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STUDIES IN THE OXIDATION OF SOME OLEFINS TO ALLYLIC HYDROPEROXIDES

BY

JOHAN HUBERT VAN DE SANDE

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
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MAY, 1968

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled

STUDIES IN THE OXIDATION OF SOME OLEFINS
TO ALLYLIC HYDROPEROXIDES

submitted by Johan Hubert van de Sande, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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Date May 30, 1968

TO MY PARENTS

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ABSTRACT

The reaction between olefins, N-chloroacetamide or 1,3-dibromo-5,5-dimethylhydantoin, and hydrogen peroxide affords β-halohydroperoxides in good yields. The β-halohydroperoxides of some tetrasubstituted olefins react with base to give high yields of the allylic hydroperoxides, which are identical to the ones prepared in the dye-sensitized photooxidation.

The intramolecular isotope effects were determined in the formation of the two β-bromohydroperoxides of 3-methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene (<u>40</u>). The major product had the hydroperoxy group on the carbon bearing the light methyl groups. The isotope effect of $k_H/k_D = 1.56$ could be explained by either hyperconjugation or relief of backstrain.

The deuterium isotope effect in the reaction of the mixture of β-bromohydroperoxides from <u>40</u> with base was found to be $k_H/k_D = 2.16$. An inversion takes place in this reaction, the major product has the hydroperoxy group on the carbon bearing the methyl-$\underline{d}_3$ groups. A similar primary deuterium isotope effect of $k_H/k_D = 2.12$ was observed in the reaction of 2-bromo-2,3-<u>bis</u>-trideuteriomethyl-3-butyl hydroperoxide (<u>56</u>) with base. These isotope effects are explained by the intermediacy of a cyclic peroxide in the reactions of β-bromohydroperoxides with base. Evidence for a cyclic peroxy intermediate was also found in the n.m.r..

The intramolecular isotope effects in the dye-sensitized photooxidation and the hypochlorite-hydrogen peroxide oxidation of <u>40</u>

and 2,3-bis-trideuteriomethyl-2-butene (41) were found to be similar. No variation in $k_H/k_D \doteq 1.37$ was found when different sensitizers are used. These small primary isotope effects are explained by the concerted addition of singlet oxygen to the olefin.

Small intermolecular deuterium isotope effects were observed in the photooxygenation of cis- and trans-dimethyl-d_6-stilbene.

The alkylations of some α-ketols were found to yield predominantly the C-alkylated products.

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INTRODUCTION

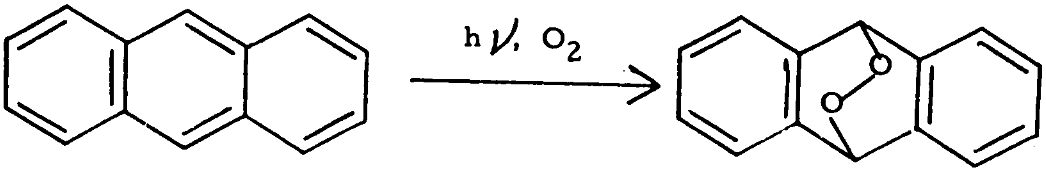
Dye-sensitized photooxygenations of organic compounds have been studied extensively during the last fifteen years. The work of Schenck's group (1, 2) has been instrumental in the development of this field. Their work showed very clearly the value of these reactions in synthetic organic chemistry. The neutral reaction conditions make the presence of different functional groups on the acceptor in the oxygenation reaction possible.

A wide variety of acceptors has been studied in the photooxygenation reactions, but most attention was given to two types of acceptors.

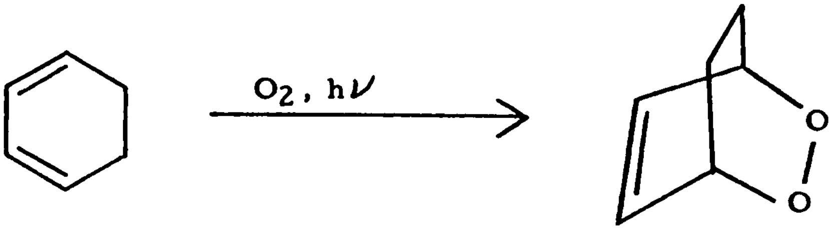
I. Conjugated Dienoids

The addition of oxygen to cyclic dienes, s-cis dienes, polyclic aromatics and some heterocycles gives 1,4-endo-peroxides as the primary products.

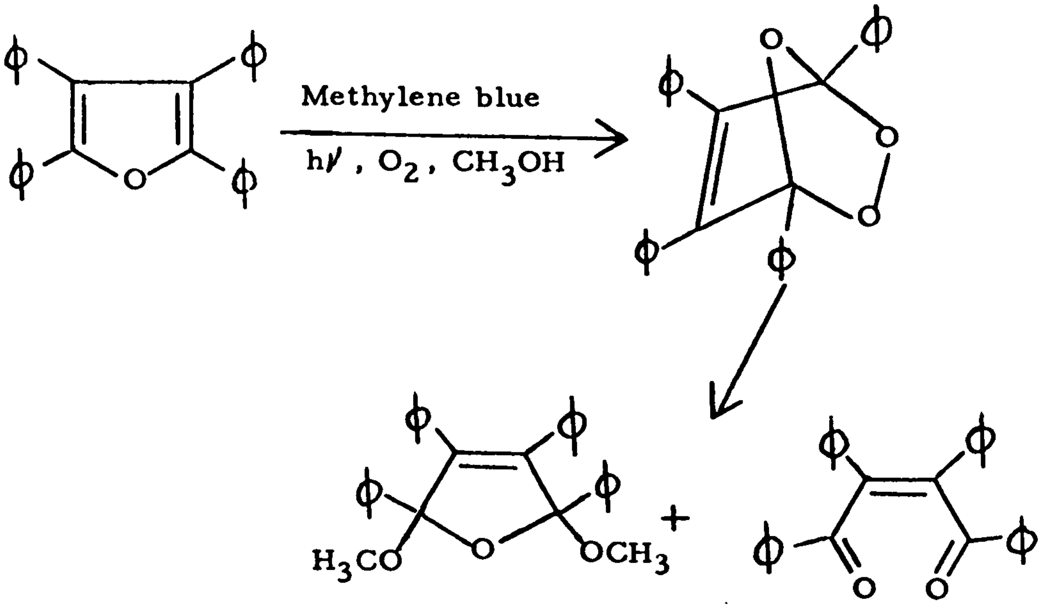
Anthracene yields the 9, 10 - transannular peroxide (3) in the dye-sensitized photooxygenation.



1,3-Cyclohexadiene gives 5,6-dioxabicyclo [2,2,2]-octene-2 ("norascaridol") (4) in the photooxygenation reaction.



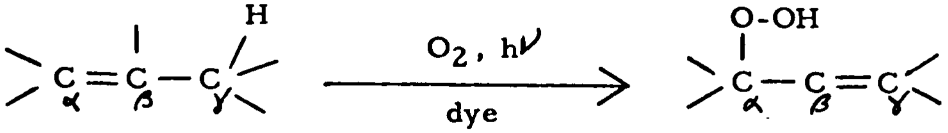
The dye-sensitized photooxidation of tetraphenylfuran in methanol gives cis-dibenzoylstilbene (5). The transannular peroxide has been isolated as an intermediate (6).



All the reactions above are analogous to the Diels-Alder reaction.

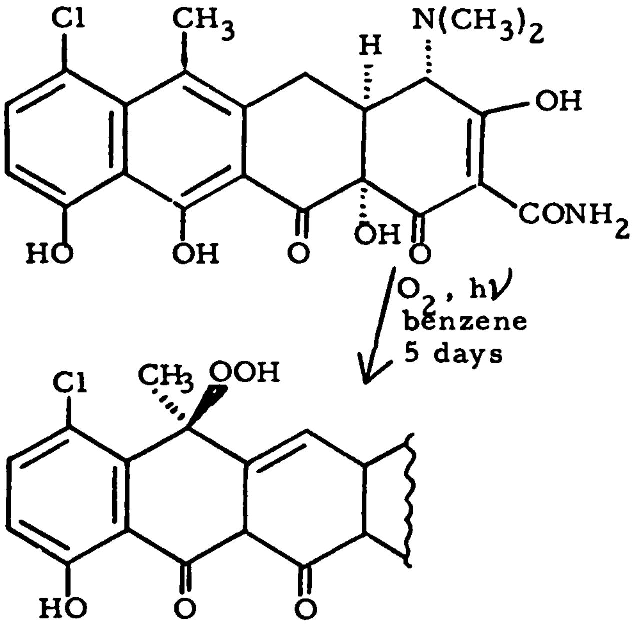
II. Olefins with Allylic Hydrogens

In the dye-sensitized photooxygenation reaction, the oxygen transferred is added to carbon α of the double bond; the double bond is shifted into the allylic position to form a double bond between carbons β and γ and the allylic hydrogen at carbon γ is moved to the free oxygen atom (1, 2).



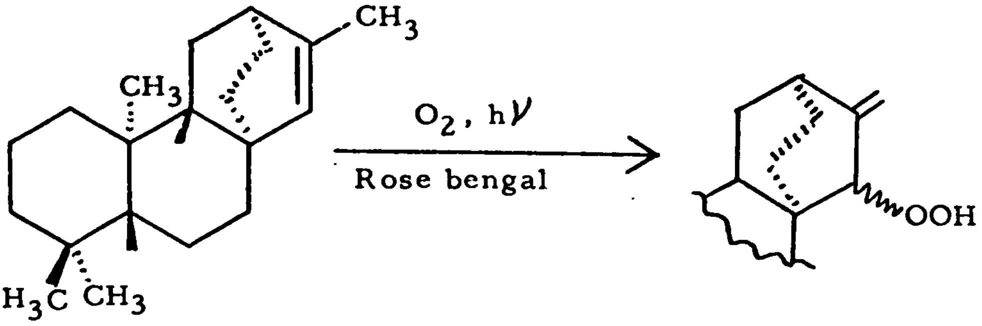
In this work we will deal mainly with reactions of type II. The allylic hydroperoxylation reaction has found wide application in synthetic chemistry.

Scott and Bedford (7) used this reaction with success in the transformation of 7-chloroanhydrotetracycline to 7-chloro-6-deoxy-6-hydroperoxy-5,5a-dihydrotetracyclin in 70% yield, a conversion which had been very difficult to achieve before.

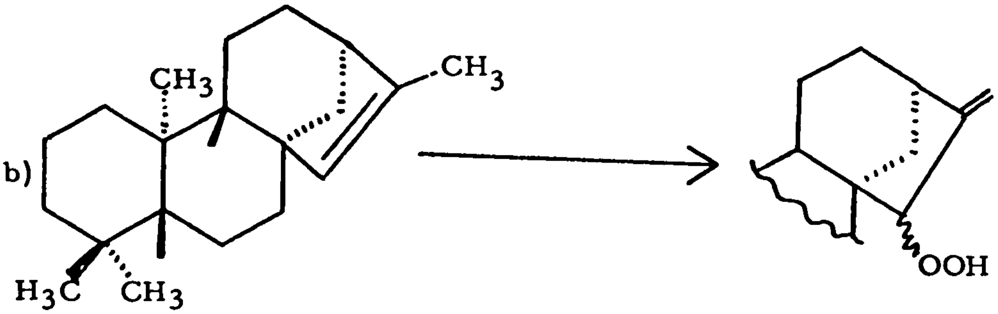


Bell and Ireland (8) used a dye-sensitized oxygenation in the construction of the C/D ring system of the diterpenoid alkaloids atesine (a) and garryfoline (b).

(a)

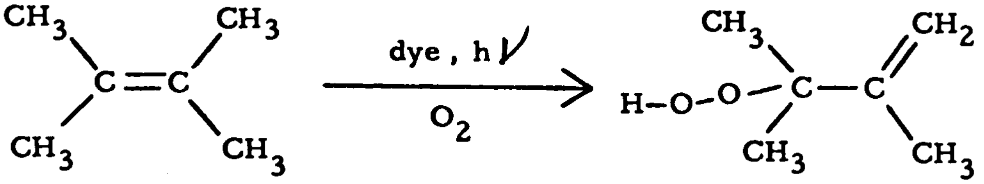


(b)



A similar transformation was carried out by Masamune (9) in the synthesis of the alkaloid garryine.

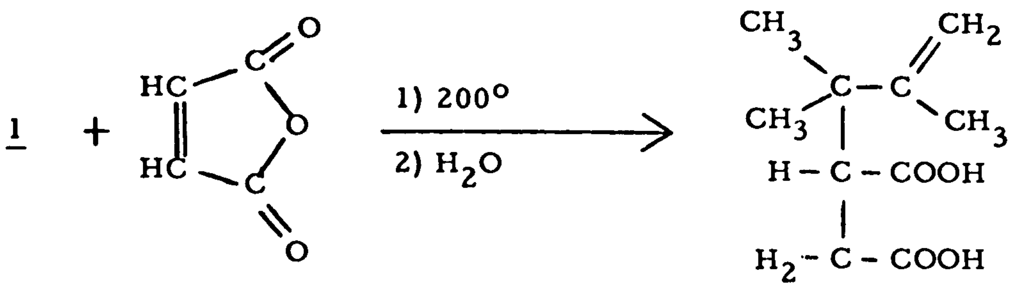
Tetramethylethylene (1) reacts under the conditions of the dye-sensitized photooxygenation to give 3-hydroperoxy-2,3-dimethyl-1-butene (2) (10).



