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Bernard David Challand

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THE SYNTHESIS OF β-HIMACHALENE
AND
STUDIES CONCERNING STEREOCHEMICAL CONTROL OF PHOTOCHEMICAL CYCLOADDITION

by

Bernard David Challand

Department of Chemistry

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of the requirements for the degree of
Doctor of Philosophy

Faculty of Graduate Studies
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ABSTRACT

In Part A is described the synthesis of racemic β-himachalene, 2, from 3-acetoxy-2-methylcyclopent-2-enone and cyclohex-2-enone ethylene ketal. A photochemical cycloaddition was the first step, and the resulting tricyclic system, 13a, was converted, by successive reduction of the ketone, esterification and fragmentation, to the substituted bicyclo[5,4,0]undecane, 14, having the 6,7 ring system of the himachalenes. The substitution pattern and degree of unsaturation of 14 were then modified by a series of alkylation and dehydration reactions. The former included hydrogenolysis of a 1,1,2-trisubstituted cyclopropane, 28, to a quaternary methyl group, 27. This reaction, and the more interesting features of the rest of the synthesis, are discussed in detail.

Part B of the thesis describes various attempts to achieve stereochemical control of intermolecular photochemical cycloadditions. The first section describes attempts to obtain stereospecificity by converting the two olefinic reactants to mixed dicarboxylic esters, thereby rendering a previously intermolecular reaction intramolecular. No cycloaddition of the olefinic bonds was observed when various allyl vinyl carbonates, other esters

(44, 46, 56, 60, 64), and an ether (54), were irradiated. In all cases the nature of the photochemical products was investigated, and generally they appeared to be derived from hydrogen abstraction reactions. Possible reasons for the lack of cycloaddition are suggested.

In the second section of Part B the results of investigations of the effect of solvent on the stereochemical course of cycloaddition reactions are described. The cycloaddition reaction of the cyclopentenone derivative, 15, with the substituted cyclohexene, 66, was examined in a variety of solvents. The relative proportions of the isomeric cycloadducts, 13a and 13b, in the product mixture were shown to be dependent mainly on the dielectric constant of the solvent. The results are explained in terms of kinetic theory and the dipole moments of the two transition states.

ACKNOWLEDGEMENTS

The author would like to express his sincere gratitude to Professor P. de Mayo for suggesting these studies and for his constant guidance and encouragement throughout this research.

The collaboration of Dr. G. Kornis and Dr. G. L. Lange in the research leading to the synthesis of β-himachalene (specifically, the preparation of intermediates 13a, 14, 20, 21, 28 and 30) is gratefully acknowledged, as is the technical assistance of Mrs. M. Heinrich and Miss L. Pinelo.

Thanks are due to all the members of the faculty of this department who have at various times offered advice and assistance to the author. Also, the author's gratitude is extended to his fellow graduate students, and to his wife, for their continued help and encouragement.

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TABLE OF CONTENTS

FIGURES AND TABLE.

PART A. THE SYNTHESIS OF β-HIMACHALENE

INTRODUCTION

The steam-volatile oils from Cedrus atlantica (Manet) and C. deodara (Loud.) were first recorded as having been investigated in 1902 by Grimal (1) and 1916 by Roberts (2). The presence of sesquiterpenes was recognised by the latter author, and there were several investigations of the nature of these compounds in subsequent years (3). Ruzicka et al. first recognised the sesquiterpenes from C. atlantica to be new compounds (4) although they did not purify them. Dev et al., in 1952, succeeded in partially purifying two new sesquiterpenes from C. deodara and named them α- and β-himachalenes (5). They noted that the properties of these hydrocarbons, and the derived hydrochlorides, closely resembled those recorded by Ruzicka. From the chemical behaviour of the himachalenes, and some physical data, Dev concluded that these sesquiterpenes were not of the cadalene, eudalene or azulene families, although they were probably bicyclic, but were of a novel type. Subsequent research (6) into the sulphur and selenium dehydrogenations and ozonolysis of the himachalenes, together with spectroscopic evidence,

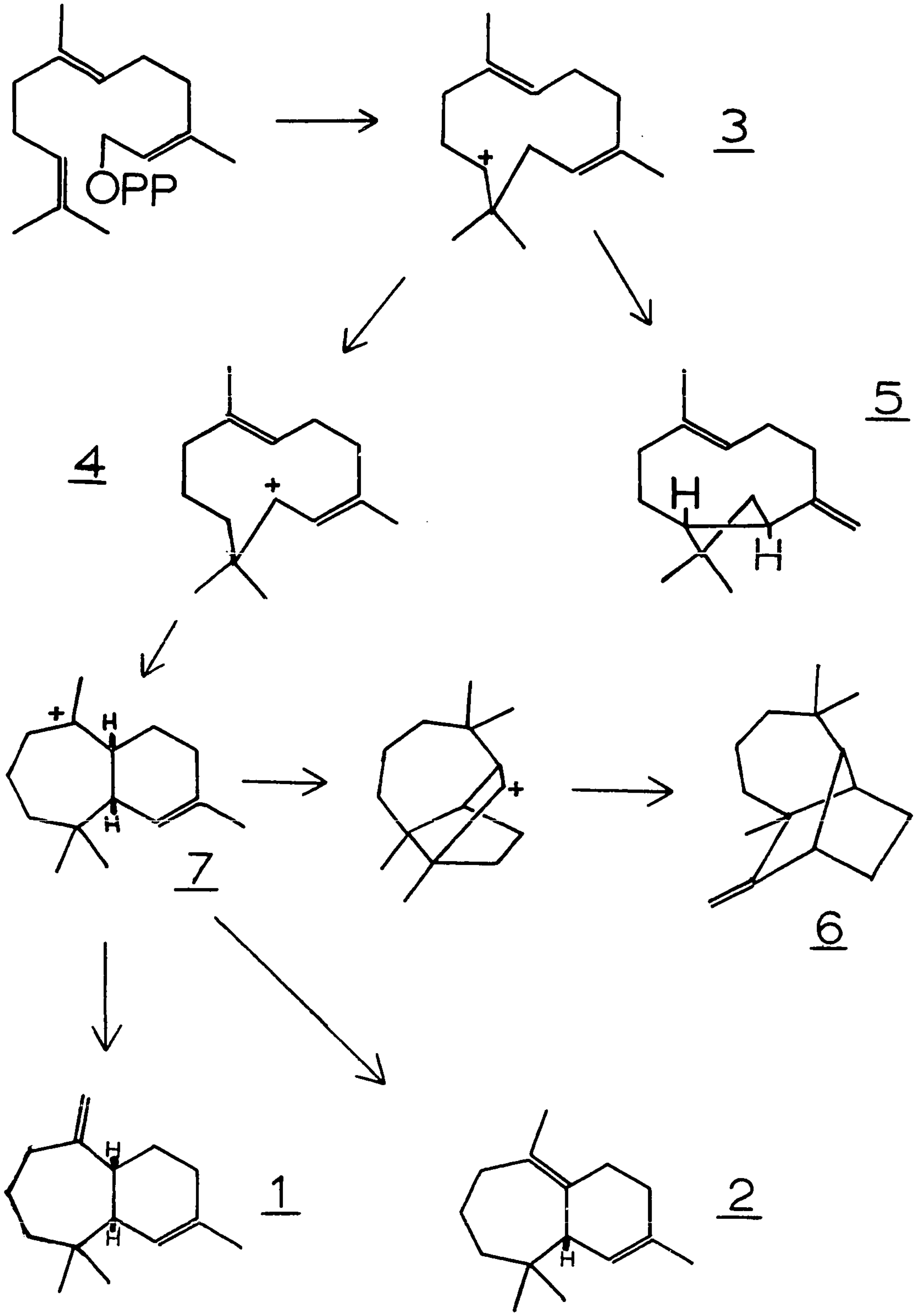
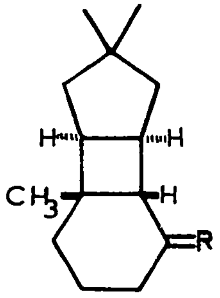


Fig. 1

allowed Dev to propose that α-himachalene was 2,4a, 5,6,7,8, 9,9a-octahydro-3,5,5-trimethyl-9-methylene-1H-benzocycloheptene (1), and β-himachalene was 2,4a,5,6,7,8-hexahydro-3,5,5,9-tetramethyl-1H-benzocycloheptene (2).

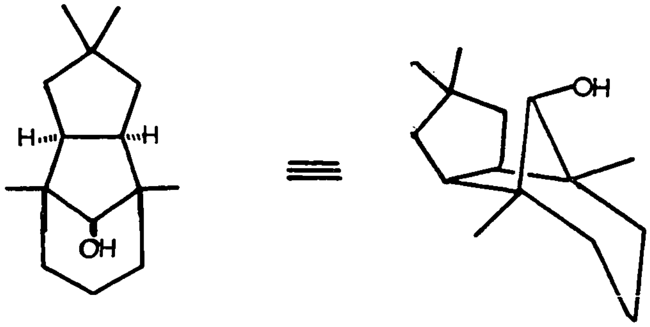
At the same time, but independently, a similar investigation by Bredenberg and Erdtman of the sesquiterpenes from C. atlantica (7) afforded sufficient evidence for them to propose the same structures for these sesquiterpenes, with the additional suggestion that the stereochemistry at the 6,7 ring junction in α-himachalene would be *cis*. On the basis of further research, Dev, *et al.*, (8) proposed the absolute stereostructures of α- and β-himachalenes as 1 and 2 respectively.

The biogenesis of sesquiterpenoids generally has been extensively reviewed recently (9) and will not be discussed here. Although the biogenesis of the himachalenes has not been investigated, the structures are in theory readily derivable from farnesyl pyrophosphate *via* the sequence shown (fig. 1). The ions 3 and 4 had been proposed (10) as intermediates in the formation of caryophyllene, 5, and longifolene, 6, as shown, but no products derived directly from the intermediate cation 7 had then been discovered. The himachalenes represent a "missing link" in this biogenetic sequence. Although these transformations are conventionally represented as involving free carbonium ions, the reactions, *in vivo*, undoubtedly involve enzyme-bound intermediates, the



8a R =O

8b R =CH_3,OH



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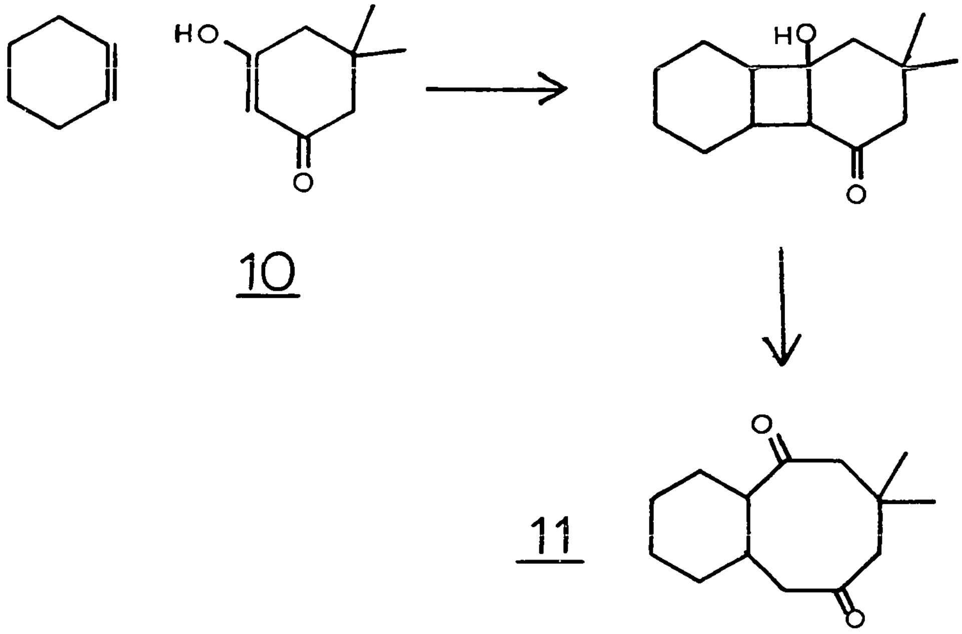


10

11

reaction course being governed by the specific nature of the enzyme. The free cation, **7**, as is shown later, when formed *in vitro*, has an extremely short lifetime, deprotonating virtually exclusively to give β-himachalene.

The reason for synthesising himachalene was primarily to demonstrate the synthetic utility of photochemical cycloaddition reactions. Only secondarily was the synthesis intended to confirm the proposed structures of the natural products, since there was little doubt of the validity of the structural assignments.

It is not the author's intention in this introduction to discuss photochemical cycloaddition reactions in general. Some aspects of the subject are introduced later, and the bulk of the subject has been extensively reviewed (11). Photochemical cycloaddition has hitherto been used synthetically principally for the generation of cyclobutane rings which have been kept intact (12) (13). Among the exceptions (14) was the synthesis of α-caryophyllene alcohol, **9**, (14a). In this case the irradiation adduct **8a** was converted to **8b**, which underwent acid-catalysed rearrangement to α-caryophyllene alcohol. Another synthetic application of cycloaddition has been the cycloaddition of enolised 1,3-diketones, *e.g.* **10**, or their esters, to olefins, and the subsequent facile cyclobutane ring scission to give 1,5-diketones, *e.g.* **11** (15) (16). The synthesis of β-himachalene was devised to utilise this type of cycloaddition and ring opening to generate the seven-membered ring.

DISCUSSION

Photochemical cycloaddition of cyclopentane-1,3-dione to a cyclohexene, and subsequent ring opening, would be expected to give the bicyclo[5,4,0]undecane-2,5-dione system 12. If a 3-substituted cyclohexene were used one of the products would have the substituent at C_8 and the other at C_{11}. The former would have a substitution pattern that would be convenient for introduction (at C_2, C_6 and C_9) of the remaining methyl groups in the carbon skeleton of the himachalenes. A further requirement for a successful synthesis would be that the ketones at C_2 and C_5 would have to have sufficiently different reactivities to enable preferential substitution at one or the other. Since this seemed to be unlikely, the ring opening step was modified so that the product would have different substituents at C_2 and C_5.

It had previously been shown (16) that cycloaddition of enol acetates of 1,3-diones to olefins gave cyclobutane adducts that were stable until hydrolysed. It was decided that a 1,4-elimination reaction to cleave the cyclobutane, similar to that used by Corey in the synthesis of caryophyllene (13), would be more useful than the retroaldol reaction. In Corey's system a fragmentation reaction (17) was used to generate a cyclonon-4-enone from a 1,7-disubstituted bicyclo[4,3,0]nonane (see fig. 2). In this case the ketone in the cycloadduct 13a, which would hopefully

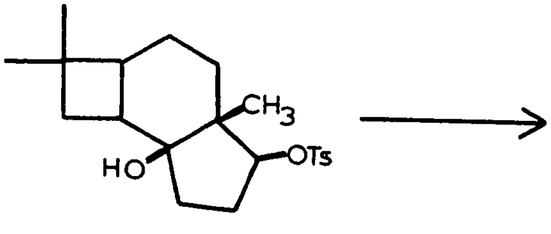
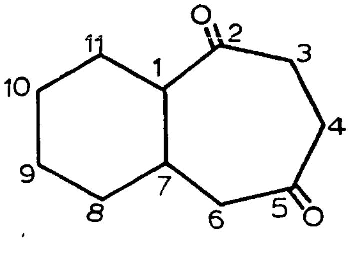


Fig. 2



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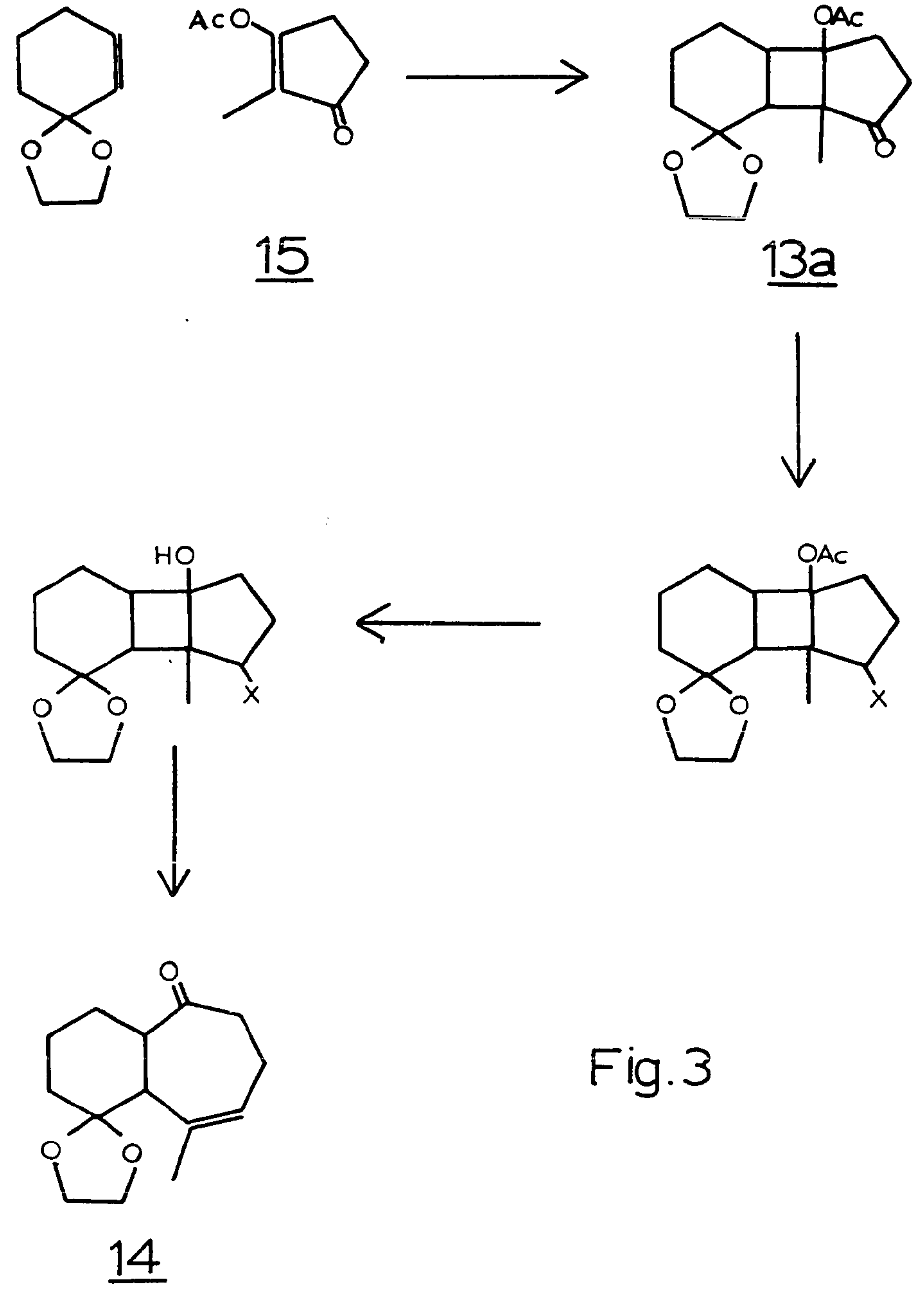


Fig.3

be formed from 15 and a suitably substituted cyclohexene, could be converted to a suitable leaving group, and hydrolysis followed by base-catalysed 1,4-elimination would then give a cyclohept-4-enone system (fig. 3). The groups at C_2 and C_5 being different would then allow different reactions to be performed at the two sites.

A dioxolan ring was chosen as the substituent at C_3 of the cyclohexene, this being convenient for subsequent hydrolysis and introduction of an α-methyl group (the methyl group in the six-membered ring of himachalene) and its symmetry minimising the number of cycloadduct isomers. The enone chosen for the synthesis was 2-methylcyclopentane-1,3-dione, the methyl group subsequently becoming one of the C_6 substituents in 14 (fig. 3).

Irradiation of 2-methylcyclopentane-1,3-dione enol acetate in cyclohexane containing the ethylene ketal of cyclohex-2-enone afforded an adduct, 13a or 13b, apparently a homogeneous simgle isomer, as judged by thin layer chromatography and n.m.r. spectrum. Eight isomeric cycloaddition adducts are possible, and some knowledge of the structure of the compound obtained was required before procedure to the next stage was attempted. A study of the ultraviolet spectra of the adduct upon treatment with base followed by acid showed no absorption which could be attributed to an $\alpha\beta$-unsaturated ketone or β-diketone. Both adducts 13a and 13b under these conditions would be expected to hydrolyse and cleave the

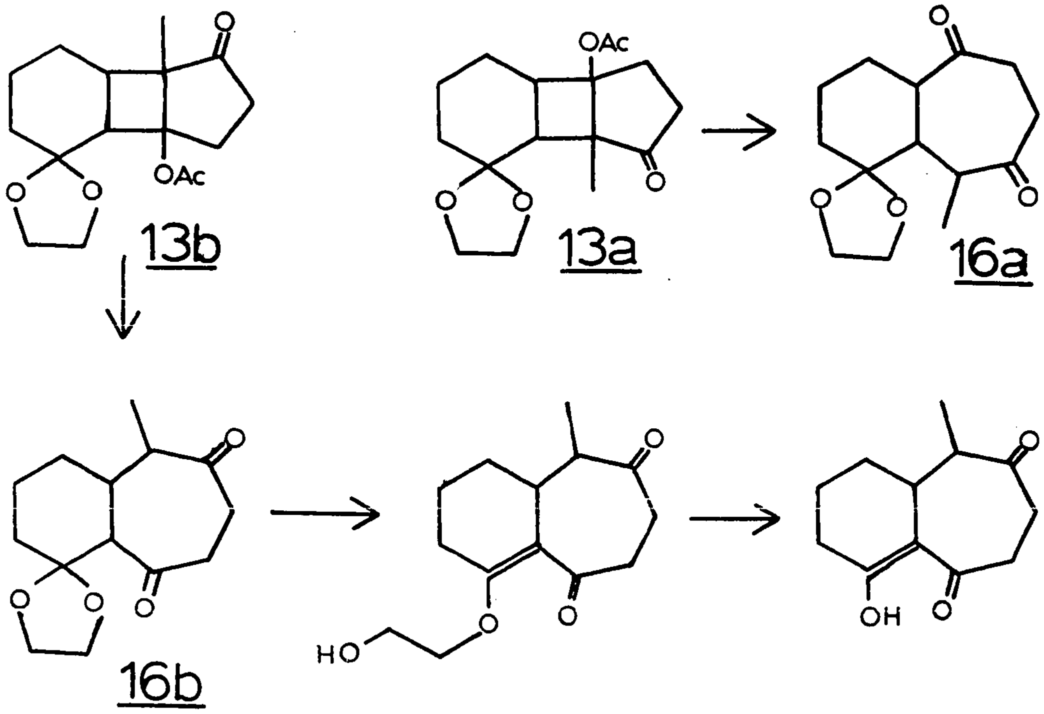


Fig. 4

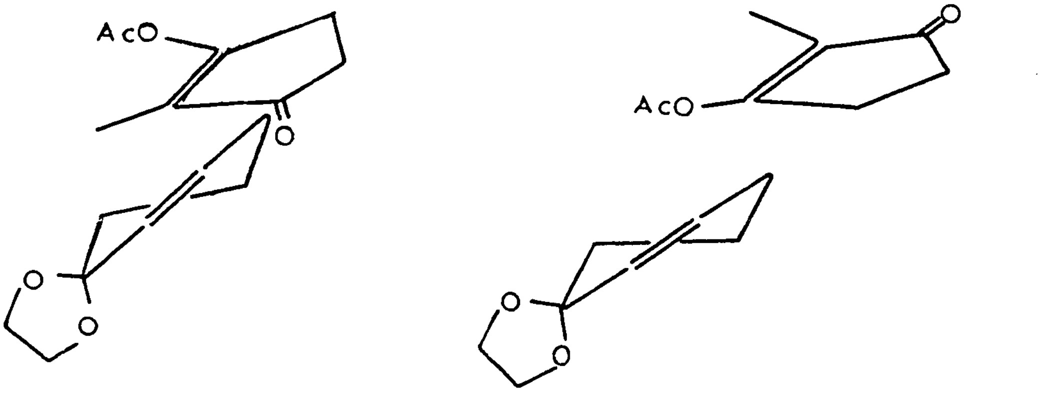
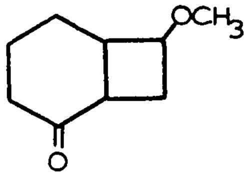


Fig. 5

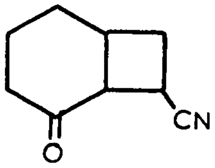
cyclobutane ring to give _16a_ and _16b_. Only one of these compounds (_16b_) could then, under the conditions used, eliminate the ethylene ketal, giving an $\alpha\beta$-unsaturated ketone chromophore (fig. 4). Since such a chromophore was not observed, the adduct must be _13a_. It was estimated that less than about 5% of adduct _13b_ could be present.

A consideration of models suggests that approach of the unsaturated ketone _15_ to the olefin must be such as to give the "anti-" adduct isomers (fig. 5), but the steric restrictions of these appear to be very similar, approach in the fashion to give _13a_ being, at most, only slightly favoured.

The work of Corey (18) has shown that the polar character of the reactants has a strong influence on the stereochemistry of cycloaddition. Whereas methoxyethylene adds to cyclohexenone to give "head-to-tail" isomers, _17_, only, acrylonitrile gives mainly "head-to-head" isomers, _18_. A consideration of the inductive effect of an allylic ketal group suggests that the double bond of the cyclohexenone ketal would be polarised as shown, _19_, only to a very small extent. The ^1H n.m.r. spectrum shows H_B downfield from H_A by only 0.29 ppm, and the ^{13}C n.m.r. spectrum shows a negligible (_ca_. 3 ppm) difference between the ^{13}C resonance positions. These figures correspond to an electron density difference of 0.03 electrons/carbon atom (19), in contrast with polar-



17



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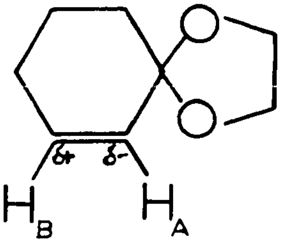

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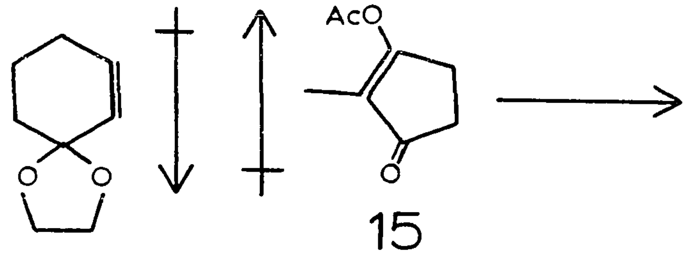


15

13a

Fig. 6

ised double bond systems (e.g. alkoxyethylenes ca. 0.3 to 0.4, and 1,1-dimethoxyethylene 0.61). These results are confirmed indirectly by tables of σ^* values which suggest very little inductive effect of alkoxy groups through C-C single bonds (84).

Another interpretation of polar effects is to consider the dipole interactions of the excited enone molecule and the olefin. The stereochemistry of cycloaddition of maleic anhydride to cis-1,2-dichloroethylene has been explained (20) by considering the dipolar interactions of the reactants, change of solvent producing an enormous change in stereospecificity (21). Cyclopent-2-enone in the n-π^* triplet excited state probably has a dipole moment, μ, very much less than 3 D, since the n-π^* excited state implies promotion of an electron from the non-bonding orbitals of the electronegative oxygen atom to the π^* orbitals of the conjugated system. Thus the n-π^* triplet excited state of 15 could, because of the effect of the acetate, be polarised towards the acetate substituent, if the dipole moment of the excited enone system is sufficiently small. Since the cyclohexenone ketal is polarised towards the ketal group, the direction of cycloaddition, if it occurs via the n-π^* triplet state, in the non-polar solvents used would be expected to be as in fig. 6. The extent of the stereospecificity would depend on the size of the dipole moment of the excited state of 15, which is not measurable, but may well be ca. 1.0 D (vinyl acetate μ 1.8 D) in the direction indicated, and this could be the real explanation for the stereospecificity of the reaction.

It has been found possible to estimate approximately the change in magnitude of one component of the dipole moment of a compound on going from the ground state to an electronically excited state, (22, 23, 24). The energy of the transition, measured as the frequency of the u.v. absorption of the compound, is dependent on the refractive index, dielectric constant, and proton-donating power of the solvent. When non-hydrogen-bonding solvents are used, it has been found that (23) the energy for the $n-\pi^*$ ketone singlet transition can be approximately expressed as a function of the dielectric constant of the solvent. This method was applied to cyclopent-2-enone using seventeen non-hydrogen-bonding solvents and a linear relationship, with a correlation coefficient of 0.88 was found (see Experimental Section, Part B of this thesis). From the slope of this line it was deduced that cyclopent-2-enone in the singlet $n-\pi^*$ excited state had a dipole component, in the direction of the ground state dipole moment, of 3.02(± 0.2)D less than the ground state moment of 3.45 D. Since it would be expected that the overall dipole moment of the excited state would be roughly collinear with the ground state moment, it can be deduced that the dipole moment of the excited singlet $n-\pi^*$ cyclopentenone is <u>ca</u>. 0.4(± 0.2)D, in the same direction as the ground state. This direction would be expected, on the basis of calculations of electron densities of enones, to be roughly parallel with the C_3-C_2 bond of cyclopentenone (24).

The dipole moment of 2-methyl-3-acetoxycyclopent-2-enone in limited conformations of the ground state was calculated (see Experimental Section, Part B, Section (2)) to be 2.5(± 0.2)D inclined at about 32° (±5°) to the C_1-O line, based on the measured dipole moments of cyclopentenone (3.45 D), phenyl acetate (1.5 D), vinyl acetate (1.80 D), (other acetates 1.7 to 1.9 D) and toluene (0.43 D). Calculation of the dipole moment of the n-π^* excited state for this compound gave 1.7(± 0.4)D at 122° (±10°) to the C_1-O line (approximately along the line of the C_3-O bond). This was based on the following assumptions: that the methyl and acetoxy substituents affect the π electron distribution of the ground and excited states in the same way, and to the same extent; that the ground state acetoxy substituents would have a dipole moment contribution less than that of the vinyl acetate, whereas in the excited state the contribution would be more like ROAc since the electron density at C_3 in the ground state is less than one electron/carbon atom and in the excited state is greater than this (24); similarly that the ground state C_2-CH_3 substituent would have a dipole moment contribution about the same as Ph-CH_3 whilst the excited state C_2-CH_3 would be more like R-CH_3. A check on the validity of this value was made by measuring the $n-\pi^*$ absorption solvent shift for 15 in the same way as had been done for cyclopentenone. The calculated component of the excited state dipole moment in the direction of the ground state moment is $-1.7(\pm0.4)\cos 90^\circ(\pm15^\circ) = 0.0(\pm0.6)$D. Thus the calculated change in dipole moment in this direction is $0.0(\pm0.6) - 2.5(\pm0.2) = -2.5(\pm0.8)$D. The measured dipole moment change, from the solvent shift studies, was -2.4 (±0.2) D. These results are at least in qualitative agreement and so there is some justification for taking the calculated value for the dipole moment of the $n-\pi^*$ excited singlet of 15 as correct within the accuracy limits given. This figure strictly applies only to the singlet $n-\pi^*$ excited state of this compound. However, the calculations and observations of Zimmerman, et al, (24) indicate that the π-electron configurations of $n-\pi^*$ $\alpha\beta$-enone singlet and triplet excited states are very similar. If the assumption is made that this also applies generally to cyclopentenone derivatives, including this 2-methyl-3-acetoxycyclopentenone, then it is apparent that the dipole moments of the $n-\pi^*$ singlet and triplet should be very similar, both in size and direction. Thus it is evident that alignment of 15 and the cyclohexenone ketal with opposed dipoles would tend to give rise to the product observed. If the cycloaddition occurs via a $\pi-\pi^*$ triplet state, this argument becomes somewhat tenuous, since Zimmerman's calculations show that the electron distribution in the $\pi-\pi^*$ state is quite different from that in the $n-\pi^*$. This aspect of the problem was studied further and the results are discussed in Part B.

In order to generate the seven-membered ring it was necessary to have the leaving group trans- to the quaternary $-CH_3$ group, as shown in fig. 7. 1,4-Elimination from this compound should give a cis-double bond in the seven-membered ring. If the configuration of the leaving group were opposite to this (i.e. cis- to the $-CH_3$), the elimination most probably would not occur, necessitating the formation of a trans-double bond in the seven-membered ring (cf. (13). A consideration of models of 13a suggested that the upper side (cis- to the $-CH_3$) would be less hindered than the lower to attack by reducing agents (irrespective of the 6,4 ring junction stereochemistry). By analogy with other systems (25) (26), it was hoped that sodium borohydride reduction would give mainly the required alcohol 20a, and this was found to be so using aqueous methanol as solvent, at 5°.

The leaving group chosen for the elimination was the methanesulphonate, sulphonates being much less susceptible to hydrolysis than carboxylate esters, thus avoiding competing hydrolysis of the leaving group during the elimination, and being good leaving groups. The methanesulphonate was conveniently prepared from sulphene, generated in situ from methanesulphonyl chloride and

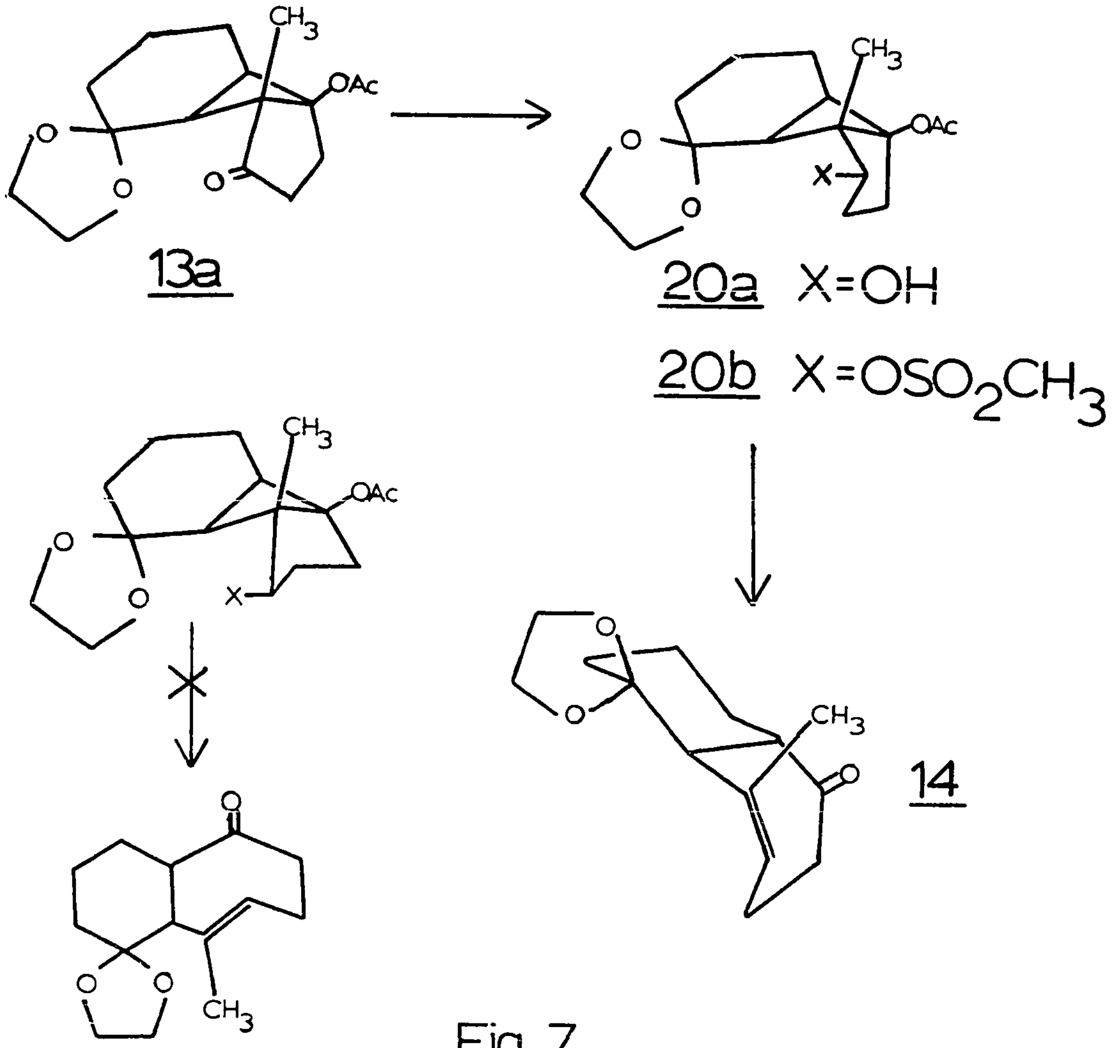

CH3
OAc
13a
CH3
OAc
X
20a X=OH
20b X=OSO2CH3
CH3
OAc
X
CH3
14
CH3

Fig. 7

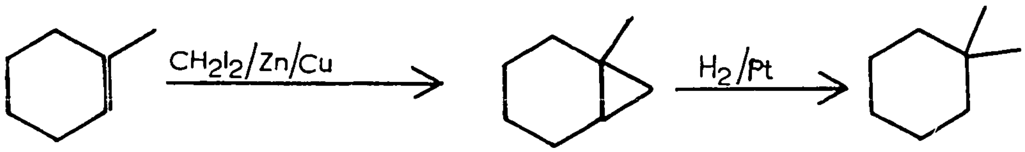

CH2I2/Zn/Cu
H2/Pt

Fig.8

triethylamine, by the method of Durst and King (27). This technique gave the sulphonate ester, 20b, in good yield (50% after several crystallisations). In practice it was unnecessary to purify the intermediate alcohol and methanesulphonate before proceeding to the next stage.

