracted with ether. The ether extract was washed with dilute hydrochloric acid and water, before drying and evaporating the solvent. The residue was found to be p-nitrophenol, m.p. 111-113°C [lit. 114°C].

Attempted Preparation of Allyl di-p-Nitrophenyl Phosphate:

Allyl bis-cyclohexyl ammonium phosphate (108) (0.335 g. 0.001 mole), prepared by the method of Maynard and Swan,[182] was suspended in pyridine (3 ml.), and p-nitrophenyl trifluoroacetate (107) (0.47 g., 0.002 mole) added. A bright yellow colouration was produced immediately, and the salt dissolved slowly in the mixture. After allowing to stand overnight at 20°C, the mixture

was diluted with water (3 ml.), and colourless needles appeared after 2 hr. These were removed by filtration and identified as N-cyclohexyl trifluoroacetamide (109), m.p. 94-95°C [lit.95°C][154] The infrared spectrum showed $\nu_{max.}^{KCl}$ 3279 (-NH-; amide), 3086 (sec. amide), 2924 and 2857 ($-CH_2-$), 1686 ($CF_3-\overset{O}{\overset{\|}{C}}-N-$), 1656 (shoulder), 1550 (amide -NH), 1449 ($-CH_2-$), 1193 and 1170 (CF_3- bands), 723 cm.$^{-1}$.

Addition of a further portion of water (5 ml.) to the filtrate caused precipitation of an oil which was identified as a mixture of N-cyclohexyl trifluoroacetamide (109) and p-nitrophenol by infrared studies.

Preparation of N-Cyclohexyl Trifluoroacetamide (109):[154] Cyclohexylamine (10 g., 0.10 mole) was treated dropwise with trifluoroacetic anhydride (20.8 g., 0.14 mole), and the reaction cooled in iced water when the temperature rose above 20°C. The mixture was then allowed to stand at room temperature for 1 hr., by which time a white precipitate had formed. The product was then treated with carbon tetrachloride (25 ml.) and the solution evaporated to dryness (repeated twice). The final residue was then allowed to crystallise as white needles, m.p. 94-95°C [lit.95°C] (yield 16 g., 95%).

PART 4: REACTIONS BETWEEN ALLYL DIPHENYL PHOSPHATE AND SULPHUR COMPOUNDS:

Reaction between Allyl Diphenyl Phosphate and Phenyl Mercaptan (116):

(a) No Solvent: Allyl diphenyl phosphate (0.314 g., 1.3×10^{-3} mole) and phenyl mercaptan (0.144 g., 1.3×10^{-3} mole) were heated together in a sealed flask for 8 hr. at 80°C. The mixture remained miscible and colourless and a g.l.c. trace at 190°C showed that only one volatile component was present, and that this was phenyl mercaptan.

(b) Excess Mercaptan: Allyl diphenyl phosphate (1.03 g., 3.55×10^{-3} mole) and phenyl mercaptan (1.41 g., 1.28×10^{-2} mole) were heated in a sealed flask at 85°C for 30 hr. After 4 hr. heating, a g.l.c. trace showed that a less volatile product was forming and after 12 hr. this product was found to be equivalent to 33% conversion of phenyl mercaptan (g.l.c. peak area method). After 30 hr. heating the ratio of the two peaks indicated that the less volatile component was being removed from the reaction mixture. The mixture was then fractionally distilled at 150°C (oil-bath)/0.1 mm. Hg., and the oily distillate was found to be allyl phenyl sulphide (117), giving a single peak on a g.l.c. trace (retention-time on column (A) at 205°C, 2.5 min. - phenyl mercaptan, 1.25 min.). The sulphide was identified by its spectral data; $\lambda_{max.}^{EtOH}$ 214, 255 mμ; $\nu_{max.}^{L.F.}$ 3040 (aryl)

2985 (CH_2=CH-), 1629 (CH_2=CH-), 1572, 1471, 1431 (all aryl), 985 and 917 (CH_2=CH-), 736 and 687 (mono-substituted phenyl) $cm.^{-1}$.

During the distillation some phenyl mercaptan was oxidised to a solid, diphenyl disulphide.

Reactions between Sulphides and Allyl Diphenyl Phosphate:

(i) Diethyl Sulphide (119): Ethyl sulphide (0.90 g., 0.01 mole) and allyl diphenyl phosphate (2.90 g., 0.01 mole) were heated at 90°C in a sealed flask for 12 hr. Addition of ether (25 ml.) to the crude, colourless mixture resulted in precipitation of a colourless, viscous oil, which solidified on cooling at 0°C. The ethereal solution was removed by micro-pipette and the solid washed six times with fresh portions (10 ml.) of dried, redistilled ether. The residual ether from the last of these operations was removed under vacuum at 15°C, leaving a free-flowing, white crystalline (plates) solid, identified as allyl diethyl sulphonium diphenyl phosphate (120) (0.95 g., 25%), m.p. 53-56°C. [Found: C,61.0; H,5.90; P,9.30; S,2.4. $C_{19}H_{25}O_4S$ requires C,60.0; H,6.6; P,8.15; S,8.4]. Considerable trouble was experienced in obtaining an analytical sample, because the product was extremely hygroscopic, as well as being low-melting. After drying over phosphorus pentoxide at 110°C and 0.01 mm., the analytical sample did not solidify on cooling.