1

2

The reactions on olefins with allylic hydrogens resemble the "ene" reaction (11). Compound 1 reacts with maleic anhydride at 200° to yield the product from an "ene" reaction.



The mechanism of the dye-sensitized photooxygenation has been studied intensively by several research groups. The discussion of this aspect can be divided into three parts:

A. Reaction of the sensitizer prior to reaction with oxygen.

B. Reaction of sensitizer with oxygen.

C. Stereochemistry of oxygen transfer to olefin.

A. The photosensitized autooxidation of anthracene has been studied in detail (3). In this reaction anthracene is both sensitizer and substrate. One molecule of anthracene sensitizes the oxidation of another molecule of anthracene.

The quantum yield for this reaction is smaller than one, indicative of a non-chain mechanism (13).

In order to study the steps of reaction of anthracene prior to reaction with oxygen, Bowen (14) looked at degassed solutions of anthracene. The following reaction sequence was set up (14, 15, 16, 2):

[1] $h\nu + A \longrightarrow A^1$ formation of first excited singlet

[2] $A^1 \longrightarrow h\nu + A$ fluorescence

[3] $A^1 \longrightarrow A^3$ intersystem crossing to triplet

[4] $A^1 \longrightarrow A$ non-radiative transition to ground state

[5] $A^1 + A \longrightarrow A_2$ dimer formation

[6] $A^1 + A \longrightarrow 2\,A$ self-quenching of fluorescence

[7] $A^3 \longrightarrow A$ non-radiative transition to ground state

Bowen (14, 16) found that fluorescence [2] is decreased by increased concentrations of anthracene. Thus the first excited singlet state can be quenched by the ground state, the product from this reaction being mainly dimer [5]. From the maximum quantum yield of dimer which is a little less than the maximum fluorescence quantum yield, Bowen (14) concluded that the singlet state is the precursor for both fluorescence and dimer formation.

Anthracene in the first excited singlet state is quenched by solvents like carbon disulfide, chloroform and bromobenzene to produce the lowest triplet state (17). Little or no fluorescence was seen in this process. Using flash photolysis and flash photography, Porter and Windsor (18, 19) were able to calculate the half-life of the anthracene triplet state. The triplet state has a half-life of 5×10^{-5} seconds, compared to approximately 10^{-8} seconds for the anthracene singlet state.

Bowen and Williams (20) did not find a relationship between the quantum yield of fluorescence in the presence of oxygen and the quantum yield for oxidation.

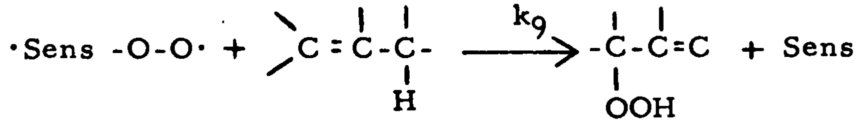
Since it was known that photooxidation is rapid in solvents which quench the fluorescence by causing singlet-triplet intersystem crossing, the triplet state of anthracene is assumed to be an intermediate in the sensitized photooxidation (17).

B. Only two mechanisms of the reaction of sensitizer with oxygen are consistent with the kinetic evidence presented by Schenck (2). Both mechanisms are in agreement with the evidence for a sensitizer in its triplet state as outlined above in the case of anthracene.

Schenck (1, 2) adapted a mechanism originally proposed by Schonberg (21) which involved the formation of a "moleoxide" from the sensitizer in the triplet state and oxygen.

[8A] $^3\mathrm{Sens} + {^3}\mathrm{O}_2 \longrightarrow \cdot\mathrm{Sens}\text{-O-O}\cdot$

[9A]



[10A] $\cdot\mathrm{Sens}\text{-O-O}\cdot \xrightarrow{k_{10}} \mathrm{Sens} + {^3}\mathrm{O}_2$

The sensitizer-oxygen complex can be represented as a triplet biradical which can either react with the olefin [9A] or collapse to give the ground state sensitizer and oxygen [10A] (21).

The second possible mechanism involves the formation of singlet oxygen ($^1O_2$) from the sensitizer in the triplet state and oxygen (27-37).

[8B] $$^3\text{Sens} + {}^3O_2 \longrightarrow \text{Sens} + {}^1O_2$$

[9B] 

$$^1O_2 + \,>C{=}C{-}\underset{H}{C}{-} \xrightarrow{k_9} {-}\underset{OOH}{C}{-}C{=}C<$$

[10B] $$^1O_2 \xrightarrow{k_{10}} {}^3O_2$$

On the basis of kinetics, the two mechanisms can not be distinguished. The ratio of the rate of collapse of the reactive intermediate to the ground state to the rate of reaction of the intermediate with the substrate is given by k_{10}/k_9.

Energy transfer from sensitizer to triplet oxygen yields the ground state sensitizer and singlet oxygen, because of conservation of electron spin angular momentum during energy transfer (25, 26).

The formation of singlet oxygen as the reactive intermediate was originally proposed by Kautsky (22, 23, 24). Sharp (27) and Kopecky (28) studied the reactivities of several olefins in the sensitized oxidation. They found that increasing substitution of the double bond greatly increased the reactivity towards the sensitized oxidation. A sensitzer oxygen complex, which acts as a biradical, can not account for the results found by Sharp (27) and Kopecky (28). Singlet oxygen acting as an electrophile can explain the results found as indicated by both these authors. Kopecky (28) also found that a variation in sensitizer used did not affect the relative rates of photooxidation of 1-methylcyclopentene. It was expected that a change in sensitizer would affect the ratio (k_{10}/k_9) of the rate of collapse of the reactive intermediate to ground state to the rate of reaction of intermediate with substrate. Schenck and Koch (38) had observed that the rate of disappearance of reactive intermediate in the dye-sensitized oxidation of α-terpinene to ascaridole is independent of sensitizer used. This reaction has, however, a very small activation energy (0.5 kcal/mole (38)) and it is incorrect to conclude that singlet oxygen is a reactive intermediate. The activation energies in the reactions studied by Kopecky (28) will be significantly different from zero. Wilson (35) also found that the product ratios in the dye-sensitized photooxidations of a number of pairs of unsaturated compounds were independent of sensitizer used. Both Kopecky (28) and Wilson (35) stated that their results were the first evidence for a "common" intermediate in reactions using different sensitizers.

An excellent support of singlet oxygen as the reactive intermediate was given by Foote (29, 30, 32, 33). Identical products to those formed in dye-sensitized photooxidations are produced when olefins are reacted with sodium hypochlorite and hydrogen peroxide. The product distribution in reactions with unsymmetrical olefins are identical in both the dye-sensitized photooxygenation and the chemical (NaOCl and H_2O_2) oxygenation (32). When optically active (+)-limone was subjected to both types of reaction, the optical activity of one of the products formed (after reduction to the alcohol), (-)-trans-carveol, was identical in the two reactions (32).

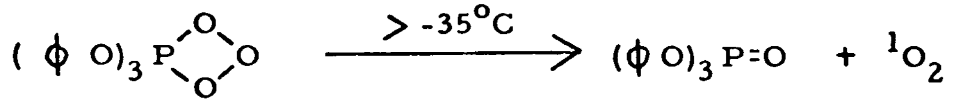
Side reactions can compete with H_2O_2/hypochlorite reaction when the acceptor is unreactive. The side reactions can be depressed by the presence of a free radical inhibitor, 2,6-di-t-butyl phenol (32).

The product ratios in the reaction of various sets of olefins with both reactions (dye-sensitized photooxidation and H_2O_2/hypochlorite) were found to be identical (33). In a recent publication Foote (38) showed that the products obtained from 1,3-cyclohexadiene, anthracene, tetraphenylcyclopentadienone. $\Delta^{9,10}$-octalin and 2,3-dimethylfuran in the hydrogen peroxide-hypochlorite oxygenation were identical to the ones produced in the dye-sensitized photooxygenation. Since Foote's work with singlet oxygen produced from hydrogen peroxide and hypochlorite, several other methods of generating singlet oxygen have been developed (31, 34, 39, 40, 41).

McKeown and Waters (34) showed that addition of bromine and alkaline hydrogen peroxide resulted in singlet oxygen which was trapped by both 9,10-diphenylanthracene and 9,10-dimethylanthracene to yield the corresponding endo-peroxides. These authors also oxidized 9-methyl-10-phenylanthracene with singlet oxygen formed in the alkaline decomposition of di-iso-peroxyphthalic acid (34).

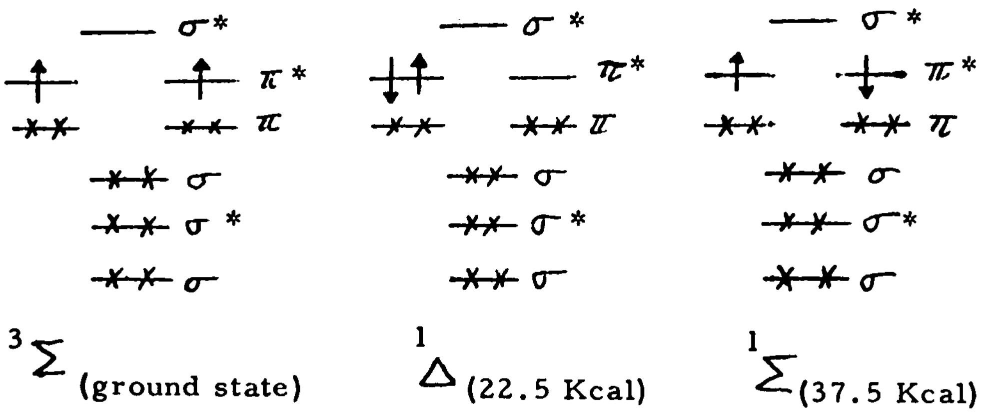
Wasserman and Scheffer (39) prepared the endo-peroxide of 9,10-diphenylanthracene in the dye-sensitized photooxidation. Slow decomposition of this "photoperoxide" in the presence of an olefin acceptor resulted in typical singlet oxygen reactions. Similar results were obtained by Kopecky and Reich (40) in the slow dissociation of 1,4-dimethoxy-9,10-diphenylanthracene peroxide.

Murray and Kaplan (41) made use of the decomposition of a triphenyl phosphite-ozone adduct to form singlet oxygen. Thompson (42) had prepared a 1:1 adduct of ozone and triphenyl phosphite (3) at -70° which was observed to lose oxygen upon warming up to room temperature.



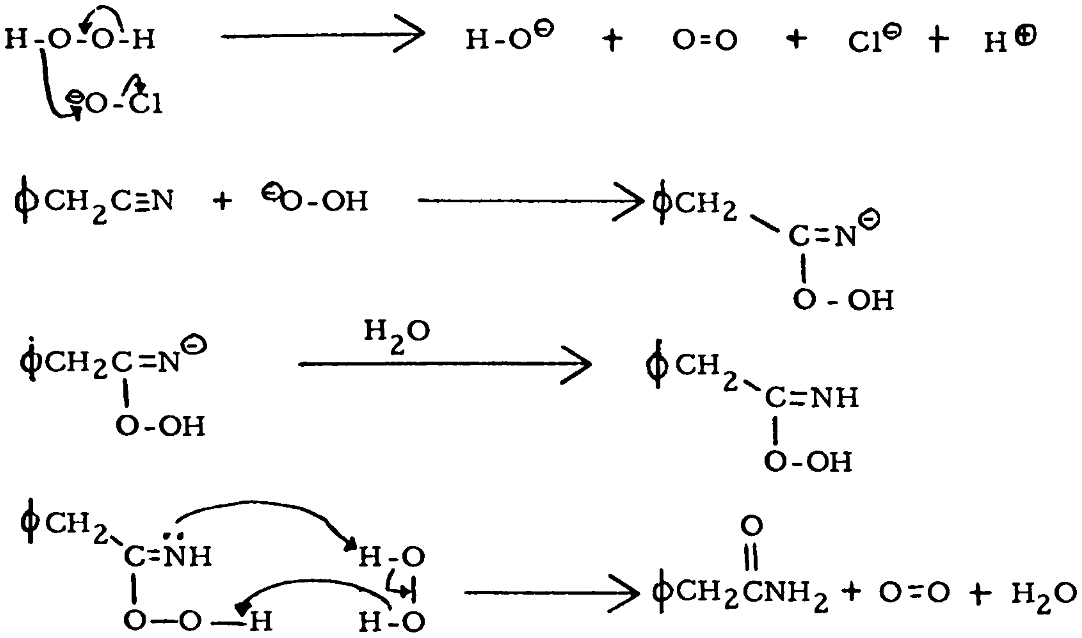
Murray (41) found that the oxygen observed had the singlet multiplicity and was able to oxidize olefinic acceptors in the usual fashion. Corey and Taylor (44) had already suggested in 1964 that oxygen formed in this decomposition had singlet multiplicity. Corey (44) also showed that singlet oxygen produced by radiofrequency discharge in gaseous oxygen (45) oxidized anthracene to the endo-peroxide.

Singlet oxygen formed in the hydrogen peroxide-hypochlorite reaction, or the bromine-alkaline hypochlorite process or by radiofrequency discharge showed chemiluminescence (43, 45, 46, 47, 48, 49 50). Bowen and Lloyd (46) showed chemiluminescence in the emission spectrum of the reaction between 30% hydrogen peroxide and hypochlorite. Oxygen can exist in two different low energy singlet states. The $'\Delta_g$ state has the electrons in one orbital, in the $'\Sigma_g$ state the two electrons are anti-parallel in two orbitals (51).