The 1,4-elimination reaction was found to proceed with great facility, only mild alkaline conditions being required (contrast the vigorous conditions required by Corey *et al* to expand the 6,5 ring system in the synthesis of caryophyllene (13)). Hydrolysis of the acetate is followed by immediate elimination of methanesulphonate anion with ring expansion to give 14, fig. 7. These conditions are sufficiently strong to equilibrate the carbon atom α- to the ketone, thus destroying the original 6,4 ring junction stereochemistry.

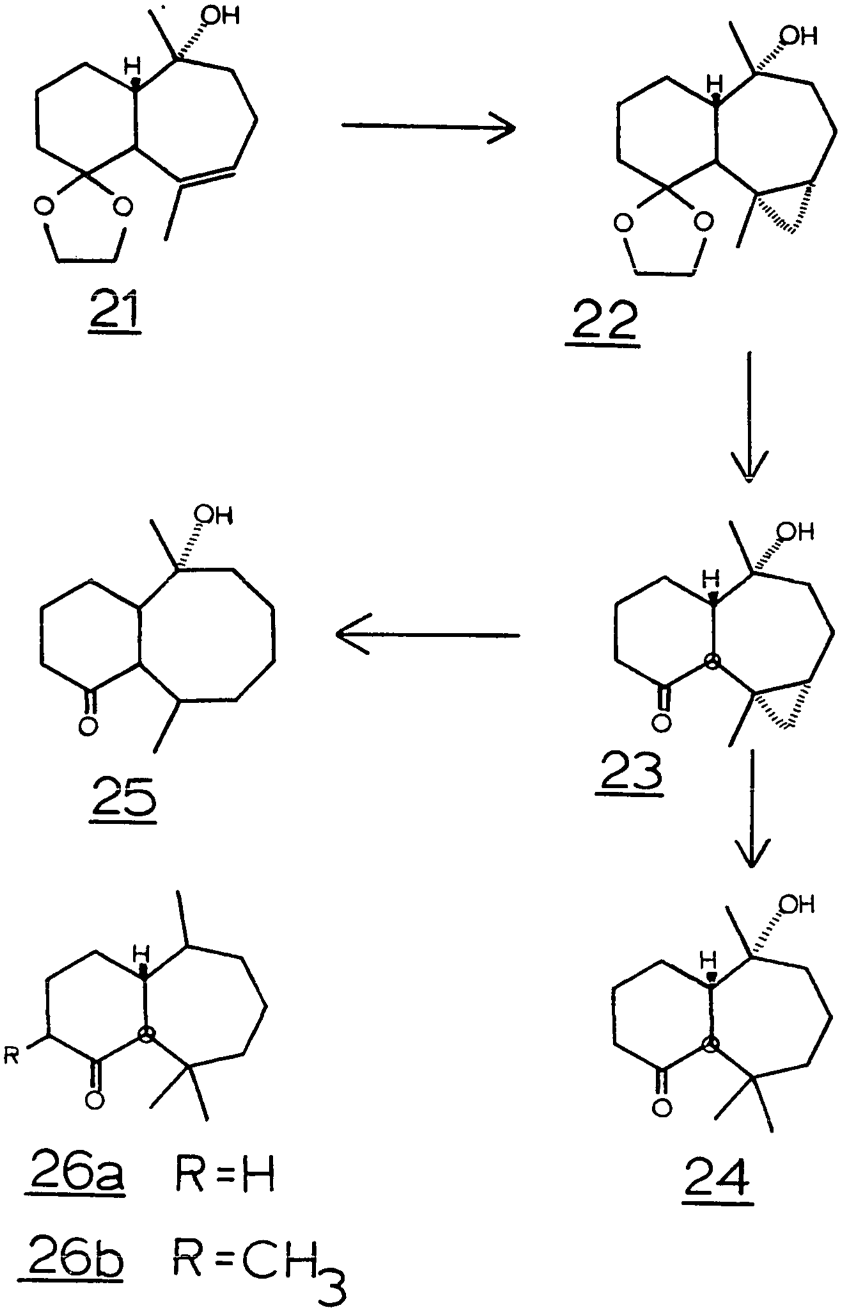
Fragmentation reactions, especially those of the 1,4-elimination type, have been extensively studied by Grob, *et al*. (28). These studies have shown that concerted fragmentations occur at greatly accelerated rates, but only when the breaking bonds are in mutually parallel, but not necessarily all mutually *trans*-, arrangements. In this system alignment of the C-mesylate bond parallel to the cyclobutane bond which is to be cleaved produces a conformationally strained state which would therefore be populated only very slightly. The fact that the reaction occurs so readily emphasises the facility of the fragmentation reaction when the conformation is correct, which itself reflects the large driving force imparted by cleavage of the cyclobutane. It is interesting to note that the compound epimeric at the C-mesylate position would be oriented to undergo fragmentation much more readily than 20b. However, such a fragmentation could not occur because of the inherent improbability of reaching a transition state to a trans-cycloheptene product (fig. 7).

Chromatography of the crude product on alumina afforded a single pure compound in 35% overall yield from 15. The trans-6,7 ring fusion was expected on the basis of the relative stabilities of the two possible modes of fusion. Introduction of one of the three remaining required methyl groups was straightforward. 14 was converted to 21 by methyl magnesium iodide in high yield. The stereochemistry shown is that predicted from analogy with other Grignard additions to ketones (29). The normal mode of addition is with the methyl group entering from the least hindered side. Consideration of models shows that this CH_3- group will always be cis- to the -H at the adjacent ring junction, irrespective of the 6,7 ring junction stereochemistry.

In theory it seemed to be possible to generate a gem-dimethyl group by reductive cleavage of a suitable cyclopropane. Quaternary methyl groups have been produced by lithium/ammonia reduction of cyclopropyl ketones (30) and by hydrogenation of substituted cyclopropanes, even under quite mild conditions (31). In order to test the feasibility of hydrogenation of a non-conjugated trisubstituted cyclopropane under relatively mild conditions, 1-methylnorcarane was prepared by the Simmons-Smith reaction (32) from 1-methylcyclohexene. Hydrogenation of this with Adams' platinum catalyst in acetic acid at atmospheric pressure was found to give 1,1-dimethylcyclohexane in high yield (fig. 8).

Accordingly 21 was treated with diiodomethane and zinc/copper couple in ether to give a mixture of 22 and 23. It is not unexpected that the zinc compounds and complexes under these conditions can cleave the dioxolan ring in the rather long reaction times involves (2 days); Blanchard and Simmons found that diethyl ether was attacked slowly by the reagent (33).

The crude mixture from this cyclopropanation reaction was treated with dilute aqueous methanolic acid to complete the removal of the ethylene ketal, and chromatography then afforded 23. The stereochemistry shown, cyclopropyl *cis*- to hydroxyl, is assigned on the basis of other studies on this reaction (34). Although these studies applied mainly to allylic alcohols, other conformationally suitable compounds should be at least as stereospecific. In this case the intermediate iodomethyl alkoxyzinc could insert the $-CH_2-$ only in the configuration *cis*- to the C-O bond, in a manner analogous to the cyclo-


OH
H
21
22
23
24
25
26a R=H
26b R=CH3

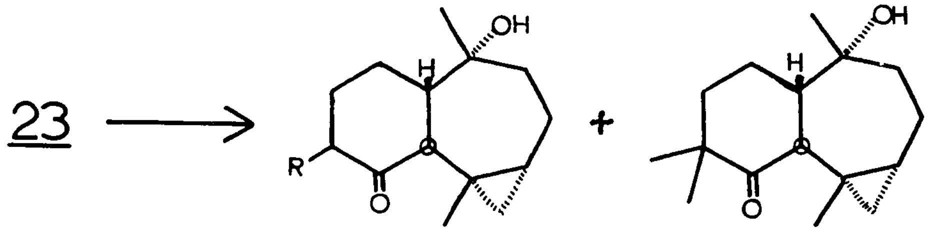
propanation of cyclopent-3-enol (35).

Hydrogenation of this compound, using the same conditions as had proved effective with 1-methylnorcarane, *i.e.* platinum in acetic acid, did not, however, give 24; 25 was produced instead. Platinum in ethanol, palladium on charcoal or rhodium on alumina in ethanol or acetic acid did not catalyse the required hydrogenation, although some hydrogenolysis of the tertiary hydroxyl occurred. However, a mixture of 73% rhodium/27% platinum, prepared according to the method of Nishimura (36), in acetic acid, was found to catalyse the conversion of 23 to 24 and 26a. There was very little hydrogenolysis of the tertiary -OH group when the solvent contained some dissolved sodium acetate, and none of the cyclooctyl product, 25, was detected.

The absence of hydrogenolysis of the C-O bond was expected on the basis of published work on hydrogenation with rhodium catalysts (36), (37). The change in the mode of cleavage of the cyclopropane in going from platinum to rhodium/platinum was surprising. This is perhaps a more striking example of an effect that has been observed in the hydrocracking of neohexane at 100° - 300° (38). Platinum and tungsten were found to cleave the most highly substituted C-C bonds, whilst nickel and rhodium catalysts preferentially cleaved the least highly substituted. From comparative studies of the rates of hydrogenolysis of neopentane and neohexane it was deduced that the principal mechanism for hydrogenolysis over rhodium involved initial adsorption of a 1,2-diradical, formed by abstraction of two vicinal H atoms by the catalyst surface, whereas over platinum catalyst other mechanisms were operative.

The ring junction stereochemistry shown for 24 is assigned on the basis of the n.m.r. spectra of this and subsequent compounds. The methine proton α- to the carbonyl is plainly distinguishable as a doublet (J=7Hz) at lower field (τ 7.3) than is normal for protons with analogous immediate environments, *e.g.* 26b or 26a (*ca.* τ 7.5). This is attributed to its being spatially close to, and hence *cis*- to, the hydroxyl group. It is interesting to note that this proton is also plainly seen in 27 (at τ 7.27), but in 28, 23 and 29 it is at higher field (τ 7.5-7.9) and obscured. A consideration of models of these compounds suggests that there would be very little difference between the H and OH positions in the two series of compounds, which leads one to conclude that the cyclopropyl group, *per se*, causes a shielding of the methine proton by about 0.3 ppm. There have been several previous reports on the long range shielding effects of cyclopropane rings (*e.g.* (85)), but the subject is not sufficiently advanced to warrant speculation on the origin of the shielding in this particular case.

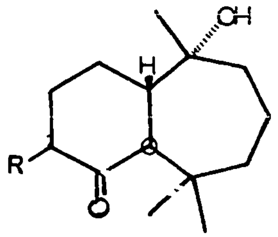
The introduction of the final carbon atom in the himachalene skeleton provided some interesting results.



28a R = β-CH_3

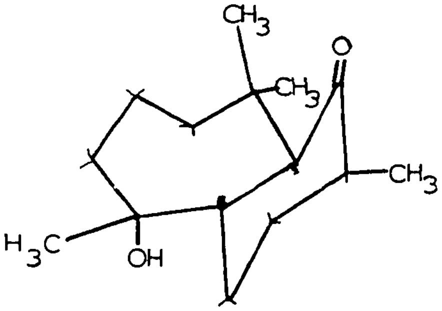
28b R = α-CH_3

29

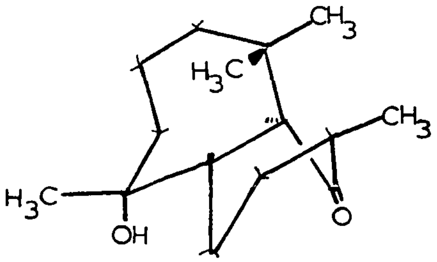


27a R = β-CH_3

27b R = α-CH_3



27a



27b

Fig. 9

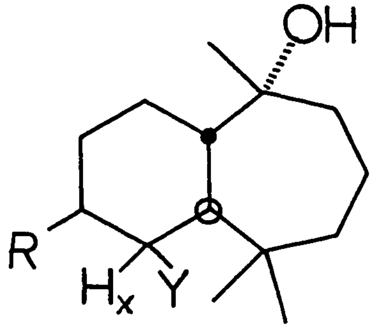
Methylation of 24 did not occur in twenty hours using conditions (methyl iodide, potassium *t*-butoxide, *t*-butanol) which were effective in methylating 23 in two hours. So 23 was alkylated to give a mixture of epimeric monomethylated products 28, and the dimethyl derivative 29. Separation of the two monomethyl derivatives by chromatography was not achieved, but the presence of two compounds was shown by the n.m.r. spectrum of the mixture. Hydrogenation of these compounds using the rhodium/platinum catalyst afforded 27, again as a mixture of two epimers which were not separated. This mixture, however, showed two carbonyl peaks in its i.r. spectrum, at 1690 cm^{-1} and 1708 cm^{-1} (in the ratio *ca.* 3:1, respectively). From this it could be deduced that the major epimer produced on alkylation was 28a, for the following reason. It had been noticed that the carbonyl stretching frequencies in the i.r. spectra of 24 and 26a were somewhat lower than is normal for saturated cyclohexanones, and this had been attributed to steric crowding of the carbonyl group by the methyl substituents. Such effects have been recorded in the literature (39), although not extensively studied. Molecular models of 23, 24, 26a, 28 and 29 show variations in carbonyl-methyl non-bonded interactions as judged from the carbonyl oxygen-methyl distances, which parallel the variation in ν_{CO}. Thus in 23, $O-CH_3$ is *ca.* 3.5Å (ν_{CO} 1702 cm^{-1}) whereas in 24 there are two O/CH_3 interactions of about 2.8-2.9Å each (ν_{CO} 1693 cm^{-1}), similarly for 26a (ν_{CO} 1694 cm^{-1}). For 29 there are two $O-CH_3$ of about 3.0Å (ν_{CO} 1697 cm^{-1}). In 27a the most likely conformation is one with the secondary methyl group equatorial, and the cyclohexanone in a slightly flattened chair form (fig. 9), and this would give rise to three O/CH_3 interactions at about 2.8-2.9Å. One would thus predict ν_{CO} lower than 1693 cm^{-1}. However, in 27b the most likely conformation is one with the cyclohexanone in a twist-boat conformation, the secondary methyl group becoming pseudo-equatorial and the gem-dimethyl substituents being twisted right away from the carbonyl group (fig. 9). This would produce no oxygen-methyl distances less than 3.0Å, and thus one would predict ν_{CO} higher than 1697 cm^{-1}. Another heavily substituted cyclohexanone, cis-2-t-butyl-5-methylcyclohexanone, has been reported (40a) to exist preferentially as a skew boat, with the $-CH_3$ group equatorial. The structural similarity between this and 27b is considerable. There has been a recent report of the measurement of the inversion barrier in cyclohexanone (40b), the smallness of which suggests that a twist-boat conformation would be of quite low energy. Assuming that there is no epimerisation during hydrogenation, this would indicate that 27a was the major product from hydrogenation and hence that 28a was the major product of methylation. During one hydrogenation experiment some product of hydrogenolysis of the hydroxyl group was obtained, 26b. The i.r. spectrum of this showed it to be a mixture, having two carbonyl peaks at 1690 and 1707 cm^{-1}, again in the approximate ratio of 3:1.

The stereochemical assignments based on the i.r. spectra are consistent with formation of the equilibrium mixture of epimers at the secondary $-CH_3$ position α- to the ketone. It is expected that the kinetically controlled product would be the compound with axial $-CH_3$, i.e. 28b (41), (42). Since 28a is the major monoalkylated product (formed under equilibrating conditions), evidently the compound with the equatorial methyl group (and cyclohexane ring in a chair conformation) is the more stable epimer.

The reason for the difference in rates of alkylation of 23 and 24 (at least a factor of 100) is unclear. It may be that the proximity of the gem-dimethyl substituents to the carbonyl group hinders the twisting of the latter, which would be necessary for attainment of a mesomeric anion. The fact that no alkylation of 23 occurs at the ring-junction is reasonable, since alkylation of the anion at that position by methyl iodide would be severely hindered sterically.

Two methods of reduction of the carbonyl group were employed. Lithium aluminium hydride reduction in ether furnished a mixture of two diols, 30a and 30b, in the ratio of 2.6:1, with a combined yield of 80%. The structure of 30a was assigned on the basis of the normal addition of lithium aluminium hydride to ketones, hydride effectively entering from the least hindered side (26), (29). The structure of 30b became apparent from its dehydration (see below). The secondary -OH group was shown to be trans- to the secondary $-CH_3$ group and trans- to the adjacent methine proton at the ring junction. This assignment is consistent with hydride attacking the carbonyl group of 27b from the least hindered side if 27b exists principally with the six-membered ring in a skew conformation. None of the other possible epimers were observed. The ratio of the epimers obtained being the same as the ratio of 27b to 27a shows that the reagent did not epimerise the centre α- to the carbonyl group (41).

Reduction of 27 by sodium in isopropanol/toluene gave the three diols 30b, 30c, and 30d in yields of 43%, 20% and 28% respectively; no 30a was detected. The structures of 30c and 30d were assigned on the basis of comparison of the n.m.r. spectra of each. Compounds 30a and 30b show H_X as a narrow multiplet with base widths 8 and 9 Hz, half-height widths 4 and 5 Hz, respectively, both at τ 6.07 ppm. Structure 30c shows the same proton at τ 6.19 ppm also as a narrow multiplet with base width about 9 Hz and Half-height width 5 Hz. Compound 30d, however (in pyridine, since the compound was only slightly soluble in more convenient solvents), shows H_X as a very broad multiplet, with base width about 25 Hz, having the approximate shape of a double doublet. Such extensive splitting is evidently caused by two vicinal axial-axial

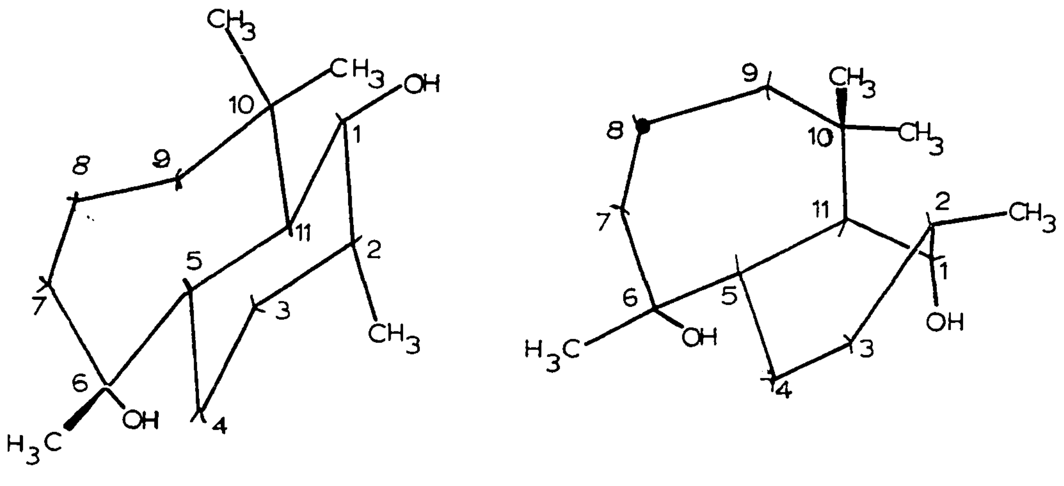


30a R = β-CH$_3$, Y = β-OH

30b R = α-CH$_3$, Y = β-OH

30c R = α-CH$_3$, Y = α-OH

30d R = β-CH$_3$, Y = α-OH



A B

Fig.10

proton couplings (J_{ax-ax} in cyclohexanes 7 to 11 Hz; J_{ax-eq} 2 to 4 Hz; J_{eq-eq} *ca.* 2 Hz) (43). Thus 30d must have the structure shown, with equatorial hydroxyl and equatorial methyl groups. Therefore 30c must, by elimination of the other three, have the structure shown.

Sodium in alcohol reduction conditions, generating sodium alkoxide, would tend to equilibrate the positions α- to the ketone prior to reduction of the latter. Isomerisation of the ring junction α- to the ketone to *cis*- is highly improbable. The proton that would be involved is extremely hindered, as has already been pointed out, and the molecules with *cis*- ring fusion have many more severe transannular interactions than those with *trans*-. Also, no α-himachalene (*cis*- ring junction) was detected from the subsequent dehydration reactions. The narrow line widths and chemical shift of H_x in 30a and 30b are consistent with the formulation of structures based on the previous conclusions, but the narrow line width of H_x in 30c is not consistent with H_x being axial in the normal sense of the word in this compound. This anomaly, together with the small difference (0.12 ppm) between H_x of 30a or 30b and 30c (normally $\Delta\tau_{ax-eq}$ is 0.4 to 0.5 ppm) suggests that H_x in 30c is not truly axial all the time and therefore that 30c has a high proportion of molecules with the cyclohexane ring in a partially mobile twist-boat form, making the secondary methyl more nearly equatorial than axial and the hydroxyl group pseudo-axial (cf.44).

Consideration of models, both flexibly bonded (Prentice-Hall F.M.M.) and rigidly bonded (Dreiding), of the various conformers of 30c leads one to the following conclusions. The lowest energy conformation with a chair cyclohexane (A in fig. 10) has five normal butane-gauche interactions and two partially eclipsed butane interactions. In addition there is a $CH_3(C_{10})$-$OH(C_1)$ interaction approximately equivalent to a 1,3-diaxial interaction in a chair cyclohexane, and a transannular interaction in the cycloheptane ring. The total enthalpy because of these interactions is estimated to be about 13 $kcal.mole^{-1}$ (45), (46). When the cyclohexane is modified to a skew-boat, the lowest energy conformation (B in fig. 10) has four butane-gauche interactions and two transannular interactions. In addition the seven-membered ring is in a regular chair conformation, which has about 0.7 $kcal.mole^{-1}$ higher energy than the normal distorted chair conformation (47). The transannular cycloheptane C-H interactions are taken into account in this figure. The total enthalpy because of these interactions is estimated to be also about 13 $kcal.mole^{-1}$. These figures are necessarily approximate, but it can be seen that only a very subtle influence would be needed to render the conformation with a skew-boat cyclohexane the more stable. Such an influence may be, at least partly, the relative entropies of the two systems.

Space-filling models and Dreiding models show that in conformation A the cyclohexane ring is rigid, flexing of the cycloheptane is limited, and rotation of one of the methyl groups is severely restricted. In conformation B, however, rotation of all the methyl groups is unhindered, and both rings are comparatively flexible. Thus it can be concluded that conformation B would have a higher entropy than conformation A. Unfortunately, quantitative estimation of this entropy difference is not possible, but if the entropy of B were of the order of 3 e.u. higher than A ($\Delta S_{boat-chair}$ for cyclohexane is 2 e.u. (46)), this would give B a lower free energy than A, at room temperature, by about 1 kcal.mole^{-1}. A free energy difference of 1 kcal.mole^{-1} between the two conformers would ensure that the more stable one were present to the extent of at least 80%.

Chair cyclohexane (conformation A).

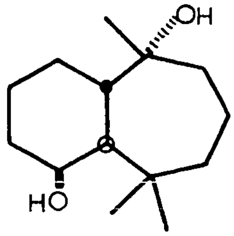
		ϕ^{o}	ΔH est'd
butane gauche	CH_3-C_2C_1-C_{11}	60	0.9
	CH_3-C_2-C_3-C_4	60	0.9
	CH_3-C_{10}-C_{11}-C_5	60	0.9
	CH_3-C_{10}-C_{11}-C_1	60	0.9
	CH_3-C_{10}-C_{11}-C_1	60	0.9
butane partially eclipsed	CH_3-C_{10}-C_9-C_8	45	1.5
	CH_3-C_6-C_5-C_4	35	3.0

transannular	$HO-C_6-HC_9$		2.0
others	$HO-C_1-C_{11}-C_{10}-CH_3$		2.0
			13.0 kcal. mole^{-1}.

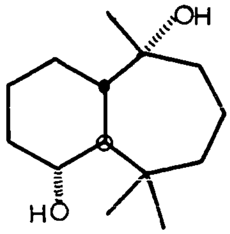
Skew-boat cyclohexane (conformation B).

butane gauche	$CH_3-C_{10}-C_{11}-C_5$	60	0.9
	$CH_3-C_{10}-C_{11}-C_1$	60	0.9
	$CH_3-C_{10}-C_{11}-C_1$	60	0.9
	$CH_3-C_6-C_5-C_4$	60	0.9
transannular	$CH_3-C_{10}-HC_2$		2.0
	$HC_{11}-OHC_6$		1.0
cycloheptane chair			0.7
cyclohexane skew-boat			5.5
			12.8 kcal. mole^{-1}.

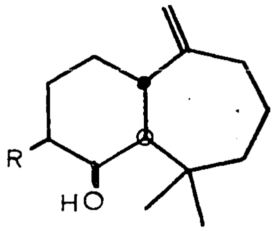
The hydrogenated compound *24* was also reduced with lithium aluminium hydride and afforded diols *40a* and *40b*, in the ratio *ca*. 3:1, the structures being tentatively assigned on the basis of the assignments for *30a* and *30b*. These served as useful models for the dehydration step. It was found that dehydration of the tertiary alcohol in *40a* could be conveniently effected by pyrolysis at 130° for ten minutes on silica. On the basis of spectra the major product appeared to be *41*. Dehydration of this mono-ol with phosphoryl chloride/pyridine afforded two dienes in the ratio 5:1 according to v.p.c. The major diene was tentatively assigned the structure *42*.



40a

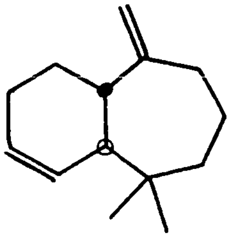


40b



41 R = H

43 $R = \beta\text{-}CH_3$

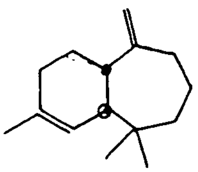
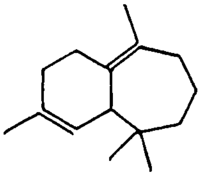
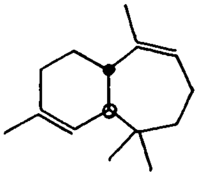
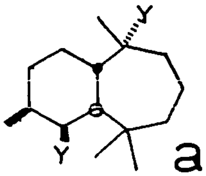
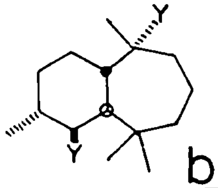
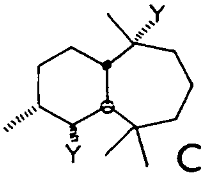
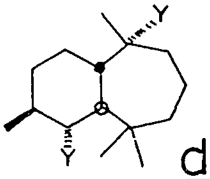


42

Dehydration of the diol 40a with phosphoryl chloride/pyridine gave the same two dienes, in the same ratio, according to v.p.c., with about 1% of another volatile product. In further preliminary experiments it was found that pyrolytic dehydration of 30a afforded a mono-ol, 43, phosphoryl chloride dehydration of which gave two dienes. A mixture of mono-ols was formed pyrolytically from diol 30b, and dehydration of this mixture gave a mixture of dienes. None of these dienes corresponded in v.p.c. retention time with α- or β- himachalenes.

Dehydration of each of the four diols, 30, with phosphoryl chloride/pyridine gave a complex mixture of dienes; these products are summarised in fig. 11. Dienes other than 2, 32, 33 were neither identified nor isolated; and it was assumed that they all contained the cyclohexene double bond exocyclic to the seven-membered ring. The three dienes 2, 32, 33 were isolated and 2 was found to be identical with the naturally occuring β-himachalene in every way (*i.e.* v.p.c. retention time, i.r. and n.m.r. spectra) except optical activity. The structures of 32 and 33 were assigned after consideration of their spectra and their chemical properties (see below).

The generally accepted mechanism for base catalysed 1,2-eliminations is preferential stereoelectronic control to give products derived from alignment of the reacting bonds in a *trans*-coplanar arrangement (45). Cases are

	 33 (%)[a]	 2 (%)[a]	 32 (%)[a]	Others (%)[a]
 a	4	2	2·5	90
 b	—	—	—[b]	98
 c	30	8	41	20
 d	25	8	29	36

30 Y = OH

31 Y = $OPOCl_2$

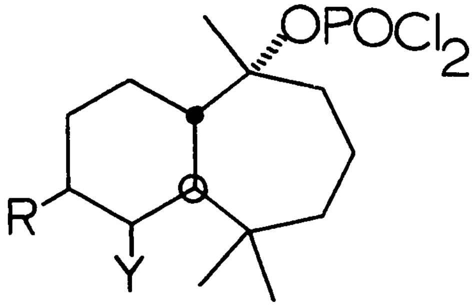
[a] ±1% (analysed by vpc)

[b] less than 0·5%

Fig. 11

known where cis-coplanar eliminations are preferred to non-coplanar (48), (49), but generally trans- elimination predominates. If there is a choice of which way an elimination should go, the acidity of the proton that is lost and the steric encumbrances around it can affect the direction of elimination, as can the relative energies of the transition states. Also to be considered is the Saytzeff elimination rule, whereby a double bond is predicted to be formed in the more highly substituted position.

The absence of dienes 2, 32 and 33 from dehydration of diol 30b indicates the hitherto unconfirmed stereochemistry of diol 30b. The secondary dichlorophosphate in the intermediate, 31b, must be trans- to the adjacent ring junction methine proton and cis- to the other adjacent proton. This would give elimination in only one direction to produce the double bond exocyclic to the seven-membered ring. Explanation of the relative yields of dienes from dehydration of the other diols requires more detailed consideration of the structures of the intermediate esters 31a, 31c and 31d. Elimination of the secondary hydroxyl group in diol 30a can, in theory, proceed in either direction with comparable facility. However, there is observed a considerable preference for elimination to give a double bond exocyclic to the seven-membered ring. If the secondary dichlorophosphate were eliminated first, elimination towards the seven-membered ring would considerably alleviate the transannular interactions and also some of the torsional strain in the seven-membered ring. This relief would probably be present to a certain extent in the transition state, reducing the activation energy required for elimination in this direction, compared with elimination in the other, and thus providing an explanation for the observed reaction. If the tertiary ester were eliminated first however, which would be more usual, α-, β- and γ- elimination would be expected (here and subsequently elimination of the tertiary ester α- signifies giving the exocyclic methylene double bond analogous to natural α-himachalene, β- signifies giving the endocyclic double bond which is exocyclic to the cyclohexane analogous to natural β-himachalene, and γ-signifies giving the other endocyclic double bond). After α- and γ- elimination there seems to be little reason for the secondary ester to eliminate towards the seven-membered ring, although after β-elimination formation of a conjugated diene would be preferred. Since all three dienes 2, 32, 33 are observed, albeit in small amounts, it is possible that the secondary dichlorophosphate is eliminated slightly faster than the tertiary. The situation is quite different in the dehydration of 31d. In this compound the secondary dichlorophosphate cannot assume a *trans*-1,2-diaxial relationship with any vicinal proton, and thus elimination of the secondary ester

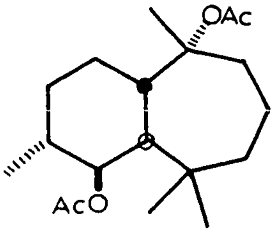


31a R = β-CH_3 , Y = β-$OPOCl_2$

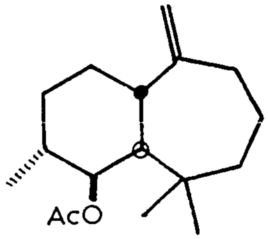
31b R = α-CH_3 , Y = β-$OPOCl_2$

31c R = α-CH_3 , Y = α-$OPOCl_2$

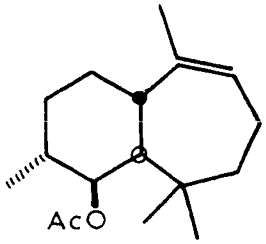
31d R = β-CH_3 , Y = α-$OPOCl_2$



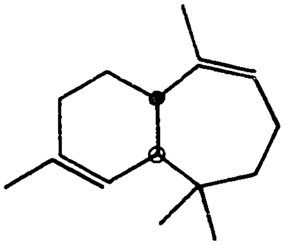
34b



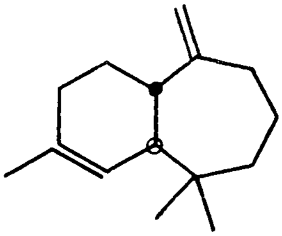
35



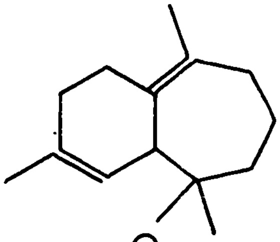
36



32



33



2

would be much slower than elimination of the tertiary. In whichever direction the tertiary ester eliminates there should be relief of torsional strain in the seven-membered ring, and so one would predict, from the Saytzeff rule, that there should be more β- elimination than γ- and more γ- than α-. When a double bond has been formed in the β- position in the seven-membered ring, this would render elimination of the secondary ester to give a conjugated diene, probably *via* a *cis*-coplanar transition state, more facile than elimination to give β-himachalene, 2. Elimination of the secondary ester from the intermediates having the α- and γ- double bonds is apparently much easier in the opposite direction. This may possibly be because approach of base to the proton involved is much less sterically restricted, in the skew-boat conformation necessary for coplanar elimination, than approach to the ring-junction proton. Compound 31c would be expected on the basis of *trans*-coplanarity to eliminate the secondary dichlorophosphate in only one direction to give ultimately dienes 2, 32 and 33 only. The fact that a higher proportion of these dienes is produced from 30c than from any other diol confirms the stereochemistry assigned to 30c. However, 20% of other dienes are observed, which must derive from *cis*-elimination of the secondary alcohol.

It has been noted earlier that there is probably a high proportion of molecules in 30c with a skew-boat cyclohexane ring. This is not likely to be the case in 31c, since a skew-boat conformation for this would require a *pseudo*-axial bulky dichlorophosphate group. A skew-boat conformation is, however, necessary for a rapid *trans*-diaxial elimination of the secondary ester. For this reason it is probable that the tertiary ester is eliminated faster than the secondary. As soon as the tertiary ester has eliminated, the skew-boat conformation of the cyclohexane ring becomes less favourable with respect to the chair conformation, thus slowing down the rate of *trans*-diaxial elimination even further. In the case where the cycloheptene double bond is in the β-position, *cis*- elimination to give the conjugated diene becomes the more rapid process, producing a much smaller amount of 2 than 32 or 33.

This interpretation of the observed dehydration results, although not rigorous, rationalises the disappointingly low yield of β-himachalene from all the diols.

Diol 30b, on vigorous acetylation, gave a mixture of the diacetate 34b and monoacetates 35 and 36. Reflux of the mixture in acetic anhydride for 12 hours completely converted 34b to the monoacetates. Pyrolysis of the mixture of 35 and 36 in the vapour phase at 560° gave a mixture of 70% 33 and 20% 32, no other dienes being detected. This is consistent with *cis*- elimination of acetate from both rings via six-centre planar transition states and concerted electron movements (45). The tertiary acetate would be expected to eliminate at a lower temperature than the secondary (50), and hence the production of dehydrated monoacetates during acetylation.

Treatment of natural α-himachalene, 1, with acid (30% formic acid/ether at 60% for 20 hours) effects isomerisation to β-himachalene (rapid and quantitative), which then undergoes much slower rearrangement to a mixture of many products. Dienes 32 and 33 undergo acid-catalysed rearrangement to β-himachalene much more slowly than α-himachalene. Treatment of 33 with 30% formic acid/ether at 80° for 20 hours gave a mixture of 40%, 33, 50% 32 and 5% 2. 32, after 600 hours under the same conditions, gave a mixture containing 48% 32, 6% 33 and 11% 2. These results can be summarised as in fig. 12.