The following spectral data was obtained: $\nu_{max}^{L.F.}$ 2967 (CH_3-), 1634 (CH_2=CH-, weak), 1587 and 1484 (aryl C=C, strong), 1202, 1264, 1211 (strong, PhO-$\overset{\|}{P}$=), 1190, 1160, 1098 (strong), 1002, 959, 906, 890, 876, 778 760 (mono-substituted benzene), 735, and 692 (mono-subst.) cm.$^{-1}$; τ^{D_2O} 4.3 (CH_2=CH, [3]), 6.15 (CH_2=CH-$\underset{\text{doublet}}{CH_2}$-$\overset{\oplus}{S}$-, [2], doublet), 6.90 ($CH_3$-$\underset{\text{quartet}}{CH_2}$-$\overset{\oplus}{S}$-, [4], quartet), 8.65 ($\underset{\text{triplet}}{CH_3}$-$CH_2$-$\overset{\oplus}{S}$-, [6], triplet).

The ethereal washings from the crude reaction product were concentrated and g.l.c. trace at 160°C showed that the only volatile component was unchanged ethyl sulphide.

(ii) Dibutyl Sulphide (121): Dibutyl sulphide (1.46 g., 0.01 mole) and allyl diphenyl phosphate (2.9 g., 0.01 mole) were heated together in a sealed flask for 72 hr. at 90°C, and the reaction followed every 24 hr. by g.l.c. at 198°C. These three traces showed that a product was being formed steadily, and that this was more volatile than the dibutyl sulphide. Addition of ether to the reaction mixture did not cause precipitation, and extraction from this ether solution with water did not yield any product. When the crude reaction mixture was distilled carefully, a distillate was obtained which contained 72% (g.l.c. peak area method) of the volatile reaction product and 28% dibutyl sulphide. This distillate contained enough volatile product to identify it

as allyl butyl sulphide (123) from its spectral characteristics, $\nu_{max.}^{L.F.}$ 3077 (wk), 1838 (very wk), 1637 (med.), 988 (strong) and 913 (strong) cm.$^{-1}$, all of which bands are characteristic of allyl groups; τ^{CCl_4} 4.0-5.2 (CH_2=CH-), 6.9 (-S-$\underset{\text{doublet}}{CH_2}$-CH=C-, doublet), 7.3-7.8 (-S-CH_2-$\overset{|}{C}$-), 8.2-9.2 (-S-$\overset{|}{C}$-CH_3-, and -$\overset{|}{C}$-CH_2-CH_3). The integral of the n.m.r. spectrum corresponded to a mixture of 70% allyl butyl sulphide in dibutyl sulphide.

In a further experiment, dibutyl sulphide (1.46 g., 0.01 mole) and allyl diphenyl phosphate (2.90 g., 0.01 mole) were heated at 120°C in a flask containing o-xylene (0.21 g. 0.002 mole) as an internal g.l.c. standard. The reaction was followed regularly over a period of 200 hr., by running g.l.c. traces at 190°C, and from these the rates of disappearance of dibutyl sulphide, and of formation of allyl butyl sulphide were estimated.

The loss of dibutyl sulphide from the system was quite rapid (30% loss after 40 hr.) initially but thereafter the rate of loss was much slower, and after 200 hr. the loss was 69%. The rate of formation of allyl butyl sulphide (123) was steady over the first 100 hr. (16%), but this too became slower as the reaction proceeded (22% after 200 hr.). Since no other volatile products were detected, there should be 47% of the theoretical amount of sulphonium salts present. Addition of ether (4ml.) caused precipitation of an oil, which was redissolved on addition of more ether, and which was not very soluble in water. The infrared

spectrum of this oil was very poor.

In a further experiment at 120°C, without added xylene, after 5 hr., an equilibrium was reached after 5 hr., containing 45% allyl butyl sulphide (123) (retention-time at 190°C, 1.25 min.) and about 1% of a substance with the same retention-time as diallyl sulphide (1.0 min., at 190°C).

(iii) Diphenyl Sulphide (118): Diphenyl sulphide (0.409 g., 0.0022 mole) and allyl diphenyl phosphate (0.583 g., 0.002 mole) were heated at 85°C for 100 hr. in a sealed flask. Addition of ether to the reaction mixture did not cause precipitation of either an oil or a solid, and extraction with water from this ether solution did not yield any product. There was no evidence from g.l.c. traces that reaction had occurred.

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