Khan and Kasha (48) assigned the chemiluminescence to emission from the $'\Sigma_g$ state of molecular oxygen. This assignment has, however, been corrected to emission from a $'\Delta_g$ dimer (45, 47, 49). Ogryzlo and coworkers (45, 49, 50) showed that in the reaction between hydrogen peroxide and hypochlorite at least 10% yield of oxygen in the $'\Delta_g$ state is produced. Oxygen in the $'\Delta_g$ state resembles ethylene electronically and might be expected to undergo two electron reactions. The $'\Sigma_g$ state however resembles the ground state and would be expected to undergo radical-like reactions.

McKeown and Waters (45) observed that only heterolytic processes which form oxygen are chemiluminescent. They could see emission in both the hydrogen peroxide/hypochlorite reaction and the benzylcyanide-alkaline hydrogen peroxide process.



If oxygen is formed in a one electron movement process, no chemiluminescence was observed. No emission of radiation could be detected during oxygen producing reactions between hydrogen peroxide and respectively $KMnO_4$, or MnO_2, or $K_3Fe(CN)_6$ or $Ce(SO_4)_2$, which are all one electron transfer processes (45). Singlet oxygen in the $'\Delta_g$ state is long lived. Several independent investigations showed that the $'\Delta_g$ state survives more than 10^8 collisions before deactivation occurs (53, 54, 55).

Bader and Ogryzlo (56) observed that the $'\Sigma_g$ state of oxygen is shorter lived than the $'\Delta_g$ state and is also rapidly quenched by water vapour (45, 56). Falick, Mahan and Meyers (57) saw a characteristic signal for $'\Delta_g$ oxygen in the e.s.r. spectrum, which was not effected by water vapour present.

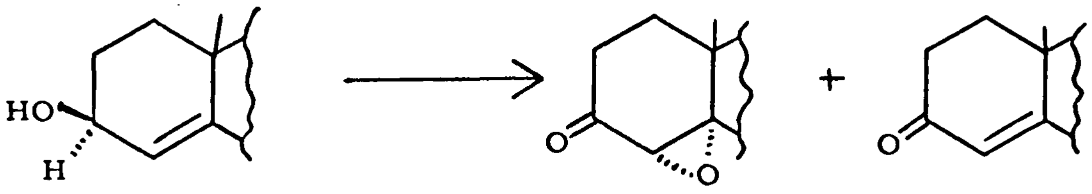
Quenching of the $'\Sigma_g$ state also presumably takes place in methanol, which in most dye-sensitized reactions acts as solvent (38).

When Kautsky (22, 23, 24) first suggested that singlet oxygen was the reactive intermediate in the dye-sensitized photooxidation, Gaffron (58) rejected this proposal on the following ground. Gaffron found that one sensitizer could effect reaction with light of 8200 Å. This wave length is of insufficient energy to excite the $'\Sigma_g$ state of oxygen. However Kautsky (23) pointed out that there was ample energy at this wave length to excite oxygen to the lower lying $'\Delta_g$ state.

Kautsky (22, 24) and later Rosenberg (59) observed that reaction occurred when sensitizer and acceptor are adsorbed on separate granules of silica gel, which would indicate that a reactive intermediate, capable of diffusion, is formed.

From all the evidence presented above, it has clearly been established that singlet oxygen in the $'\Delta_g$ state is the reactive intermediate in the dye-sensitized photooxygenation.

However, Nickon (60) observed that in the dye-sensitized photooxidation of cholest-4-ene-3-ol the ratio of the two products (4 and 5) depends on the sensitizer used.

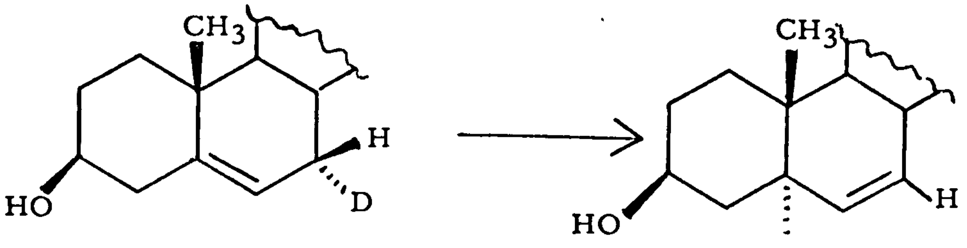


4 5

The same results on this system were found by Kearns and coworkers (36, 37). They observed a relationship between the triplet state energy of the sensitizer and the product ratio 5/4. If a high energy sensitizer was used, fluorescein, more of compound 5 was formed, while a low energy sensitizer, methylene blue, gave rise to predominant formation of 4. The formation of 5 was also very concentration dependent, indicative of a radical reaction. With riboflavin as a sensitizer and acceptor concentration of 1.3×10^{-2} mole/liter the product ratio 5/4 was 30, at a concentration of 7.5×10^{-5} mole/liter the ratio observed was 0.2. Kearns (36, 37) explains these results by the presence of $'\Sigma_g$ singlet oxygen as well as $'\Delta_g$ singlet oxygen. The high energy sensitizers will give rise to more $'\Sigma_g$ oxygen which will produce compound 5. The low energy sensitizers have only sufficient energy to excite $'\Delta_g$ singlet oxygen, which they propose produces compound 4. The concentration dependance of the formation of 5 seems to be in agreement with the presence of $'\Sigma_g$ singlet oxygen. Kearns and coworkers (36, 37) did not show, however, the presence of a radical reaction.

C. The mechanism of the approach of singlet oxygen to the double bond has been studied quite intensively by Nickon and his group (60-66).

The photosensitized oxygenation of cholesterol-7α-d (6) yields 3β-hydroxy-5α-hydroperoxy-Δ^6-cholestene (7) which had only 8.5% of the original deuterium retained. Similarly cholesterol-7β-d (8) produced the corresponding hydroperoxide (9) which had 95% of the original deuterium retained (61 , 62).



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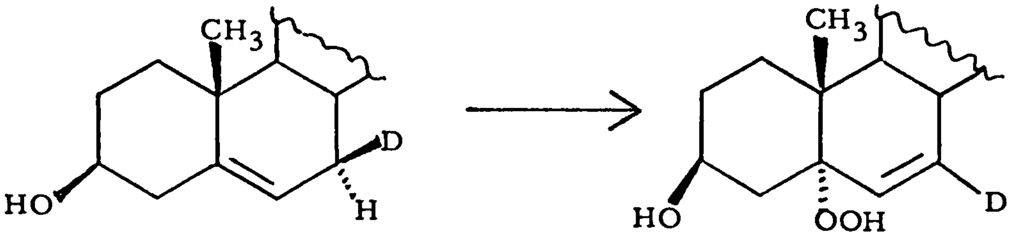

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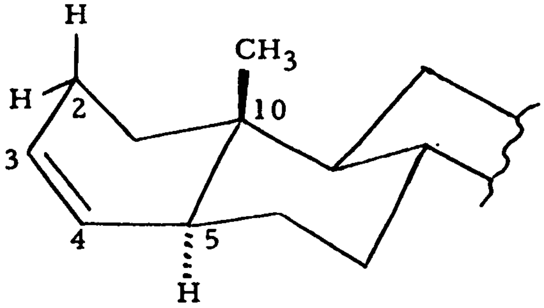
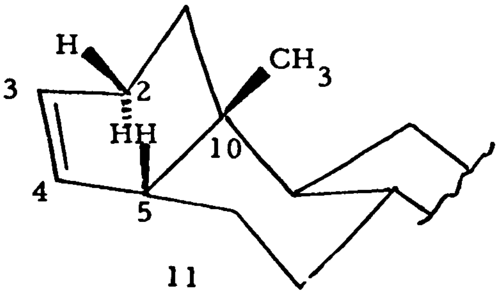
From this and some more evidence in the cholesterol compounds, Nickon concluded that the reaction was very stereospecific and required an axial hydrogen on the same side as where the oxygen came in. In other words the singlet oxygen must necessarily attack the π-orbital from a direction perpendicular to the olefinic plane and the allylic hydrogen must be suitably orientated to allow transfer to oxygen. In cyclohexenoid systems with half-chair conformations, a quasi-axial hydrogen should be in a better position for cyclic transfer than a quasi-equatorial hydrogen (63). Nickon (63) looked at the products obtained from 5α- and 5β-cholest-3-ene (10 and 11). The abstraction of the axial hydrogens at either C_2 or C_5 was studied in compound 10.



10

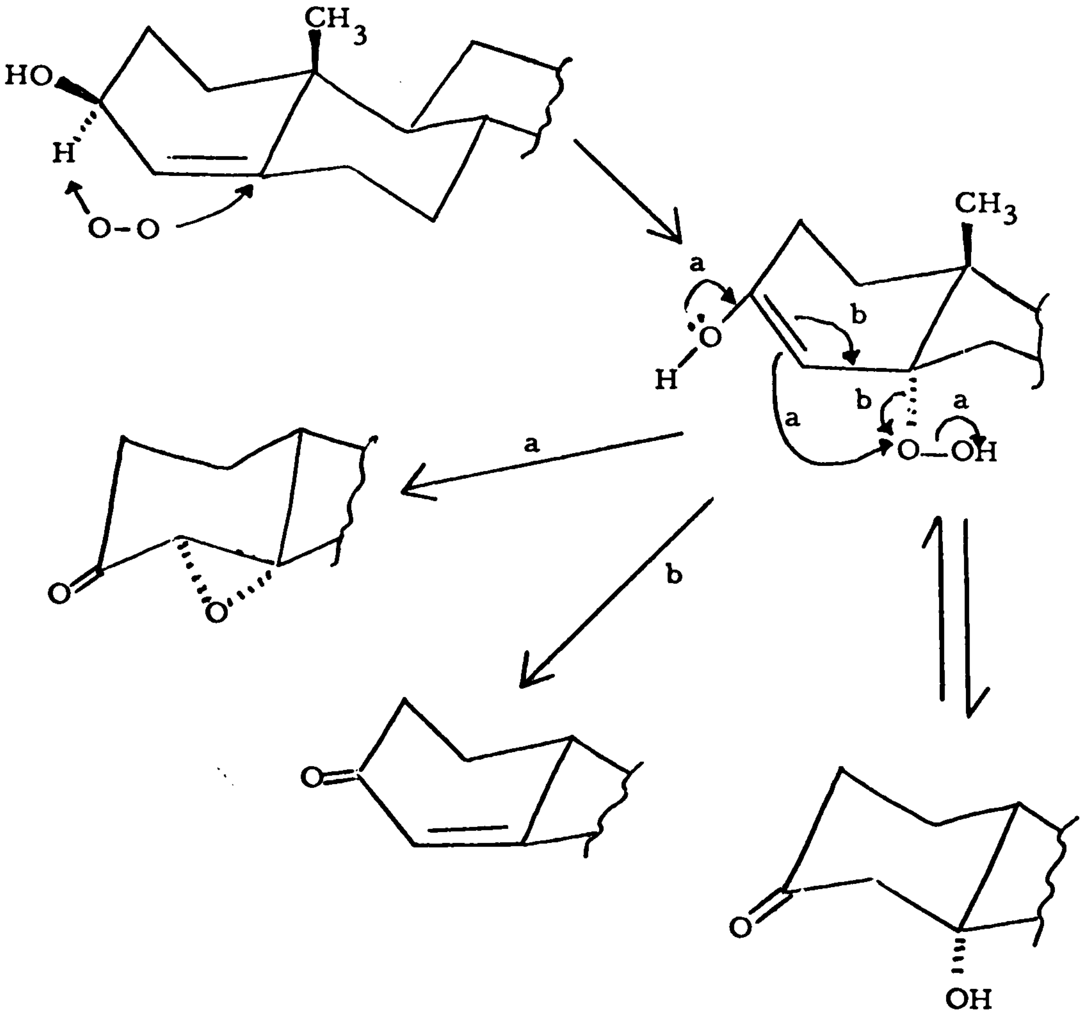
The methyl group interferes with β-approach and abstraction of the axial C_2-hydrogen, while no interference is felt in α-attack and axial C_5-hydrogen abstraction. In fact, the ratio of C_2-hydrogen:C_5-hydrogen abstraction observed was 1:17 (63). In the compound 11 the same ratio was studied.