The very rapid isomerisation of α-himachalene can be rationalised on the basis of the relative energies of the *cis*- and *trans*- fused six- and seven-membered rings. The substitution pattern is such that a *cis*- fused system necessarily has several severe transannular interactions. Protonation of the exocyclic methylene in α-himachalene would give the carbonium ion 7. Although 7 could then lose a proton to give a double bond in any of three positions, formation of the tetrasubstituted double bond would be so energetically favourable, because of the simultaneous removal of most of the steric interactions in the seven-membered ring, as to virtually exclude formation of the other two, *cis*- ring junction, possibilities. In

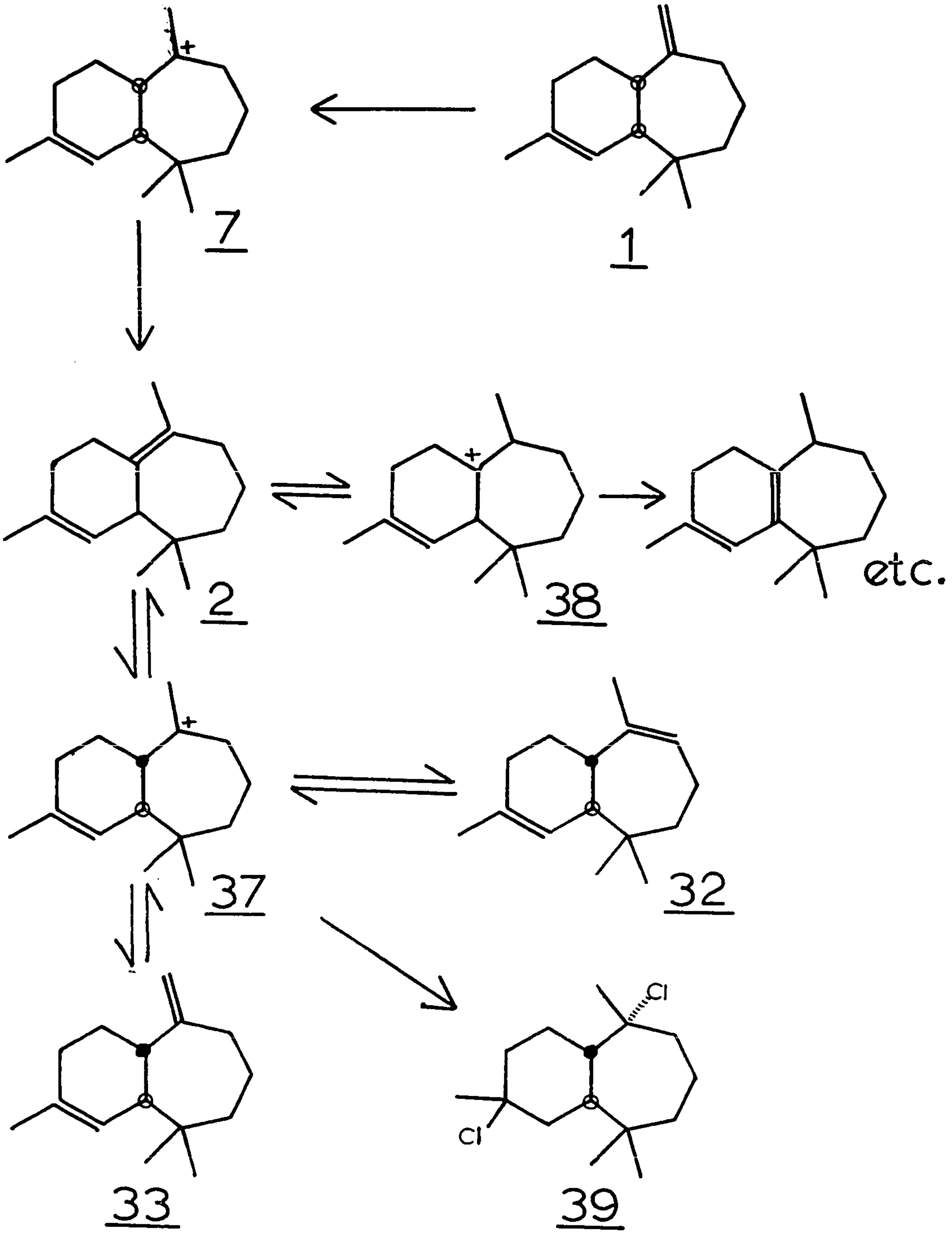


Fig.12

contrast, the carbonium ion 37, derived from the *trans*-ring junction dienes, would have much greater stability than 7, and would tend to partition elimination of a proton to give 2, 32, and 33 in comparable proportions. β-Himachalene would be expected to protonate the tetrasubstituted double bond at either carbon, giving 37 and 38. The latter carbonium ion could probably then either revert to 2 or lose a proton irreversibly to give a conjugated diene and hence the other acid-catalysed isomerisation products of β-himachalene.

The instability of the cation 7 is demonstrated effectively by the reaction of hydrogen chloride with α- and β- himachalenes (5),(7). Both give the same dihydrochloride in rather low yield. When dienes 32 and 33 were treated with hydrogen chloride gas under the same conditions, a dihydrochloride 39 was formed in somewhat higher yield. The i.r. and n.m.r. spectra of this compound were superimposable on those of the himachalene dihydrochloride. Base catalysed dehydrochlorination of the latter gave 10% 2, 20% 33, and no trace of α-himachalene. These results show that the dihydrochloride of the himachalenes has the *trans*- ring junction structure 39, derived from 37. This means that the cation 7, a necessary intermediate in the conversion of α-himachalene to 2 and 37, decomposes much faster than it can react with a chloride ion. The low yield of 39 from the himachalenes is then partly due to the competing formation of 38 rather than 37 from 2. Since β-himachalene is one of the products of base-catalysed, presumably *trans*-, dehydrochlorination of 39, the stereochemistry of one of the tertiary chloride positions can be assigned tentatively as shown. There is no evidence on which to base an assignment of the other asymmetric centre.

PART B. STEREOCHEMICAL CONTROL OF PHOTOCHEMICAL CYCLOADDITION.

INTRODUCTION.

Intermolecular photochemical cycloaddition of $\alpha\beta$-unsaturated ketones to olefinic double bonds is a comparatively recently discovered subject, the first publications being in 1962 (15), (53). Since that time many examples of the reaction have been discovered, and it appears to be a general phenomenon of which $\alpha\beta$-unsaturated ketone photodimerisation is a specific category. One feature that is apparent in the general case, at least insofar as liquid phase irradiations are concerned, is the large number of isomers that are formed in the reactions, and the variability of their ratios. "Head-to-head", X, "head-to-tail", Y, and *cis*, *trans*- isomeric adducts (fig. 13) are all formed in various ratios under different conditions of reactant structure, solvent and irradiation, (11a), (53a), (54).

No mechanisms have been accepted which are of general applicability in explaining the variation in product ratios. In some cases, *e.g.* preferential formation of anti-fused systems, steric effects would be expected to

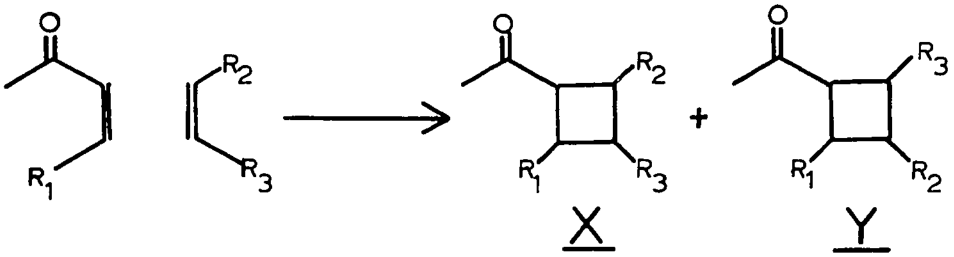


Fig. 13

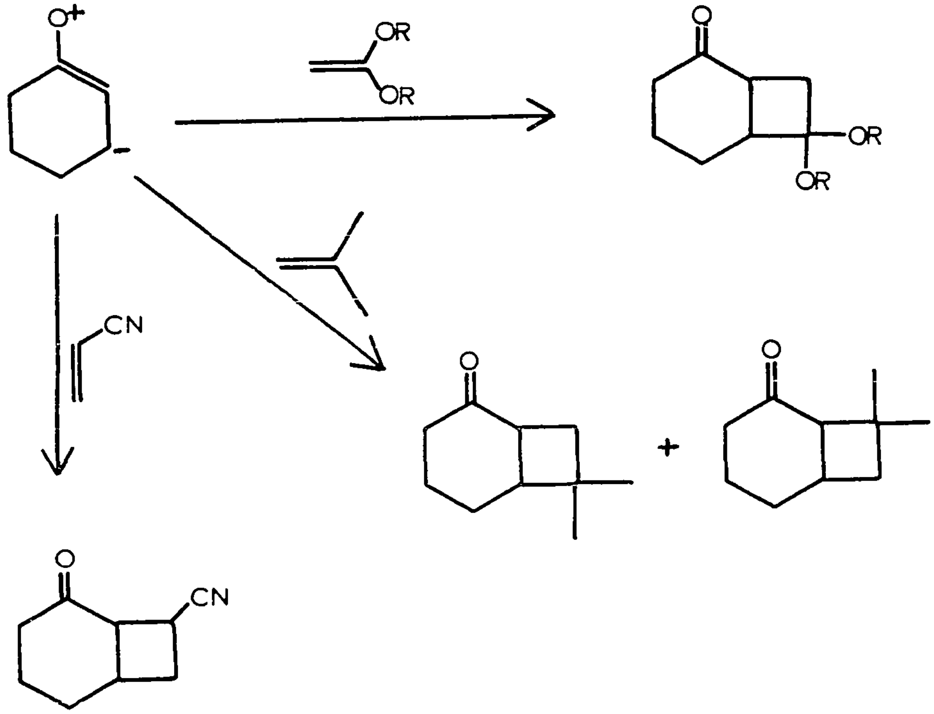


Fig. 14

play a major role in determining the product structure (e.g. dimerisation of ketosteroids, (55)).

Two explanations for the variations have involved postulating that different cycloadducts result from different spin multiplicities of the excited ketone (53a), (54a), or from different electronic distributions in the excited state ($n-\pi^*$ or $\pi-\pi^*$, (54b)). Another explanation for the particular isomers obtained in some cases is that of Corey (18) who proposed that the polar character of the reacting double bonds governed the type of product (head-to-head or head-to-tail) obtained (see Part A of this thesis). His explanation assumed that the excited state cyclohexenone reacted as if it were a charged species. Addition to olefins was then an electrophilic process and highly stereospecific with olefins that had considerable polar character, e.g. fig. 14.

The variability and general lack of predictability of the stereochemical course of cycloaddition seriously limits the use of the reaction as a synthetic tool. At the commencement of the research described in Part A, it was considered remarkably fortuitous that the cycloaddition reaction described there should have been so stereospecifically head-to-head.

In contrast with intermolecular cycloadditions, intramolecular reactions have been known for many years (11c) (one of the first was the irradiation of carvone (56)). A feature of these is that the reaction course is freq-

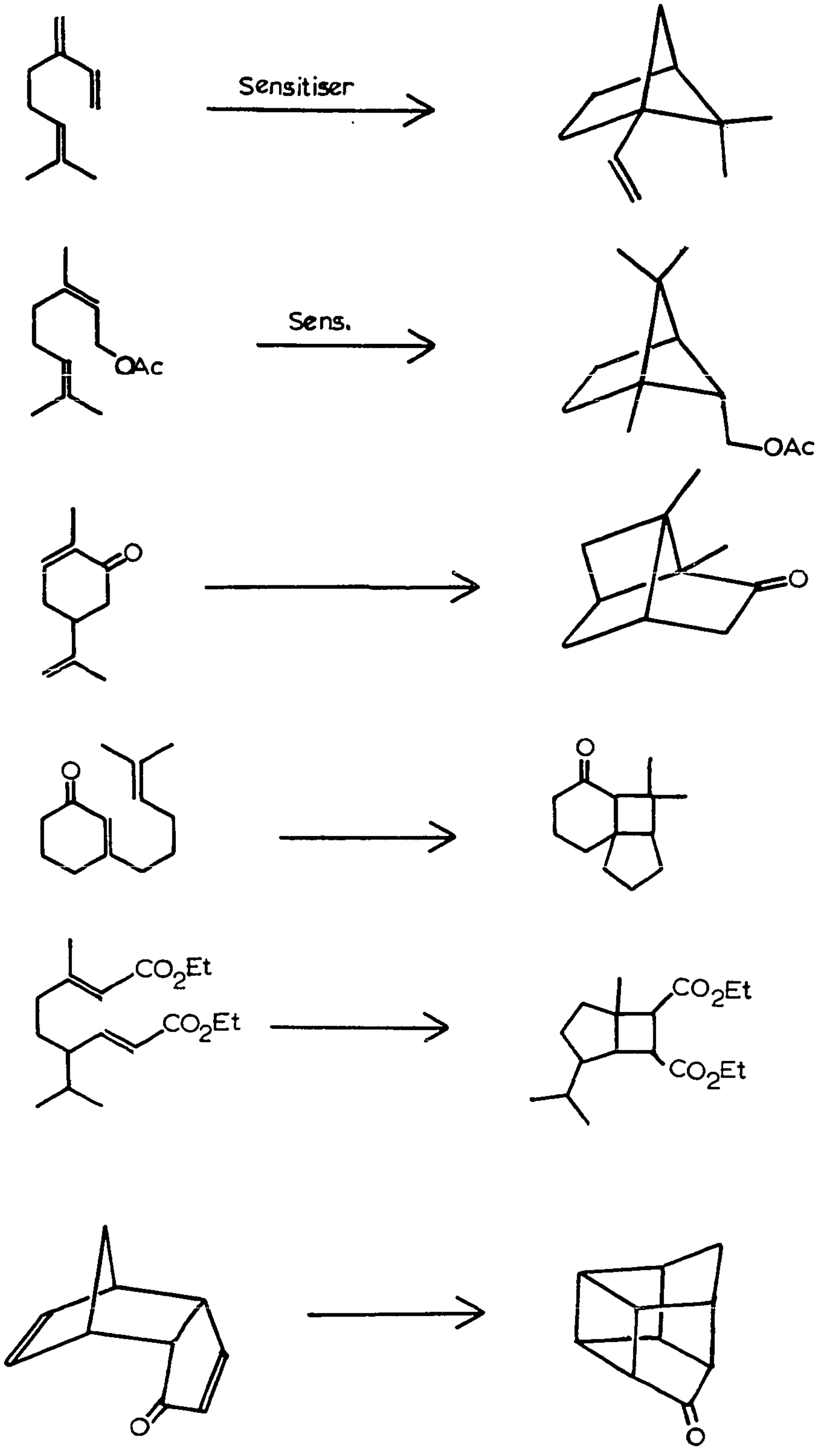


Fig.15

uently highly stereospecific, particularly when the reaction is sensitised. Some examples of these are shown in fig. 15 (57). It is noteworthy that in many cases the preferred mode of cycloaddition gives systems containing 5-membered rings rather than 4- or 6- whenever possible. This forms the basis for Srinivasan's empirical "rule of five" (58) which states that when there is a choice of ring size to be formed initially, five-membered ring formation is preferred to four- or six- membered. Subsequent coupling of the diradical formed by this process gives the bicyclic product.

It was thought possible that two olefinic double bonds, separated by between two and six atoms which were not all carbon, might undergo cycloaddition as stereospecifically as the examples mentioned previously. If the "linking group" of atoms were chosen so that it could be readily removed after cycloaddition a potential method of controlling predictably the stereochemical course of a cycloaddition reaction would have been found. Much of the research following (in Section (1)) is an attempt to achieve this by using various ester and ether linking groups.

Dimedone enol esters are known to undergo cycloaddition reactions with facility (16), and a chain of six atoms was arbitrarily chosen as the first linking group; it seemed likely that a longer chain between the reacting centres would inhibit intramolecular reaction. This was the basis for the choice of the first substrate, a dimedone enol succinate.

Subsequently, difficulties were encountered in attempted preparations of dimedone enol carbonates, and so a different unsaturated ketone was used. Cyclopentane-1,2-dione enol esters had previously been shown to give photochemical cycloadducts (86), and so enol oxalates and carbonates of this compound were prepared and irradiated.

After the unsuccessful work described in Section (1), it was decided to follow up the observation of stereospecificity in the cycloaddition reaction described in Part A. Section (2) comprises a study of the effect of solvent on this cycloaddition reaction.

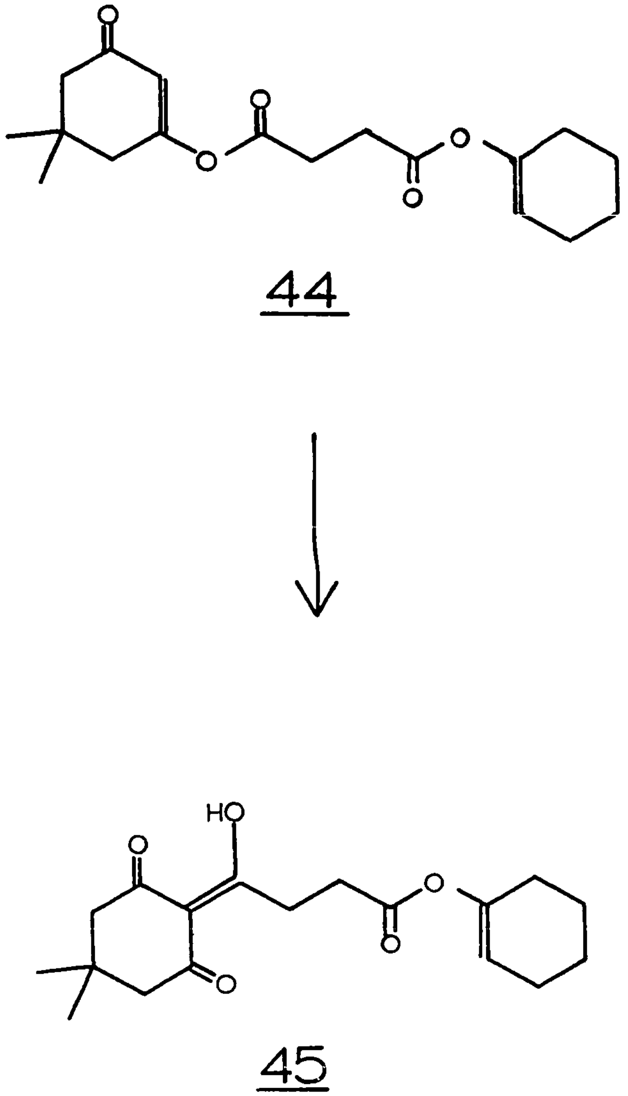
DISCUSSION.

SECTION (1).

$-O_2C.CH_2.CH_2.CO_2-$ Linking Group.

A 0.013M solution of cyclohex-1-enyl 3-keto-5,5-dimethylcyclohex-1-enyl succinate, 44, conveniently prepared from dimedone, succinyl chloride and cyclohexanone, was irradiated (in cyclohexane) and a smooth disappearance of starting material was observed. It was evident from the spectra of the product, after isolation, that cycloaddition had not occurred, but that the major product was the β-triketone 45.

Acyl group migration in this system is not unexpected and has ample analogy. Enol acetates and benzoates are known to rearrange photochemically (59) in this manner (fig. 16), and a similar reversible thermal arrangement is known (60). The mechanism for the photochemical rearrangement is thought to be *via* a pair of radicals which generally recombine in a solvent cage (fig. 16A). The major difference between the previously known cases and this one is that probably it is the ester carbonyl group that absorbs the light in the enol acetates and benzoates. In this case, since a pyrex filter was used, the cyclohexenone chromophore must have been the absorber, and the enol double bond excited initially. The mechanism would then probably be as in fig. 16B.



44
45

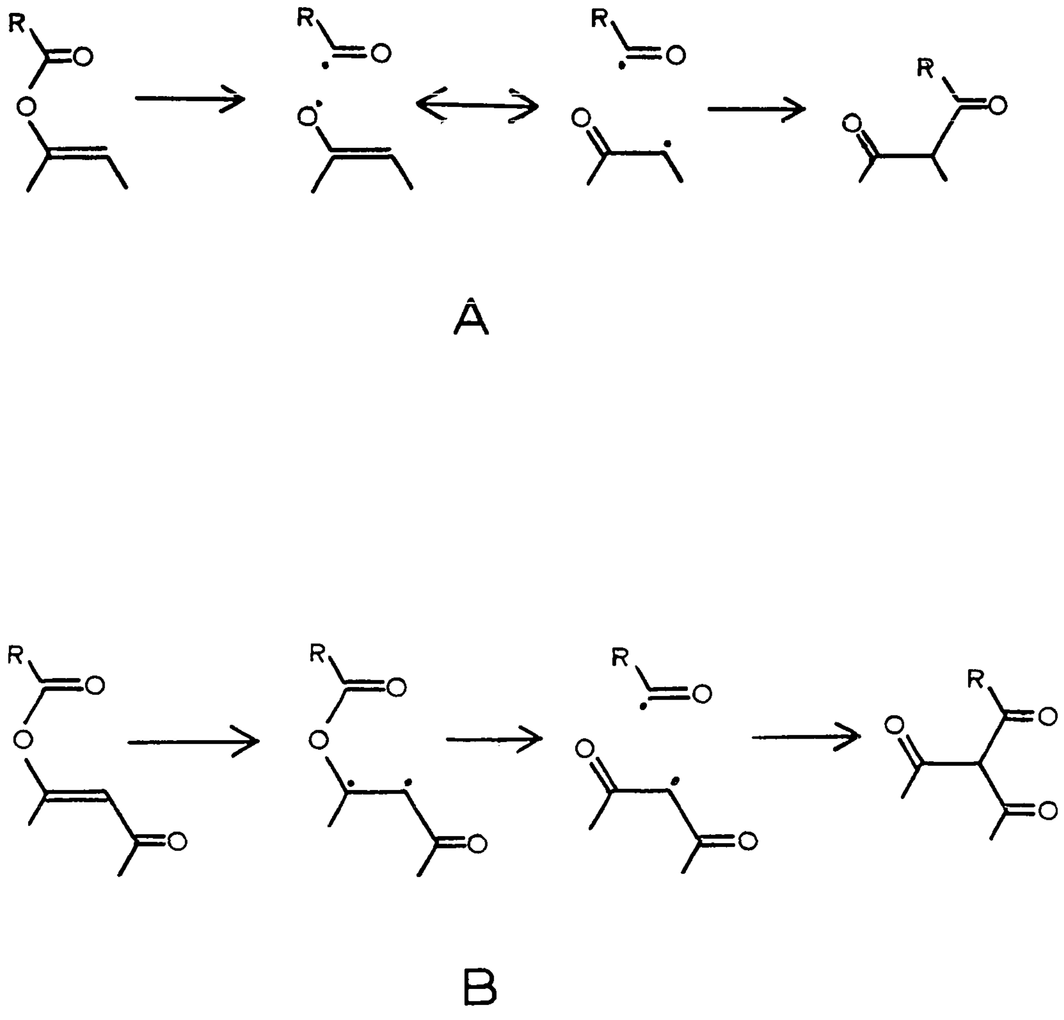
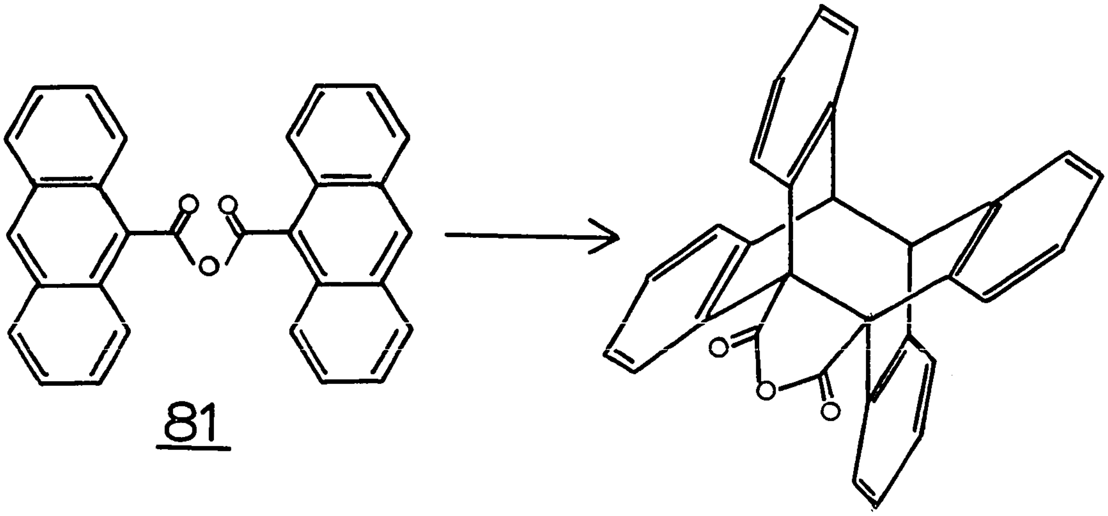


Fig. 16

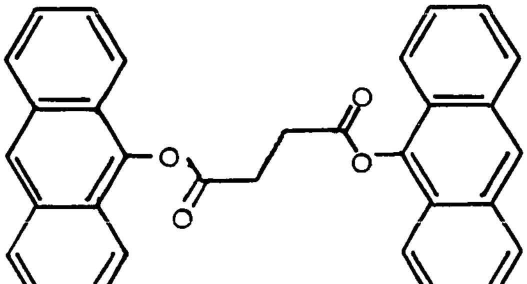
Dimedone enol esters are known to undergo intermolecular cycloaddition (16), so it is evident that the succinate linking group of six atoms places such a great distance between the double bond systems that fission to the pair of radicals becomes a more efficient process than cycloaddition of the excited enone to the isolated double bond. It is noteworthy that a simiiar situation occurs in di-anthracen-9-yl succinate, <u>80</u>. Irradiation does not give the monomeric cycloaddition product (as anthracene-9-carboxylic anhydride, <u>81</u>, does (61)) but gives a head-to-tail polymer (62).

<u>-COO- Linking Group</u>.

Cycloaddition of two olefins, connected by a carboxylate group, would give as the product a hydroxycyclobutanecarboxylic acid lactone, either β- or γ-. This would be expected to undergo facile hydrolysis and subsequent reactions could be performed specifically on the carboxylic acid residue or the hydroxyl function. In view of the high stereospecificity normally encountered in intramolecular cycloadditions it was expected that either the β-lactone (a bicyclo[2,2,0] system) or the γ-lactone (a bicyclo[2,1,1] system) would be formed, but probably not both, thus eliminating the difficulty of separation of mixtures of cycloadducts. In order to provide a synthetic goal, should the reaction proceed as planned, the system cyclopent-1-en-5-onyl 2-methyl-4-isopropylcyclohex-1-



81



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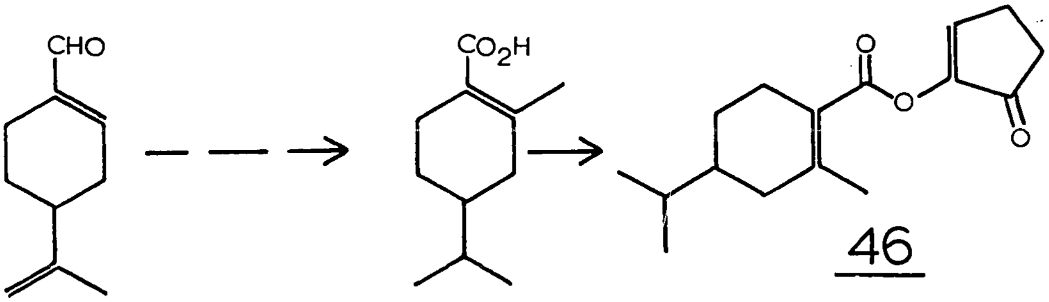


48

47

46

enecarboxylate was chosen, 46. This was conveniently prepared from the optically active acid 47 and cyclopentane-1,2-dione. The acid had been previously prepared from natural perillaldehyde 48, isolated from Shiso oil (by H. Hikino, in these laboratories). It was thought that either of the cycloadducts would then provide convenient intermediates for a short synthesis of hydroxyvaleranone 49, (63).

Irradiation of the ester, 46, in cyclohexane (.02M) with 350 nm wavelength light gave a mixture of mainly hydroxylic material and, apparently, a cycloadduct. The spectra and analysis of the cycloadduct showed that intramolecular reaction of both double bonds had occurred; the i.r. spectrum showed the presence of a strained γ-lactone and a saturated cyclopentanone, but no singlet methyl group was visible in the n.m.r. Hoping that this anomaly had a trivial origin, the cycloadduct was hydrolysed with dilute aqueous methanolic alkali. This treatment was expected to cause spontaneous rearrangement of the 1-hydroxybicyclo[3,2,0]heptan-2-one system initially formed, to a 1-hydroxybicyclo[2,2,1]heptan-7-one (fig. 17). This acyloin rearrangement has been observed in these laboratories to be extremely rapid (86). The product from this treatment was expected to be 50. The i.r. spectrum of the carboxylic acid product was consistent with this formulation, but methylation with diazomethane afforded two products, and not one, as anticipated. One of these com-

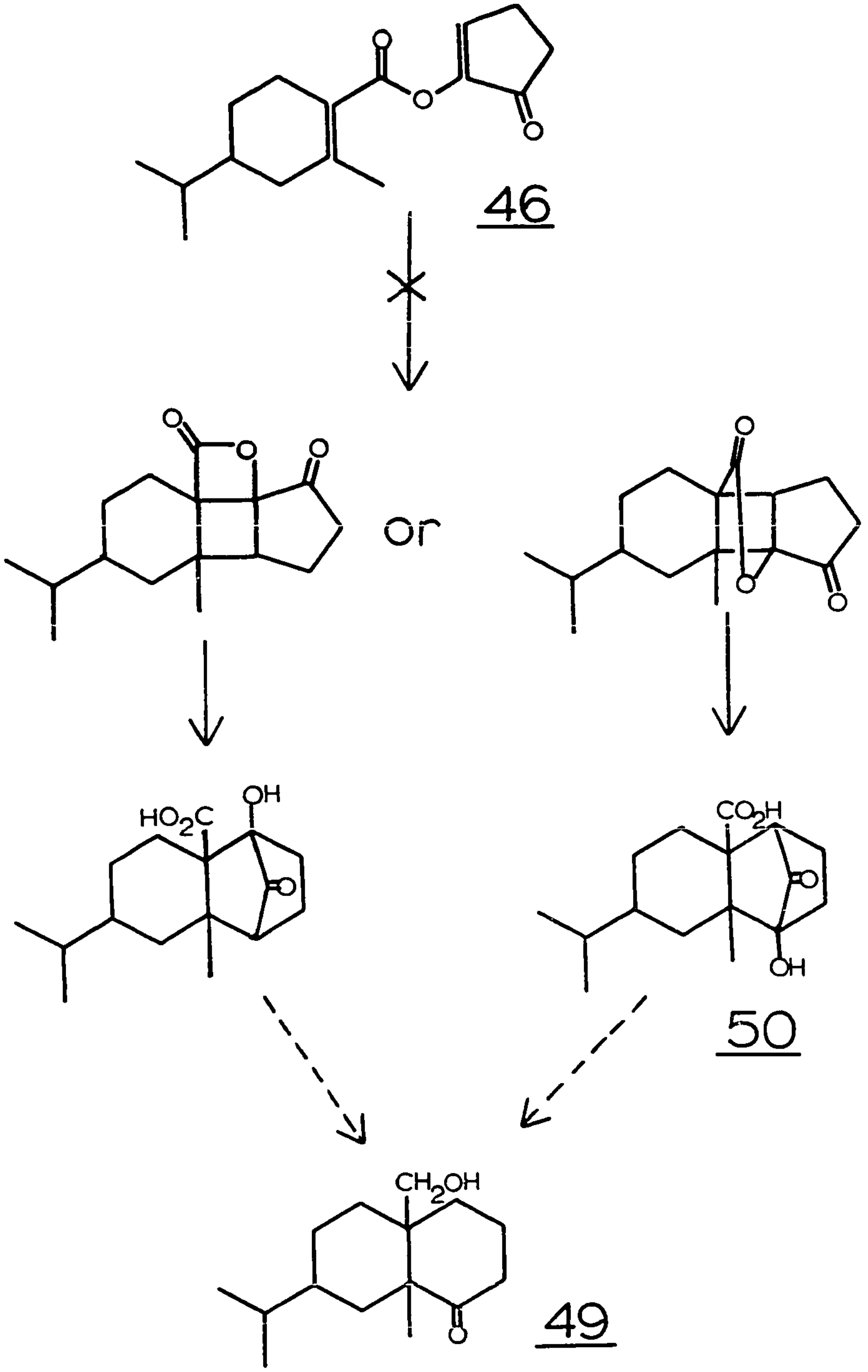


Fig. 17

pounds was evidently the methyl ester of the carboxyclic acid, whilst the other had an i.r. spectrum indicating the presence of two constrained carbonyl groups and no hydroxyl. In addition the n.m.r. spectrum of the ester again showed the absence of a quaternary methyl group.

The only explanation consistent with all these observations appeared to be that outlined in fig. 18. The tetrasubstituted double bond must have rearranged out of conjugation prior to cycloaddition to the cyclopentenone. The cycloadduct would then have a spirocyclic structure as shown, 51. Hydrolysis and rearrangement of this compound gave 5-isopropyl-1'-hydroxyspiro[cyclohexane-1,2'-norbornan-7'-one]-2-carboxylic acid, 52a. The possible alternative structure, 53, derived from a δ-lactone cycloadduct, was rejected when it was found that pyrolysis of the ester 52b converted it to a strained lactone, 87, identical with the byproduct isolated from methylation of the acid 52a. Such a lactone could only arise from the reaction sequence shown.

The cycloaddition reaction involved here has one interesting feature, that being the initial rearrangement of the cyclohexene double bond. Photochemically induced rearrangement of αβ-unsaturated ketones and esters to βγ-unsaturated is well-known in acyclic systems, and the mechanism is apparently well-established, (64). The excited carbonyl is considered to abstract a hydrogen atom from the γ- position *via* a 6-centre transition state (fig.

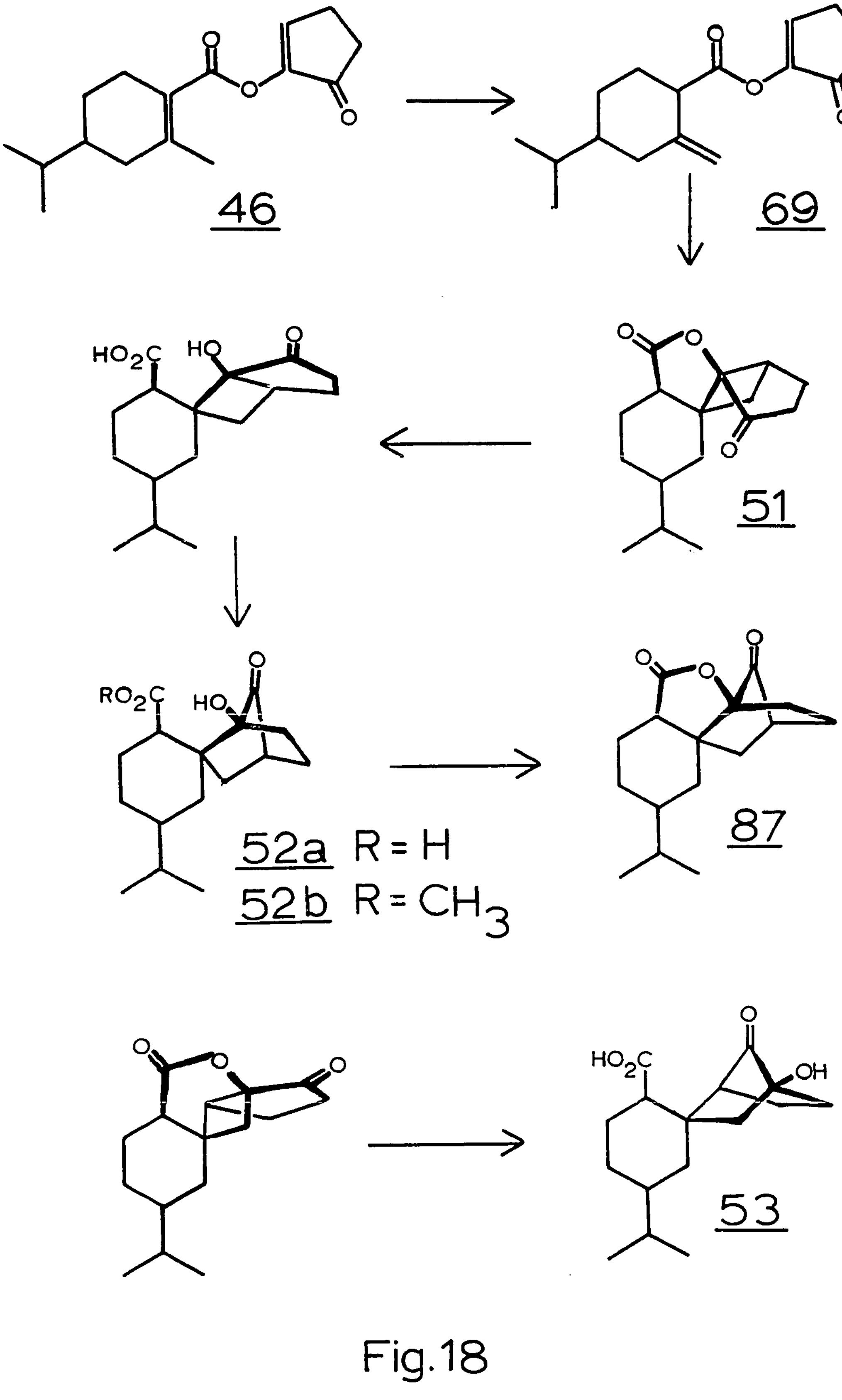


Fig.18

19). The electron distribution in the excited state is thought to be n-π^* (64), (65), and the multiplicity triplet, since compounds known to be in π-π^* states have been found to be resistant to hydrogen transfer reactions (64), (66), and the reactions are triplet-sensitised. One author has, however, suggested (67) that some results contradict a n-π^* excited state. A significant point is that radiation of wavelength less than 260 nm must be used to excite $\alpha\beta$-unsaturated esters (67). In this case the wavelength of the light used was greater than 300 nm. The principal absorption band in 46 at these wavelengths ($\lambda_{max.}$ 320 nm) was assumed to be due to the n-π^* singlet transition of the cyclopentenone moiety. However, the overlapping π-π^* of the enone and n-π^* and π-π^* absorption bands of 46 tail considerably to long wavelengths, and it is possible that there could be a measurable extinction because of these bands at wavelengths above 300 nm, i.e. under the enone n-π^* band.

The simplest explanation for the observed reaction is that it is the unsaturated ester that absorbs the light directly. Although such an absorption would be very inefficient at the wavelengths used, it may be that the subsequent deconjugation of the double bond is a much faster reaction than intramolecular cycloaddition of 46, making double bond rearrangement the favoured reaction.