11

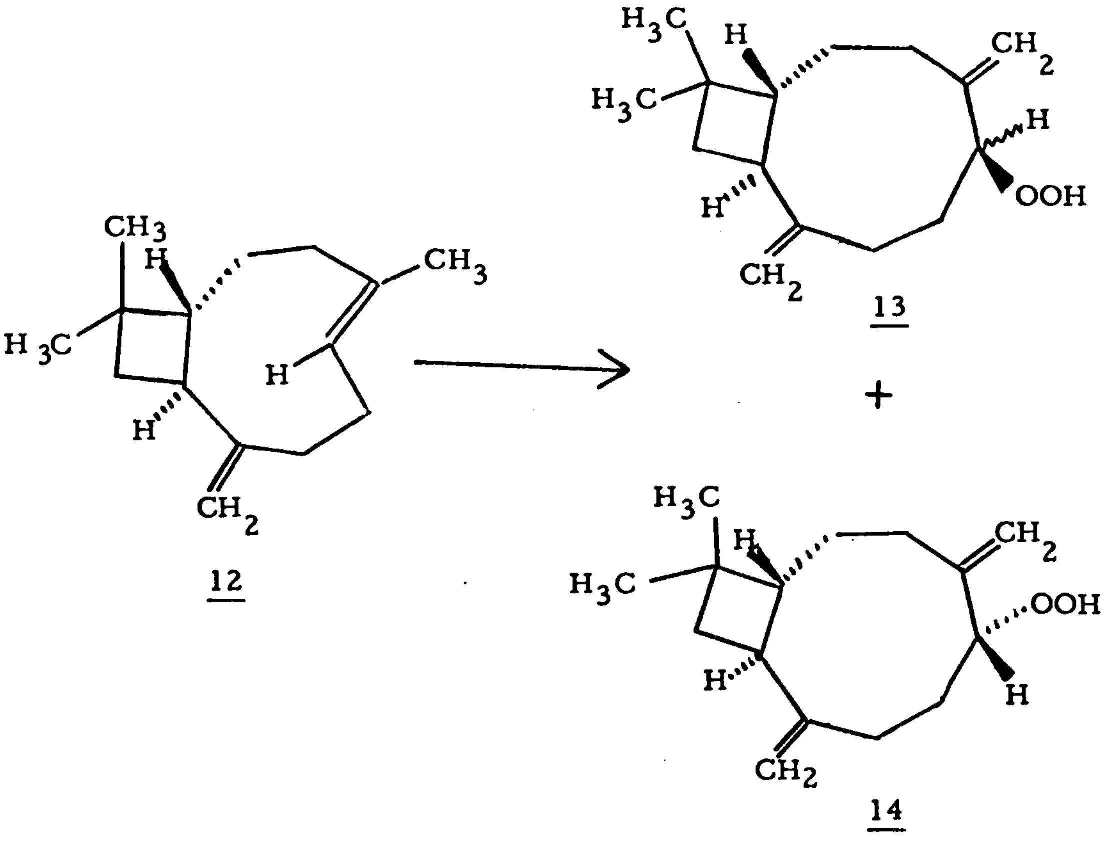
The attack on α side is favoured by the right conformation of the C_2-hydrogen. However, oxygen attack is impeded by the congested concave face of the α-fused rings. No interaction is expected by β-attack and C_5-hydrogen abstraction (63). Not such a large ratio as in the α-compound was expected and these authors found the ratio of C_2-hydrogen:C_5-hydrogen abstracted was 1:6.

Nickon and Mendelson (65) found that allylic oxygen functions deactivated the double bond towards photooxygenation. Acetylation or benzoylation is an effective way to protect an allylic alcohol when oxygenation at another site is required. The inductive effect is the explanation for this observation (65). Allylic alcohols can be oxygenated but a mixture of products are formed from the primary product. This was illustrated by Nickon (65) in the case of cholest-4-ene-3β-ol as shown below.

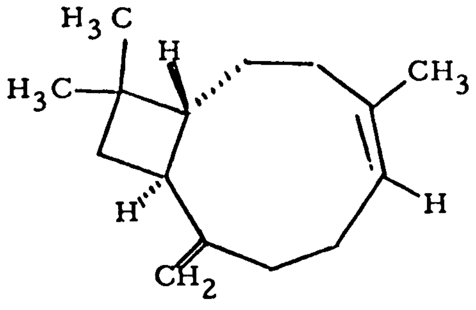


They showed the presence of an epoxy-ketone, α,β-unsaturated ketone, and a hydroperoxy ketone (65). Nickon and Mendelson (66) also carried out photooxygenation on some steroids with conformationally flexible rings.

From all the results obtained, Nickon concluded that the reaction was stereospecific, subject to steric hindrance and needed specific conformational requirements. Recently Gollnick and Schade (70) showed a difference in products formed from a trans- and a cis-cyclic olefin. The photosensitized oxygenation of (-)-caryophyllene (12) yielded two exocyclic olefinic hydroperoxides (13, 14) in a combined yield of 80%.



The cis-isomer (-)-isocaryophyllene (15) produced the compounds 13 and 14 and four endocyclic olefinic hydroperoxides, formed by abstraction of allylic ring hydrogens.



15

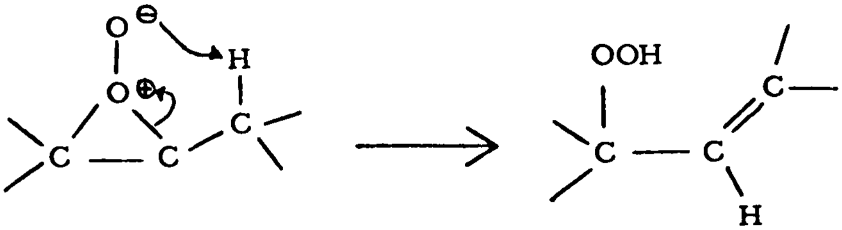
Gollnick and Schade (70) found the results above in good agreement with a concerted mechanism as proposed by Schenck (2) and Foote (33).

Klein and Rojahn (67) showed that the dye-sensitized photooxygenation of exocyclic double bonds was highly sterically controlled. Methylene cyclohexane and methylene cyclopentane could not be oxygenated, while methylene cycloheptane and β-pinene produced the expected allylic hydroperoxides. They suggested that the distance between the vinyl carbon and the axial or quasi-axial allylic hydrogen is too large to form a cyclic transition state in the case of methylene cyclopentane and methylene cyclohexane (67).

Kenny and Fischer (68) explained the product ratio in the dye-sensitized photooxidation of carvomenthene in one paper by a concerted mechanism. In their next paper (69), they concluded from the same evidence that a non-selective attack of oxygen took place on one end of the double bond of carvomenthene followed by non-selective transfer of a cis-axial hydrogen.

Nickon (60-66) and Foote (29, 30, 32, 33) both feel that a concerted "ene" type mechanism takes place. Foote (33) found that the product distribution from the reaction of trimethyl styrene did not change with different substituents on the phenyl ring. This is in good agreement with a concerted mechanism.

Sharp (27) and Kopecky (28) explained the different reactivities of a series of alkenes by the formation of an intermediate perepoxide which rearranges with a concurrent proton shift to yield the allylic hydroperoxide.

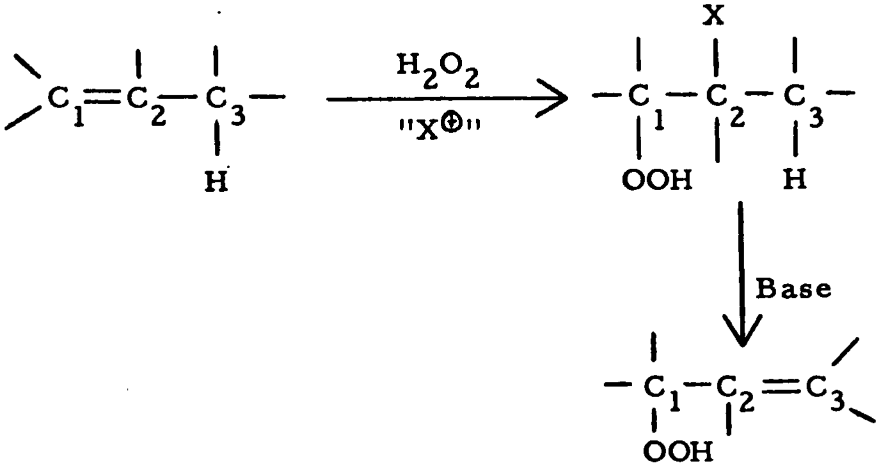


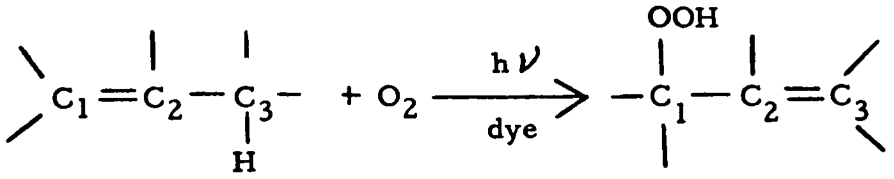
To obtain more information concerning the mechanism of the oxygen transfer to olefins, deuterium isotope effects of several deuterated alkenes were studied in this work. An alternate route for the preparation of allylic hydroperoxides was developed. The results are shown in the formation of β-halohydroperoxides and their reactions with base. Deuterium isotope effects were studied in the reactions of some deuterated β-halohydroperoxides with base. A convenient alkylation procedure of α-ketols was developed during this work.

CHAPTER I

PREPARATION AND BASE-CATALYSED REACTIONS OF SOME β-HALOHYDROPEROXIDES.

An investigation into an alternate way to the sensitized photooxidation route of preparing allylic hydroperoxides was carried out. It seemed that the reaction between base and β-halohydroperoxides could produce allylic hydroperoxides. Thus, conversion of an olefin to the β-halohydroperoxide and subsequent elimination of the elements of hydrogen halide would constitute a simple two step, chemical transformation of the olefin to an allylic hydroperoxide, equation [11]. This reaction sequence would introduce the hydroperoxy group and shift the double bond of an olefin into the same positions as is observed in the photosensitized reaction, equation [12].

[11] 

[12] 

The formation of a four membered cyclic peroxide could occur in the reaction of β-halohydroperoxides with base. A cyclic peroxide could also be involved in the dye-sensitized photooxidation. Four membered cyclic peroxides were suggested as intermediates in the chemiluminescent reaction between lophine (2,4,5-triphenylimidazole) and base and oxygen (71) and in the chemiluminescent reaction between 9-cyano-10-methylacridinium nitrate with hydrogen peroxide (72).

When the work on the subject was well in hand, several reports appeared on the reactions of β-halo- and β-cyanohydroperoxides with base (73, 74, 75). Richardson, Peters and Konopka (73) reported that acetone and formaldehyde are formed rapidly in the reaction of 1-chloro-2-methyl-2-propyl hydroperoxide with base. These authors proposed a four membered cyclic peroxide as an intermediate. Schulz, Rieche and Kirschke (74) report that on treatment with base the bromo analog, 1-bromo-2-methyl-2-propyl hydroperoxide is converted partly to isobutylene oxide as well as to acetone and formaldehyde. A similar cleavage reaction was observed by Dulog and Vogt (75) in the reaction of 2-methyl-2-hydroperoxypropionitrile with base. Acetone and cyanate ion are produced. The above β-halohydroperoxides have halogen on the terminal carbon atom and a simple elimination route to allylic hydroperoxides is not available to these materials.

The preparation of the β-halohydroperoxides of some tetrasubstituted alkenes and reactions of these with base are presented (76).

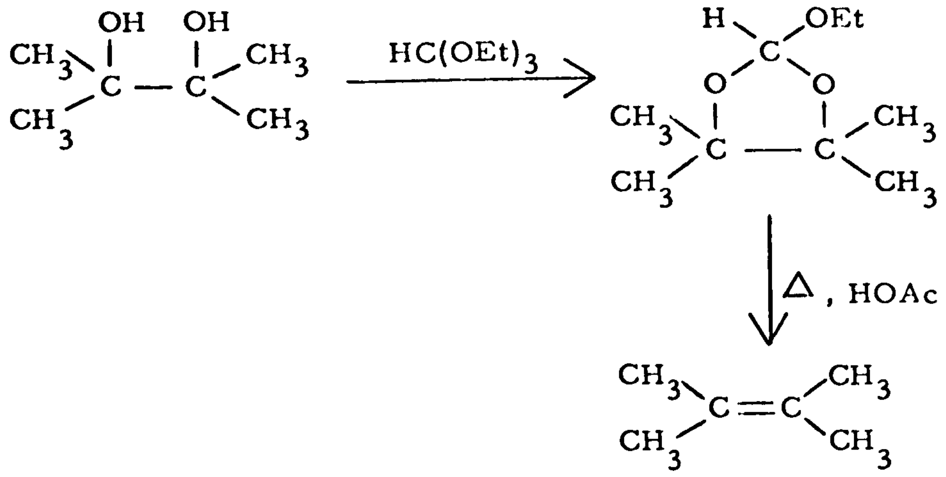
RESULTS AND DISCUSSION

THE PREPARATION OF SOME β-HALOHYDROPEROXIDES.

At the time when the investigations were started, no convenient method for the preparation of β-halohydroperoxides was known. β-Halohydroperoxides had been prepared by the autooxidation of halogenated hydrocarbons, which was not a very clean reaction (77, 78). Weissermel and Lederer (79) prepared β-halohydroperoxides in low yield (<25%) by the reaction between olefins, hydrogen peroxide and t-butyl hypochlorite.

A reactive olefin for electrophilic reactions,2,3-dimethyl-2-butene (1), was chosen as a model compound. Compound 1 was prepared in two different ways. The reaction between 3-methyl-2-butanone and methylmagnesium iodide, followed by dehydration of the resulting alcohol affords a 23% overall yield of 1. The g.l.c. analysis (FFAP, 70°) indicated that the material was > 99% pure. The second route to compound 1 was by means of a reaction developed by Cranck and Eastwood (80). Pinacol reacts with ethyl orthoformate to form 2-ethoxy-4,4,5,5-tetramethyl-1,3-dioxolan which upon pyrolysis produces compound 1 in 82 % yield, equation [13].

[13]

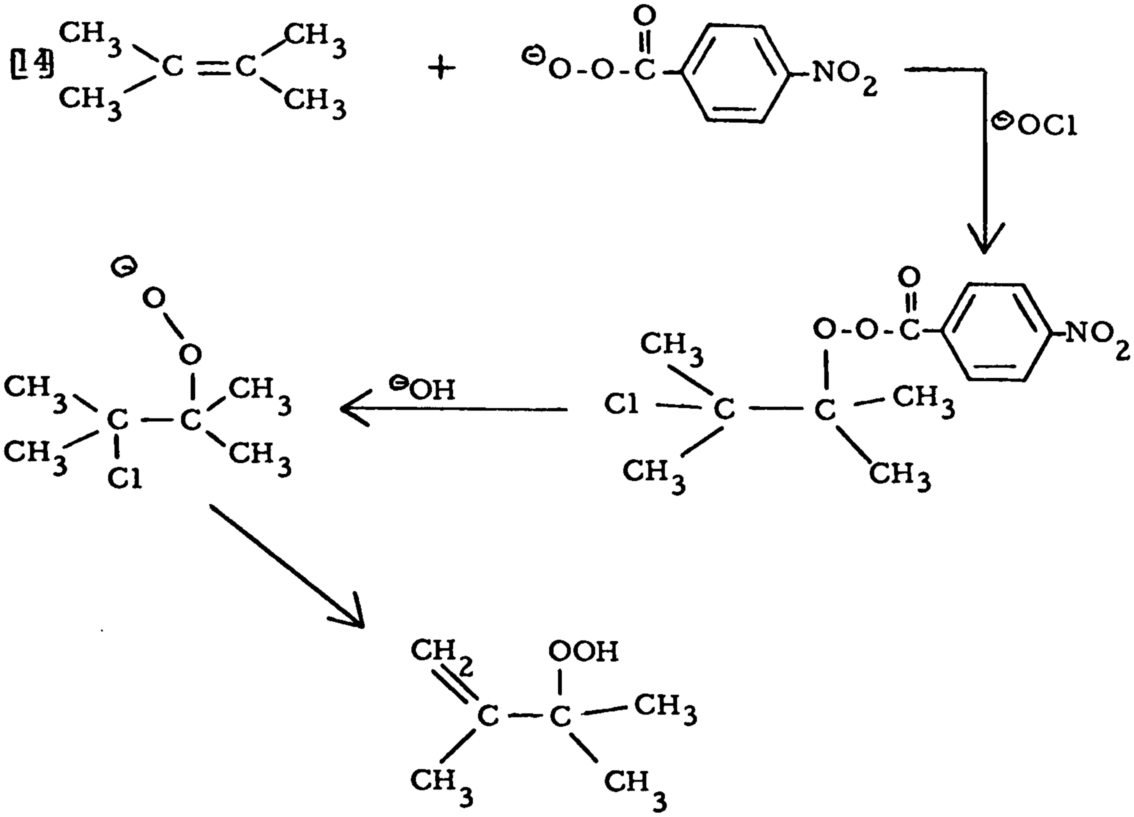


1

A dye-sensitized photooxygenation was carried out on compound 1 to give 2,3-dimethyl-3-hydroperoxy-1-butene (2) in 50% yield (10). The infrared spectrum (CCl_4) showed absorption bands at 3560 and 3300-3500 cm^{-1} (free and bonded -OOH stretching vibrations), and 3100 and 1645 cm^{-1} (olefinic stretching vibrations). The n.m.r. spectrum (CCl_4) showed absorption at τ1.6-1.8 (broad singlet) for the hydroperoxy proton, τ5.1-5.2 (multiplet) for the vinyl protons, τ8.22 (multiplet) for the protons of the allylic methyl group and τ8.70 (singlet) for the protons of the gem-dimethyl group. Compound 2 was also prepared by the method of Foote (29), using sodium hypochlorite and hydrogen peroxide. The infrared and n.m.r. spectra of compound 2 prepared this way were identical to the ones described above of the product from the dye-sensitized photooxidation.

Some preliminary investigations into the preparation of β-halohydroperoxides were carried out using 2-hydroperoxytetrahydropyran (81) or p-nitroperoxybenzoic acid (82). A vigorous explosion occurred during the distillation of 2-hydroperoxytetrahydropyran and further work with this compound was abandoned. Compound 1 was treated with the sodium salt of *p*-nitroperoxybenzoic acid and sodium hypochlorite and the reaction mixture subsequently treated with methanolic base. An infrared spectrum (CCl_4) of the undistilled product showed absorption bands at 3600 and 3300 -3500 cm^{-1} for the free and bonded -OOH stretching vibrations and absorptions at 3100 and 1620 cm^{-1} for the olefinic stretching vibrations. The infrared spectrum was identical to the spectrum of compound 2. The formation of the allylic hydroperoxide can be explained by the reaction sequence of equation [14].

[14]



2

This reaction provides some information about the possible presence of a chlorohydroperoxide. The presence of base in the sodium hypochlorite may make it impossible to isolate the chlorohydroperoxide, since it is expected to be unstable in the presence of base. The work with p-nitroperoxybenzoic acid was abandoned in favour of the methods described below.

The reaction between N-haloamides, water and olefins is well known to give β-halohydrins (83, 84). It seemed that a possible method for the preparation of β-halohydroperoxides could be the reaction between olefins, N-haloamides and 98% hydrogen peroxide. As a chlorinating agent N-chloroacetamide (18) was chosen. Compound 18 was prepared from acetamide and chlorine according to the method of Orton (85). Iodometric analysis showed that compound 18 contained the theoretical amount of active chlorine. The reaction between equivalent amounts of N-chloroacetamide and compound 1 and a ten-fold excess of 98% hydrogen peroxide in ether gave 2-chloro-2,3-dimethyl-3-hydroperoxybutane (19) in 60% yield based on iodometric titration. Compound 19 gave a positive chlorine test (Beilstein) and a positive hydroperoxide test (iodometric). Concentration of the ether solution, followed by low-temperature crystallization of the residue from pentane resulted in a 30% yield of 19. The infrared spectrum (CCl_4) of 19 showed absorption bands at 3550 and 3200-3500 cm^{-1} for the free and bonded -OOH stretching vibrations. The n.m.r. spectrum (CCl_4) showed absorption at τ1.9-2.1 (broad singlet) for the hydroperoxy proton and at τ8.38

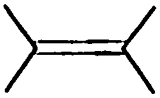
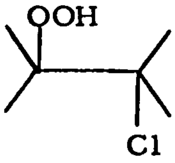
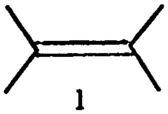
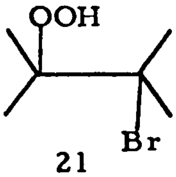
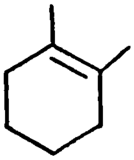
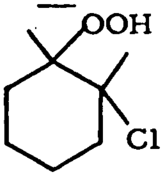
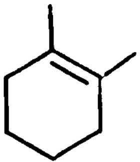
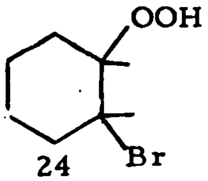
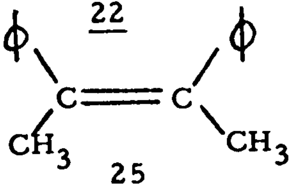
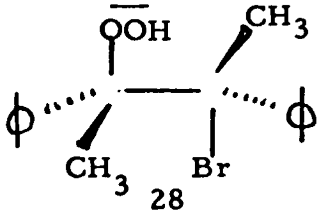
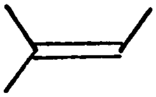
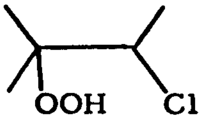
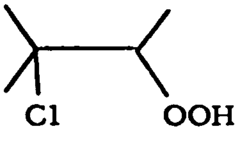
(singlet) and 8.60 (singlet) for the protons of the *gem*-dimethyl groups. The *p*-nitrobenzoate ester of 19 was prepared, its infrared spectrum (benzene) showed an absorption band at 1765 cm^{-1} (-C=O stretching vibration). The n.m.r. spectrum (benzene) of the *p*-nitrobenzoate ester showed absorption at τ 2.40 (singlet) for the aromatic protons and at τ 8.43 (singlet) and 8.68 (singlet) for the protons of the *gem*-dimethyl groups. Compound 19 was reduced with lithium aluminium hydride to 3-chloro-2,3-dimethyl-2-butanol (46). The infrared and n.m.r. spectra of 46 were identical to those of authentic 46, prepared from N-chloroacetamide, water and tetramethylethylene (86). The preparation of the chlorohydroperoxide 19 was a very slow reaction at room temperature; however a vigorous, exothermic reaction occurred when a trace of *p*-toluenesulfonic acid was added to the reaction mixture at 0°. Once a temperature of 150° was recorded after addition of a trace of *p*-toluenesulfonic acid, but normally the solution ceases to boil after one minute.

The reaction between equivalent amounts of 1,3-dibromo-5,5-dimethylhydantoin (20), tetramethylethylene and a five-fold excess of hydrogen peroxide resulted in the isolation of crystalline 3-bromo-2,3-dimethyl-2-hydroperoxybutane (21) in 76% yield. This reaction proceeded rapidly at 0°, but some coloring occurred and some dibromide was formed. Dibromide formation in general could be entirely eliminated by adding the brominating agent to a solution of olefin and hydrogen peroxide in ether at -40°. The infrared spectrum (CCl_4) of 21 showed absorption bands at 3550 and 3250-3500 cm^{-1} for the free and bonded -OOH stretching vibrations. The n.m.r. spectrum (CCl_4) showed absorption at τ 1.8-2.3 (broad singlet) for the hydroperoxy proton and at τ 8.19 (singlet) and τ 8.55 (singlet) for the protons of the two gem-dimethyl groups. Iodometric titrations on 21 showed 96.75% of the theoretical amount of active oxygen present.

The β-halohydroperoxides, prepared in similar manner as outlined above, are listed in Table I. 1,2-Dimethylcyclohexene (22) was kindly donated by Dr. K. R. Kopecky. Compound 22 was reacted with N-chloroacetamide and hydrogen peroxide. Several attempts at isolation of 2-chloro-1,2-dimethylcyclohexyl hydroperoxide (23) resulted in explosions. It was possible to obtain spectral data for compound 23, by pumping off the ether from the ether solution of 23, in the presence of some carbon tetrachloride. The infrared spectrum (CCl_4) showed absorption bands at 3540 and 3200-3500 cm^{-1} for the free and bonded -OOH stretching vibrations. The n.m.r. spectrum (CCl_4) showed two singlets for the protons of the methyl groups at τ 8.42 and τ 8.67. The yield of 23 was estimated to be 57% based on starting material left as determined by g.l.c.. 2-Bromo-1,2-dimethylcyclohexyl hydroperoxide (24) was prepared from 22 in 86% yield based on iodometric titration. In view of the explosions with compound 23 no attempts at isolation of 24 were made. The next tetrasubstituted olefin subjected to β-halohydroperoxide formation was cis-dimethylstilbene (25).

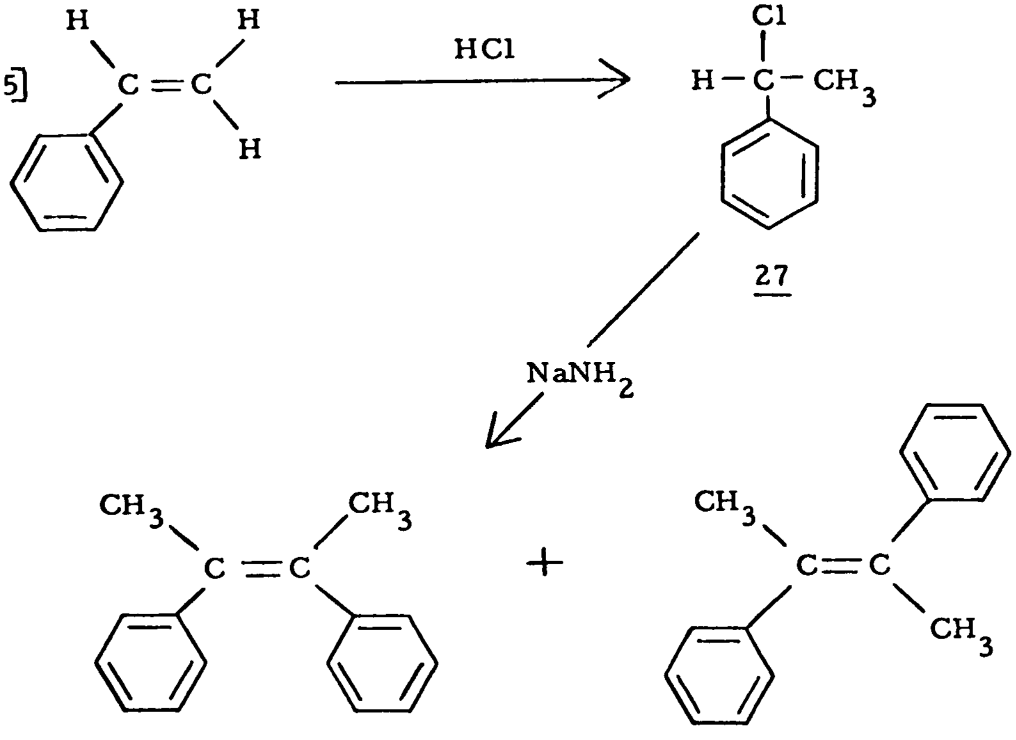
TABLE I

Yield of β-Halohydroperoxides from Olefins.