An alternative explanation is that energy is being transferred to the ester function from the enone. Such

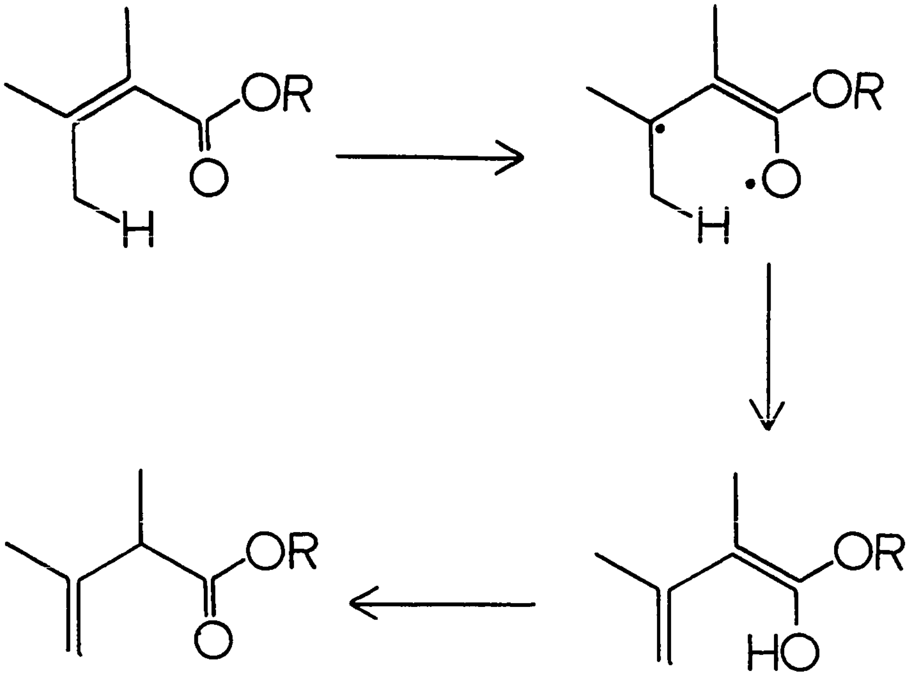


Fig.19

intramolecular energy transfers have been observed in both triplet and singlet excited aromatic systems, and there is a recent observation of such an effect in a non-aromatic enone (69). This explanation implies that there is an excited state, or a high vibrational level thereof, of the unsaturated ester group of lower energy than the cyclopentenone singlet or triplet. This must be either the $n-\pi^*$ or $\pi-\pi^*$ triplet states, since the singlet states are known to be of much higher energy. Alternatively, an "uphill" transfer of energy must be postulated, possibly via a "non-vertical" process (70).

-CH_2O- Linking Group.

In order to circumvent the possibility that the double bond rearrangement in 46, described above, was caused by energy transfer through the ester carbonyl group in some way, it was decided to attempt insulation of the two double bonds with a saturated carbon atom. The allylic enol ether, 54, was prepared by acid-catalysed condensation of the allylic alcohol, 55, and cyclopentane-1,2-dione. It was hoped that irradiation of this compound would produce a normal cycloadduct. Irradiation with 350 nm light in ether/cyclohexane gave a complex mixture of products; i.r. spectra after chromatographic separation showed that no cycloaddition product was present in greater than about 5% yield (only traces of material containing a saturated cyclopentanone carbonyl group).

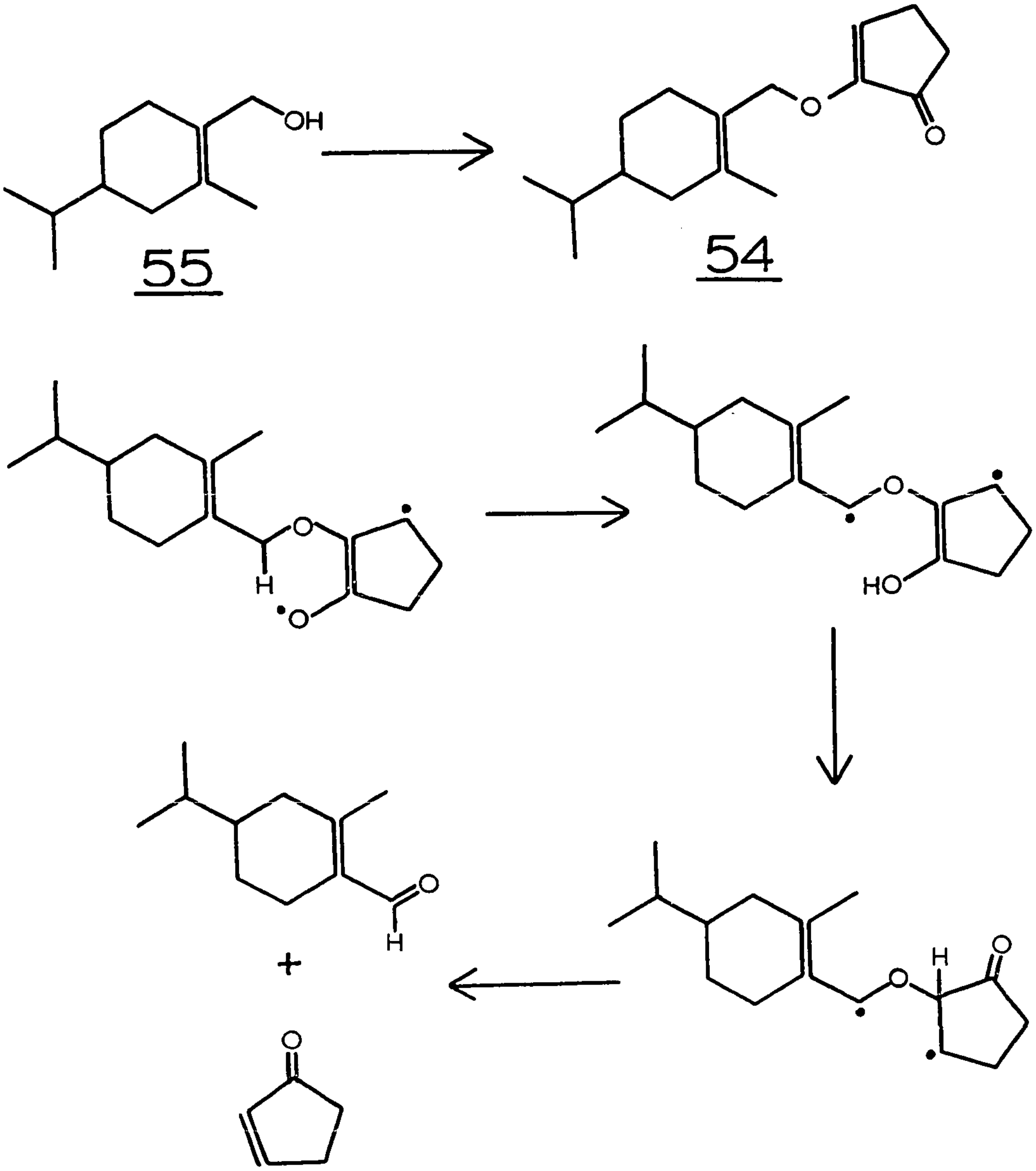


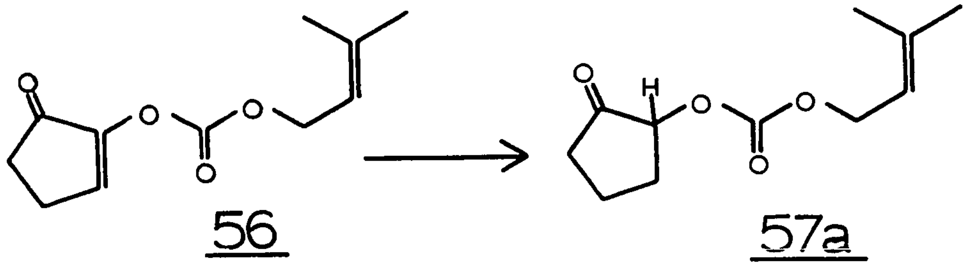
Fig. 20

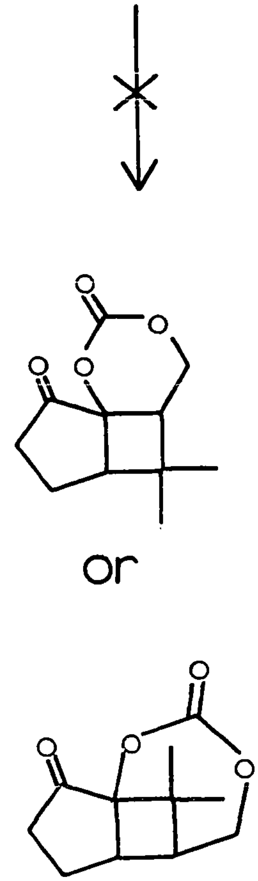
Most of the material was hydroxylic and very polar, but there was a significant production of 2-methyl-4-isopropylcyclohexene-1-carboxaldehyde (ca. 18% yield after purification). Sensitisation of the irradiation with triphenylene gave the same mixture of products, as did sensitisation with acetophenone. In this latter case there were several other products derived from the sensitiser (see Appendix).

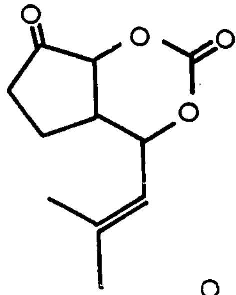
The aldehydic product was identified by comparison of the spectra with a sample prepared by oxidation of the alcohol 55. Formation of the aldehyde during the irradiation, rather than during the workup, was checked by following the appearance of the aldehyde by i.r. during the reaction. Its formation can be readily rationalised as in fig. 20. A six-centre abstraction of the activated hydrogen atom by the excited enone would be expected to be a facile reaction and a two-step mechanistic process as shown is likely. The cyclopentenone formed would react further under the conditions used, probably giving rise to some of the other observed products. There was no immediately obvious reason why the enone in 54 should abstract hydrogen rather than give a cycloaddition product. Some possible reasons for this, and the following observed reactions, are discussed at the end of this section.

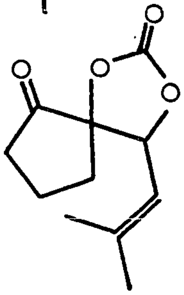
$-OCOOCH_2-$ Linking Group.

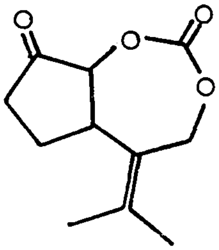
3-Methylbut-2-enyl cyclopent-2-enone-2-yl carbonate, 56, was prepared in good yield *via* the 2-chloroformylcyclopent-2-enone. This carbonate (.021 M in 10% ether/cyclohexane) was irradiated with "black light" ultraviolet ($\lambda_{max.}$ 350 nm), following the disappearance of the starting material by thin-layer chromatography. When no starting material remained the solution was evaporated. Spectra on the residue suggested that the material consisted of about 80-90% of one compound, but attempted chromatography showed that extensive decomposition occurred on silica gel. Elucidation of the structure of the major product was rendered more difficult by this facile decomposition. The i.r. spectrum showed that the product contained a saturated cyclopentanone, and a carbonate function and no hydroxyl. This ruled out the possibility of an acyl group migration analogous to that observed with the succinate, and suggested that cycloaddition had occurred. This possibility was also rejected after consideration of the n.m.r. spectrum, which showed that the two methyl groups were still attached to a double bond (six proton narrow multiplet at τ 8.21). Evidently then, the cyclopentenone had either been photoreduced by the solvent, to give 57a, or an intramolecular addition or hydrogen transfer of some kind, to give 57b-e, had occurred (the possibility of addition of solvent to the cyclopentenone was rejected

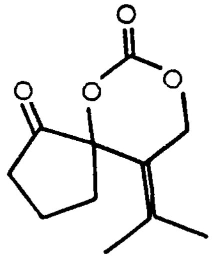





57b


57c


57d


57e

after consideration of the n.m.r. spectrum). The presence of a small amount of a normal cycloaddition product (less than 10%) was suggested by the presence of two small singlet peaks in the n.m.r. at τ 9.13 and τ 8.98. The presence of three protons appearing in the n.m.r. spectrum between τ 4.3 and 5.6 suggested that 57b or 57d were more likely structures than the others.

A decision between the possible structures was made after a few degradative experiments. Reduction of the crude irradiation product with lithium aluminum hydride afforded a mixture of very polar alcohols, which could be partially purified by chromatography. This reaction was expected to destroy the carbonate and give diols or triols from all the likely possible structures. All of these alcohols reacted smoothly and fairly rapidly with sodium periodate, and assuming that one mole of periodate was absorbed by one mole of each diol, titration gave the molecular weight of each diol as about 190. This confirmed that there was still an oxygen function at C_2 on the cyclopentanone in the irradiation product, and that the two halves of the molecule were joined together by a bond or bonds, other than those of the carbonate. This eliminated possibility 57a. Isolation of the oxidised products and examination of the u.v. spectra in neutral, acidic, and basic solutions showed that there were no $\alpha\beta$-unsaturated ketones present. This eliminated structure 57e (see fig. 21), and probably also 57b and 57c. To choose between the

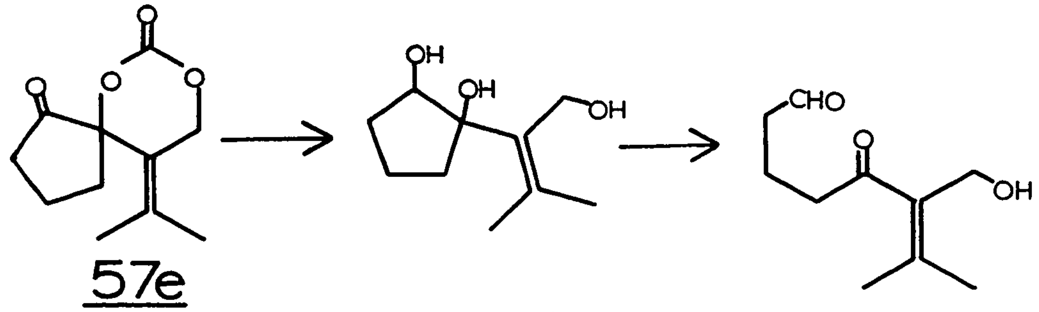

57e
OH
OH
OH
CHO
O
OH

Fig. 21

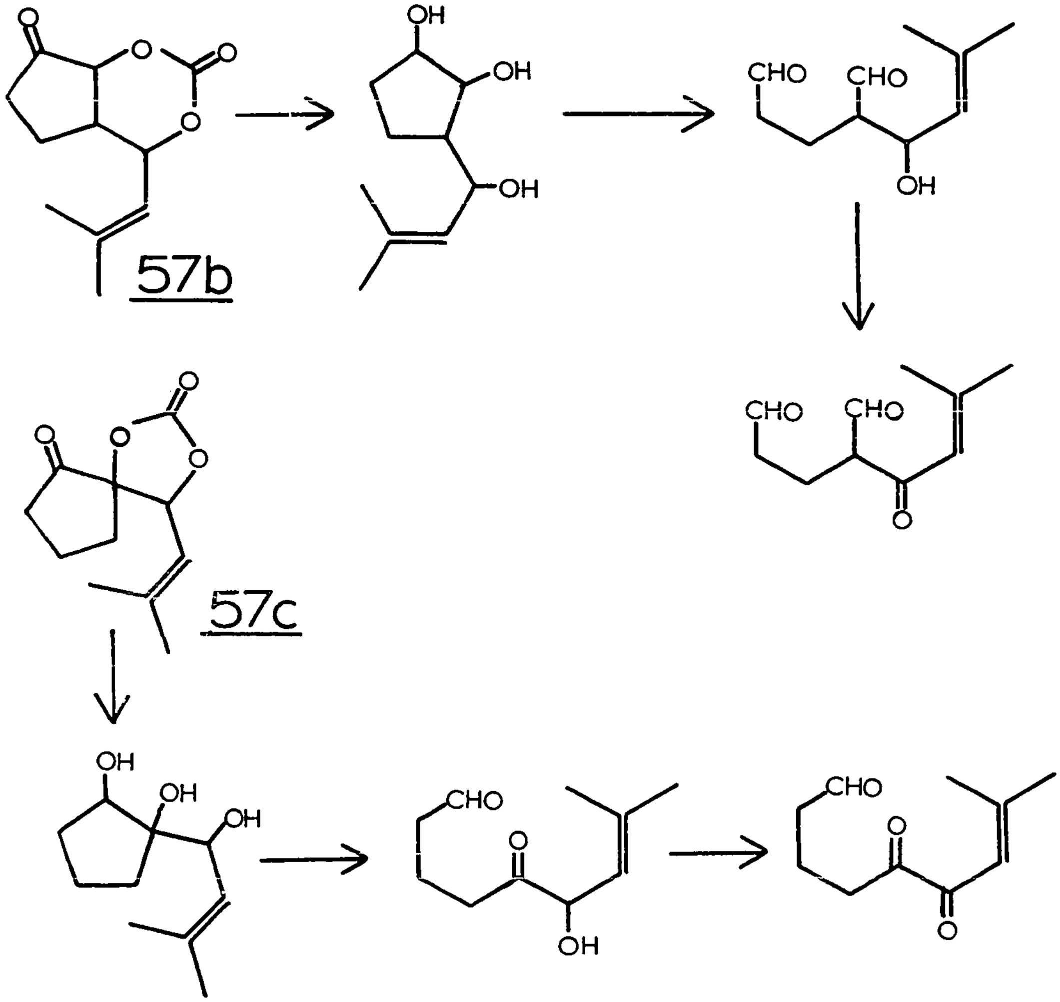

57b
57c
OH
OH
OH
CHO
CHO
OH
CHO
CHO
O
OH
OH
OH
CHO
O
OH
CHO
O
O

Fig. 22

remaining possibilities, the alcohols were oxidised with active manganese dioxide, a reagent known to be specific for allylic alcohols in short reaction times (41). Reaction was completed rapidly, all the alcohols giving only two products, which were separated chromatographically. One of these showed the presence of hydroxyl and an ester carbonyl group in the i.r., and the other showed hydroxyl, a γ-lactone, and a 1,1-disubstituted olefin. Neither showed strong u.v. absorption above λ=225 nm, even when treated with acid or base. These observations are consistent with only one of the remaining structures for the irradiation product, that being 57d. The triols derived from structures 57b and 57c would both give $\alpha\beta$-unsaturated ketones upon treatment with manganese dioxide, which would be stable to further oxidation (fig. 22). Structure 57d, however, would be expected to give the $\alpha\beta$-unsaturated aldehyde, 58a, which would cyclise to the hemi-acetal and then be further oxidised to the lactone 58b as shown (fig. 23). This would be the structure of the product showing the ester carbonyl group. The other compound, showing a saturated γ-lactone carbonyl, is probably 58c. This would be expected to be formed by migration of the double bond in 58b, if the latter had the strained trans- ring fusion.

Since one of the triols appeared to give the conjugated lactone, and the others the non-conjugated, it seems likely that both cis- and trans-ring junctions were present, and hence that both cis- and trans- fused irradiation

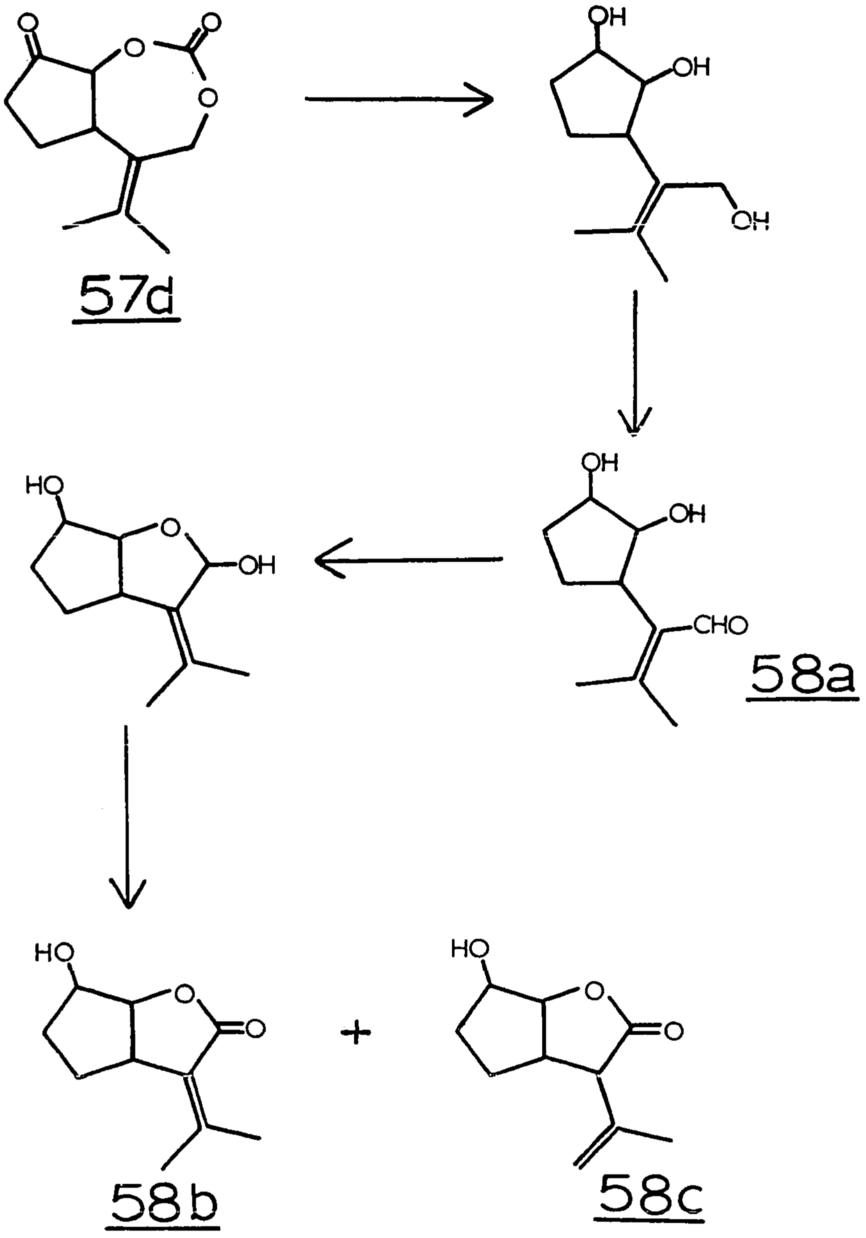


Fig. 23

adducts were formed.

To confirm the structural assignment further, another experiment was performed. Basic hydrolysis of the crude irradiation product under mild conditions afforded a complex mixture of products from which two could be isolated by chromatography. One of these was assigned the structure 59 on the basis of spectra, and its mode of formation. The u.v. spectrum was typical of a 3-alkylcyclopentane-1,2-dione, and under the mild conditions of formation, this could be reconciled only with hydrolysis and prototropic rearrangement of the product as shown in fig. 24. The i.r. and n.m.r. spectra are in complete accord with this assignment. The other compound isolated from the hydrolysis was crystalline and had elemental analysis suggesting dehydration of 59. The u.v. spectrum showed that it had an enolised cyclopentane-1,2-dione chromophore, and the i.r. and n.m.r. spectra suggested that it was dimeric.

-OCO.COO-CH_2 Linking Group.

The oxalate, 60, analogous to the carbonate, 56, was prepared in a similar manner *via* cyclopentane-1,2-dione enol chloroglyoxalate. Irradiation of this diester (0.008 M in 20% ether/cyclohexane), under the same conditions as irradiation of the carbonate, afforded an unstable product, the spectra of which were very similar to those of the carbonate irradiation product, and suggested that the struc-

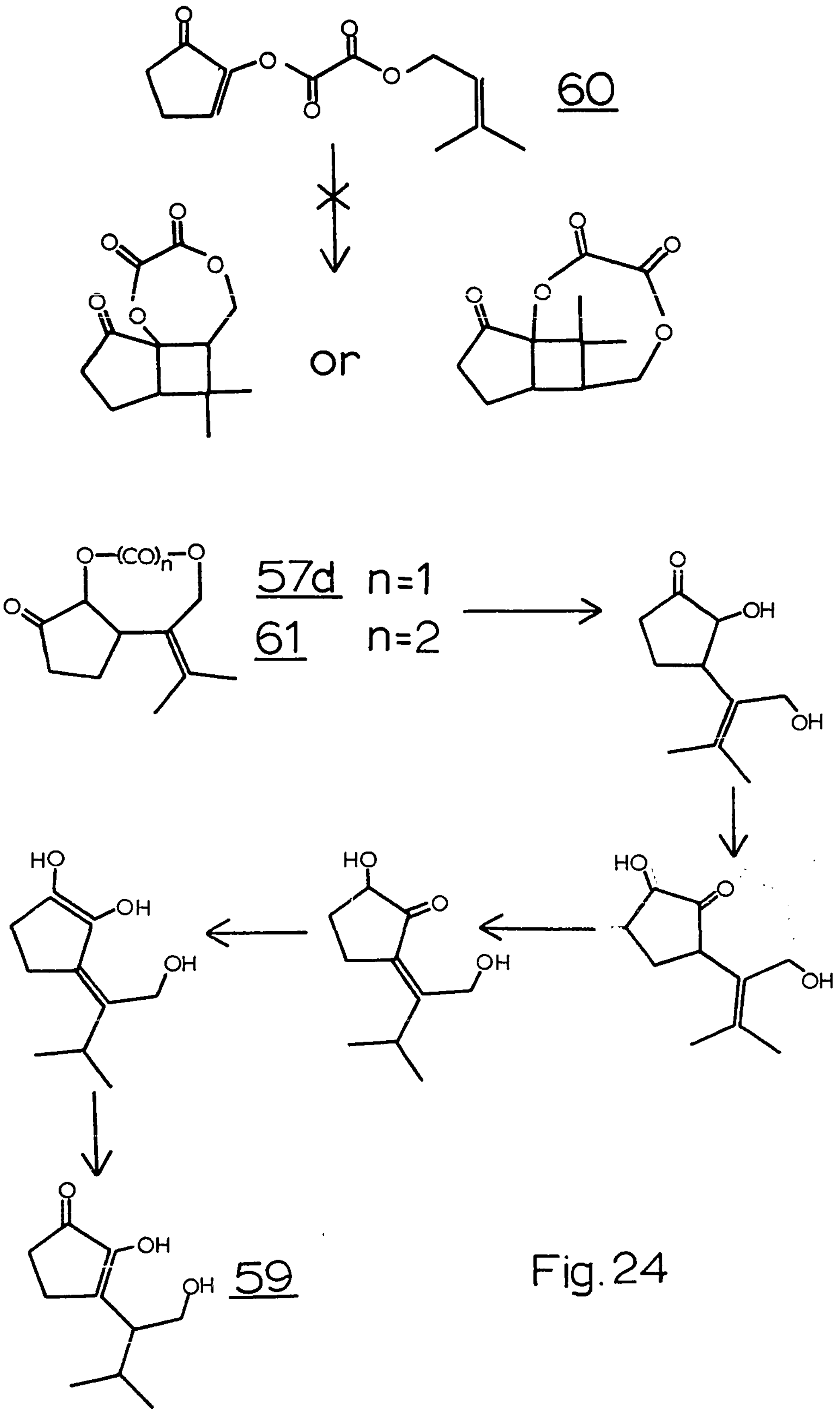


Fig. 24

ture was analogous, i.e. 61. This was confirmed by basic hydrolysis of the product under mild conditions. From the complex mixture of products two compounds were isolated which were identical, according to chromatographic R_f, i.r. and u.v. spectra, and mixed m.p. (for the crystalline compound) with the two isolated products from the hydrolysis of 57d.

It is interesting to speculate on how these two compounds, 57d and 61, could have arisen by irradiation. They are evidently the products of a two-step reaction, namely, hydrogen transfer and addition.

Intermolecular photoreduction of αβ-unsaturated ketones (71), and of other systems (72), by various solvents is known, and ether (the use of which, as a co-solvent, was necessary because of the low solubility of the carbonate and oxalate in hydrocarbons) is a good hydrogen donor. However, an initial abstraction of a hydrogen atom from the solvent by the excited enone, path A, fig. 25, followed by coupling of the radical to the isolated double bond would require either that a non-activated H atom (H^2) then be abstracted from 62 in order for the product to be formed, or that an intramolecular hydrogen atom migration occur after abstraction of an activated hydrogen atom. Neither of these pathways seems satisfactory. Initial intramolecular abstraction of H^1, path B, seems much more plausible, but then the product would be expected to be 57b and not 57d (cf. (69), (73)). Initial addition of the

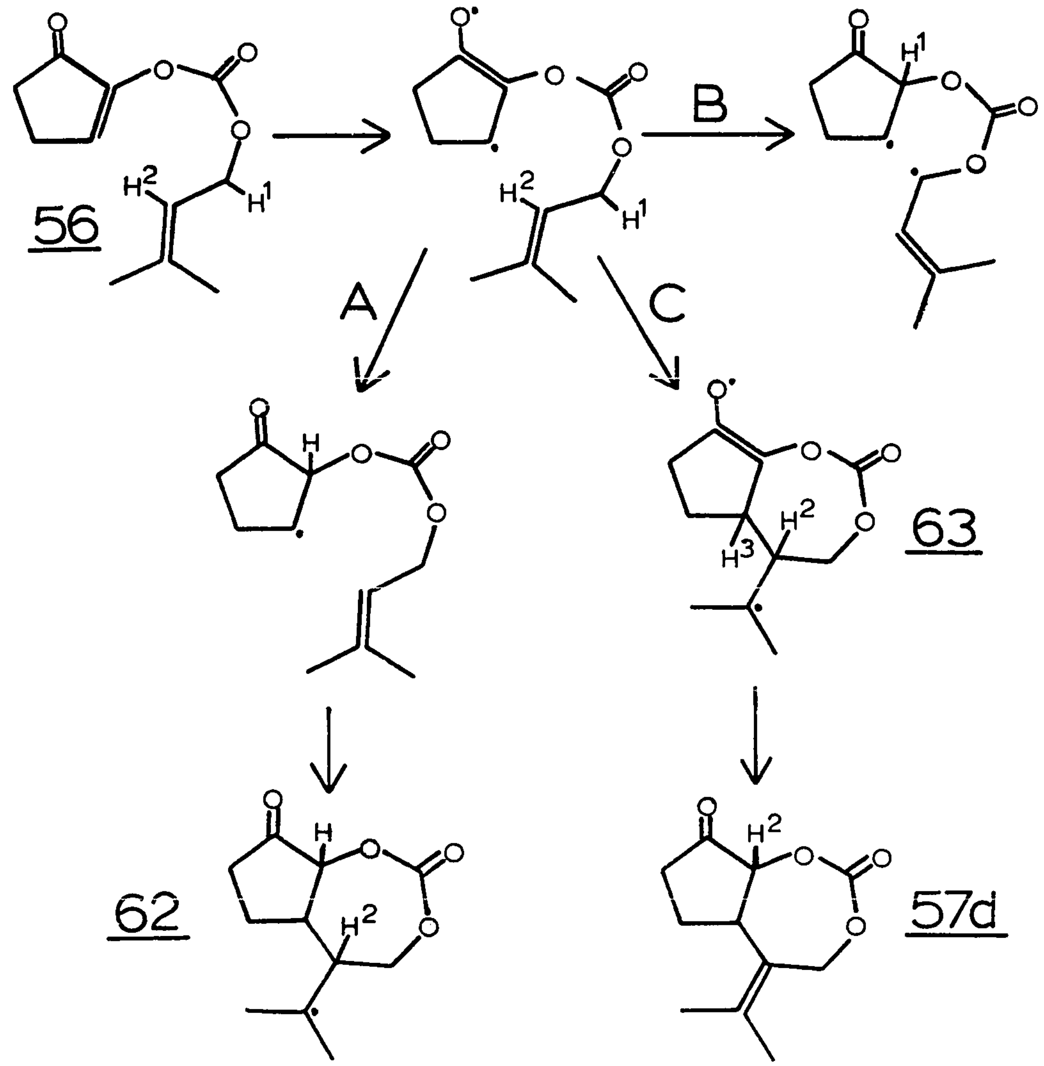
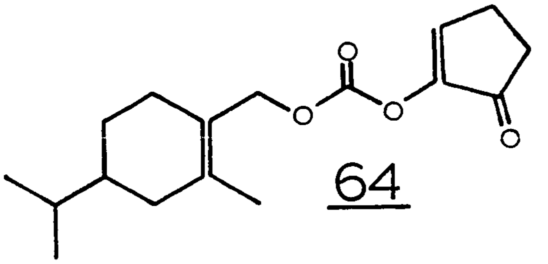


Fig. 25



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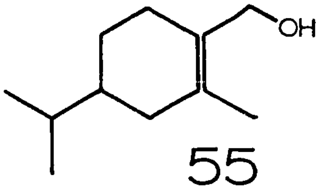
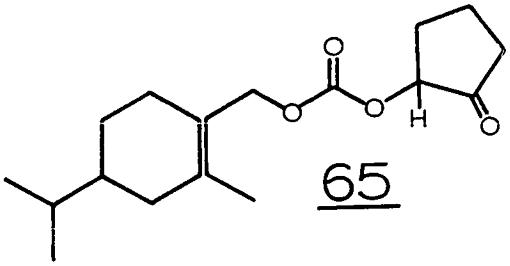


55



65

excited enone to the isolated double bond (path C), followed by transfer of a hydrogen atom across the ring seems to be the most acceptable mechanism. Since two diastereomeric diradicals, 63, could be formed, and these could transfer H^2 to opposite sides of the cyclopentanone (cis- and trans- to H^3), this mechanism would also explain the supposed production of both cis- and trans- cycloadducts.

It seemed possible to test this hypothetical mechanism of initial addition of the chromophore to the double bond and subsequent hydrogen atom migration by irradiating a similar system with H^2 replaced by an alkyl group. If an intermediate analogous to 63 were formed, the addition to a cyclobutane would be expected to be completed, since there would then be no convenient hydrogen atom to migrate. Accordingly the carbonate 64 was prepared, and irradiated under various conditions. Irradiation in cyclohexane with 350 nm u.v. light gave a complex mixture of products, including hydroxylic material, and several compounds that apparently had lost the carbonate function. An n.m.r. spectrum on the mixture of products showed no vinyl protons, and apparently there had been no cycloaddition. Irradiation in ether gave rapid conversion to 65. This was identified by its spectra and hydrolysis to the alcohol 55. Irradiation of 64 in acetone (350 nm) gave no reaction, and attempted photosensitisation of cycloaddition by benzene in cyclohexane again gave a complex mixture of products, with little or no cycloaddition.

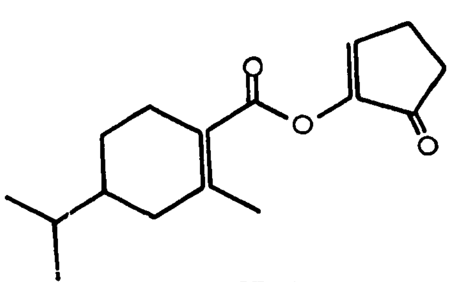
Evidently this compound seems to react principally by intermolecular hydrogen abstraction (71). It is therefore possible that the compounds 56 and 60 initially abstract a hydrogen atom either from the solvent or intramolecularly, and subsequently add to give the observed products 57d and 61.

Attempts to produce stereospecific intramolecular cycloaddition of all the compounds considered here have been abortive. It is of interest to speculate on the possible reasons for this lack of cycloaddition. The reason in the case of the succinate derivative seems to be apparent; the two olefinic centres are too far apart to permit ready cyclisation. However, this cannot be the reason for lack of cyclobutane formation in the carbonate and oxalate systems, since intramolecular addition does occur in two cases.

In the case of unsubstituted cyclopentenone (74) it is known that two triplet states are involved in different photochemical reactions, and that decay from one triplet state to the other is a comparatively slow process. The higher energy triplet, T_2, undergoes cycloaddition, whereas the lower, T_1, abstracts hydrogen and does not cycloadd. It is probable that one is $n-\pi^*$ and the other $\pi-\pi^*$, but it is not apparent which is which. The comparative energies of the $n-\pi^*$ and $\pi-\pi^*$ singlet excited states of enones are known (75), and the change in these when the chromophore is substituted is also known. The energy level of the n electrons is considered to be between the π and π^*, and substitution of electron-donating groups on the ethylenic double bond raises both the π and π^* levels, thus increasing the energy of the n-π^* state and decreasing that of the π-π^* state. The corresponding effect of substitution on the energies of n-π^* and π-π^* triplet states is not known for $\alpha\beta$-unsaturated ketones, nor is it often known whether n-π^* or π-π^* excited species are responsible for phosphorescence in other compounds. However, certain compounds which are thought to phosphoresce from n-π^* states, e.g. acetophenone and benzophenone, show an increase in E_T when substituted by electron donors. This parallels the corresponding singlet n-π^* effect, and if it is assumed that the substituent effect on E_T of π-π^* also corresponds to the effect on the energy of the singlet π-π^*, then it can be seen that the difference between the energies of the n-π^* and π-π^* triplet states could vary considerably depending on the substituent and the solvent used. This may well produce different reactions from differently substituted cyclopentenones, depending on which triplet has the lower energy, the energy separation of the two triplets, and the ease of internal conversion between them.