Olefin	Halogen Source	β-Halo-hydroperoxides	% Yield
 1	18	 19	60
 1	20	 21	76
	18	 23	57
 22	20	 24	86
 25	20	 28	70
	18	 + 	40 10

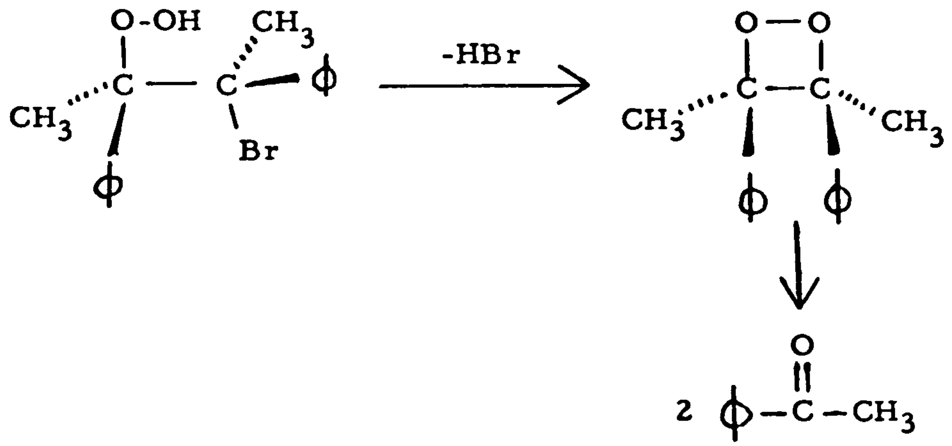
Compound 25 was prepared following the reaction sequence outlined in equation [15].

[15]



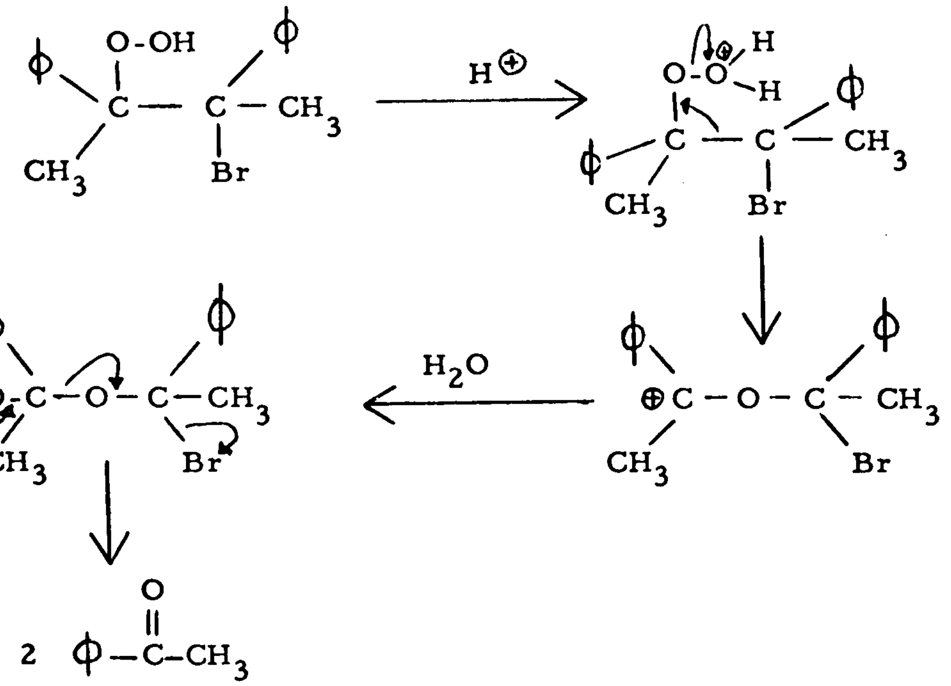
Styrene was reacted with hydrochloric acid to give α-phenylethyl chloride (27) in 83% yield (87). Reaction of 27 with sodium amide resulted in the formation of a mixture of cis- and trans-dimethylstilbene (88). Fractional recrystallization from methanol gave a 15% yield of trans-dimethylstilbene (26) and a 40% yield of cis-dimethylstilbene (25). The n.m.r. spectrum (CCl_4) of 25 showed absorption at $\tau 3.09$ (singlet) for the aromatic protons and at $\tau 7.87$ (singlet) for the protons of the methyl group. A n.m.r. spectrum (CCl_4) of 26 showed absorption at $\tau 2.82$ (singlet) for the aromatic protons and at $\tau 8.15$ (singlet) for the protons of the methyl group. The *cis* compound *25* has a higher electron density on the double bond (steric effect of the *cis* phenyl groups inhibits conjugation of the double bond with the phenyl groups) and was chosen to react with the brominating agent and hydrogen peroxide. A 70% yield (iodometric titration) of the *threo*-3-bromo-2,3-diphenyl-2-butylhydroperoxide (*28*) was obtained. Compound *28* could be isolated as a crystalline solid which, however, decomposed on standing. The n.m.r. spectrum ($CDCl_3$) showed absorption at τ2.6-2.9 (multiplet) for the aromatic protons and the hydroperoxy proton and at τ 7.78 and 8.06 for the protons of the methyl groups. The n.m.r. sample in $CDCl_3$ decomposed upon standing. New absorptions appeared in the spectrum at τ7.40 and τ2.2-2.4 and τ2.4-2.6, which are characteristic for the n.m.r. spectrum of acetophenone. Acetophenone can be visualized to be formed by the sequence of equation [16].

[16]



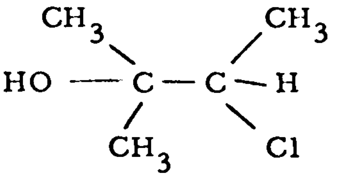
The presence of a trace of acid could also be responsible for the formation of acetophenone, equation [17].

[17]

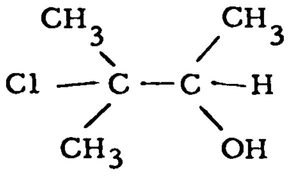


This observation was not investigated any further.

One trisubstituted olefin, 2-methyl-2-butene was transformed to the chlorohydroperoxide in 50% yield as determined by iodometric titration. Two possible chlorohydroperoxides can be formed from 2-methyl-2-butene, 3-chloro-3-methyl-2-butyl hydroperoxide and 3-chloro-2-methyl-2-butyl hydroperoxide. The reaction mixture was reduced to the corresponding chlorohydrins with lithium aluminium hydride and the product of reduction analysed by g.l.c. (hallcomid 180-L, 115°). Two products were present in a 4:1 ratio which were both collected from the effluent stream of the g.l.c.. The infrared spectrum (CCl_4) of the major product showed absorption bands at 3580 and 3200-3500 cm^{-1} for the free and bonded -OH stretching vibrations. The n.m.r. spectrum (CCl_4) showed absorption at τ6.05 (quartet, J= 7 c.p.s.) for the methine proton, at τ 7.85 (broad singlet) for the hydroxyl proton, at τ 8.48 (doublet, J= 7 c.p.s.) for the protons of the methyl group and at τ= 8.72 (singlet) for the protons of the *gem*-dimethyl group. The two possible chlorohydrins are 2-chloro-2-methyl-3-butanol (30) and 3-chloro-2-methyl-2-butanol (29).



29



30

The major product expected in the formation of β-chlorohydroperoxides from 2-methyl-2-butene is 3-chloro-2-methyl-2-butyl hydroperoxide and consequently, after reduction, the expected major product is 29. Evidence for 29 as the major product was obtained from the n.m.r. spectrum described above. Protons of a *gem*-dimethyl group on a tertiary carbon bearing a hydroxyl group are expected to absorb at *ca*. τ 8.75 ($(CH_3)_3C\text{-}OH$ – τ 8.78) while protons of a *gem*-dimethyl group on a tertiary carbon bearing a chlorine are expected at *ca*. τ 8.45 ($(CH_3)_3C\text{-}Cl$ – τ 8.42) (89). Reaction of the major compound with potassium dichromate did not occur, indicative of a tertiary alcohol. Compound 29 was prepared from 2-methyl-2-butene, N-chloracetamide and water in 11% yield (86). The n.m.r. and infrared spectra of 29 were identical to those of the collected major product, which thus has been shown to be compound 29. The infrared spectrum (CCl_4) of the minor compound showed absorption bands at 3575 and 3300-3500 cm^{-1} for the free and bonded -OH stretching vibration. The n.m.r. spectrum (CCl_4) showed absorption at τ6.31 (quartet, J=7 c.p.s.) for the methine hydrogen, at τ7.09 (singlet) for the hydroxyl proton, at τ8.46 (doublet, J=2 c.p.s.) for the protons of the *gem*-dimethyl group and at τ8.79 (doublet, J=7 c.p.s.) for the protons of the methyl group. The n.m.r. spectrum is in agreement with the expected structure of the minor compound, 3-chloro-3-methyl-2-butanol (30). The protons of the dimethyl group on the carbon bearing chlorine absorb at the expected position (*ca.* τ 8.45) and the protons of the methyl group are expected to absorb at *ca.* τ 8.75 as was observed. Compound 30 was also prepared in a two-step reaction sequence. The method for chlorination of *n*-propyl methyl ketone was adapted for the chlorination of methyl *iso*-propyl ketone (90). The product 3-chloro-3-methyl-2-butanone was obtained in 46% yield. The n.m.r. spectrum (CCl_4) of 31 showed absorption at τ7.68 (singlet) for the protons of the *gem*-dimethyl group. Reduction of compound 31 with lithium aluminium hydride gave a 58% yield of compound 30. The infrared and n.m.r. spectra and the g.l.c. retention time of compound 30 were identical to those of the minor product collected from the g.l.c.. It can be concluded that the chlorohydroperoxylation reaction of 2-methyl-2-butene results in the formation of two products, 2-chloro-2-methyl-3-butyl hydroperoxide and 3-chloro-2-methyl-2-butyl hydroperoxide in a 1:4 ratio.

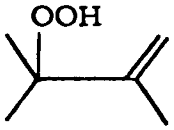
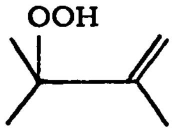
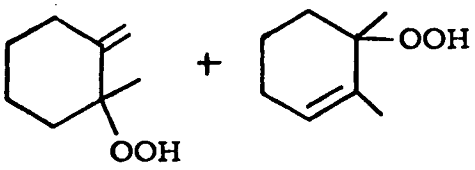
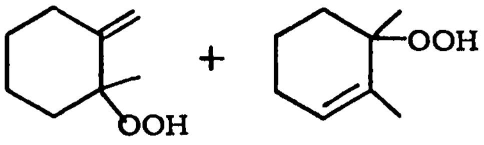
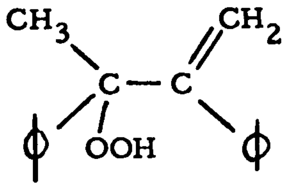
At the time when the work on the preparation of β-halohydroperoxides was well on the way, two reports appeared in the literature on this subject. Rieche, Schulz and Kirschke (91, 92) synthesized β-halohydroperoxides by reaction between an olefin, hydrogen peroxide and molecular halogen. The main disadvantage of this procedure is the side reaction of formation of dihalides. No dihalides are detected in the preparation of β-halohydroperoxides in the manner described in this work. It has been shown that the reaction between olefins, N-chloracetamide or 1,3-dibromo-5,5-dimethylhydantoin, and 98% hydrogen peroxide affords β-halohydroperoxides in good yields. β-Bromohydroperoxides are formed in higher yields than β-chlorohydroperoxides.

Reactions of β-Halohydroperoxides with Base.

It was found that all the β-halohydroperoxides reacted extremely rapidly with base. The products formed from reaction of the tetrasubstituted β-halohydroperoxides with base are listed in Table II. The reactions were carried out by mixing the β-halohydroperoxides in methanol or ether solution with a methanolic solution of base at 0°. After stirring the reaction mixtures for one to two hours at 0°, they were poured into icewater and extracted with ether. In the reaction of 23 with base, however, sodium borohydride was added to the reaction mixture prior to workup to reduce the allylic hydroperoxide. The yield of products obtained from the reactions of base with the β-halohydroperoxides are yields of products actually isolated by distillation. The β-chlorohydroperoxide 19 upon treatment with methanolic base resulted in a 70%

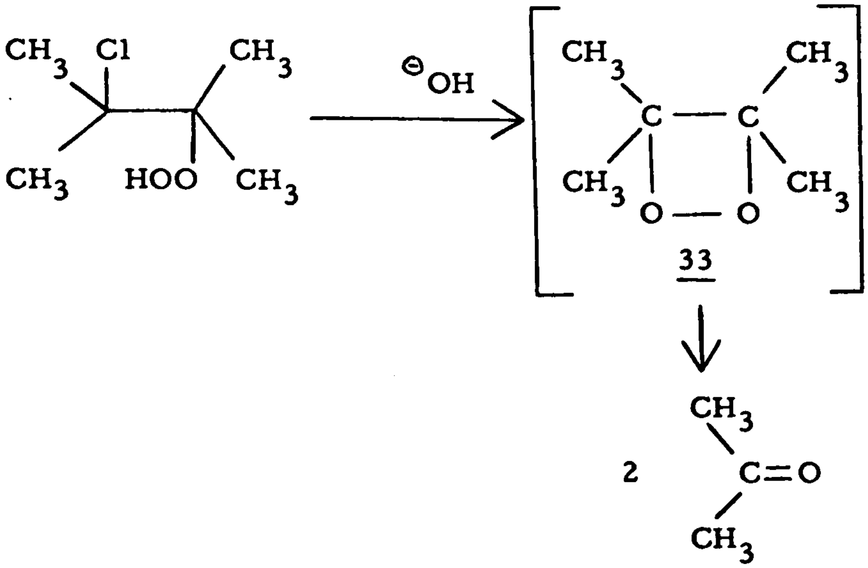
TABLE II

Products from Reaction Between β-Halohydroperoxides and Base.