It is noteworthy that most of the systems that have been observed to undergo intramolecular cycloaddition in solution have had two or three saturated carbon atoms between the olefinic double bonds (11c), (58). In the cases here, the compound, 69, with three atoms, not all saturated carbon, between the double bonds, also undergoes cycloaddition (although 54 does not). However, the carbonate and oxalate systems considered have four and five atoms between the double bonds and normal cycloaddition does not occur. This suggests that in systems where the rate of cycloaddition, because of the conformational strains involved, would be expected to be small, and where other reactions (such as hydrogen abstraction) can occur, then the other reactions involved become seriously competitive with cycloaddition. This suggestion can be modified to fit the observation of two excited triplets undergoing different reactions by postulating that certain substituted cyclopentenones could have much faster rates of internal conversion between the excited triplet states T_1 and T_2 (which may be of very similar energy) than cyclopentenone itself has. The predominant observed reaction would then be whichever chemical reaction proceeded faster.

Although no other systems were investigated, it seems possible that compounds of the types 82 (divinyl carbonates), 83 (unsaturated acid anhydrides) and 84 (unsaturated allyl carboxylates) would be worth investigating as probably more suitable for intramolecular cycloaddition than those described here.



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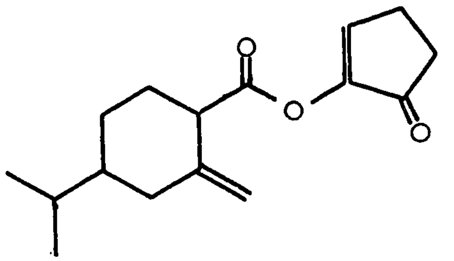

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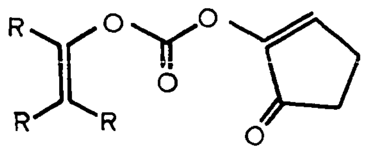

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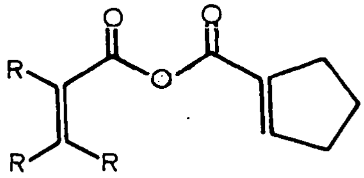

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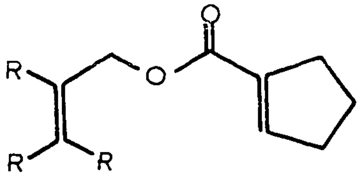
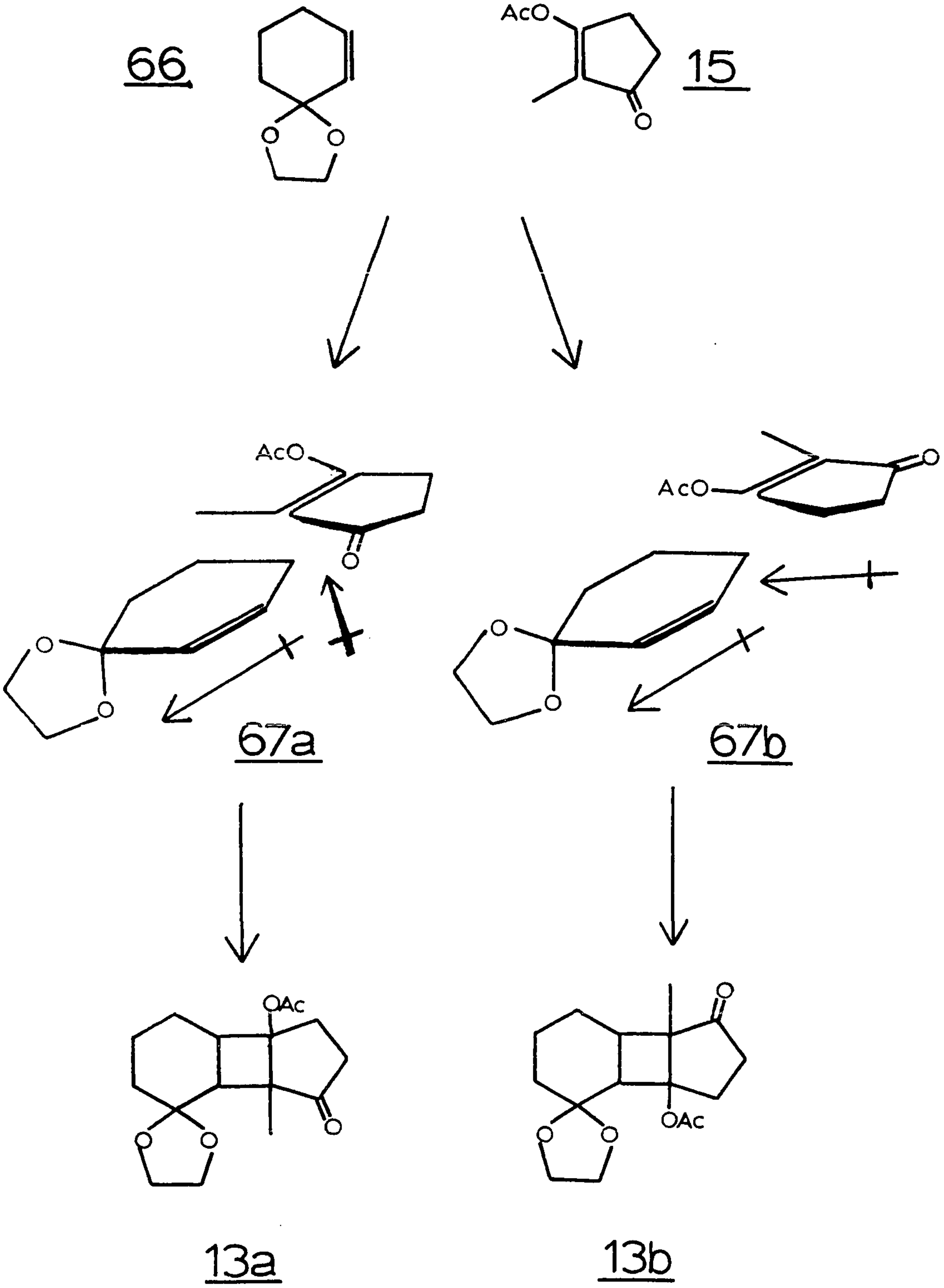


84

SECTION (2).

In Part A of this thesis some of the possible causes of the stereospecificity of the cycloaddition of 15 to 66 were discussed at length. The polar character of the double bond of 66 was considered in the light of Corey's findings regarding stereospecific cycloadditions (18) and the steric restrictions of the two modes of addition were examined. Both of these explanations were rejected in favour of a third, that being that the orientation of the dipoles of the reactants at the moment of reaction exerted a considerable effect on the direction of cycloaddition. Calculations of the dipole moment of the excited enone (which appear in the experimental section) suggested that this moment was appreciable and its direction was such as to give rise to 13a when opposed to the dipole moment of 66. If this explanation is valid, then a significant change in the stereospecificity of the reaction should be observable when a reaction solvent of high dielectric constant is used in place of cyclohexane. In order to confirm that this was so, and to investigate a potential method of controlling the direction of cycloaddition reactions, the effect of different solvents on this system was studied.

The theory behind these studies is derived from elementary kinetics and Kirkwood and Onsager's equations, and is basically the same as that used by Berson (21) in his studies of solvent effects on Diels-Alder reactions.


66
AcO
15
AcO
AcO
67a
67b
OAc
OAc
13a
13b

The molecular geometry of the two transition states for formation of the two anti-adducts is considered as being approximately expressed by **67a** and **67b**. Since the methods are the same in both cases and it is assumed that both reaction paths would follow the same rate laws, and that kinetic control is observed, then the product ratio P_A/P_B is equal to k_A/k_B, where k is the rate constant for the first stage (assumed to be the slower) of the reaction path A or B. Also $\ln(k_A/k_B)$ is proportional to the difference in the free energies of activation of the two paths, *i.e.* the difference between the free energies of the two transition states, ΔF_{A-B}. The free energy of a transition state depends on many things, which can be grouped into "steric" and "electronic" factors, taking the meaning of these terms in the widest possible sense.

$$\Delta F_{A-B} = \Sigma(F_A^{\mathrm{steric}} + F_A^{\mathrm{elect.}}) - \Sigma(F_B^{\mathrm{steric}} + F_B^{\mathrm{elect.}})$$

If all the contributing factors to F_A and F_B are the same, then $\Delta F_{A-B} = 0$, and the two reaction paths will be equally probable. If all these factors are not the same, then the two reaction paths will not be equally probable.

Considering the particular case involved here, the two transition states are very similar in size and shape, and little difference would be expected between the steric contributions to their energies, in any environment. The "electronic" factors can be divided into two categories: (a) specific internal electronic interactions of the two reactants, and (b) the overall electronic distribution throughout the transition state. Category (a) would be extremely difficult to estimate quantitatively; the electrostatic interactions of highly polarised molecules, and the mechanism of Corey (18), would be the type of interactions included. The double bond in the reacting olefin in this case, 66, has already been shown (Part A) to have little polar character, and so most of the electrostatic interactions between 66 and 15 in the transition states correspond to mutual induced polarisation of the reactants. Category (b) corresponds to the resultant dipole moment of the transition state as a whole. This is the resultant of the dipole moments of the two reactants, at the instant of reaction, modified by the induced polarisation. Since there is no convenient method of calculating this polarisation, one must assume that it is independent of the environment surrounding the reactants.

From Kirkwood's (76) and Onsager's (77) equations, the change in free energy upon moving a dipole from a vacuum to a solvent is given by

$$\Delta F = F_{\text{solution}} - F_{\text{vacuum}} = \frac{-\mu^2(\epsilon-1)}{a^3(2\epsilon+1)}$$

where μ is the permanent electric dipole moment, ϵ is the solvent dielectric constant, and 'a' is the so-called "cavity radius", generally considered to be a constant for the particle having the dipole. For two different dipoles, A and B, corresponding to the resultant dipole moments of the two transition states, the difference in electrostatic stabilisation (i.e. the difference between the free energy changes of the two) on moving both dipoles from a vacuum to the same solvent is

$$\Delta F_A - \Delta F_B = \left(\frac{\mu_B^2}{a_B^3} - \frac{\mu_A^2}{a_A^3}\right) \cdot \frac{(\epsilon - 1)}{(2\epsilon + 1)}$$

When the transition states can be considered to be of approximately the same size and shape, as are 67a and 67b, this becomes

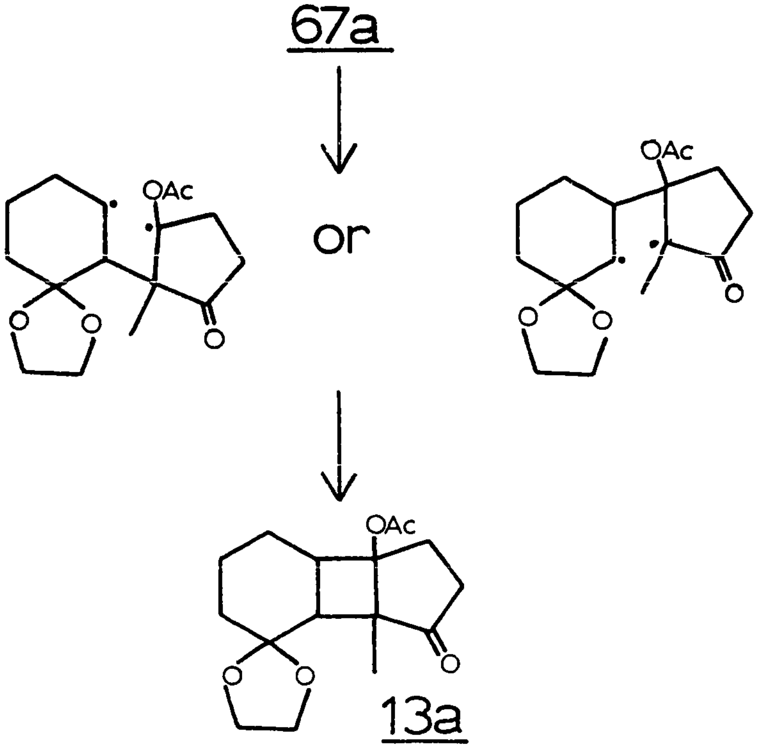
$$\Delta F_A - \Delta F_B = \frac{(\mu_B^2 - \mu_A^2)}{a^3} \cdot \frac{(\epsilon - 1)}{(2\epsilon + 1)} \qquad \text{(equation A)}$$

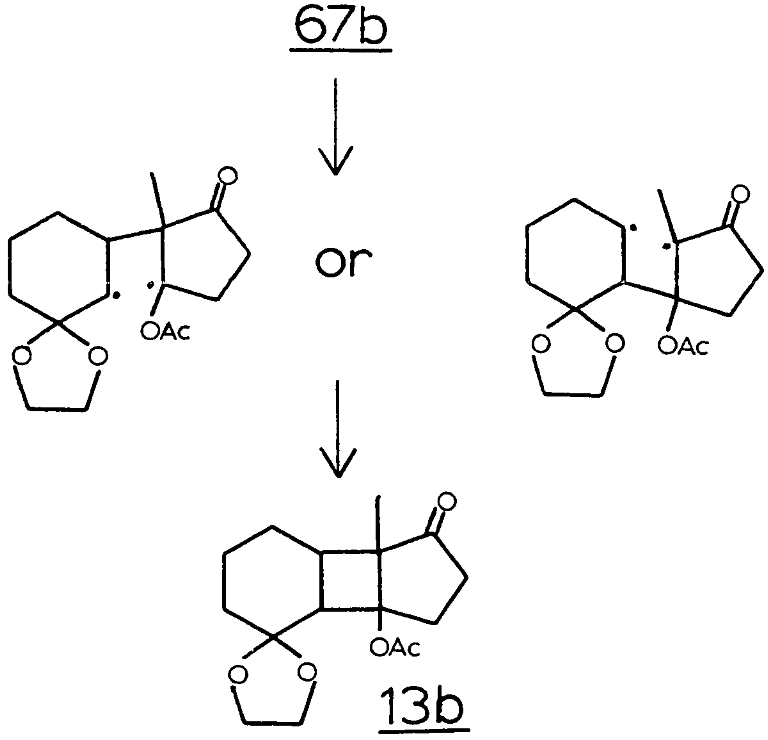
Since μ_B and μ_A are considered to be approximately independent of the environment, this means that the difference between the free energies of two systems having different dipole moments should be linearly dependent on this function of the dielectric constant of the solvent. It has already been noted that $\ln(P_A/P_B)$ is proportional to the difference between the free energies of the transition states 67a and 67b, so the relationship

$$\ln\frac{(P_A)}{(P_B)} \propto \frac{(\epsilon - 1)}{(2\epsilon + 1)}$$

should apply to this reaction.

Irradiations were carried out in several solvents of greatly varying dielectric constant, and at various con-


67a
OAc
or
OAc
OAc
13a


67b
or
OAc
OAc
OAc
13b

centrations of 66, as described in the experimental section. Apparently six cycloaddition products were produced, together with other compounds, visible as four peaks on v.p.c. analysis, called 13a', 13a, 13b, 13b'; these were tentatively identified as cycloadducts from the way the yield of these products varied with the concentrations of 15 and 66, all of them being present in all solvents (see experimental section). A partial separation of 13a, 13b and 13b' was obtained by column chromatography on silicic acid, and the structures elucidated as described below. The other compound obtained, 13a', was formed in smaller quantity and not isolated.

The material called 13a was found to be one compound identified by comparison with the previously characterised material. However, 13b and 13b', although appearing as one peak each on v.p.c., were each shown to be mixtures of two compounds by their n.m.r. spectra; attempted further separation was unsuccessful.

When treated with dilute methanolic acid for a few minutes, followed by dilute methanolic alkali, 13b' was rapidly converted to a compound having a chromophore consistent with the β-diketone structure 68. The rapidity of the hydrolysis of the tertiary acetate was thought to be very unusual, and the mechanism of fig. 4 (see Part A) was discarded when it was discovered that initial treatment with base, followed by acid, gave no reaction. Further treatment with base was required to produce 68. Evi-

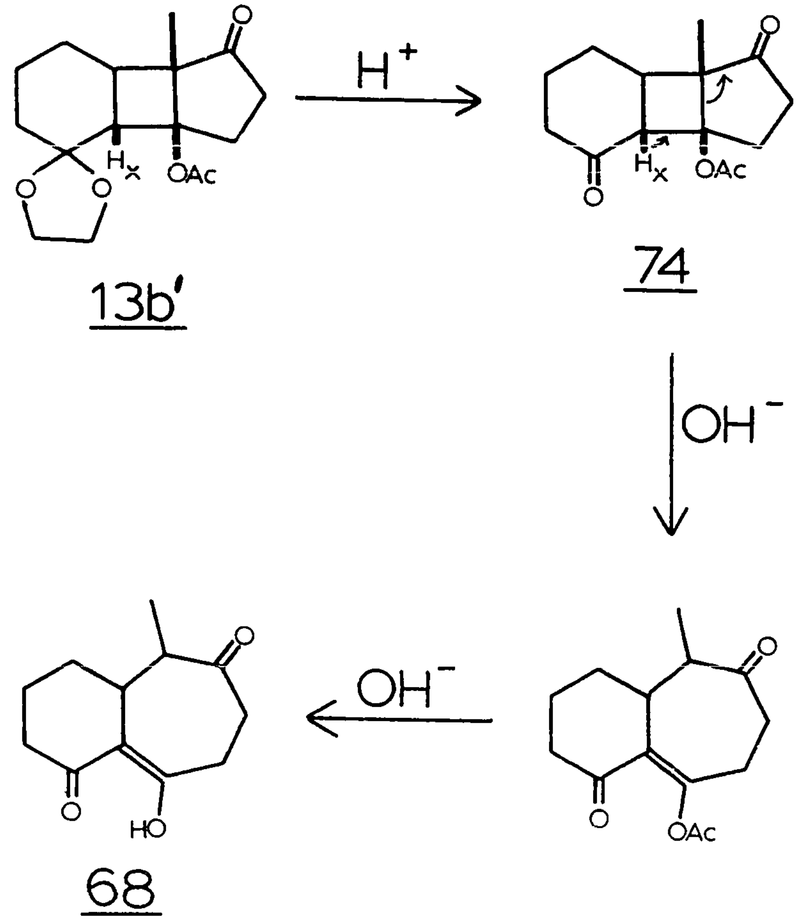


Fig. 26

dently initial acidic hydrolysis of the ketal was required; then base-catalysed cyclobutane ring cleavage of a head-to-tail cycloadduct occurred as shown in fig. 26. That both compoents of the mixture in 13b' underwent this reaction sequence was shown by the extinction of the chromophore produced. No such chromophore could arise from a head-to-head adduct like 13a.

Upon treatment of 13b with dilute methanolic acid, slow formation of a chromophore indicated that acetic acid was being eliminated after hydrolysis of the ethylene ketal. When the product was treated with base, it was converted to an orange compound, which was also formed rapidly when 13b was treated with acid for only a short time, followed by base. This second product was not isolated, since it decomposed rapidly in air, but it was tentatively assigned a partial structure on the basis of its u.v. spectrum. It was apparently diketonic, having $\lambda_{max.}$ 255 nm in acid which changed reversibly to $\lambda_{max.}$ 505 nm in base, the anion evidently having a very extended chromophore. A small amount of the compound 73, formed slowly from 13b by acid treatment, was isolated, and from the extinction of the u.v. absorption of this it was deduced that both components of the mixture 13b must have been converted quantitatively to this compound on prolonged acid treatment. Hence this compound must necessarily be an intermediate in the formation of the orange compound on treatment with base. This also implies

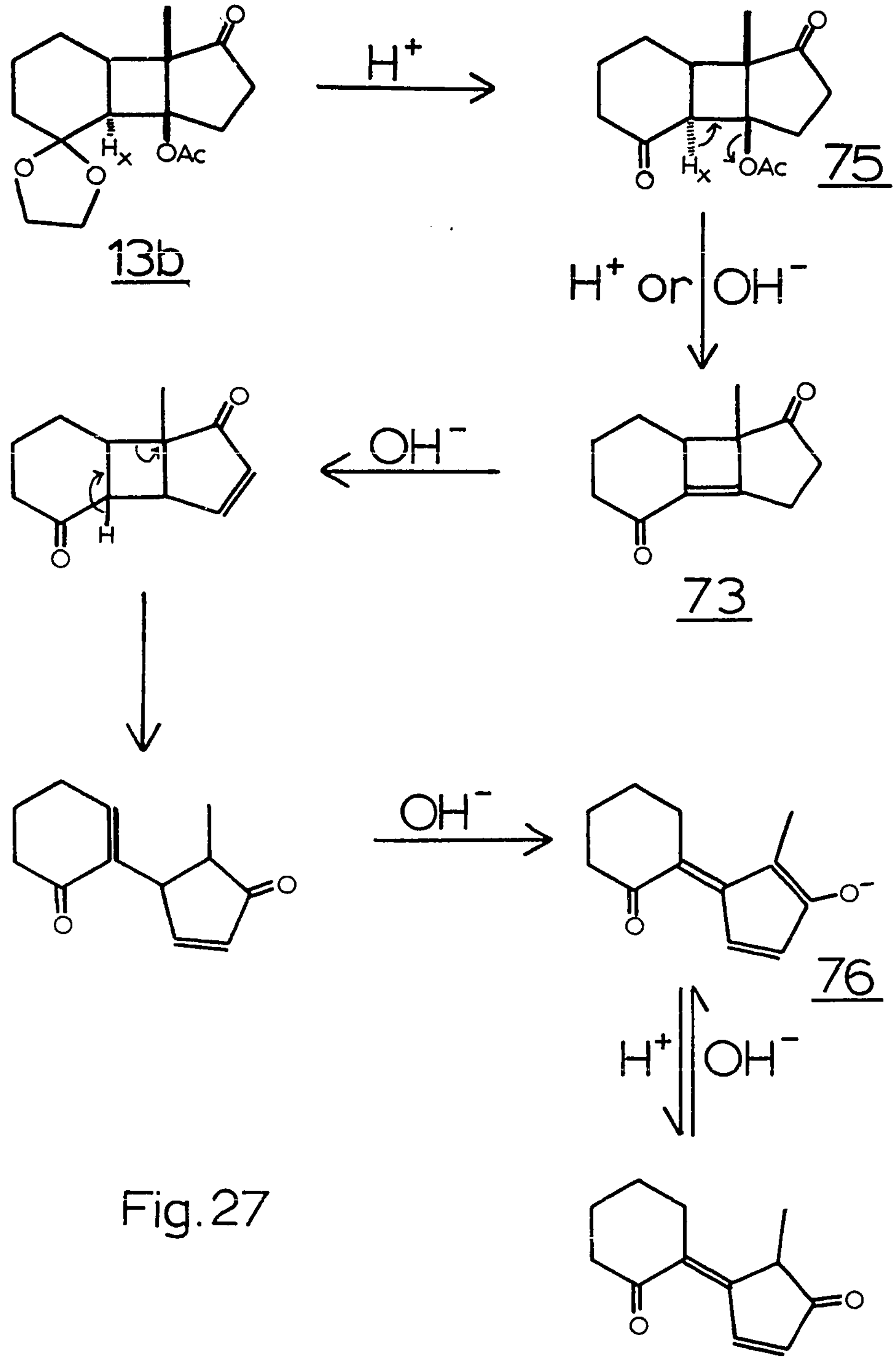


Fig. 27

that 73 is formed very rapidly by alkaline treatment of the diketone, 75, derived from 13b by hydrolysis of the ethylene ketal. Thus the acetate must be β- to the cyclohexanone ketone, and both components of 13b must have the head-to-tail stereochemistry. A possible mechanism for the formation of the orange compound, 76, is outlined in fig. 27.

Since basic treatment of 75 caused initial elimination of the acetate, rather than cleavage of the cyclobutane (as had occurred with 74, from 13b') it is probable that the protons H_x in 13b and 13b' have opposite orientations with respect to the acetate and the stereochemistry of H_x in 13b and 13b' is tentatively assigned as shown in fig. 26 and fig. 27. Thus the fractions 13b and 13b' contain all the possible head-to-tail cycloadducts.

The compound (or mixture of compounds), 13a', was considered to be a 6,4-ring junction epimer of 13a, since the ratio of 13a' to 13a was approximately 1:10 from all irradiations, no systematic variation being apparent. Likewise the ratio of 13b' to 13b was approximately constant at 1:3. There was, however, a marked variation in the ratio 13a' + 13a : 13b' + 13b; in non-polar solvents this ratio tended to 98:2, and in polar solvents to 45:55. Concentration effects were also observed; higher concentrations of 66 and 15 produced a smaller variation in the 13a : 13b ratio.

The possibility that the solvent effect could be attributed to preferential reaction of one transition state to give products other than cycloadducts was considered, and rejected. Although the most noticeable changes in the ratio of 13a to 13b were at low concentrations of 66, when the yields of cycloadducts were also low (ca. 15%), these low yields were reproduced in all solvents at low concentrations of 66, including both the most and the least polar. Also, a distinct solvent effect was observed when the total yield of 13 was high (70%).

The concentration effect mentioned above appeared, in the cases of iso-octane, cyclohexane, acetonitrile and methanol, to be a result of the difference between the dielectric constants of the solvent and solute. The ratios of 13a : 13b in solutions with a high concentration of 66 fell between the ratios for dilute solutions and the ratio for products formed by irradiation in neat 66 (see figs. 28 and 29). However, in ethyl acetate and diethyl ether, there was a definite tendency to formation of higher proportions of 13b at an intermediate concentration of about 20 mol.% of 66 (fig. 30). Above and below this concentration there was a pronounced decrease in the proportion of 13b. No reason can be confidently proposed for this effect, although guesses can be made. Since the ethyl acetate and diethyl ether molecules are very similar in size and shape, and both quite different from all the others used, it is conceivable that the effect is the result of preferential solvation of one of the transition

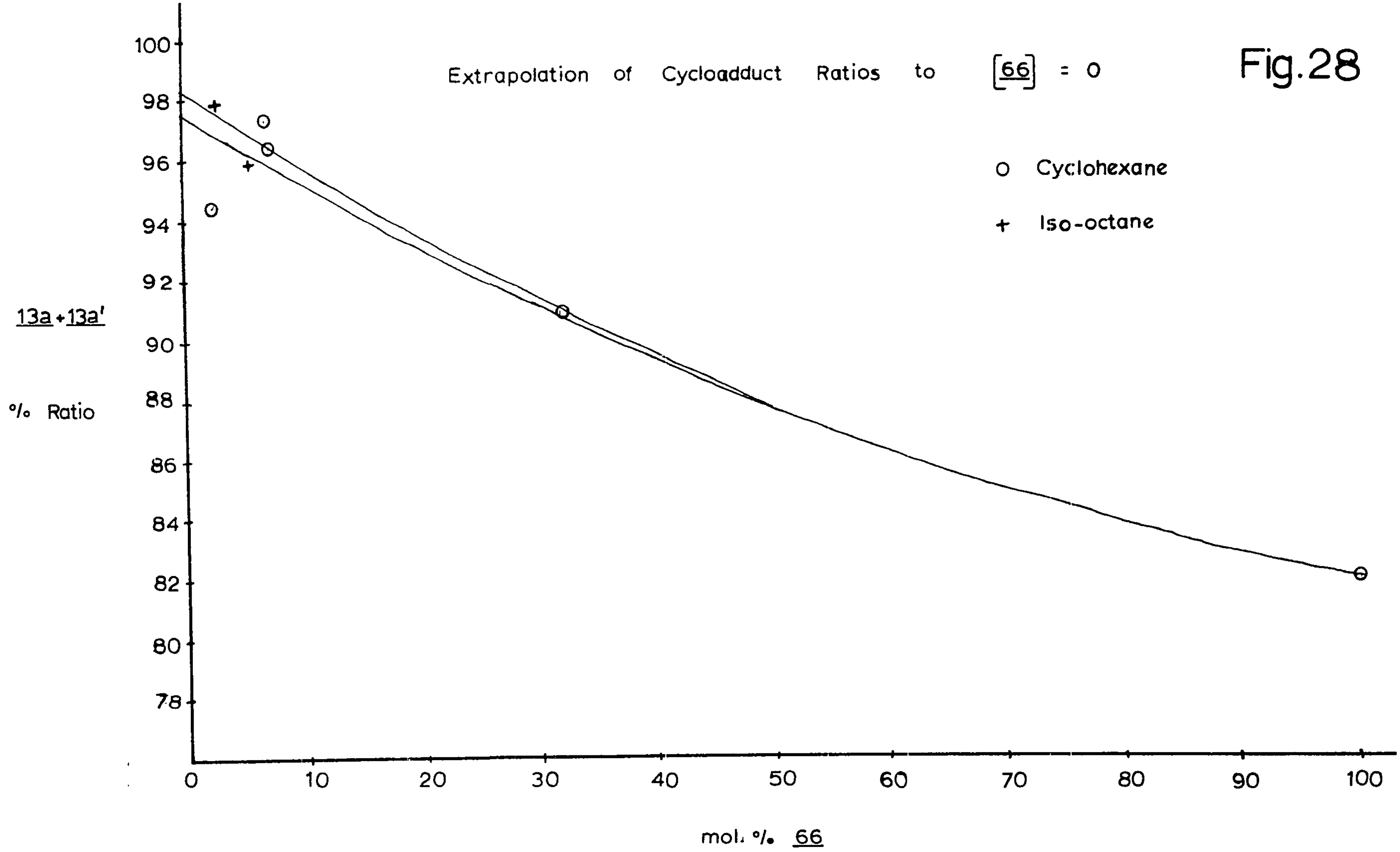


Fig.28

Extrapolation of Cycloadduct Ratios to [66] = 0

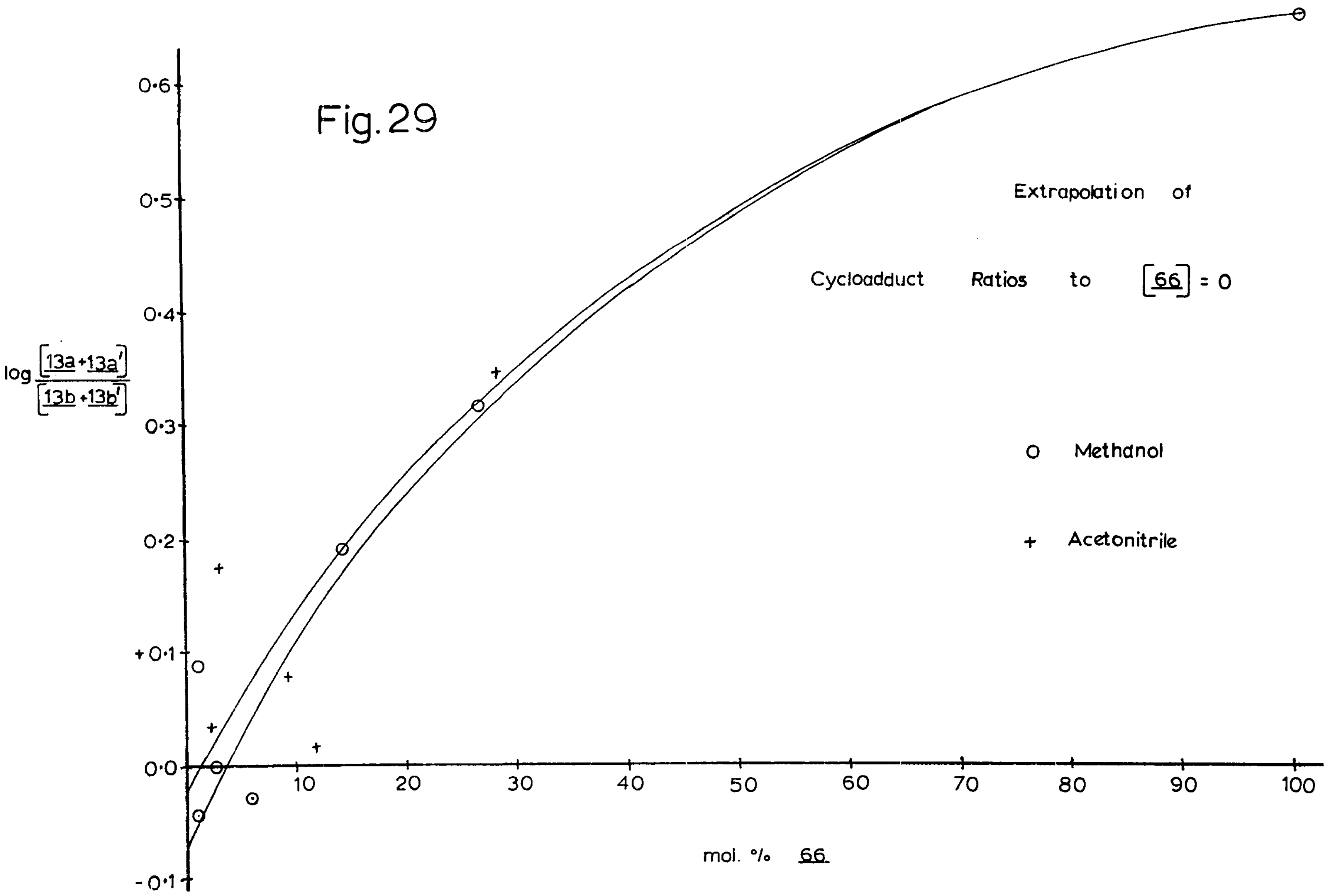


Fig. 29

Extrapolation of Cycloadduct Ratios to [66] = 0

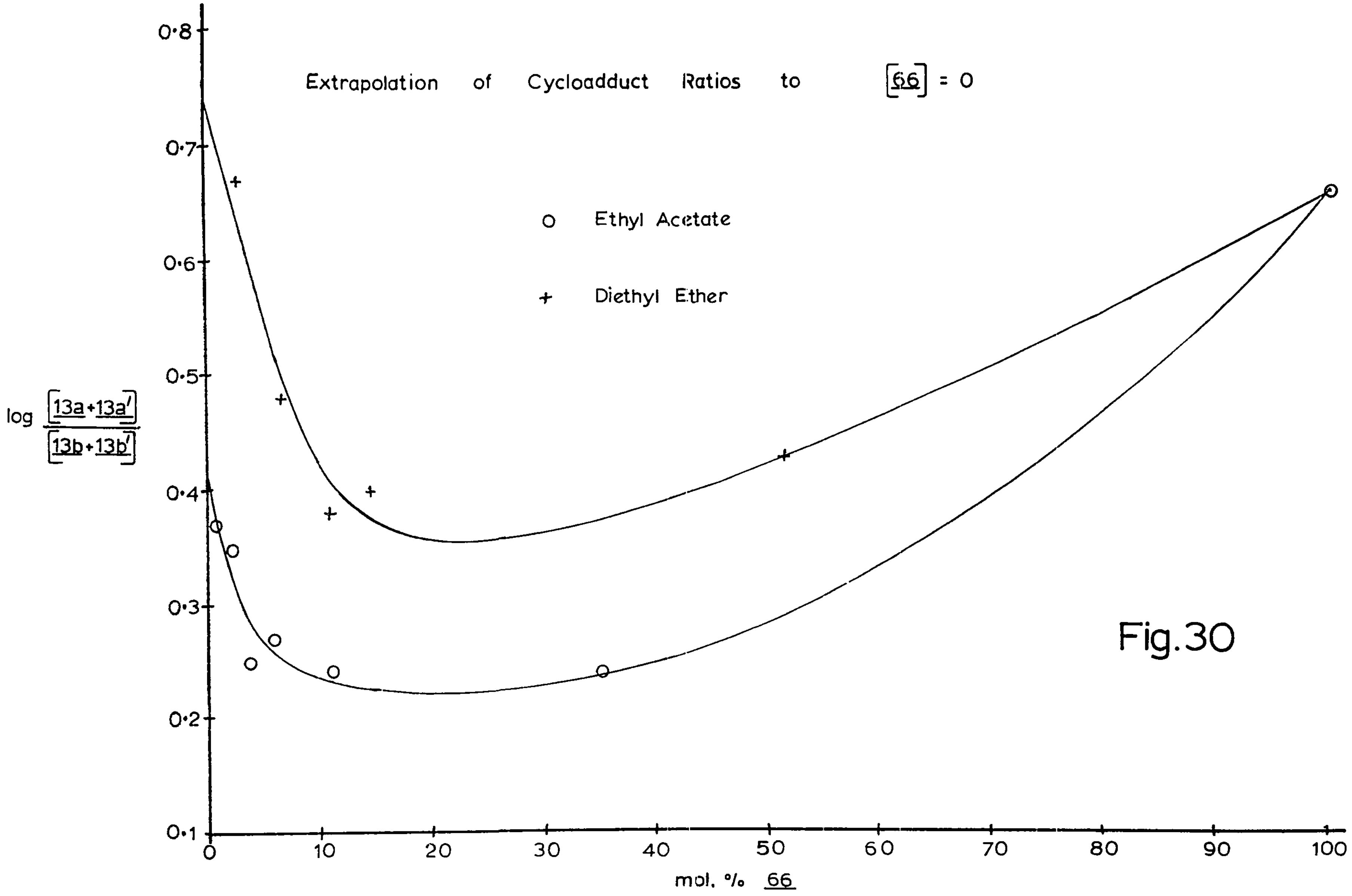
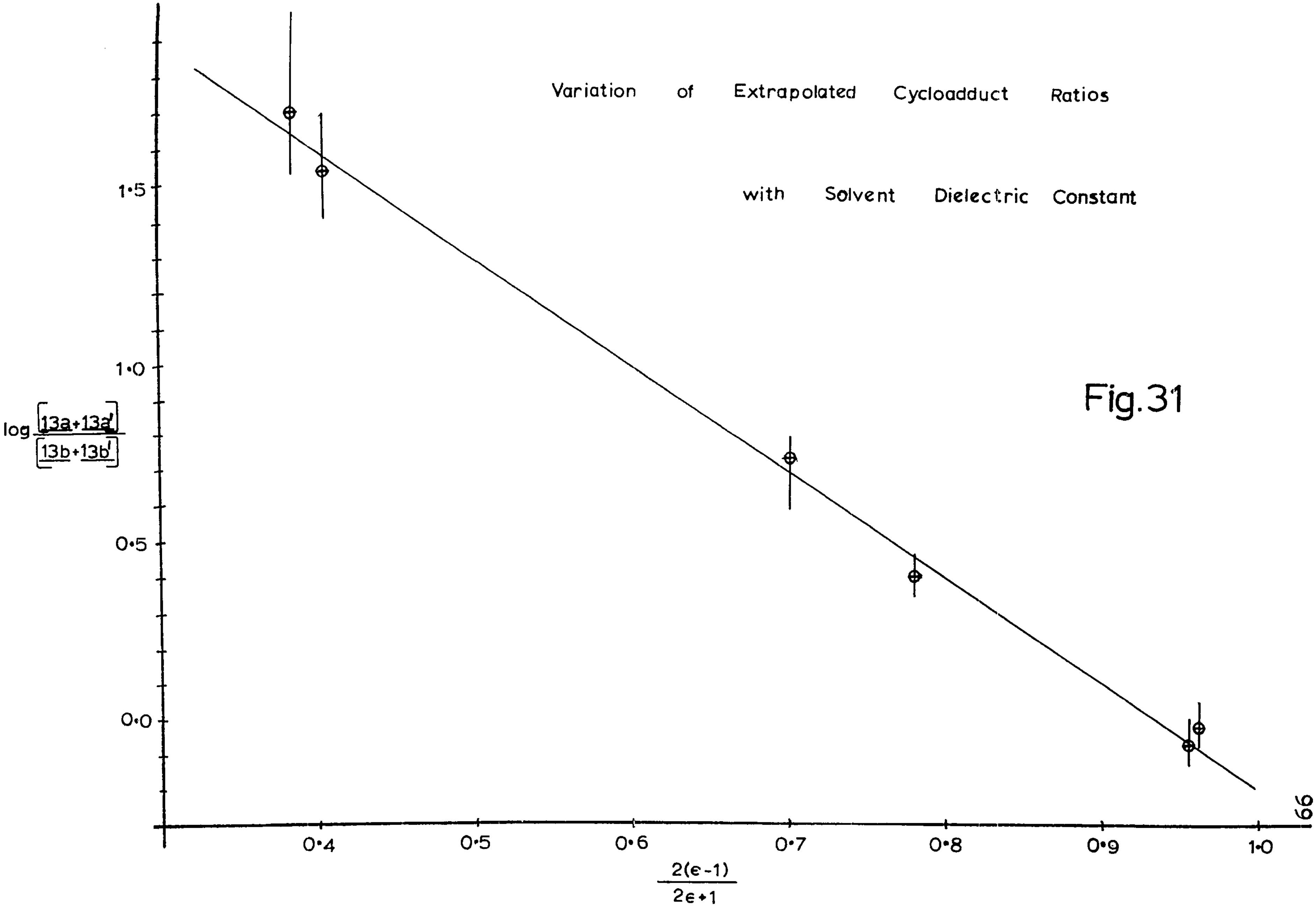

Extrapolation of Cycloadduct Ratios to [66] = 0

Fig.30

states (producing stabilisation) by a molecular cluster of about five molecules of solvent to one of <u>66</u> (acting as a "co-solvent"). Any such effect would be expected to depend primarily on solvent molecular shape and size, and to be highly specific.

In view of this concentration effect it was decided to extrapolate the concentration of <u>66</u> to zero for all solvents in order to obtain a variation of the ratio <u>13a</u> : <u>13b</u> that was dependent only on the properties of the solvent. Then log(<u>13a</u> + <u>13a'</u>)/(<u>13b</u> + <u>13b'</u>) was plotted <u>vs</u>. $2(\epsilon-1)/(2\epsilon+1)$ ($=2f(\epsilon)$). The six points obtained thus were then fitted to a line by a least-squares approximation, the correlation coefficient (r, being a criterion of linearity; a perfect fit would have r = 1.000) being 0.998 (see fig. 31).

This result is ample verification of the theoretical treatment outlined above, and demonstrates that the dielectric constant of the solvent, and the dipole moment of the transition states in photochemical cycloadditions can greatly affect the course of the reaction. It is noteworthy that the solvent effect described here is considerably greater than that described by Berson (21) in Diels-Alder reactions (typical changes in ratio were 23:77 in non-polar to 41:59 in polar solvents). Large changes in ratios of products with change of solvent have also been observed by Schenck <u>et al</u>. (20) in the photodimerisation of acenaphthylene and the cycloaddition of <u>cis</u>-1,2-dichlo-



Variation of Extrapolated Cycloadduct Ratios

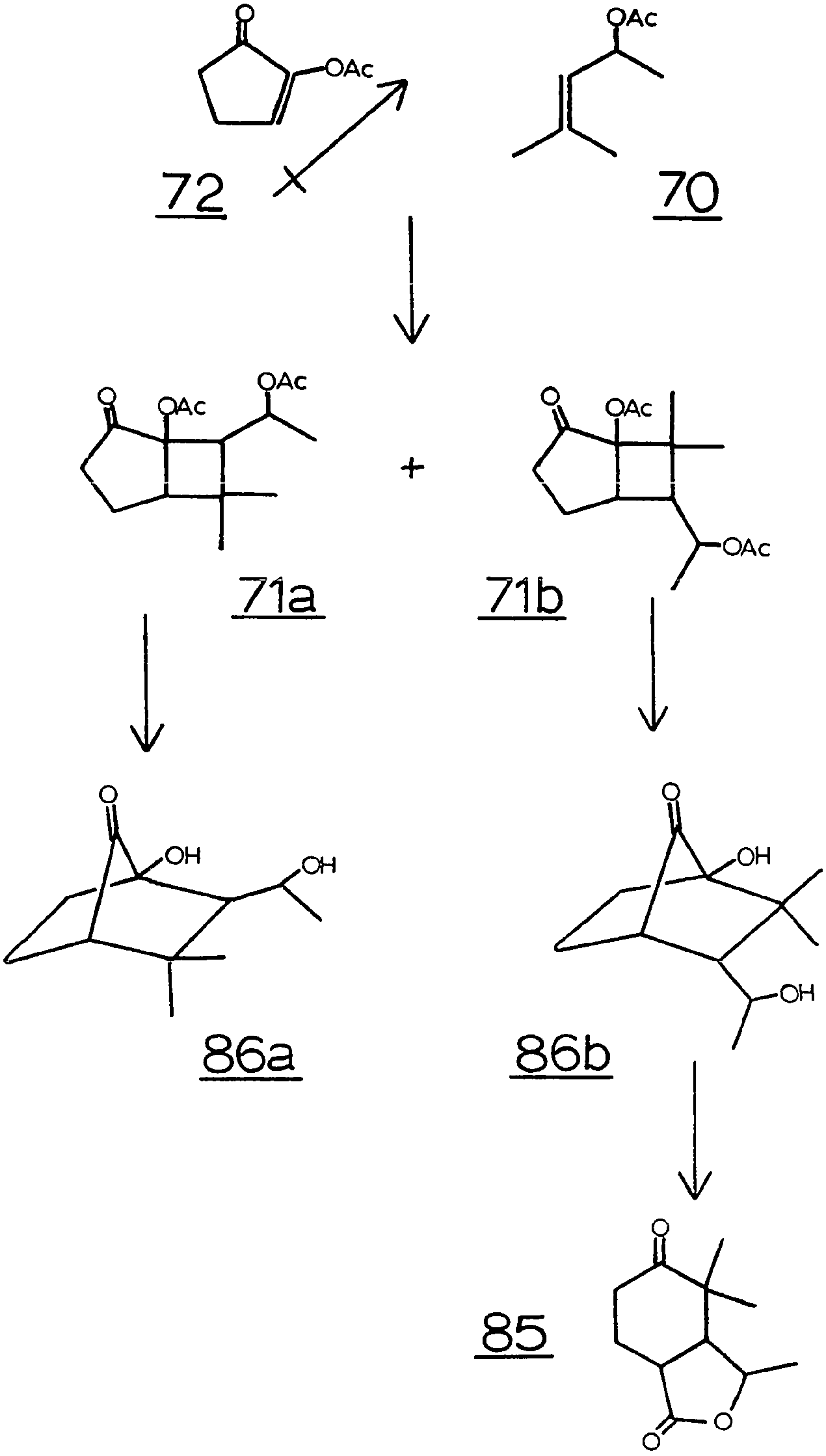
with Solvent Dielectric Constant

Fig. 31

roethylene to maleic anhydride. In both of these reactions the product variation is in the syn- to anti- ratio, since the dipole moments of the reactants are orthogonal to the reacting double bonds. In this case the variation is in the head-to-head to head-to-tail ratio, since the dipole moments are approximately parallel to the reacting double bonds. Another point of interest is that both of these, and other, workers were obliged to substitute the molar volume of the solvent for $1/a^3$ in equation A in order to obtain a linear relationship between $f(\epsilon)$ and the ratio of products. In the case described here such a correction was found to be unnecessary.

These results suggest that stereochemical control of cycloaddition could be achieved in synthetic sequences by introduction of the required polar groups (such as ketals or halides) at, for example, allylic positions in the reactants, and subsequent removal of them after cycloaddition. As was implied earlier, during the discussion of the theory, polar solvents would not necessarily give a mixture of equal amounts of both products; the actual ratio would depend on any other factors involved, e.g. $F_{A\ steric} - F_{B\ steric} \neq 0$. This is apparent from the studies of Berson and Schenck (20), (21).

In order to test the generality of the technique 2-acetoxycyclopent-2-enone, 72, and 4-methylpent-3-en-2-yl acetate, 70, were irradiated in a variety of solvents in the same way as 15 and 66. In this case the dipole moment


72
70
71a
71b
86a
86b
85
OAc
OH

of the excited state of 72 would be expected to be as shown. Application of the arguments previously proposed is made more difficult because of the large number of conformations of 70, and hence the uncertainty involved in predicting the instantaneous dipole moments of the reaction transition states. However, irradiation in non-polar solvents produced a mixture of at least six compounds (v.p.c. analysis), apparently all cycloadducts, 71a and 71b, and the proportion of three of these in the mixture was greatly reduced by irradiation in polar solvents (ca. 50% in non-polar to ca. 5% in polar solvents).

Because of the number of the irradiation products, no attempt was made to isolate and characterise any of them individually. The assignment of cycloadduct structures was confirmed by hydrolysis and rearrangement to mixtures of norbornan-7-one derivatives, 86a and 86b, and periodate oxidation of these to a mixture of hydroxy-keto-acids and the lactone 85, which was identified by its i.r. and n.m.r. spectra.

These irradiations showed that a significant solvent effect occurred, and that the subject generally warranted further investigation.

EXPERIMENTAL SECTION.

Melting points were taken on a Kofler heating block and are uncorrected. Infrared and N.m.r. spectra were run in spectral grade carbon tetrachloride solution unless otherwise stated, and recorded on Beckmann IR 10 or IR 7 and Varian A60 spectrometers, respectively.

PART A. SYNTHESIS OF β-HIMACHALENE.

Preparation of cyclohex-2-enone, ethylene ketal.

The method of Wanzlick *et al.* (51) was found to give a mixture of double bond isomers, and so was modified as follows.

Potassium hydroxide pellets (59 g.) were dissolved in diethylene glycol (336 ml.) at 190°. To this solution was added 2-chlorocyclohexanone ethylene ketal (84 g.) (51) at 50° whilst agitating slightly. The mixture was kept at 160-165° for $3\frac{1}{2}$ hours and then cooled. If a higher temperature were used appreciable quantities of cyclohex-3-enone ethylene ketal were formed. The mixture was then distilled to 115°/3mm. and the distillate was extracted with ether (5 times), washed with water (3 times), dried and distilled. The fraction b.p. 55-7°/ 6.5mm. consisted of pure material (44 g., 73%), containing none of the isomer according to v.p.c. (on 10% silver nitrate/10% carbowax, 6' x 1/4"; 140°; which had been shown to be effective in separating the isomers).

N.m.r. τ 7.7-8.5(m.; 6H), 6.12(m.; 4H), 4.47(d.J = 10Hz; t.J = 1.7Hz; 1H), 4.18(d.J=10Hz; t.J = 3.2Hz; 1H).

Acetylation of 2-methylcyclopentane-1,3-dione.

Ketene gas was passed through a dry ethereal suspension (200 ml.) of the methyldione (3.14 g.) at 10° for six hours. The resulting clear solution was then evaporated down and distilled to give 2-methyl-3-acetoxy-cyclopent-2-enone (4.02 g.; 91%), b.p. 84-87°/2mm., spectra

I.r. $\nu_{max.}$ 2920, 1778, 1710, 1670, 1180 cm^{-1}.

N.m.r. τ 8.48 (t.J = 1Hz; 3H), 7.72 (s.; 3H), 7.0 to 7.8 (m.; 4H).

Analysis: Calc. for $C_8H_{10}O_3$: C 62.32, H 6.54%
Found : C 62.26, H 6.54%

Irradiation of 15 and cyclohex-2-enone ethylene ketal.

A solution of the ketal (100 g.) in cyclohexane (120 ml., alumina-filtered) was degassed by bubbling nitrogen for one hour. The dione acetate (2.0 g.) was then added and the degassing continued for ten minutes more. The solution was then irradiated with a 450 watt high pressure mercury lamp through pyrex, following the reaction by I.r. almost to completion. Distillation of the reaction mixture fractionally then removed successively cyclohexane, the ketal (b.p. 84°/15 mm.), unchanged dione acetate, and the irradiation adduct (b.p. ca. 200°/ 0.5mm., 3.3 g., 90%). Crystallisation of this last from ether to m.p. 124-5° gave material with spectra and analysis:

I.r. $\nu_{max.}$ 2940, 1735, 1370, 1245, 1155, 1115, 1045 cm^{-1}

N.m.r. τ 8.80(s.), 8.0-8.7(m.), 7.99(s.), 7.1-7.8(m.), 6.05(m.).

Analysis: Calc. for $C_{16}H_{22}O_5$: C 65.29, H 7.53, O 27.18%

Found : C 65.66, H 7.39, O 26.86%

The u.v. spectrum showed no intense peaks, even on addition of cold dilute aqueous sodium hydroxide. The alkaline solution was heated under reflux for 45 minutes, giving no observable change in u.v.. The solution was treated with dilute hydrochloric acid, and then made alkaline again, still with no appearance of peaks in the u.v. Acidification with acetic acid produced no change. The limit of detection of an enolised β-diketone was estimated to be about 5%, thus indicating that there could not be more than 5% of 13b in the cycloaddition product.

Reduction of the irradiation adduct, 13a.

The distilled irradiation adduct (3.7 g.) in methanol (60 ml.) was added at 5° to a cold solution of sodium borohydride (1.35 g.) in water (8 ml.)/methanol (40 ml.) during five minutes. The mixture was kept at 5° for 25 minutes, then diluted with water (500 ml.) and extracted with ether. After washing, drying, and evaporation 3.1 g. of crystalline material was obtained (85%). Good analyses were not obtained after crystallisation from petroleum ether (m.p. 132-133°) or methanol (m.p. 178-9°) or after sublimation (m.p. 119-126°); e.g. from methanol/water: found C 63.75, H 8.35%; $C_{16}H_{24}O_5$ requires C 64.84, H 8.16%; $C_{16}H_{24}O_5,\frac{1}{2}CH_3OH$ requires C 63.44, H 8.39%.

I.r. $\nu_{max.}$ 3560, 3460, 2950, 1735, 1250, 1033 cm^{-1}

N.m.r. τ 8.73(s.; 3H), 8.0-8.6(m.; 7H), 8.04(s.; 3H), 7.2-8.0(m.; 6H), 6.04(m.; 5H).

Preparation of 20b.

To the dry alcohol 20a (3.3 g.) in dry CH_2Cl_2 (160 ml.) was added triethylamine (54 ml.) in CH_2Cl_2 (100 ml.) whilst stirring and cooling in an ice bath. To the solution was then added methanesulphonyl chloride (9 ml.) in methylene chloride (100 ml.) during five minutes, with continued stirring and cooling. The red solution was then stirred for ten minutes at room temperature, and then washed with water (10x100 ml). The aqueous extracts were back-extracted with methylene chloride and the combined organic solutions were washed again, dried thoroughly ($MgSO_4$), and evaporated togive 5.8 g. dark oil.

This sulphonate was crystallised for spectra and analysis from ethyl acetate/petrol to m.p. 145-145.5°.

I.r. $\nu_{max.}$ 2940, 1735, 1365, 1340, 1247, 1177, 955 cm^{-1}

N.m.r. τ 8.70(s.; 3H), 8.1-8.5(m.; 7H), 8.02(s.; 3H), 7.2-8.9(m.; 5H), 6.07(m.; 4H), 5.04(m.; 1H).

Analysis:	Calc. for $C_{17}H_{26}O_7S$:	C 54.54, H 7.00%
	Found:	C 54.58, H 6.83%

Hydrolysis of 20b.

The crude methanesulphonate (5.5 g.), in dioxan (175 ml.), was treated with a solution of sodium hydroxide (1.77 g., 3 moles) in water (95 ml.). The solution was kept at 70° for one hour, then diluted with water (1000 ml.) and extracted with ether (10x100 ml.). After drying, the extracts were evaporated to give yellowish crystals. This material was purified by chromatography on a column of neutral alumina (benzene eluent) and afforded 1.0 g. 6-methylbicyclo[5,4,0]undec-5-en-2,8-dione, 8-ethylene ketal, 14 (30% yield from dione acetate). After recrystallisation from petrol the m.p. was 124-124.5°.

I.r. $\nu_{max.}$ 2950, 1717, 1174 cm^{-1}.

N.m.r. τ 8.2-8.6(m.; 4H), 8.20(m.; 3H), 7.3-8.1(m.; 8H), 6.06(m.; 4H), 4.29(m.; 1H).

Analysis:	Calc. for $C_{14}H_{20}O_3$:	C 71.16, H 8.53%
	Found:	C 71.28, H 8.27%

Preparation of 21.

To a suspension of Mg turnings (1.0 g.) in ether (6 ml.) was added methyl iodide (4 ml.) in ether (18 ml.). The reaction mixture was heated under reflux and a further 10 ml. ether was added. When all the magnesium had dissolved, a solution of 14 (970 mg.) in ether (70 ml.) was added and reflux continued 1½ hours. The solution was then carefully treated with water (50 ml.), and the layers were separated. The ethereal layer was dried and evaporated to give white crystals (965 mg.).

After recrystallisation from petrol the m.p. was 70-71°.

I.r. $\nu_{max.}$ 3580, 2960, 1255, 1165, 1075, 870 cm^{-1}

N.m.r. τ 8.99(s.; 3H), 8.2-8.8(m.; 8H), 8.14(m.; 3H), 7.2-7.9(m.; 4H), 6.16(m.; 4H), 4.33(m.; 1H).

Analysis:	Calc. for $C_{15}H_{24}O_3$:	C 71.39, H 9.59%
	Found:	C 71.08, H 9.11%

Preparation of 1-methylbicyclo[4.1.0]heptane (1-methylnorcarane).

To a zinc/copper couple (8 g.) in ether (25 ml.) containing methylene iodide (0.5 ml.), was added 1-methylcyclohexene (6 g.) in methylene iodide (23 g.) during 20 minutes, maintaining a steady reflux. The mixture was stirred at reflux temperature for 20 hours. The ethereal solution was then poured into ice/1NHCl, shaken and separated, washed with water, dried (K_2CO_3) and evaporated to 10 ml.

The solution was then fractionally distilled (b.p. 122°) to give 1-methylnorcarane (2 g.), containing about 5% of the starting material.

I.r. $\nu_{max.}$ 3070 (cyclopropyl CH), 1018 cm^{-1} (cyclopropyl def.).

N.m.r. τ 8.98(s.; 3H), 9.0-10.0(m.; 3H).

This compound has since been reported in the literature (52), prepared by the same method.

Hydrogenation of 1-methylnorcarane.

A mixture (1.76 g.) of 1-methylnorcarane (ca. 60%) and 1-methylcyclohexene was hydrogenated at atmospheric temperature and pressure in acetic acid (30 ml.) using PtO_2 (257 mg.) catalyst. After hydrogenation, ether was added to the solution and the acetic acid was washed, dried and separated by v.p.c. (5' x $\frac{1}{4}$" silicone SE 30 column, 58°). The major product obtained was shown to be 1,1-dimethylcyclohexane by the following spectral details.

I.r. $\nu_{max.}$ 1470, 1455, 1385, 1365, 1177, 1150 cm^{-1}

N.m.r. τ 9.11(s.; 6H).

Preparation of 23.

Zinc/copper couple, prepared by the method of LeGoff (32b) was moistened with ether (2.5 ml.) and methylene iodide (0.31 ml.), and 21 (4.2 g.) in ether (18 ml.) was added, followed by more methylene iodide (1.68 ml.). The mixture was heated under reflux with vigorous stirring for twenty hours. More zinc/copper couple (2.0 g.) and methylene iodide (1.5 ml.) were added and the heating and stirring were resumed for 22 hours. The mixture was then poured into 3% aqueous hydrochloric acid (100 ml.), and extracted with ether (10 x 30 ml.). After drying over magnesium sulphate and evaporation of the extract, the residue (5.62 g.) was dissolved in 1½% methanolic hydrochloric acid (50 ml.) and left to stand at room temperature for 50 mins. The solution was then evaporated down to 20 ml., poured into water, and extracted with ether (10 x 30 ml.). After drying over magnesium sulphate, the ethereal solution was evaporated to dryness, yielding 23 as sticky crystals. Recrystallisation from ether afforded white needles m.p. 122-3 (dec.), (550 mg.). The mother liquors were chromatographed on silicic acid powder, using 20% ethyl acetate/benzene eluent, to give a further 3.1 g. (35% yield from 15).

I.r. $\nu_{max.}$ 3620 cm^{-1} (OH), 3065 cm^{-1} (cyclopropyl CH), 1700 cm^{-1} (CO).

N.m.r. τ 8.70(s.; 3H), 9.04(s.; 3H), 9.35(m.; 3H).

Analysis:	Calc. for $C_{14}H_{22}O_2$:	C 75.63, H 9.97%
	Found:	C 75.32, H 9.61%

PtO_2-catalysed Hydrogenation of 23.

The cyclopropyl ketone compound 23 (60 mg.) was hydrogenated with PtO_2 (50 mg.) in acetic acid (6 ml.) during two hours. The solution was then evaporated and separated by t.l.c. into three components; starting material (21 mg.), a polar compound (5 mg.), and a compound which appeared to be 25 (11 mg.).

I.r. $\nu_{max.}$ 3610 (OH), 1695 cm^{-1} (CO).

N.m.r. τ 8.79(3H), 9.23 (d.; 3H).

Attempted hydrogenations of 23 and 22 with PtO_2 in ethanol, 5% Pd/charcoal and 5% Rh/alumina in ethanol and acetic acid gave only starting material and other cyclopropyl-containing compounds, which were not characterised.

Rh/PtO_2-catalysed hydrogenation of 23.

The cyclopropyl ketone compound 23 was hydrogenated in acetic acid (10 ml.) with Rh/PtO_2 catalyst (274 mg.) The solution was evaporated down and extraction with chloroform afforded 95 mg. Separation of this by t.l.c. gave 24 (40 mg.), i.r. showing peaks at 1695 (CO) and 3610 cm^{-1} (OH), and n.m.r. at τ 8.82(s.; 3H), 9.03(s.; 3H), 9.10(s.; 3H), 7.30(d.; 1H, J=7c.p.s.); and 26a (17 mg.), i.r. showing no OH, CO at 1695 cm^{-1}, n.m.r. peaks at 9.04 (s.; 3H), 9.08(s.; 3H), 9.14(d.; 3H).

Methylation of 23.

To a refluxing solution of potassium (270 mg.) in dry *t*-butanol (9 ml.) under nitrogen was added a solution of 23 (600 mg.) in dry benzene (1.0 ml.). A solution of methyl iodide (0.45 ml.) in dry benzene (1.0 ml.) was added to the refluxing mixture during one hour. After decomposition of the reaction mixture with water the product (650 mg.) was isolated with ether. It was separated by t.l.c., R_f 0.5, (eluent 50% petrol/ether). The monomethylated material (205 mg., 50% based on consumed ketone) was crystallised from ether, m.p. 124-125°.

I.r. $\nu_{max.}$ 3610, 3500, 3060, 2920, 1700, 1450, 1380, 1140, 1020 cm^{-1}.

N.m.r. τ 9.2-9.7 (m.; 3H), 9.13 (s.; 3H), 9.01 (d.J=5Hz;

ca. 2H), 9.00 (d.J=6.5 Hz; ca. 1H), 8.75 (s.; 3H), 8.40 (1H-OH).

Analysis:	Calc. for $C_{15}H_{24}O_2$:	C 76.23, H 10.23%
	Found:	C 75.99, H 10.27%

The starting material, R_f 0.3, and the dimethylated compound 29, R_f 0.6, (140 mg.) were also separated. 29 had

I.r. $\nu_{max.}$ 3610, 3500, 3060, 3060, 2920, 1695 cm^{-1}

N.m.r. τ 9.2-9.6(m.; 3H), 9.13(s.; 3H), 9.00(s.; 3H), 8.97(s.; 3H), 8.83(s.; 3H).

Hydrogenation of 28.

A catalyst prepared according to the method of S. Nishimura (36), being a fused mixture of rhodium and platinum oxides in the ratio 8:3, was used.

The catalyst (50 mg.) was saturated with hydrogen at atmospheric temperature and pressure in glacial acetic acid (5 ml.) containing anhydrous sodium acetate (50 mg.). The compound 28 was then added and the mixture shaken until hydrogen uptake ceased (ca. 15 hours). The solution was then separated from the catalyst and evaporated under reduced pressure to dryness. The solid was dissolved in water (5 ml.) and extracted with chloroform. Evaporation of this gave sticky crystals of 27. Although the spectra and subsequent reactions of this product showed it to be a mixture, a chromatographic separation into the epimers 27a and 27b was not obtained. Recrystallisation from ether/petrol gave material with m.p. 97-99°.

I.r. $v_{max.}$ 3610 (OH), 1710 (CO), 1690 (CO) cm^{-1}.

N.m.r. τ 8.79(s.; 3H), 8.94(s.; 3H), 9.14(s.; 3H), 8.92(d.;J=11Hz), 8.98(d.;J=10Hz), 7.27(d.;J=7Hz; 1H).

Reduction of 27 (i).

A solution of the ketol (81 mg.) in dry ether (6 ml.) was stirred with excess lithium aluminium hydride (50 mg.) for 30 minutes. The mixture was decomposed with aqueous sodium potassium tartrate, and the product isolated with ether (70 mg.). Separation by t.l.c. (eluent 50% petrol/ether) gave 30a (R_f 0.7, 44 mg., 54%) and 30b (R_f 0.5, 21 mg., 26%).

(ii).

To a refluxing suspension of sodium (1.3 g.) in toluene (25 ml.) was added the ketol (650 mg.) in isopropanol (8.0 ml.) and the mixture refluxed for two hours, by which time all the sodium had reacted. After dilution with water the product was isolated with ether. The crude product (650 mg.) was separated by t.l.c. (eluent 65% ether/petrol) to give 30b (R_f 0.56, 257 mg., 40%), 30c (R_f 0.28, 120 mg., 18%) and 30d (R_f 0.21, 167 mg., 26%).

30a was a glass.

I.r. $\nu_{max.}$ 3620, 3500, 2920, 1130, 1070, 1010, 975, 960cm^{-1}

N.m.r. τ 9.10(d.;J=6.5Hz, 3H), 8.94(s.; 6H), 8.78(s.; 3H), 6.06(m.; 1H).

Analysis: Calc. for $C_{15}H_{28}O_2$: C 74.95, H 11.74%
Found: C 75.22, H 11.92%

<u>30b</u>, m.p.85-86° (light petroleum).
I.r. $\nu_{max.}^{CHCl_3}$ 3600, 3460, 2920, 1075, 1010, 980 cm^{-1}

N.m.r. τ 9.06(d.;J=6.5Hz, 3H), 8.94(s.; 3H), 8.92(s.; 3H), 8.75(s.; 3H), 6.06(m.; 1H), 8.56(1H-OH), 8.54 (1H-OH)

Analysis: Found: C 75.10, H 11.72%

<u>30c</u>, m.p.116.5-117.5° (light petroleum).
I.r. $\nu_{max.}$ 3620, 3440, 2920, 1070, 950, 900 cm^{-1}

N.m.r. τ 9.18(s.; 3H), 9.01(d.;J=6.5Hz, 3H), 8.96(s.; 3H), 8.80(s.; 3H), 6.19(m.; 1H), 7.80(2H-OH).

Analysis: Found: C 74.67, H 11.62%

<u>30d</u>, m.p.173-174° (dec.) (ether)
I.r. $\nu_{max.}^{CHCl_3}$ 3590, 3440, 2910 cm^{-1}

N.m.r. τ (pyridine) 8.96(s.; 3H), 8.79(d.;J=6.5Hz, 3H), 8.67(s.; 3H), 8.59(s.; 3H), 6.25-6.7(m.; 1H).

Analysis: Found: C 74.84, H 11.75%

Reduction of 24.

To 24 (20 mg.) in dry ether (2.5 ml.) was added lithium aluminium hydride (25 mg.) and the reaction mixture stirred at room temperature for 40 hours. Decomposition of the excess hydride with water, followed by extraction with ether, afforded diols 40 (30 mg.). Separation of the mixture was effected by t.l.c. (40% ethyl acetate/benzene eluent). The first fraction, 40a, (R_f 0.7, 10 mg.) had

I.r. $\nu_{max.}$ 3615, 3490, 2930, 1070, 980 cm^{-1}

The second, 40b, (R_f 0.25, 4 mg.) had

I.r. $\nu_{max.}$ 3410, 2930, 1045, 960 cm^{-1}.

Pyrolytic dehydration of 40a.

The diol 40a (20 mg.), in chloroform solution, was spread in a narrow line, 10cm. long, on a 1mm. thickness of silica on a t.l.c. plate. The plate was then heated at 130° for twenty minutes, developed in 5% ethyl acetate/benzene, and the major fraction, 41 (*ca*. 10 mg.) was separated.

I.r. $\nu_{max.}$ 3620, 3065, 1635, 890 cm^{-1}

N.m.r. τ 5.35(s.; 2H), 9.00(s.; 3H), 9.03(s.; 3H).

Pyrolytic dehydration of 30a.

Diol 30a (25 mg.) was treated in the same manner as the model diol 40a above, and afforded the mono-ol 43 (20 mg.).

I.r. $\nu_{max.}$ 3640, 3070, 1635, 890 cm^{-1}

N.m.r. τ 5.33(s.; 2H), 6.14(m.; 1H), 9.00(s.; 6H), 9.05 (d.; 3H).

Pyrolytic dehydration of 30b.

Diol 30b (30 mg.) was treated in the same manner as the model diol 40a above, and afforded a crystalline mono-ol (20 mg.).

I.r. $\nu_{max.}$ 3620, 3065, 3020, 890 cm^{-1}, suggests that the material was a mixture.

N.m.r. τ 5.32(s.; 2H), 6.10(m.; 1H), 9.00(s.; 6H), 9.05 (d.; 3H).

Dehydrations of 40a and 41.

The mono-ol 41 (10 mg.) was treated with a solution of phosphorus oxychloride (1 mequiv.) and pyridine (10 mequivs.) in benzene (2 ml.) at 50° overnight. T.l.c. then showed that the starting material was completely destroyed, so the solution was poured into water and extracted with benzene. V.p.c. (5' x $\frac{1}{4}$" 20% carbowax, 146°) on the solution showed the presence of two dienes in the ratio 5:1. After v.p.c. separation of these, the major isomer (thought to be 42) had

I.r. $\nu_{max.}$ 3070, 3050, 2930, 1630, 1450, 885 cm^{-1}

Dehydration of 40a and workup in the same manner gave the same two products, in the ratio 5:1, and less than 5% other dienes.

Dehydration of 43.

The mono-ol 43 (20 mg.) was treated with a solution (3 ml.) containing 1 mequiv. of phosphorus oxychloride and 10 mequiv. of pyridine in 3 ml. benzene at 50° for 15 hours, when t.l.c. showed no starting material to be present. The solution was poured into water and extracted with benzene. V.p.c. (5' x $\frac{1}{4}$" 20% carbowax, 140°) showed the presence of four constituents in the ratio 65:7:25:3 in the order of elution. Separation by v.p.c. gave a compound (major fraction) with

I.r. $\nu_{max.}$ 3075, 3040, 1630, 890, 870 cm^{-1}

N.m.r. τ 4.60(m.; 1H), 5.32(s.; 2H), 8.91(s.; 3H), 8.98 (s.; 3H), 9.05(d.;J=7Hz, 3H).

The second largest fraction had

I.r. $\nu_{max.}$ 3070, 3010, 1635, 890 cm^{-1},

N.m.r. τ 9.04(s.), 9.30(s.).

These latter spectra showed the same features as spectra of 33 prepared from authentic himachalene dihydrochloride, and the v.p.c. retention times of the two samples were the same.

Dehydration of the mono-ols from diol 30b.

The mono-ols (*ca.* 20 mg.) were treated with a solution (2 ml.) of phosphorus oxychloride in pyridine/benzene as above. V.p.c. (5' x $\frac{1}{4}$" 3% 810 silicone, 142°) on the products after separation showed a mixture of four components in the approximate ratio 60:30:4:6 in order of elution. The first compound had the same v.p.c. retention time (on the same column) and a similar i.r. spectrum to the major product from mono-ol 43 above, but the three other compounds appeared not to correspond with the three others above. None of the compounds from this dehydration or from dehydration of 43 had v.p.c. retention times corresponding with either natural himachalene.

Dehydration of 30c.

Diol 30c (12 mg.) was treated with phosphoryl chloride solution in pyridine/benzene (3 ml.), in the same manner as had been the mono-ols, at 50° under nitrogen overnight. Water was added and the solution was extracted with benzene; the extract was filtered through magnesium sulphate and evaporated. V.p.c. on the residue (9' x $\frac{1}{4}$" 20% 20M carbowax, 150°) showed about six peaks corresponding to 33 30%

2 8%

32 41%

others 21% (all ± 1%)

Dehydration of 30d.

Diol 30d (8 mg.) was treated with the phosphoryl chloride reagent (2 ml.) and worked up as before. Analysis of the diene products by v.p.c. showed

33	25%
2	8%
32	29%
others	38% (all ± 1%)

Dehydration of 30b.

Diol 30b (10 mg.) was likewise treated with excess of the phosphoryl chloride reagent (2 ml.). The same workup procedure as previously gave a mixture of dienes containing negligible 33, 2 or 32 according to v.p.c. analysis.

Dehydration of 30a.

Diol 30a (12 mg.) was treated with an excess of the phosphoryl chloride reagent as above (3 ml.). Extraction and v.p.c. analysis of the diene products showed

33	*ca*.4%
2	*ca*.2%
32	*ca*.2.5%
others	92%

Dehydration of a Mixture of Diols 30c and 30d.

A mixture of diols 30c and 30d (144 mg.), in the approximate ratio 2:3, was treated with a solution (25 ml.) of phosphoryl chloride (9 times excess), and pyridine (90 times excess), in benzene under nitrogen at 50° for twelve hours. Water was then added and the mixture was extracted with benzene, washed, dried and evaporated to give a diene mixture (95 mg.). This material was separated by v.p.c. (20' x 3/8" 20% 20M carbowax, 170° to give

2, i.r. and n.m.r. spectra identical with those of natural β-himachalene.

32, I.r. $\nu_{max.}$ 3015, 1440, 1389, 1379, 1367, 1160, 1152
878, 825 cm^{-1}.

N.m.r. τ 9.21(s.; 3H), 9.02(s.; 3H), 8.31(m.; 6H),
4.70(m.; 1H), 4.50(m.; 1H).

33, I.r. $\nu_{max.}$ 3070, 3015, 1638, 1450, 1390, 1366, 1150,
890 cm^{-1}.

N.m.r. τ 9.30(s.; 3H), 9.03(s.; 3H), 8.33(m.; 3H),
5.33(m.; 1H), 5.27(m.; 1H), 4.72(m.; 1H).

Analysis: Calc. for $C_{15}H_{24}$: C 88.16, H 11.84%
Found: C 88.10, H 11.62%.

Acetylation of the Mono-ol from Diol 30b.

The mono-ol (6 mg.) and sodium acetate (9 mg.) were refluxed in acetic anhydride (1 ml.) for four hours. The solution was then evaporated to dryness below 60° and water (5 ml.) was added. Extraction with ether furnished an oil (8 mg.), i.r. and t.l.c. showing it to be mainly one compound, 35.

Preparation of 35 from 30b.

Diol 30b (479 mg.), in acetic anhydride (25 ml.), was heated under reflux with sodium acetate (490 mg.) for twelve hours, (shorter reaction times gave a mixture of 35 and 34b). The solution was then evaporated to about 5 ml., water (25 ml.) was added and the mixture extracted with ether. The extract was washed, dried and evaporated, and separated by t.l.c. to give 35 (462 mg.) as an oil.