β-Halohydroperoxide	Product	% Yield
19		70
21		77
23		33, 1
24		76, 2
28		60

yield of 2,3-dimethyl-3-hydroperoxy-1-butene (2). This material was identical (n.m.r. and infrared spectra) with a sample of 2 prepared by the photosensitized oxidation of 2,3-dimethyl-2-butene. An investigation was made into the possible presence of acetone, 3-chloro-2,3-dimethyl-2-butanol and 2,3-epoxy-2,3-dimethyl butane (32) from the reaction between 19 and base. Tertiary hydroperoxides, like α-cumylhydroperoxide, are well known to give the corresponding alcohols on treatment with base (93). This would explain the possible presence of the chlorohydrin. The formation of epoxides from the reaction between chlorohydrins and base is a well established process. The formation of acetone could be pictured as follows. An analogous reaction to the formation of epoxides from β-chlorohydrins could occur with β-chlorohydroperoxides. The resulting product will be the four membered perepoxide (33). Decomposition of the perepoxide 33 could lead to formation of acetone, equation [18].

[18]

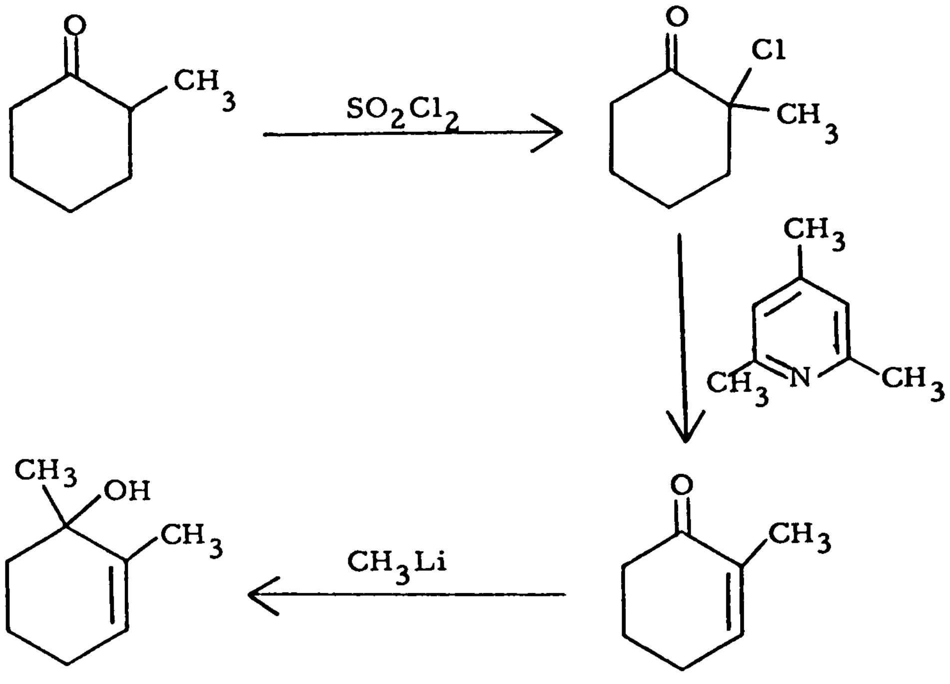


The epoxide 32 was prepared following the procedure of Eliel and Rerick (94). Reaction between 1 and *meta*-chloroperoxybenzoic acid resulted in a 35% yield of 2,3-epoxy-2,3-dimethylbutane (32). The n.m.r. spectrum (CCl_4) showed a singlet at τ 8.78. G.l.c. analysis of the reaction mixture containing 2 from the reaction between 2-chloro-2,3-dimethyl-3-butyl hydroperoxide and base, showed no evidence for the presence of any chlorohydrin or oxide. Traces of material (*ca.* 1%) with the retention time of acetone were detected by the g.l.c. analysis.

The reaction between 2-bromo-2,3-dimethyl-3-butyl hydroperoxide (21) and base resulted in a 77% yield of distilled allylic hydroperoxide 2. The infrared and n.m.r. spectra showed that this product was identical to the one obtained in the dye-sensitized photooxygenation. The reaction mixtures, from the reaction between the 2-halo-1,2-dimethylcyclohexyl hydroperoxides and base, containing 2-methylene-1-methyl-cyclohexyl hydroperoxide and 1,2-dimethyl-2-cyclohexenyl hydroperoxide were reduced to the corresponding alcohols, 2-methylene-1-methylcyclohexanol (34) and 1,2-dimethyl-2-cyclohexen-1-ol (35), and characterized as such. The two possible products, 34 and 35, were synthesized for comparison by different routes. 2-Methylene-1-methylcyclohexanol (34) was prepared via a modified procedure of Mannich (95). The reaction between cyclohexanone, formaldehyde and dimethylamine hydrochloride resulted in a 55% yield of 2-(dimethylaminomethyl)-cyclohexanone hydrochloride (36). This salt was pyrolysed under vacuum and the product, 2-methylenecyclohexanone (37), stored at -70°. Compound 37 is known to be unstable at room temperature; dimerization occurs readily (96). Reaction between 2-methylenecyclohexanone and methylmagnesium iodide was carried out at -70°. Analysis by g.l.c. (FFAP, 132°) showed the presence of two products in a 60:40 ratio, which were isolated by trapping from the effluent of the g.l.c.. The major product showed absorption bands in the infrared spectrum (CCl_4) at 3660 (sharp) and 3550-3200 (broad) cm^{-1} for the free and bonded -OH stretching vibrations and at 1640 cm^{-1} for the olefinic stretching vibration and at 885 and 895 cm^{-1} for the C-H out of plane vibrations. The n.m.r. spectrum (CCl_4) showed absorption at τ 5.15 (multiplet) and τ 5.39 (multiplet) for the olefinic protons, τ 7.6-8.6 (broad) for the ring and hydroxyl protons and at τ 8.72 (singlet) for the protons of the methyl group. The spectra are in excellent agreement with structure 34 for the major compound. The second product had no absorption below τ 6 in the n.m.r. and showed hydroxyl but no olefinic absorption in the infrared spectrum. The compound was not identified.

1,2-Dimethyl-2-cyclohexen-1-ol (35) was prepared in the following manner: Scheme 1.

Scheme 1



35

38

The method of Warnhoff and Johnson (97) was followed to prepare 2-methylcyclohexenone (38) in 29% yield. This compound 38 was reacted with methyllithium at -40° (98) and g.l.c. analysis (FFAP, 120°) of the distillate showed two products present in a 60:40 ratio. The two products were collected from the effluent of the g.l.c.. The major product's n.m.r. spectrum (CCl_4) showed absorption at τ4.68 (multiplet) for the olefinic proton, τ7.9-8.6 (broad) for the ring, hydroxyl, and allylic methyl protons, and at τ8.80 (singlet) for the protons of the second methyl group. The spectrum was in good agreement with structure 35 for the major compound. The minor product showed no absorption characteristic of an olefin in the infrared spectrum and had no absorption in the n.m.r. spectrum below τ6. It was not investigated further. Distillation of the reaction mixture from the reaction between 23 and base after reduction, gave a 33% yield of compound 34, whose infrared and n.m.r. spectra were identical to authentic 34. The analysis by g.l.c. indicated the presence of ca. 1% of a material with the same retention time as the isomeric alcohol 35. Similarly, the reaction between 2-bromo-1,2-dimethylcyclohexyl hydroperoxide (24) and base resulted in a 42% yield of isolated 1-methyl-2-methylenecyclohexanol (34). The infrared and n.m.r. spectra were identical to those of authentic 34. G. l.c. analysis before distillation showed 12% 1,2-dimethylcyclohexene and 76% of product 34, based on the hydroperoxide yield. Also present was ca. 2% of a material with the same retention time as the isomeric alcohol, 1,2-dimethyl-2-cyclohexenol (35). The dye-sensitized photooxygenation of 22, after reduction, resulted in a 59% yield of alcohol 34, whose infrared and n.m.r. spectra were identical to those of authentic 34. G.l.c. analysis indicated the presence of ca. 5% of a material with the same retention time as 35. It has been shown that the same ca. 97-3 mixture of alcohols was produced in the dye-sensitized photooxidation as well as in the reactions of 23 and 24 with base. The isomeric alcohol 35 was only detectable by g.l.c. and was identified in the reaction mixtures only by comparison of its g.l.c. retention time with that of an authentic sample. In this case where two possible products are possible, the selectivities of the two processes are identical. The photo-sensitized reaction of 1,2-dimethylcyclohexene is rather selective compared with most examples in which more than one product is possible (1, 2). However, α-pinene also gives a high yield (94%) of the exocyclic olefin in the dye-sensitized photooxidation.

The dye-sensitized photooxidation of cis-dimethylstilbene, followed by reduction of the product by lithium aluminium hydride, affords 2,3-diphenyl-3-hydroxy-1-butene (39) in 48% yield. The n.m.r. spectrum (CCl_4) shows absorption at τ 2.5-3.2 (multiplet) for the aromatic protons, τ4.55 (doublet, J=1.5 c.p.s.) and τ4.82 (doublet, J=1.5 c.p.s.) for the vinylic protons, τ8.05 (broad) for the hydroxyl proton, and at τ 8.40 (singlet) for the protons of the methyl group. The infrared spectrum ($CHCl_3$) showed absorption bands at 3560 and 3300-3500 cm^{-1} for the free and bonded -OH stretching vibrations, and 3060 and 1640 cm^{-1} for the olefinic stretching vibrations and at 905 cm^{-1} for the C-H out of plane bending vibration of the terminal methylene group.

The reaction between threo-2-bromo-2,3-diphenyl-3-butylhydroperoxide (28) and base, followed by reduction, gives a 60% yield of 39. The product obtained in this reaction was identical (infrared and n.m.r. spectra) with the one obtained in the dye-sensitized oxidation.

Brief investigations into the products from the reaction between the chlorohydroperoxides of 2-methyl-2-butene, and base were carried out. Dye-sensitized photooxygenation of 2-methyl-2-butene was known (1, 2) to give a mixture of the two possible allylic hydroperoxides in a 1:1 ratio. The retention time of the corresponding alcohols, obtained from lithium aluminium hydride reduction of the dye-sensitized reaction product of 2-methyl-2-butene, in the g.l.c. was obtained. The reaction mixture from the reaction between the chlorohydroperoxides from 2-methyl-2-butene and base, was reduced with lithium aluminium hydride, and subsequently analysed in the g.l.c.. No products with the same retention times as the allylic alcohols were present. The course of this reaction has been further investigated in detail by Mumford (76).

It has been shown that β-halohydroperoxides from tetrasubstituted alkenes, react with base to give allylic hydroperoxides, identical to those obtained from the dye-sensitized oxidation. No allylic hydroperoxides were obtained from the reaction of β-halohydroperoxides, prepared from trisubstituted alkenes, and base. Mumford (76) observed that carbon-carbon bond cleavage occurs in the reaction of base with β-halohydroperoxides prepared from alkenes other than tetrasubstituted ones. The mechanism of this addition elimination reaction will be discussed in more detail in the next chapter.

EXPERIMENTAL

Melting points and boiling points reported are not corrected. Refractive indices were measured on a Bausch and Lomb Abbe-3 L Refractometer. Infrared spectra were recorded on Perkin-Elmer model 421 and model 337 spectrophotometers and only characteristic absorption bands are cited. Nuclear magnetic resonance spectra (n.m.r.) were determined with Varian analytical spectrometers, models A-60 and HR-100 with tetramethylsilane (TMS) as internal standard. Gas-liquid chromatography (g.l.c.) was carried out on Aerograph 202 and A-90-P3 gas chromatographs. Quantitative g.l.c. analyses were made with calibrated internal standards. Mass spectra were obtained on A.E.I. MS-2-H mass spectrometer.

The photolysis cell consisted of a 2.5 cm x 25 cm water-jacketed test tube fitted with a ground glass stopper containing an outlet tube and an inlet tube with a fritted disk which reached to the bottom of the test tube. The inlet tube was connected to the exhaust port of a Dynaport air pump. The outlet tube was connected to a T-tube which was, in turn, connected to an oxygen buret and to the inlet port of the air pump.

All preparations of β-halohydroperoxides were carried out behind shields. Apparatus containing these compounds was manipulated with the aid of tongs and hands were protected with heavy canvas gloves.

2,3-Dimethyl-2-butanol (16):

A methylmagnesium iodide solution was prepared from 300 g (2.0 mole) of magnesium and 300 g (2.1 mole) of methyl iodide in 1200 ml ether, all contained in a two liter three-necked flask fitted with a mechanical stirrer, reflux condenser and dropping funnel. A solution of 3-methyl-2-butanone (172 g, 2 mole) in anhydrous ether (200 ml) was added at such a rate as to maintain mild reflux of the ether. The reaction mixture was then hydrolysed by pouring into ice/HCl. The ether layer was separated from the aqueous layer and dried over magnesium sulfate. The solvent was removed by distillation through a 30 cm Vigreux column. The residue was distilled to yield 113 g (46%) of 16, b.p. 114-119°, η_D^{25} = 1.4139. Reported (99) b.p. 118.9-119.2° (759 mm), η_D^{26}= 1.4169.