I.r. $\nu_{max.}$ 3070, 1735, 1635, 1245, 1020, 890 cm^{-1}.
The presence of small peaks at 3020 and 860 cm^{-1} suggested that 36 was an impurity.

N.m.r. τ 9.16(s.; 3H), 9.10(s.; 3H), 9.00(d.J=3Hz; 3H),
8.02(s.; 3H), 5.32(s.; 2H), 5.09(m.; 1H).

Pyrolysis of 35 and 36.

The mixture of 35 and 36, as prepared above, without further purification, was pyrolysed in the vapour phase by passing it through a quartz tube at 540-570° under 1-2mm. nitrogen pressure several times until decomposition was almost complete according to i.r. analysis. I.r. indicated less than about 10% acetate remaining, and v.p.c. (20' x 3/8" 20% 20M carbowax, 170°) showed that the mixture (285 mg.) contained about 70% 33 and about 20% 32, with negligible quantities of other dienes.

Preparation of Himachalene Dihydrochloride, 39.

A mixture of authentic α- and β-himachalenes (2.21 g.), containing about 20% of impurity of unknown constitution, retention time on v.p.c. 0.95 relative to β-himachalene (12' x ¼" 20% 20M carbowax, 150°), was filtered through a short column of active alumina, dissolved in ether (10 ml.), and saturated with dry hydrogen chloride gas during 1¼ hours, at 0°. The solution was kept sealed at 0° overnight, then evaporated to dryness below 10°. The solid residue was crystallised from light petrol to give 39 (700 mg.), m.p. 115-118° (fast heating).

I.r. $\nu_{max.}$ 1449, 1385, 1370, 1110, 570 cm^{-1}.

N.m.r. τ 9.15(s.; 3H), 9.03(s.; 3H), 8.40(s.; 6H).

Analysis: Calc. for $C_{15}H_{26}Cl_2$: C 64.97, H 9.45, Cl 25.58%
Found: C 64.87, H 9.32, Cl 25.61%.

The dihydrochloride was found to be quite stable for at least 24 hours at room temperature under nitrogen as crystals or in carbon tetrachloride solution, but could not be recovered from methanol or nitromethane solutions.

39 from Synthetic 32.

32 (19 mg.) was saturated with dry hydrogen chloride gas in ether solution (1 ml.) at 0°, sealed and kept at 0° for forty hours. Evaporation to dryness and recrystallisation from light petrol afforded 39 (17 mg.), m.p. 108-112°. A mixed m.p. with authentic, optically active, 39 was depressed. The i.r. spectra of the two compounds were superimposably identical.

39 from Synthetic 33.

A mixture of 32 and 33 (285 mg.) was converted to 39 (115 mg. after recrystallisation) using the same procedure as above. The i.r. and n.m.r. spectra of the product were identical with those of authentic 39. Recrystallisation gave m.p. 107-110° (fast heating).

Analysis: Found: C 65.39, H 9.51% (i)
C 64.99, H 9.20, Cl 25.56 (ii).

Dehydrochlorination of 39.

It had been found that pyrolytic decomposition of authentic himachalene monohydrochloride (a sample obtained from H. Erdtman), by injection of small amounts, in solution, on a v.p.c. column, gave two major products, one having the same retention time as 33 (synthetic).

Authentic 39 (10 mg.) was filtered through a 4 x 1 cm. column of neutral alumina in carbon tetrachloride solution. I.r. on the eluent was identical with that of himachalene monohydrochloride, and v.p.c. decomposition gave the same pattern.

Authentic 39 (96 mg.) was dissolved in pyridine and the solution refluxed for 6½ hours under nitrogen. V.p.c. on the super-natant liquid after cooling showed three components, with retention times corresponding to 33, β-himachalene and the second major product from v.p.c. decomposition of himachalene monohydrochloride. Separation by v.p.c. gave 33 with i.r. identical with the synthetic material (ca. 20% of total diene product); β-himachalene, i.r. identical with the natural material (ca. 8%); the third product, i.r. showing peaks at 3070, 3025, 1635, 1448, 1390, 1380, 1366, 890 cm^{-1} (ca. 70%).

Acid-catalysed rearrangement of α-himachalene.

Authentic α-himachalene (17 mg.) was dissolved in 30% formic acid/ether (about 0.05ml.) in a capillary tube. The tube was sealed and kept at 60° for about fifty hours. V.p.c. analysis of the contents showed almost entirely (ca. 85%) one peak, corresponding to β-himachalene, by a retention time comparison with an authentic sample. The tube contents were poured into water and extracted with carbon tetrachloride, and the extract separated on v.p.c. I.r. of the separated diene was almost identical with that of authentic β-himachalene.

Acid-catalysed rearrangement of 33.

33, obtained from himachalene dihydrochloride, 39, (95 mg.) was dissolved in 50% formic acid/ether (0.3 ml.) in a capillary tube. The tube was sealed and heated at 80° for twenty-four hours. The contents were then separated by v.p.c. The compound having the same retention time as β-himachalene was repurified by v.p.c., and had an i.r. spectrum identical with that of β-himachalene.

A sample of 33, dissolved in 30% formic acid/ether in a sealed capillary tube, was heated at 70° for 2 hours. V.p.c. analysis (9' x $\frac{1}{4}$" carbowax column) of the contents then showed mainly starting material with a trace (*ca.* 2%) of β-himachalene and *ca.* 4% 32. The tube was then resealed and heated at 80° for a further 18 hours, the contents being analysed at intervals. After six hours there were present 65% 33, 2% 2, 25% 32, and *ca.* 3% of material of much shorter retention time. After eighteen hours, analysis showed about 40% 33, 5% 2, 50% 32 and *ca.* 5% others. V.p.c. separation of the compound 32 gave

I.r. $\nu_{max.}$ 3015, 1440, 1389, 1379, 1366, 1150, 878 cm^{-1}

N.m.r. τ 4.50(m.; 1H), 4.70(m.; 1H), 8.31(m.; 6H), 9.02 (s.; 3H), 9.21(s.; 3H).

PART B: STEREOCHEMICAL CONTROL OF PHOTOCHEMICAL CYCLOADDITION.

Preparation of cyclohex-1-enyl 3-keto-5,5-dimethylcyclohex-1-enyl succinate, 44.

A slurry of dimedone (5,5-dimethylcyclohexane-1,3-dione) (3 g.) in chloroform (20 ml.) was added during five minutes to succinyl chloride (redistilled, 10 g.) with vigorous stirring. After a further five minutes the solution was heated on a steam bath under nitrogen and refluxed for three hours. The solvent and excess succinyl chloride (b.p. _ca_. 100°, 0.2mm.) were then distilled out of the reaction mixture under vacuum. Spectra on the liquid residue showed it to be mainly 3-keto-5,5-dimethylcyclohex-1-enyl succinyl chloride:

I.r. $\nu_{max.}$ 1795, 1765, 1680, 1125 cm^{-1}

N.m.r. τ 8.92(s.; 6H), 7.87(s.; 2H), 7.66(m.; 2H), 7.26 (s.; 2H), 6.76(s.; 2H), 4.30(m.; 1H).

τ 7.31, 7.12, 5.00, 4.55 were probably due to impurities.

To this material, without attempting purification, was added carbon tetrachloride (15 ml.) and cyclohexanone

(2 ml). The solution was heated under reflux for four hours and then the solvent and excess cyclohexanone were removed by distillation. More carbon tetrachloride (20 ml.) was added and the solution filtered to remove some succinic anhydride. Distillation of the filtrate under high vacuum afforded the di-enol ester product 44, as a viscous pale greenish-yellow liquid, b.p. *ca.* 170°, 0.2mm. (0.94 g.) On cooling to -70° the glass solidified and could be crystallised from ether. Recrystallisation afforded white prisms (700 mg.), m.p. 73-76°.

I.r. $v_{max.}$ 3016, 1760, 1750, 1679, 1646, 1120 cm^{-1}

N.m.r. τ 8.90(s.; 6H), 8.32(m.; 4H), 7.85(s.; 2H), 7.89 (m.; 4H), 7.64(m.; 2H), 7.33(m.; 4H), 4.72(m.; 1H), 4.29 (m.; 1H).

U.V. $\lambda^{ether}_{max.}$ 226 nm (ϵ 14400).

Analysis: Calc. for $C_{18}H_{24}O_5$: C 67.48, H 7.55%
Found: C 67.79, H 7.96%.

Irradiation of 44.

The di-ester (495 mg.) was dissolved in benzene (90 ml.)/cyclohexane (120 ml.), both previously filtered through active alumina, and the solution was degassed by bubbling nitrogen through it for 30 minutes. The solution was then irradiated with light from a 450 watt high-pressure lamp through a pyrex filter, under nitrogen for eight hours. After this time no further change was visible in the i.r. spectrum, so the irradiation was stopped and the solution evaporated to dryness. No attempts were made to purify the product beyond unsuccessful attempts at crystallisation, but its identity was established by the following spectral data and chemical tests:

U.v. $\lambda^{C_6H_{12}}_{max.}$ 232 nm (ϵ *ca.* 10^4).
274 nm (ϵ *ca.* 7×10^3).

I.r. $\nu_{max.}$ 3030, 1750, 1670, 1570, 1150 cm^{-1}

N.m.r. τ 8.92(s.; 6H), 8.38(m.; 4H), 7.93(m.; 4H), 7.67, 7.50, 7.38, 7.27, 7.06, 6.62 (not analysed, total 9H), 4.69(m.; 1H), *-7.75*(m.; 1H).

a) An ethereal solution of the compound gave a reddish brown colour with methanolic ferric chloride whereas the di-ester starting material did not.

b) Treatment of aqueous cupric acetate with an ethereal solution of the compound caused the blue colour to be extracted into the ether layer, whereas similar treatment with an ethereal solution of the di-ester did not.

From these data the β-triketo- structure, cyclohex-1-enyl 4-keto-4-(2,6-diketo-4,4-dimethylcyclohexyl) butanoate, *45*, was assigned to the irradiation product. The alternative structure, a β-diketone from rearrangement of the cyclohexenyl ester, was rejected after comparison of the u.v. maxima with those of 2-acetyl-5,5-dimethylcyclohexane-1,3-dione, which has

$$\lambda_{\text{max.}} \quad \begin{array}{l} 273 \text{ nm } (\epsilon\ 10800) \\ 231 \text{ nm } (\epsilon\ 10620). \end{array}$$

Preparation of 46.

The acid, 47, (1.76 gm.) was warmed with thionyl chloride (5 ml., redistilled) on a steam bath for ten minutes and then evaporated to dryness. Cyclopentane-1,2-dione (0.85 g., recrystallised from ether) was then added in chloroform (15 ml., previously filtered through active alumina), and the solution heated at reflux under nitrogen for one hour. Evaporation to dryness and chromatography on 120 g. silicic acid powder using 4% ethyl acetate/benzene as eluent afforded the enol ester, 46, (1.76 g., 77% from 47).

I.r. $\nu_{\text{max.}}$ 1740, 1730, 1635, 1620, 1190, 1085 cm^{-1}

N.m.r. τ 9.10(d.;J=5Hz, 6H), 7.95(m.; 3H), 2.78(t.;J=2.5 Hz, 1H).

U.v. $\lambda^{\text{ether}}_{\text{max.}}$ 227 nm (ϵ 11200), 320 nm (ϵ 60).

Analysis: Calc. for $C_{16}H_{22}O_3$: C 73.25, H 8.45%

Found: C 73.37, H 8.52%.

Irradiation of 46.

A solution of 46 (250 mg.), in cyclohexane (freshly filtered through alumina, 50 ml.) was degassed by bubbling nitrogen for one hour. Irradiation of the solution (Rayonet reactor, 24 watt "black light" phosphor lamps, $\lambda_{max.}$ 350 nm) for eight hours, followed by thin layer chromatographic separation on silica, using 50% ether/petrol as eluent, afforded starting material, R_f ca. 0.3, (ca. 20 mg.), a cycloaddition adduct, R_f ca. 0.25, (71 mg.), less polar material (40 mg.), and hydroxyl-containing material, R_f ca. 0.1, (74 mg.).

The cycloaddition product 51, after further chromatographic purification, had spectral data:

I.r. $\nu_{max.}$ 1790, 1747, 1150, 1030, 1020 cm^{-1}

N.m.r. τ 9.18(d.;J=6Hz, 6H).
$\tau(C_6H_6)$ 9.37(d.;J=6Hz, 6H).

Analysis: Calc. for $C_{16}H_{22}O_3$: C 73.25, H 8.45%
Found: C 73.05, H 8.27%.

Irradiation of the ester in benzene with 350 nm hv gave the same material but in no higher yield.

Irradiation of the ester (90 mg.) in benzene with 350 nm hv with triphenylene (330 mg.) as sensitiser gave the same product, and the reaction proceeded somewhat faster.

Irradiation of the ester in cyclohexane with 450 watt high pressure mercury lamp with a pyrex filter gave the same adduct as the only isolable product, but in even lower yields.

Rearrangement of 51.

The irradiation adduct (71 mg.) was treated with 1% sodium hydroxide (in 90% methanol/water, 6 ml.) at reflux under nitrogen for one hour. The solution was poured into water, washed with ether, acidified and extracted with ether to give acidic material, 52a, (30 mg.). This was purified chromatographically on silica t.l.c. plates, with 10% acetic acid/benzene eluent, and had i.r. spectral peaks at 3400, 1780, 1705 cm^{-1}. Treatment with diazomethane and separation by t.l.c. (silica, 50% ether/petrol) afforded a non-polar material (9 mg.), the i.r. spectrum showing no hydroxyl, and carbonyl peaks at 1802 and 1790 cm^{-1}, and the ester, 52b, (12 mg.). This ester was recrystallised from petroleum ether, m.p. 79.0-79.5°.

I.r. $\nu_{max.}$ 3520, 1780, 1740, 1155 cm^{-1}.

N.m.r. τ 9.06(d.;J=5.5Hz, 6H), 7.44(1H-OH), 6.45(s.; 3H).
$\tau(C_6H_6)$ 9.06(d.;J=5.5Hz, 6H), 6.58(s.; 3H).

Analysis: Calc. for $C_{17}H_{26}O_4$: C 69.36, H 8.90%
Found: C 69.35, H 8.77%.

Lactonisation of 52b.

The methyl ester (21 mg.) was heated under nitrogen at 190° for thirty minutes, cooled, and evacuated briefly. The liquid product of this pyrolysis was purified (thin layer chromatography) and found to have an i.r. spectrum identical with that of the byproduct from treatment of the acid, 52a, with diazomethane.

I.r. $\nu_{max.}$ 1802, 1790, 1084 cm^{-1}

N.m.r. τ 9.10(d.; 6H)

Analysis:	Calc. for $C_{16}H_{22}O_3$:	C 73.25, H 8.45%
	Found:	C 74.30, H 8.40%.

Preparation of 2-methyl-4-isopropylcyclohex-1-enylmethyl cyclopent-1-en-5-onyl ether, 54.

The allylic alcohol, 55 (ca. 70% pure after fractional distillation of very impure material), (3.8 g.), cyclopenta-1,2-dione (4.2 g.) and p-toluenesulphonic acid (50 mg.) were mixed and kept at room temperature for four days. Dione which had crystallised (1.8 g.) was then removed and the remaining liquors chromatographed quickly on silicic acid (100 g.) using 7% ethyl acetate/benzene as eluent. All fractions containing the desired product were chromatographed, after combining them (2.15 g.), on 220 g. silicic acid with 10% ethyl acetate/chloroform as eluent. This afforded a mixture of liquid allylic alcohols (1.2 g.) and the liquid allylic enol ether 54 (930 mg., 42% based on 55).

I.r. $\nu_{max.}$ 3070, 1725, 1625, 1108 cm^{-1}.

N.m.r. τ 9.12(d.;J=5Hz, 6H), 8.31(m.; 3H), 5.68(s.; 2H), 3.67(t.;J=2.5Hz, 1H).

U.v. $\lambda^{\text{ether}}_{\text{max.}}$ 246 nm (ϵ 7900), 308 nm (ϵ 125).

Analysis: Calc. for $C_{16}H_{24}O_2$: C 77.37, H 9.74%

Found: C 77.34, H 9.72%.

Irradiations of 54.

(i) The allylic ether (188 mg.) was dissolved in 50% ether/cyclohexane (alumina-filtered, 50 ml.) and the solution degassed by bubbling nitrogen for one hour. The solution was then irradiated (24 watt 350 nm phosphor lamps, Rayonet reactor) for 3¼ hours, by which time the starting material was almost completely destroyed. Separation of the products by thin layer chromatography in 7% ethyl acetate/benzene and examination of them by infrared showed that no desired cycloaddition product was present to greater than <u>ca</u>. 5%. The major product was 2-methyl-4-isopropylcyclohexene-1-carboxaldehyde (20 mg.), shown by comparison of the i.r. and n.m.r. spectra with those of an authentic sample, produced together with several hydroxyl-containing, very polar compounds.

(ii) In a similar manner, the allylic ether (126 mg.) in 75% ether/cyclohexane (100 ml.) containing triphenylene (290 mg.) was irradiated 70 minutes, giving apparently the same mixture of products as above.

(iii) The allylic ether (300 mg.) and acetophenone (1.95 g.) in 50% ether/cyclohexane (100 ml.) were similarly irradiated for 50 minutes until the starting material was destroyed. Chromatography of the products on a silicic acid column with 20% ether/cyclohexane eluent gave many fractions, the principal products being derived from acetophenone. These were acetophenone pinacol (108 mg.), an unidentified alcohol, and a compound which, from its i.r. and n.m.r. spectra, appeared to be p-(1-ethoxyethyl)acetophenone. There was no indication that any of the desired cycloaddition product had been formed in greater than 5% yield.

Preparation of 2-methyl-4-isopropylcyclohexene-1-carboxaldehyde.

The allylic alcohol, 55, (500 mg., 70% pure), and active manganese dioxide (4.0 g.) in petroleum ether (60/80, 25 ml.), were shaken at room temperature for twenty hours. The solution was filtered, washed (H_2O), dried (magnesium sulphate), and evaporated. Thin layer chromatographic separation (silica, 5% ether/benzene eluent) afforded the liquid aldehyde (122 mg., ca. 35% yield).

I.r. $\nu_{max.}$ 2750, 1670, 1642, 1247 cm^{-1}

N.m.r. τ 9.08(d.;J=6Hz, 6H), 7.90(m.; 3H), 0.02(s.; 1H).

U.v. $\lambda_{max.}^{C_6H_{12}}$ 243 nm (ϵ 11800), 320 nm (ϵ 74).

Preparation of 2-chloroformylcyclopent-2-enone.

Cyclopentane-1,2-dione (3.1 g.) was dissolved in a solution of 12½% phosgene in benzene (70 ml.), containing calcium carbonate (4 g.), and the suspension was heated under reflux for seven hours. The reaction was followed by i.r., and when complete the solution was filtered and evaporated to give 4.5 g. of crude chloroformate, as a mobile liquid.

After distillation (b.p. 77°, 1.5mm.) this compound had

I.r. $\nu_{max.}^{neat}$ 1790, 1722, 1630, 1120 cm^{-1}

N.m.r. τ 7.1-7.8(m.; 4H), 2.51(t.;J=2.5Hz, 1H).

U.v. $\lambda_{max.}^{ether}$ 220 nm, 312 nm.

<u>Preparation of 3-methylbut-2-enyl cyclopent-2-enon-2-yl carbonate, 56</u>.

To a solution of chloroformylcyclopentenone (1.6 g.) in carbon tetrachloride (15 ml.) was added isopentenol (1.0 g.). The solution was refluxed two hours and then evaporated to give 2.0 g. Chromatography of this on 170 g. silicic acid column (12% ether/benzene eluent) afforded the required compound (1.19 g., 57%).

I.r. $\nu_{max.}$ 1765, 1728, 1630, 1270, 1220, 925 cm^{-1}

N.m.r. τ 8.22(m.; 6H), 7.2-7.7(m.; 4H), 5.28(d.;J=7Hz, 2H), 4.53(t.;J=7Hz, m.; 1H), 2.65(t.;J=2.5Hz, 1H).

U.v. $\lambda_{max.}^{ether}$ 223 nm (ϵ 9150), 321 nm (ϵ 60).

Analysis: Calc. for $C_{12}H_{14}O_4$: C 62.84, H 6.71%

Found: C 62.57, H 6.62%.

Preparation of 3-methylbut-2-enyl cyclopent-2-enon-2-yl oxalate, 60.

To oxalyl chloride (8 ml.) and calcium carbonate 1.07 g.) in carbon tetrachloride (30 ml.) was added cyclopentane-1,2-dione (904 mg.) in carbon tetrachloride (30 ml.) during half an hour whilst maintaining the solution at reflux temperature. Heating was continued a further two hours and then the excess oxalyl chloride was removed by distilling out 50 ml. of the solvent through a Vigreux column, whilst adding a further 60 ml. carbon tetrachloride to the stillpot. Reflux was then resumed and isopentenol (900 mg.) in carbon tetrachloride (10 ml.) was added during five minutes. After a further twenty minutes heating the solution was filtered, evaporated, and cooled to -20°. The crystals were separated and recrystallised from ether to m.p. 40.5-41.5° (1.23 g., 56% yield).

I.r. $\nu_{max.}$ 1786, 1751, 1730, 1293, 1198, 1140, 930 cm^{-1}

N.m.r. τ 8.21(m.; 6H), 7.1-7.7(m.; 4H), 5.20(d.;J=7Hz, 2H), 4.56(t.;J=7Hz, m.; 1H), 2.60(t.J=2.5Hz, 1H).

U.v. $\lambda_{max.}^{ether}$ 220 nm (ϵ 13500), 320 nm (ϵ 74).

Analysis: Calc. for $C_{12}H_{14}O_5$: C 60.50, H 5.92%

Found: C 60.43, H 6.03%.

The intermediate chloroglyoxalate had spectra:

I.r. $\nu_{max.}$ 1788, 1733, 1232, 1070, 950 cm^{-1}

N.m.r. τ 7.1-7.8(m.; 4H), 2.50(t.;J=2.5Hz, 1H).

Irradiation of 56.

The carbonate (449 mg.), in 10% ether/cyclohexane (100 ml., filtered through alumina), was degassed by bubbling nitrogen for one hour, and irradiated (350 nm, Rayonet reactor) for three and a half hours, following the disappearance of starting material by t.l.c. The solution was then evaporated to dryness below room temperature. Since the product, 57d, was not stable on silica gel, or on distillation, the experimental elucidation of the structure was performed without attempting purification.

I.r. $\nu_{max.}$ 1760, 1745, 1250 cm^{-1}

N.m.r. τ 8.21(m.; 6H), 7.2-8.8(m.; ca. 4-6H), 5.38(m.; 2H), 4.60(m.; 1H). Additional small singlet peaks at 9.13 and 8.98 suggested the presence of less than 10% cycloaddition product.

Irradiation of 60.

The oxalate (93 mg.), in 20% ether/cyclohexane (50 ml.), was degassed and irradiated as above for one and a half hours. Evaporation then afforded an oil, 61, unstable on t.l.c., having spectra:

I.r. $\nu_{max.}$ 1780-1740, 1160 cm^{-1}

N.m.r. τ 8.21(m.; 6H), 7.1-9.0(m.; ca. 4-6H), 5.25(m.; 2H), 4.60(m.; 1H). Additional small singlet at 9.13.

Reduction of 57d.

Reduction of the products from irradiation of 449 mg. of the carbonate was achieved by adding them, in ether (20 ml.), to 257 mg. lithium aluminium hydride in ether (20 ml.) and stirring for one and a half hours at room temperature. T.l.c. separation (silica; ethyl acetate eluent) of the products gave 110 mg. of a mixture of polar alcohols, having no vinyl protons. The remainder of the products was apparently a mixture of decomposition products. The polar reduction products were separated into three fractions according to R_f values on t.l.c.; 43 mg. (R_f 0.3, ethyl acetate), 33 mg. (R_f 0.2, ethyl acetate), 32 mg. (R_f 0.1, ethyl acetate).

Periodate titrations.

A portion of each of the three alcohol fractions was treated with sodium periodate solution and at intervals aliquots were treated with sodium arsenite solution and back-titrated with standard iodine solution. The 43 mg. fraction was found to react with one mole of periodate within two hours, and the other two with one mole within half an hour, after which no more was taken up, assuming M.W. of the alcohols to be 186. After isolation of the products from periodate titrations, and examination of the u.v. spectra in neutral, basic, and acidic solutions, αβ-unsaturated ketones were shown to be absent.

Manganese dioxide oxidations.

The remainder of each of the alcohol fractions was treated with active manganese dioxide (200 mg.) in chloroform (2 ml.), and reaction was followed by t.l.c. In all cases an immediate reaction occurred and was complete in fifteen minutes. The products from the 32 mg. and 43 mg. fractions were different, and both of these compounds were apparently present in the 33 mg. fraction products. Separation on t.l.c. (50% ethyl acetate/benzene, R_f 0.4 and 0.45) afforded 9 mg., i.r. showing hydroxyl, carbonyl at 1728 cm^{-1} for the faster-running compound, and 14 mg., i.r. showing hydroxyl, carbonyl at 1770 cm^{-1}, $C=CH_2$ at 890 cm^{-1}, n.m.r. τ 5.15, for the slower. U.v. spectra showed no strong absorption above $\lambda_{max.}$=225 nm, even when treated with acid or base. These observations are consistent only with the formulation 57d for the irradiation product. The reduction product is then the corresponding triol, and the manganese dioxide oxidation products are 58b and 58c.

Hydrolysis of 57d.

Hydrolysis of the products (190 mg.) from irradiation of the carbonate in 20% water/methanol (25 ml.) containing sodium hydroxide (64 mg.; ca. 1 equiv.) at room temperature for forty minutes afforded a complex mixture of products from which could be isolated two fractions (from t.l.c.; 20% ethyl acetate/benzene). Fraction A (R_f 0.4), 13 mg., crystalline, m.p. 111-112° (after recrystallisation from ether), had spectra:

I.r. $\nu_{max.}$ 3500, 3340, 2925, 2855, 1730, 1710, 1700, 1665, 1655, 1410, 1395 cm^{-1}

N.m.r. τ 8.0-9.1(m.; ca. 40), 7.65(m.; ca. 8), 6.75(s.; ca. 0.4, imp?).

U.v. $\lambda_{max.}^{MeOH}$ 263 nm (ϵ 11400), on treatment with base changes reversibly to 298 nm (ϵ 8000) (for $(C_{10}H_{14}O_2)_n$).

Analysis:	Found:	C 73.59, H 8.83%
	Calc. for $(C_{10}H_{14}O_2)_n$:	C 72.26, H 8.49%

Fraction B (R_f 0.22), 59, 17 mg., had spectra:

I.r. $\nu_{max.}$ 3500, 3340, 2980, 2930, 2870, 1705, 1660, 1410, 1395, 1200, 1100 cm^{-1}

N.m.r. τ 7.79(d.;J=5Hz, 3H), 7.69(d.;J=5Hz, 3H), 8.0-8.5 (m.; 1H), 7.60(m.; 5H), 6.58(m.; 2H).

U.v. $\lambda_{max.}^{MeOH}$ 258 nm (ϵ 10200), on treatment with base changes reversibly to 296 nm (ϵ 6800).

Hydrolysis of the products from irradiation of the oxalate, 60.

The mixture, 61, from irradiation of the oxalate could be hydrolysed by either excess sodium bicarbonate in 40% water/methanol, or by one equivalent of sodium hydroxide in 50% water/methanol. In both cases a complex mixture of products was produced. From 350 mg. irradiation products by the latter procedure was obtained 170 mg. non-acidic products, from which were separated two fractions, 22 mg. and 26 mg. which were identical with fractions A and B respectively from hydrolysis of the carbonate irradiation products, according to R_f on t.l.c., and i.r. spectra, and mixed m.p. (for fraction A).

From the spectra (particularly u.v.; cf. cyclopentane-1,2-dione $\lambda^{MeOH}_{max.}$ 253 nm (ϵ 8140) in neutral, and $\lambda^{MeOH}_{max.}$ 290 nm (ϵ 6080) in basic solution; lit. u.v. $\lambda^{EtOH}_{max.}$ 251 nm; 3-methylcyclopentane-1,2-dione lit. u.v. $\lambda^{EtOH}_{nax.}$ 259 nm (ϵ 11000)) the structure of fraction B was assigned as 3-(1-hydroxy-3-methylbut-2-yl)-cyclopentane-1,2-dione, 59.

Such a structure could only arise under such mild conditions if the structure of the irradiation product were 61, analogous to that of the carbonate irradiation product.

Preparation of 64.

To 2-chloroformylcyclopent-2-enone (600 mg.) in carbon tetrachloride (12 ml.) was added the alcohol, 55 (600 mg.), and the solution was refluxed for three hours. Evaporation followed by rapid column chromatography of the residue (on 50 g. silicic acid, 10% ether/benzene eluent) gave a mixture (695 mg.) which was further purified by t.l.c. (10% ether/benzene eluent) to give 64 (512 mg.).

I.r. $\nu_{max.}$ 2960, 2920, 2870, 1765, 1730, 1625, 1230 cm^{-1}

N.m.r. τ 9.10(d.;J=6Hz, 6H), 8.24(m.; 3H), 7.2-7.7(m.; 4H), 5.30(m.; 2H), 2.69(t.;J=3Hz, 1H).

U.v. $\lambda_{max.}^{cyclohexane}$ 221 nm (ϵ 6000)
325 nm (ϵ 30).

Irradiations of 64.

A solution of 64 (119 mg.) in cyclohexane (50 ml., alumina filtered) was degassed with bubbling nitrogen and irradiated (350 nm) for one and a half hours. A complex mixture of products was formed, separation of which by t.l.c. (5% ether/benzene) and examination of the fractions by i.r. showed that no cycloaddition had occurred, although none of the products was identified.

Irradiation of 64 (248 mg.) in anhydrous ether (50 ml.) in the same manner for three hours afforded one major product which was separated by t.l.c. (5% ether/benzene eluent). This was identified as 65.

I.r. $\nu_{max.}$ 2950, 2920, 2870, 1765, 1745, 1250 cm^{-1}

N.m.r. τ 9.10(d.;J=6Hz, 6H), 8.25(m.; 3H), 5.35(m.; 2H), 5.11(d.;J=9Hz, 1H).

Compound 65 (45 mg.) was hydrolysed in 10% water/methanol (10 ml.) containing sodium hydroxide (40 mg.) at room temperature for forty minutes. Two products only were formed. Separation of these by t.l.c. (50% ethyl acetate/benzene eluent) gave 55, having i.r. and n.m.r. spectra, and R_f on t.l.c. identical with authentic material, and cyclopentane-1,2-dione, apparently contaminated with 2-hydroxycyclopentanone. This aerial oxidation of the acyloin on silica was confirmed by preparation of the authentic 2-hydroxycyclopentanone by hydrolysis of 2-chlorocyclopentanone. Attempted purification on t.l.c. gave substantial decomposition to cyclopenta-1,2-dione. Attempted preparations of the 3,5-dinitrobenzoate of the acyloin were unsuccessful, despite one literature report of this derivative.

Irradiation of 64 in acetone solvent gave no observable reaction in one and a half hours; attempted sensitisation of the irradiation of 64 in cyclohexane (1000 ml.) with benzene (6 ml.) (254 nm hv) gave a more complex mixture than had irradiation without the sensitiser, and there was no evidence of cycloaddition.

Estimation of the dipole moment of 15.

Ground state of cyclopentenone.

The direction and magnitude of the dipole moment of cyclopent-2-enone were calculated by taking the bond lengths

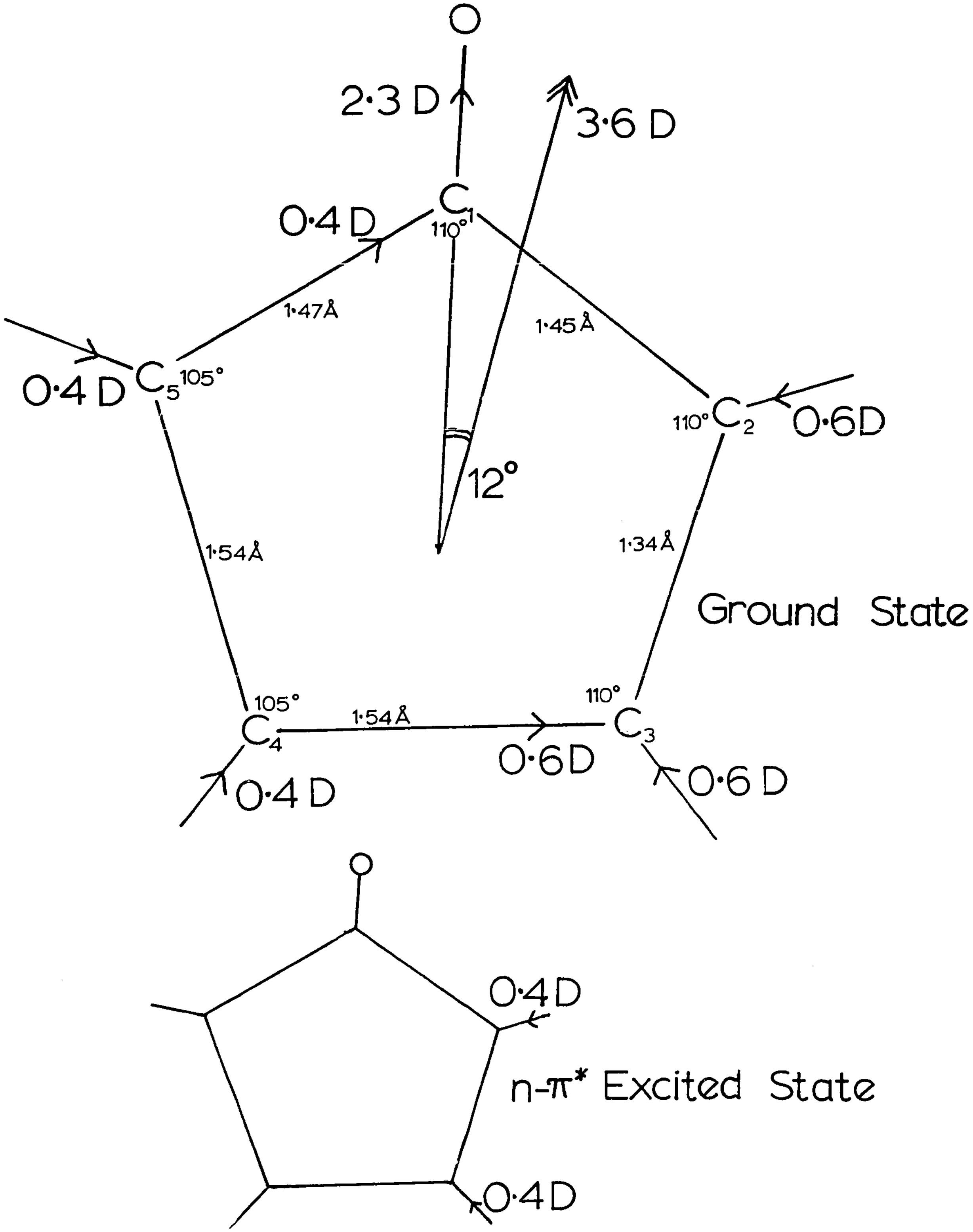

O
2·3 D
3·6 D
C_1
110°
0·4 D
1·47Å
1·45Å
0·4 D
C_5
105°
110°
C_2
0·6D
12°
1·54Å
1·34Å
Ground State
105°
110°
C_4
1·54Å
C_3
0·6D
0·4 D
0·6 D
0·4D
n-π* Excited State
0·4D

Fig. 32

and angles of the molecule as shown in fig. 32 and estimated bond moments from literature values (78), (79). The resultant of these bond moments is 3.60 D inclined at 12° to the C_1-O line. The magnitude of this moment is in good agreement with the experimental value of 3.45 D (78), implying that the bond moment figures are fairly reliable, and that the direction is probably correct within 5°.

n-π^* Excited state of cyclopentenone.

The u.v. spectrum of cyclopentenone was run in seventeen non-hydrogen-bonding solvents (all alumina-filtered prior to use) and the frequency of the n-π^* singlet absorption maximum plotted vs. $f(\epsilon)$ (23), where ϵ is the solvent dielectric constant and $f(\epsilon) = \frac{2(\epsilon-1)}{2\epsilon+1}$. The change in magnitude of the dipole moment component along the line of the ground state moment upon excitation could then be calculated from the formula (23):

$$\Delta\mu_{e-g} = \frac{-\Delta E}{\Delta f(\epsilon)} \cdot \frac{V \cdot 3}{\mu_g \cdot 4\pi}$$

where $\Delta\mu_{e-g}$ is the change in dipole moment upon excitation

μ_g is the ground state dipole moment

ΔE is the energy of the absorption maximum

V is the molecular volume of cyclopentenone.

The observed points were fitted to a line having a slope

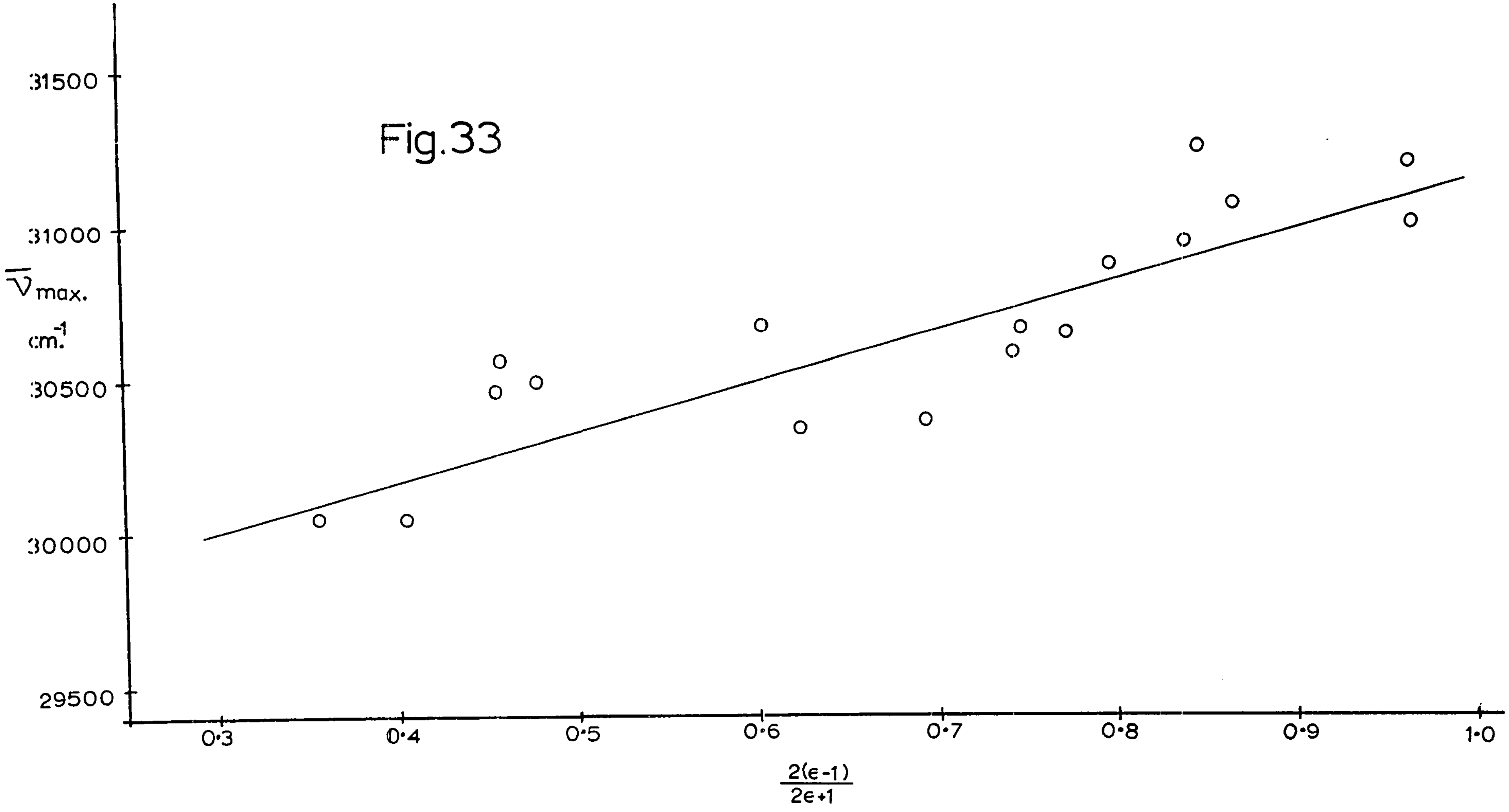


Fig.33

Variation of $^1n\text{-}\pi^*$ Absorption of Cyclopentenone with Solvent Dielectric Constant

$\left(\frac{\Delta E}{\Delta f(\epsilon)}\right)$ of 1612 cm^{-1} with a correlation coefficient, r, of 0.88, by a least-squares approximation (fig. 33). Since

$$\frac{\Delta E}{\Delta f(\epsilon)} = 1612xhxc \quad c.g.s.$$

$$V = \frac{V_m}{N_{Av.}}$$

$$\mu_g = 3.45 \times 10^{-18} e.s.u.$$

where

$$h = 6.63 \times 10^{-27}$$

$$c = 3 \times 10^{10} \ cm.sec^{-1}$$

$$V_m = 82 \ cm^3 \ mole^{-1}$$

$$N_{Av.} = 6.02 \times 10^{23} \ molecules.mole^{-1}$$

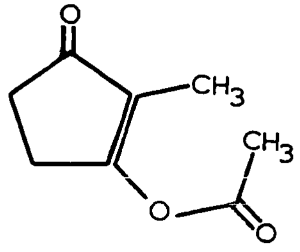
it could be deduced that

$$\Delta\mu_{e-g} = -3.02 \ D \ (\text{probably } \pm 0.2D).$$

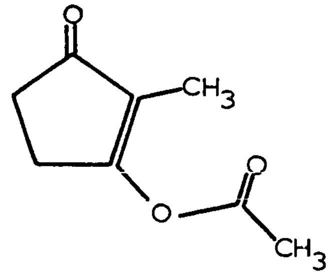
Consequently the component of the excited state dipole moment along the line of the ground state moment is 3.45 - 3.02 = 0.43(±0.2)D. The direction of the excited state dipole moment cannot be determined but a guess of between 12° and 50° to the C_1-O bond seems reasonable, since the n-π^* state involves promotion of an electron from the n orbitals of the oxygen to the π^* orbitals distributed throughout C_1, C_2 and C_3. This would give the absolute magnitude of the excited state dipole moment as between 0.2 and 0.8 inclined at between 12° and 50° to C_1-O.

Ground state of 15.

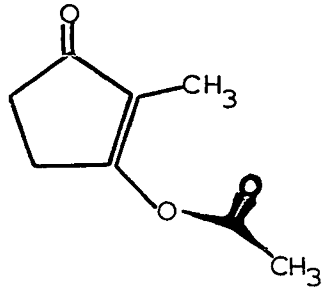
Since 15 has an acetoxy group which can rotate fairly freely, the instantaneous dipole moment of the molecule would tend to vary considerably, both in magnitude and direction, depending on the molecular conformation. It is required that some estimate of the magnitude and direction of the likely conformations be known. Conformations of 15 with the methyl group of the acetate, or the acetate carbonyl group close to the C_2-CH_3 group (fig. 34, A and B) are not likely to be populated greatly because of the bulk of the C_2-CH_3 group. The remaining conformations of the acetate group would give an average resultant dipole roughly along the $C_3(sp^2)$-O bond. This average was taken as 0.9 D, based on the dipole moments of vinyl acetate and phenyl acetate (78). The bond moment of CH_3-$C_2(sp^2)$ was taken as 1.0 (±0.2) D, and the experimental magnitude and calculated direction of the moment of cyclopentenone were used to calculate the dipole moment of 15 (fig. 35). This calculated resultant was 2.48 (±0.2) D at 32° (±5°) to C_1-O. This, however, is an average for most of the conformations of the molecule. The instantaneous dipole moment probably varies from about 3.2 D at 20° to C_1-O (for conformation C, fig. 34) to about 1.0 D at 250° to C_1-O (for conformation D, fig. 34), together with variations of the direction of the moment out of the plane of the cyclopentenone ring.



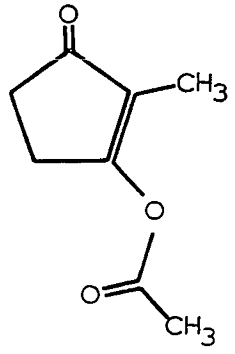
A



B



C



D

Fig. 34

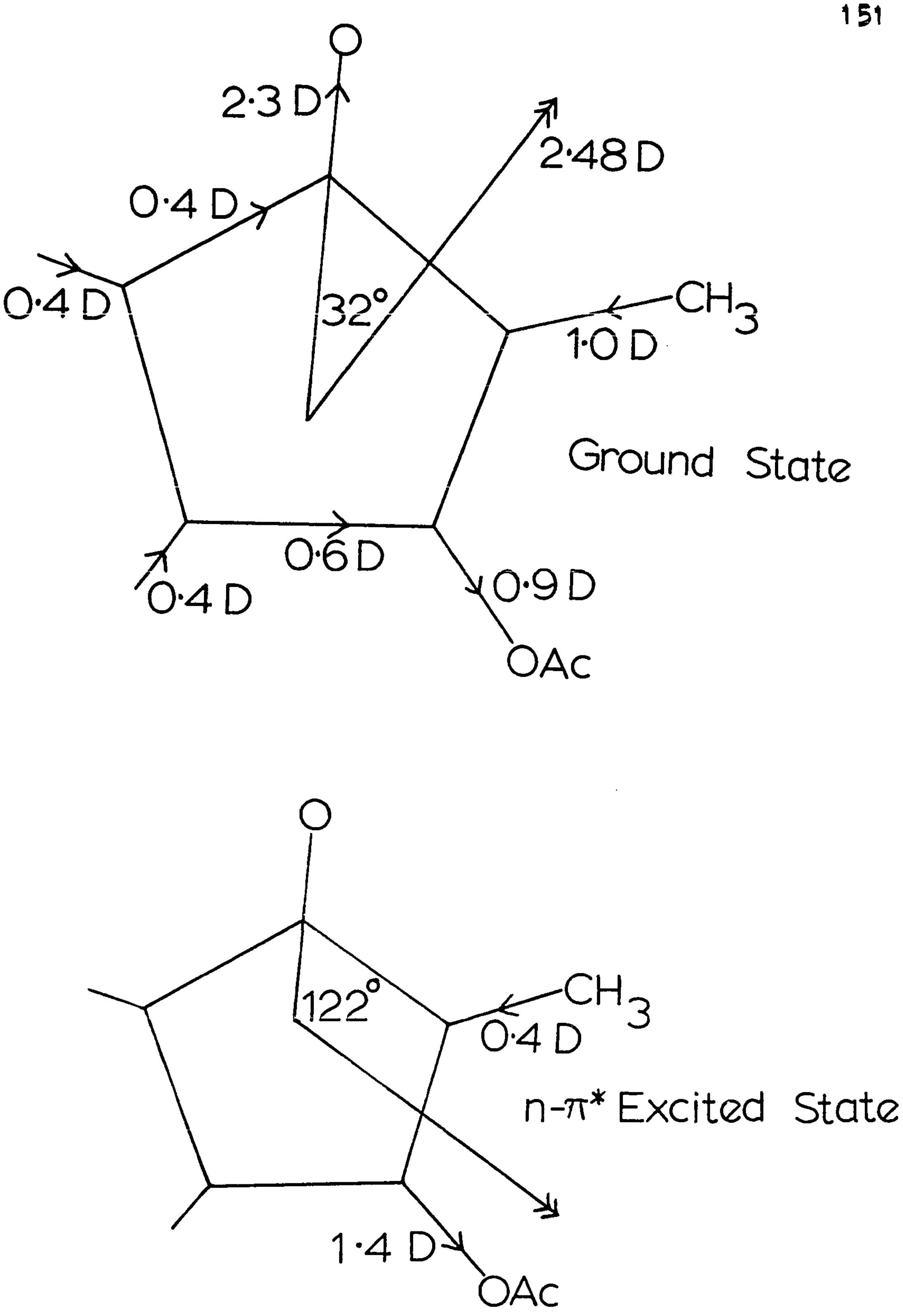

O
2·3 D
2·48 D
0·4 D
0·4 D
32°
CH3
1·0 D
Ground State
0·6 D
0·4 D
0·9 D
OAc
O
122°
CH3
0·4 D
n-π* Excited State
1·4 D
OAc

Fig. 35

The dipole moment of 15, in carbon tetrachloride solution at room temperature, was measured and found to be 3.84 D. This is larger than the calculated moment, and larger than would be expected for 15. This may be because of experimental error in the determination (15 hydrolyses readily, and the material used may have been impure), or because 15 may exist in a preferred conformation, such as fig. 34 B, in dilute carbon tetrachloride solution.

n-π^* Excited state of 15.

Since the π-electron density at C_2 and C_3 is expected to be increased in the n-π^* excited state of the enone, the C_2-CH_3 bond moment was considered to be approximately equal to the C_2-H bond moment in excited cyclopentenone, and the average C_3-O bond moment (including the average for the acetate conformations) was taken as 1.4 D. The dipole moment of the n-π^* excited state of 15 was then calculated from the previously estimated dipole moment of excited cyclopentenone, with these corrections for the acetate and methyl substituents, to be 1.74 (±0.4) D at 122° (±10°) to C_1-O. Allowing for the variations in conformation of the acetoxy group the instantaneous dipole moment of excited 15 would probably be between 1.2 and 2.5 D at between 100° and 200° to C_1-O. This variation is much smaller than the corresponding variation in the ground state of 15 since the dipole moment contribution of the cyclopentenone is so much smaller.

It was hoped that these figures could be conveniently checked by measuring the dipole moment change on excitation to the n-π^* singlet state, as had been done for cyclopentenone. Using the same seventeen solvents, the maximum absorption frequencies were plotted against f(ϵ) (fig. 36). Again, the best straight line, r = 0.86, was determined by a least squares approximation, and had a slope of 489 cm^{-1}. From this it was deduced that

$$\Delta\mu_{e-g} = -2.40(\pm0.2)D.$$

If the previous calculation of the average dipole moment of excited <u>15</u> has any validity, then the component of that moment along the line of the ground state moment should be equal to $\Delta\mu_{e-g} + \mu_g$. Resolving the calculated moment (1.74D at 122° to C_1-O) gives the component along 32° to C_1-O as 0.0($\pm$0.55)D.

$$\Delta\mu_{e-g} + \mu_g = 2.48(\pm0.2) - 2.40(\pm0.4)$$

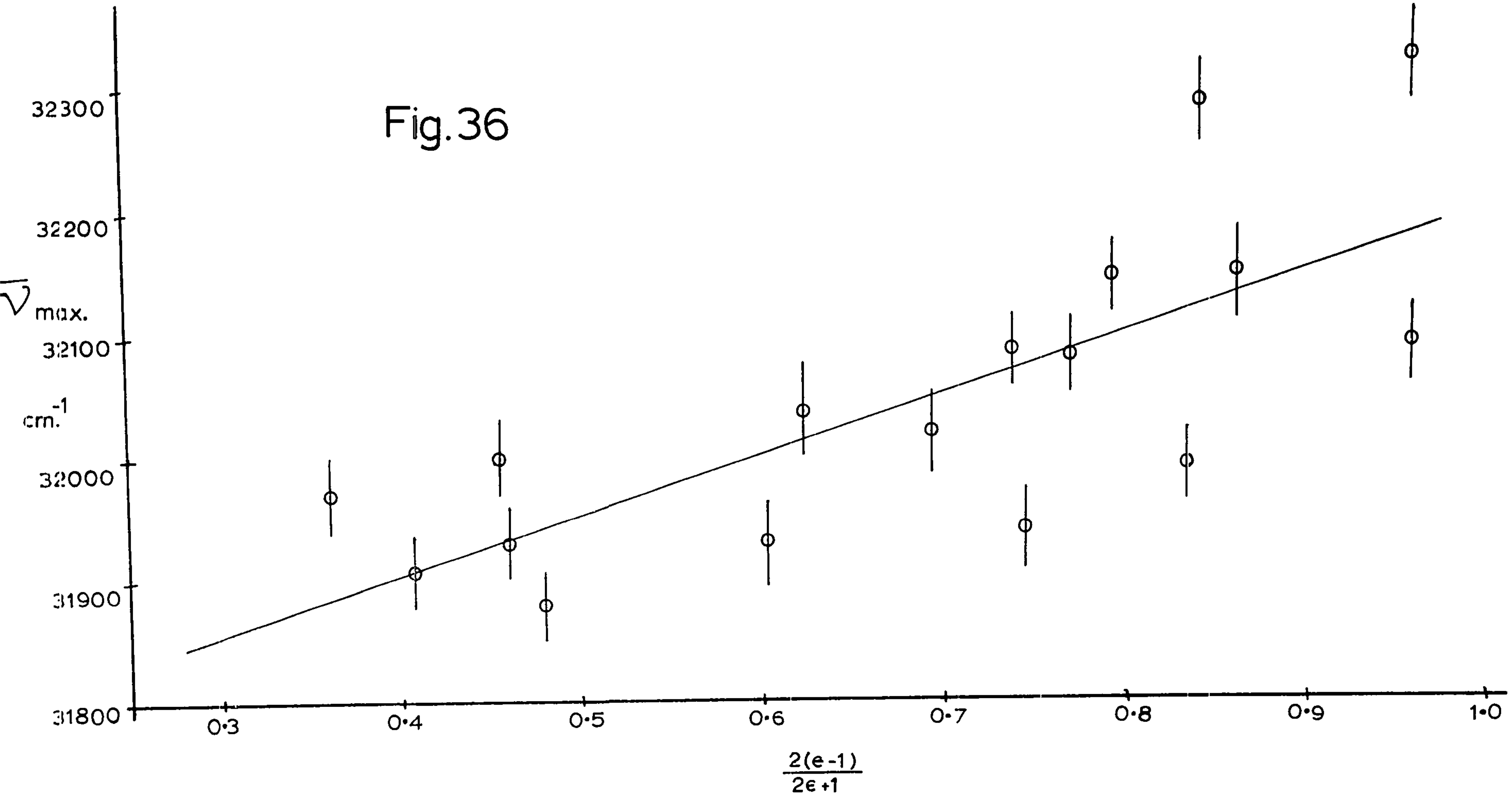
$$= 0.08(\pm0.6)D.$$

Thus there is some justification for taking these calculated dipole moment figures as reasonably correct:

Ground state of <u>15</u> (average for most conformations) 2.5 ($\pm$0.2) D at 32° ($\pm$5°) to C_1-O,

n-π^* Excited state of <u>15</u> (average for most conformations) 1.7 ($\pm$0.4) D at 122° ($\pm$10°) to C_1-O.

Fig.36



Variation of ^{1}n-π^{*} Absorption of <u>15</u> with Solvent Dielectric Constant

It is apparent from these figures that the dipole moment component of excited 15 along the $C_2=C_3$ double bond is directed towards C_3 for most conformations of 15. If the experimentally determined value for the ground state dipole moment (3.8 D) is assumed to be correct, the excited state dipole moment derived from this would be approximately perpendicular to the $C_2=C_3$ double bond. From this one would predict a negligible solvent effect on the cycloaddition reaction.

Irradiations of 15 and 66 in various solvents.

The preparations of 15 and 66 have been described previously (in Part A). The solvents used for the irradiations were the purest grades available, cyclohexane, iso-octane and methanol being Fisher "spectranalysed" grades, ethyl acetate being B.D.H. "Analar", and ether being Mallinckrodt "anhydrous". The acetonitrile was distilled from phosphoric oxide, and all solvents were filtered through alumina immediately prior to use.

To a weighed amount of 66 in a pyrex tube was added a measured volume of 15 and the solvent. The solution was degassed by bubbling nitrogen for at least half an hour and the volume was then measured to allow for solvent evaporation. The tube was stoppered and placed in a cold water bath (ca. 10°) in a Rayonet reactor and irradiated (350 nm) for one hour. This time gave about 10% to 30% destruction of 15. Concentrations of 66 used were 0.8

to 52 mol.%, and the ratio of 66 to 15 weighed out was approximately constant at 20:1.

Analysis of the products was performed by v.p.c. (7' x 1/8" 5% FFAP on diatoport, 235^{o}). The major product at high concentrations of 66 and 15 in cyclohexane had retention time 26 minutes and was identical with 13a, prepared under very similar conditions, and previously characterised. Other compounds appeared at retention times of 24 minutes (13a'), 28 minutes (13b) and 30 minutes (13b'). All other peaks, in all solvents, had retention times less than about 20 minutes, their retention times varied according to the irradiation solvent, and they were most significant at low concentrations of 15 and 66. These were assumed to be products of hydrogen abstraction mainly from the solvent and not of cycloaddition. Two or three injections of each irradiation sample were made, and the disc integrations were averaged; reproducibility was about ±10% of the peak size. The approximate yield (based on v.p.c. analysis) of 13 varied mainly with the concentration of 15 used. The results are summarised in the table.

Identification of 13b and 13b'.

A solution of 15 (1.0 g) and 66 (5.5 g.) in acetonitrie (20 ml.) was degassed with nitrogen for forty minutes, and irradiated with 350 nm light in a pyrex tube. The reaction was followed by i.r. and stopped at 23 hours (*ca*.

TABLE

Solvent.	[66] mol.%	Ratios (%)				Total Yield 13 approx. %	log $\frac{(13a+13a')}{(13b+13b')}$
		13a'	13a	13b	13b'		
C_8H_{18}	2.6	10	88	1	1	20	1.69
C_8H_{18}	5.5	6	90	3	1	30	1.38
C_6H_{12}	2.4	12	82.5	4	1.5	15	1.24
C_6H_{12}	6.9	4.5	93	2	0.5	30	1.59
C_6H_{12}	7.1	6.5	90	2	1.5	50	1.44
C_6H_{12}	32	5	86	8	1	70	1.00
Ether	2.6	8.5	74	12.5	5	15	0.67
Ether	6.6	8	67	17	8	20	0.48
Ether	11.0	7	63.5	22.5	7	25	0.38
Ether	14.6	6.5	65	21.5	7	30	0.40
Ether	51.6	8	65	19	8	40	0.43
EtOAc	0.8	9	61	21	9	15	0.37
EtOAc	2.2	8	61	23	8	20	0.35
EtOAc	3.6	10	54	26	10	20	0.25
EtOAc	5.8	8	57	24	11	25	0.27
EtOAc	11.2	8.5	55	26	10.5	25	0.24
EtOAc	35.2	8.5	55	23.5	13	40	0.24
CH_3CN	2.3	9	43	32	16	15	0.034
CH_3CN	3.15	2.5	57.5	31.5	8.5	15	0.175
CH_3CN	9.3	7.5	47	33	12.5	30	0.079
CH_3CN	11.7	10	41	33	16	40	0.017
CH_3CN	28.2	4	65	24	7	60	0.347
CH_3OH	1.05	5	42.5	37	15.5	15	-0.044
CH_3OH	1.08	4.5	50.5	35	9	15	0.087
CH_3OH	2.68	7	43	36	14	20	0.000
CH_3OH	5.9	7	41.5	36.5	15	25	-0.026
CH_3OH	14.3	4.5	56.5	30	9	30	0.194
CH_3OH	26.6	5	62.5	28	4.5	40	0.317
None	100	6	76	14	4	70	0.659

80% conversion of 15). Evaporation of the solvent followed by distillation of 66 and the unchanged 15, and distillation of the residue afforded a glassy, viscous liquid (1.4 g.), b.p. ca. 160°/0.03mm. A portion of this material (800 mg.) was chromatographed on a silicic acid column (80 g.; eluent 60% ethyl acetate/petrol) to give a partial separation of 13a (98 mg., ca. 90% pure by v.p.c.), 13b (90 mg., ca. 85% pure) and 13b' (80 mg., ca. 90% pure) according to v.p.c. analysis.

13a, crystallised from ether; m.p., m.m.p. and i.r. confirmed identity with the previously characterised compound.

I.r. $\nu_{max.}$ 2940, 2890, 1738, 1370, 1245, 1200, 1180, 1115, 1045, 985, 950, 920, 880 cm^{-1}.

13b; from the n.m.r., apparently a mixture of two compounds in the approximate ratio 3:1; τ values of the major isomer given first in each pair.

I.r. $\nu_{max.}$ 2940, 2890, 1738, 1370, 1235, 1185, 1085, 1045, 945, 860 cm^{-1}.

N.m.r. τ 9.00, 8.90 (s.; 3H), 8.02, 7.99 (s.; 3H), 6.15 (s.; 4H).

Analysis:	Calc. for $C_{16}H_{22}O_5$:	C 65.29, H 7.53%
	Found:	C 65.43, H 7.55%

13b'; also apparently a mixture of two compounds in the ratio 3:2; τ values of the major isomer given first.

I.r. $\nu_{max.}$ 2940, 2890, 1738, 1370, 1230, 1150, 1090, 1045, 1020, 945, 860 cm^{-1}.

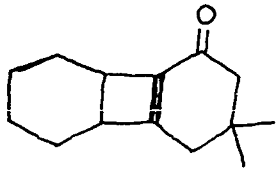
N.m.r. τ 9.00, 8.85 (s.; 3H), 8.03, 8.00 (s.; 3H), 6.17, 6.12 (s.; 4H).

Analysis: Found: C 65.49, H 7.44%

The head-to-tail nature of the components of the mixtures 13b and 13b' was verified by acid and base degradation to chromophores, followed by u.v. measurements. A methanolic solution of 13b' (1.0 mg.ml.$^{-1}$) had no u.v. absorption. Treatment with dilute hydrochloric acid at room temperature for fifteen minutes followed by dilute methanolic sodium hydroxide caused a very rapid reaction (complete in one minute) to give a chromophore with $\lambda^{OH^-}_{max.}$ 304 nm (ϵ ca. 3000, assuming quantitative conversion), $\lambda^{H^+}_{max.}$ 285 nm (ϵ ca.1500). These chromophores were stable to further treatment with acid or base, and the wavelengths and extinctions are consistent with formation of 68 from both components of the mixture 13b'. Initial treatment of 13b' with dilute base had no observable effect in the u.v., even after acidification.

A methanolic solution of 13b (0.8 mg.ml.$^{-1}$) had no u.v. absorption. Upon treatment with dilute acid, slow formation of a chromophore, $\lambda_{max.}$ 241 (ϵ ca. 4000 after one hour, assuming complete conversion of 13b), indicated that acetic acid was being lost as well as the ethylene ketal. The structure 73 appeared to be reasonable for the compound formed (cf. 89, $\lambda_{max.}$ 249 nm, (80)). Upon treatment with base this compound was rapidly destroyed and a transient ($t_{\frac{1}{2}}$ *ca.* 4 mins. in air) chromophore was

89



formed, $\lambda_{max.}^{OH^-}$ 505 nm (ϵ greater than 6000), rapid acidification of which gave $\lambda_{max.}$ 255 nm, a change which was reversible. This chromophore was also formed, with the same extinction, by treatment of a solution of 13b with acid for five minutes, followed by base. Under these conditions no 73 was observed. At no time was the compound 68 formed. Initial treatment of 13b with base had no observable effect.

Treatment of 13a with acid and base under the same conditions gave no chromophores visible in the u.v.

A mixture of 13b and 13b' (*ca.* 50 mg.) was treated with 1% methanolic hydrochloric acid at room temperature for one hour. Half of the solution was then separated by preparative t.l.c. (eluent: 20% ethyl acetate/benzene) collecting 73 (R_f 0.3, 5 mg.).

I.r. $\nu_{max.}$ 2940, 1740-1690 (broad), 1650 cm^{-1}.

U.v. $\lambda_{max.}^{CH_3OH}$ 242 nm (ϵ *ca.* 4000)

The remainder of the solution was made alkaline with methanolic sodium hydroxide and the red solution was stoppered and left at room temperature for five minutes. Acidification and separation of the products by preparative t.l.c. afforded impure 68 (R_f 0.5, eluent: 20% methanol/ethyl acetate; 12 mg.). Repurification by t.l.c. twice more gave 68 (6 mg.).

I.r. $\nu_{max.}$ 2940, 1705 (broad), 1610 (broad) cm^{-1}

U.v. $\lambda_{max.}^{CH_3OH}$ 285 nm (ϵ ca. 1600)

$\lambda_{max.}^{OH^-}$ 304 nm (ϵ ca. 3000)

Irradiations of 72 and 70 in various solvents.

These irradiations were performed in the same way as those of 15 and 66. V.p.c. analysis of the products (7' x 1/8", 5% FFAP on diatoport, 190°) from irradiations in non-polar solvents (n-pentane, cyclohexane) showed six peaks occurring in two groups, with approximate ratios 5:30:30:3 in the first group, and 30:2 in the second. Irradiations in polar solvents (acetonitrile, methanol) gave the same products in the approximate ratios 1:3:40:1 and 50:5. Separation of both groups of peaks by preparative v.p.c., gave material with n.m.r. spectra indicating a mixture of several components in each, all apparently cycloadducts. The i.r. spectra were consistent with this assignment.

Group (1) I.r. $\nu_{max.}$ 2960, 1740, 1370, 1240 cm^{-1}

Group (2) I.r. $\nu_{max.}$ 2960, 1740, 1370, 1240 cm^{-1}

Confirmation of the assignment of cycloadduct structures was obtained by degradation. Hydrolysis of both the separated fractions gave material with spectra showing only one carbonyl peak, that being a strained bicyclic cyclopentanone. Such structures can be explained as deriving from acyloin rearrangement of 1-hydroxybicyclo[3,2,0]-heptan-2-one derivatives, i.e. cyclobutane adducts of 72 and 70.

Group (1) I.r. $\nu_{max.}$ 3450, 2960, 1775 cm^{-1}

Group (2) I.r. $\nu_{max.}$ 3450, 2960, 1775 cm^{-1}

These alcohols were considered to be mixtures of isomeric 1-(and 4-)-hydroxy-2,2-dimethyl-3-(1-hydroxyethyl)-norbornan-7-ones.

Periodate oxidation of the group (2) alcohols gave several products, the principal one being 2-(1-hydroxyethyl)-3,3-dimethyl-4-ketocyclohexane-1-carboxylic acid lactone, the structure being assigned on the basis of the following spectra:

I.r. $\nu_{max.}$ 2970, 1785, 1712, 1390, 1170, 965 cm^{-1}

N.m.r. τ 8.85(s.; 6H), 8.55(d.;J=6Hz, 3H), 7.8-8.5(m.; 3H), 7.4-7.7(m.; 3H), 5.65(d.;J=9Hz, q.;J=6Hz, 1H).

This compound was also produced in high yield by aqueous dichromate/ether oxidation of the group (2) alcohols.

Periodate oxidation of the group (1) alcohols gave a mixture of hydroxy-keto-acids, the lactone above not being formed.

APPENDIX.

Irradiation of Acetophenone in Ether/Cyclohexane.

It had been observed, during the irradiation of 54 with acetophenone as sensitiser, that many products were formed from the sensitiser. It was confirmed that the presence of 54 was unnecessary to the formation of these by the following.

Acetophenone (4.73 g.) in 50% ether/cyclohexane (250 ml.) was degassed by bubbling nitrogen for one hour, and then irradiated under nitrogen (350 nm) for 2¼ hours. Evaporation and chromatography on a silicic acid column with 5% ether/benzene afforded acetophenone (2.54 g.); 3-ethoxy-2-phenylbutan-2-ol, 88a, (162 mg., 7% yield), 88b (150 mg., 6% yield), p-(1-ethoxyethyl)acetophenone, 79, (70 mg., 3% yield) and a mixture of the acetophenone pinacols (1.3 g.). The three hitherto unknown compounds were identified conclusively by their spectra and analyses as follows:

3-ethoxy-2-phenylbutan-2-ol:

88a I.r. $\nu_{max.}$ 3580, 2980, 1450, 1197, 1105, 703, 678, 637, 575 cm^{-1}

N.m.r. τ 9.16(d.J=6.5Hz, 3H), 8.84(t. J=7Hz, 3H), 8.49(s.; 3H), 7.30(s.; 1H, exchanges with D_2O, 6.1-6.9(m.; 3H), 2.5-3.0(m.; 5H).

U.v. $\lambda_{\text{max.}}^{C_6H_{12}}$ 206 nm (ϵ 8600), 258 nm (ϵ 190).

Analysis: Calc. for $C_{12}H_{18}O_2$: C 74.19, H 9.34%

Found: C 74.17, H 9.42%

<u>88b</u> I.r. $\nu_{\text{max.}}$ 3560, 2980, 1448, 1378, 1105, 705, 680, 645, 630, 570 cm^{-1}

N.m.r. τ 9.00(d.J=6.5Hz, 3H), 8.93(t.J=7Hz, 3H), 8.61(s.; 3H), 7.21 (broad, 1H, exchanges with D_2O), 6.2-7.1(m.; 3H), 2.5-3.0(m.; 5H).

U.v. $\lambda_{\text{max.}}^{C_6H_{12}}$ 206 nm (ϵ 8400), 258 nm (ϵ 200).

Analysis: Calc. for $C_{12}H_{18}O_2$: C 74.19, H 9.34%

Found: C 74.35, H 9.32%.

p-(1-ethoxyethyl)acetophenone:

I.r. $\nu_{\text{max.}}$ 2975, 1685, 1608, 1265, 1100, 600 cm^{-1}

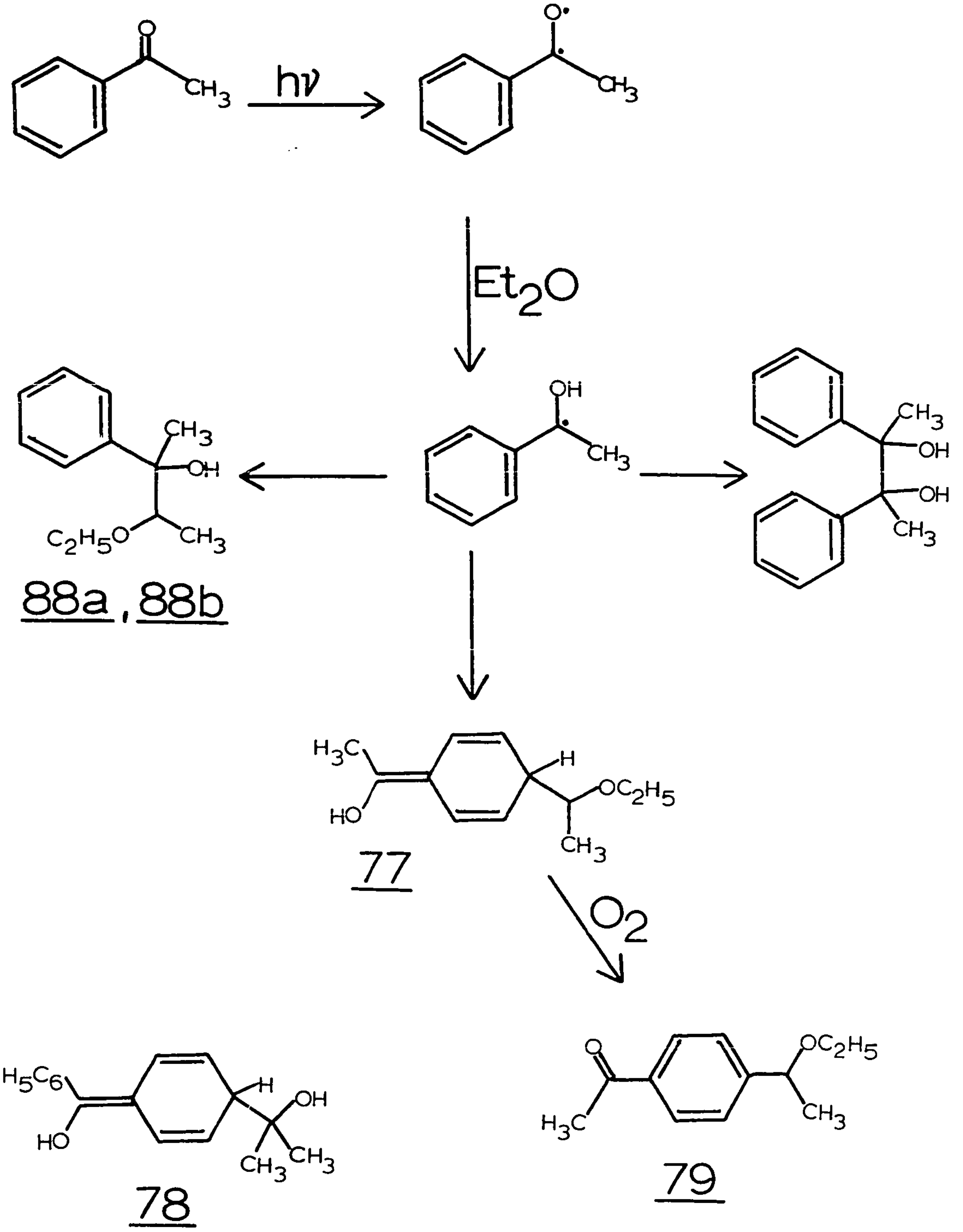
N.m.r. τ 8.83(t.J=7Hz, 3H), 8.62(d.J=6.5Hz, 3H), 7.51 (s.; 3H), 6.69(q.J=7Hz, 2H), 5.62(q.J=6.5Hz, 1H), 2.68(d.J=8Hz, 2H), 2.18(d.J=8Hz, 2H).

U.v. $\lambda_{\text{max.}}^{C_6H_{12}}$ 248 nm (ϵ 15000, ϵ_{203} <u>ca</u>. 24000), 320 nm (ϵ 670).

Analysis: Calc. for $C_{12}H_{16}O_2$: C 74.97, H 8.39%

C 75.07, H 8.45%.

The derivation of the two alcohols from the acetophenone ketyl radical and ethoxyethyl radical was reasonable.


hν
Et₂O
88a, 88b
77
O₂
78
79

However, formation of the p-substituted acetophenone requires that the ketyl radical be delocalised and attacked in the p-position by the ethoxyethyl radical. The product from such a reaction (1-hydroxyethylidene-4-(1-ethoxyethyl)-cyclohexa-2,5-diene, 77), is analogous to the intermediate, 78, recently demonstrated (82) (83) to be present in the photoreduction of benzophenone by isopropanol. It is highly probable that 77 was oxidised to 79 by traces of atmospheric oxygen either during the reaction or during the workup. The alternative mechanism, abstraction of two hydrogen atoms from 77 by other excited ketones, does not seem likely since no dihydroacetophenone derivatives were observed. It is noteworthy that Filipescu and Minn (82) observed that 78 was unstable to air, although they suggested that the oxidation product was benzophenone, rather than the para-alkylated derivative, on the basis of the emission spectrum of the product.

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