2,3-Dimethyl-2-butene (1):

a) From dehydration of alcohol 16

Compound 16 (113 g, 1.1 mole) was dropped slowly into 150 ml of 85% phosphoric acid heated at 160°, contained in a three-necked flask equipped with a magnetic stirrer, dropping funnel and distillation take-off. The organic layer was separated from the distilled material and dried over magnesium sulfate. The product was distilled through a 30 cm Vigreux column and the fraction boiling from 65°-71° collected. This fraction was distilled through a Nestor-Faust annular teflon spinning band column to yield 41 g (44%) of 1, b.p. 70-71° (700 mm), η_D^{25} = 1.4075. Reported (100) b.p.

73°, η_D^{25} = 1.4094. The n.m.r. spectrum (CCl_4) showed a singlet at τ 8.41. The g.l.c. analysis (5 ft x 1/4 in FFAP, 70°) indicated that the product was $>$ 99% pure.

b) From 2,3-dimethyl-2,3-butanediol

Compound 1 was prepared according to the method of Cranck (80). Pinacol (118 g, 1.0 mole) and freshly distilled ethyl orthoformate (148 g, 1.0 mole) were heated at 135° (bath temperature) until 85 g (92%) of ethanol distilled over (10 hours). Two drops of acetic acid were added and the bath temperature raised to 175°. The mixture was heated until no more product distilled over (8 hrs). The distillate was washed three times with 40 ml portions of ice-water and dried over magnesium sulfate. Fractional distillation through a Nestor-Faust annular teflon spinning band column yielded 69 g (82%) of 1, b.p. 69-70°, η_D^{25} = 1.4025. The n.m.r. spectrum (CCl_4) showed a singlet at τ8.41.

2,3-Dimethyl-3-hydroperoxy-1-butene (2):

a) From Sensitized oxidation of 1

A solution of 1.0 g (11.9 mmoles) 2,3-dimethyl-2-butene and 30 mg of methylene blue in 30 ml methanol was placed in the photolysis cell. The pump was turned on and after pressure equilibrium was reached the cell was illuminated with two 200 W frosted light bulbs placed against the cell on either side. Oxygen uptake became very slow after 45 minutes when 300 ml (STP) had been consumed (theoretical 265 ml). The solution was poured into 100 ml ice-water and the resulting mixture extracted three times with 50 ml ether. The combined ether extracts were washed with water and with saturated sodium chloride solution. The ether solution was dried and the solvent removed by distillation through a Nestor-Faust annular teflon spinning band column. Distillation of the residue gave 0.7 g (50%) of 2, b.p. 55-56° (15 mm), $\eta_D^{25} = 1.4401$. Reported (10) b.p. 55° (12 mm), $\eta_D^{20} = 1.4428$. The infrared spectrum (CCl_4) showed absorption bands at 3560, 3300-3500, 3100 and 1645 cm^{-1}. The n.m.r. spectrum (CCl_4) showed peaks at τ1.6-1.8 (s), τ5.1-5.2 (m), τ8.22 (m) and τ 8.70 (s), in the ratio 0.85:1.85:3:5.71, required 1:2:3:6.

b) From sodium hypochlorite-hydrogen peroxide oxidation of 1

The reaction was carried out following the procedure of Foote and Wexler (29). To a solution of 5.05 g (60 mmoles) of 1 in 300 ml of methanol was added 19.2 ml of 30% H_2O_2 (180 mmoles). The solution was stirred at 10°, and 150 ml of 1.02 M sodium hypochlorite solution (150 mequiv.) was added in the course of 90 minutes. The solution was diluted with water and extracted with ether. Ether was distilled from the dried extracts through a 2 ft Podbielniak column. Distillation of the residue gave 2.2 g (28%) of compound 2, b.p. 59-59.5° (17 mm), $\eta_D^{24.5} = 1.4408$. This material was identical (n.m.r. and infrared spectra) with compound 2 prepared in the dye-sensitized photooxidation.

N-Chloroacetamide (18):

This was prepared according to the method of Orton and

Bradfield (85). A solution of acetamide (70 g, 0.83 mole) and sodium bicarbonate (100 g, 1.2 mole) in 160 ml of water was stirred at 0°. A rapid current of chlorine gas was introduced for 30 minutes, while the mixture was kept cool. The precipitate of sodium chloride and 18 was filtered off and another 60 g (0.7 mole) of sodium bicarbonate added to the filtrate. Chlorine was passed in again and after 30 minutes the precipitate was filtered off. The combined solids were extracted with hot chloroform and upon cooling 45 g (40%) of compound 18 crystallized, m.p. 111°. Reported (101) m.p. 111°. Iodometric titration: Found 38.18% Cl; required 37.97% Cl.

3-Chloro-2,3-dimethyl-2-butyl Hydroperoxide (19):

To a solution of 9.0 g (0.107 mole) of 1, 9.45 g (0.101 mole) N-chloroacetamide and 50 ml ether in a three-necked flask, fitted with a thermometer and reflux condenser and cooled in an ice bath, was added 15 g (0.4 mole) of 98% hydrogen peroxide (FMC Corp.) at a rate to keep the temperature from rising above 10°. After the resulting solution had cooled to 0° *ca.* 1 g of p-toluenesulfonic acid was added. The temperature rose rapidly and the solution began to boil. It was stirred in the ice bath for 1 hr. (Usually, the solution ceased boiling after a few minutes. However, in some reactions the reaction was so exothermic that all the ether was driven out and temperatures of up to 150° were observed in the reaction flask.) The reaction mixture was then washed with four portions of water and with 10% sodium bicarbonate solution. Twenty per cent of the dried ether solution was concentrated on a bath at 40^{o} and the residue taken up in 15 ml pentane. The pentane solution was cooled to -65^{o}. The precipitate formed was filtered in a low-temperature filtration apparatus. This material (1.0 g, 30%), m.p. $72\text{-}73^{o}$ (decomposition), appeared to be hygroscopic. The infrared spectrum (CCl_4) of 19 showed absorption bands at 3550 and 3200-3500 cm^{-1}. The n.m.r. spectrum (CCl_4) showed peaks at τ 1.9-2.1 (b.s.), τ 8.38 (s) and τ 8.60 (s) in the ratio 0.9:6.4:6.0, required 1:6:6. A satisfactory elemental analysis could not be obtained on this material, but iodometric titration showed 99% of the theoretical active oxygen content. The p-nitrobenzoate ester was prepared, m.p. $104.5\text{-}105^{o}$. The infrared spectrum (benzene) showed an absorption band at 1765 cm^{-1}. The n.m.r. spectrum (benzene) showed peaks at τ 2.40 (s), τ 8.43 (s) and τ 8.68 (s) in the ratio 4.28:6.0:5.65, required 4:6:6. Analysis calculated for $C_{13}H_{16}NO_5Cl$: C, 51.75: H, 5.35. Found: C, 51.25; H, 5.56.

Ten per cent of the ether solution of 19 was added to a stirred slurry of 0.3 g of lithium aluminium hydride in 20 ml ether at 0^{o}. The mixture was hydrolysed after 10 minutes with 15% potassium hydroxide. G.l.c. analysis using a 5 ft x 1/4 in. column of 10% DEGS on Chromosorb W at 70^{o} showed the presence of only one product in addition to some starting olefin 1. The product, 3-chloro-2,3-dimethyl-2-butanol (20) was collected from the effluent stream of the g.l.c.. The n.m.r. spectrum (CCl_4) showed absorption at τ8.07 (b.s.), τ8.36 (s) and τ8.69 (s) in the ratio

1 : 5.5 : 6.0, required 1 : 6 : 6.

3-Bromo-2,3-dimethyl-2-butyl Hydroperoxide (21):

To a solution of 4.8 g (0.057 mole) of 1 and 9.0 g (0.26 mole) of 98% hydrogen peroxide in 50 ml ether stirred at -40° was added 8.1 g (0.029 mole) of 1,3-dibromo-5,5-dimethylhydantoin (20) (Matheson, Coleman, and Bell, 98% theoretical active bromine) in small portions over a 10 minute period. The reaction mixture, protected with a calcium chloride tube, was allowed to come to room temperature, washed with 25 ml cold, saturated sodium bicarbonate solution and four times with water. Ether was distilled from the dried material through a 2 ft Podbielniak column using a 40° water bath. The residual oil crystallized when the remainder of the ether was removed under vacuum. Two recrystallizations from pentane gave 8.5 g (76%) of constant melting product 21, m.p. 93-94°. Reported (91) m.p. 93°. Two iodometric titrations indicated 96.77% and 96.75% of the theoretical amount of active oxygen. The infrared spectrum (CCl_4) showed absorption bands at 3550 and 3250-3500 cm^{-1}. The n.m.r. spectrum (CCl_4) showed peaks at τ1.8-2.3 (b), τ8.19 (s) and τ8.55 (s) in the ratio 0.71 : 6.0 : 6.1, required 1:6:6.

2-Chloro-1,2-dimethylcyclohexyl Hydroperoxide (23):

A solution of 23 in ether was prepared from 9.6 g (0.086 mole) of 1,2-dimethylcyclohexene, 11 g (0.5 mole) of 98% hydrogen peroxide and 8.4 g (0.086 mole) of 18 and 50 ml of ether using the procedure described above for the preparation of 19. An aliquot of the dried solution, after removal of hydrogen peroxide and acetamide, was analysed by g.l.c. (FFAP column, 125°) using chlorobenzene as an internal standard. It was found that 43% of the original 1,2-dimethylcyclohexene had not reacted. By difference from unreacted starting material, compound 23 was formed in 57% yield. The relative thermal response factors are: chlorobenzene 100, 1,2-dimethylcyclohexene 84. The n.m.r. spectrum (CCl_4) of crude 23 showed peaks at τ 8.42 (s) and τ 8.67 on top of a broad absorption at τ 7.6-8.8. Several attempts to isolate 23 resulted in explosions.

2-Bromo-1,2-dimethylcyclohexyl Hydroperoxide (24):

The procedure described for the preparation of 21 was used to prepare a solution of 24 from 2.0 g (0.0182 mole) 1,2-dimethylcyclohexene, 2 ml (0.082 mole) of 98% hydrogen peroxide and 2.6 g (0.009 mole) of 20 in 20 ml of ether. Iodometric titration of an aliquot of the solution showed that 86% of hydroperoxide had formed.

α-Phenylethyl Chloride (27):

This was prepared according to the method of Goerner and Hines (87). Styrene (156 g, 1.5 mole) was stirred in a 250 ml three-necked flask fitted with a mercury-sealed stirrer, a gas inlet and an outlet tube. The flask was cooled in an ice salt bath and hydrochloric acid introduced until the solution was saturated (8 hours). The mixture was fractionally distilled to give 175 g (83%)

of 27, b.p. 86° (25 mm), n_D^{26} = 1.5274. Reported (87) b.p. 73° (11 mm). The n.m.r. spectrum (neat) showed peaks at τ 2.7-3.0 (m), τ 5.11 (q) and τ 8.39 (d, J= 7 c.p.s.) in the ratio 5.18 : 1.0 : 2.93, required 5 : 1 :3.

cis- and trans-Dimethylstilbene (25 and 26):

These were prepared following a procedure of Hauser and coworkers (88). To a stirred suspension of 19.5 g (0.52 mole) of sodium amide in 500 ml of liquid ammonia was added, during 10 minutes, a solution of 70 g (0.5 mole) of 27 in 300 ml of dry ether. The mixture was stirred for 1.5 hr, while the ammonia was allowed to evaporate. Ether and 2 M hydrochloric acid were added and the layers separated. The ethereal layer was washed with hydrochloric acid, followed by water and dried over calcium chloride. The ethereal solution was freed of solvent and fractional crystallization from methanol of the residue gave 8 g (15%) of 26, m.p. 103-105°, and 21 g (40%) of 25, m.p. 62-64°. Reported (102) m.p. of 26 is 107° and m.p. of 25 is 66°. The n.m.r. spectrum (CCl_4) of 26 showed peaks at τ 2.82 (s) and τ 8.15 (s) in the ratio 5.86 : 3.0, required 5:3. The cis compound 25 is free of 26 by n.m.r., the trans compound 26 contains 7% of 25 by n.m.r..

threo-3-Bromo-2,3-diphenyl-2-butyl Hydroperoxide (28):

A solution of 28 in ether was prepared from 3.0 g (0.014 mole) of 25, 2.5 g (0.073 mole) of 98% hydrogen peroxide and 2.0 g (0.007 mole) of 20 and 50 ml ether using the procedure described above for the preparation of 19. Iodometric titration of an aliquot of the solution showed 70% of hydroperoxide had formed. Compound 28 could be crystallized from pentane, m.p. 63-65°, but decomposed on standing. The n.m.r. spectrum ($CDCl_3$) showed peaks at τ 2.6-2.9 (m), τ 7.78 (s) and τ 8.06 (s) in the ratio 11.7 : 3.0 : 2.88, required 11 : 3 : 3. Upon standing new peaks appeared in the n.m.r. spectrum at τ 2.2-2.4 (m) and τ 2.4-2.6 (m) and τ 7.40 (s).

3-Chloro-3-methyl-2-butanol (30) and 3-Chloro-2-methyl-2-butanol (29):

The procedure described for the preparation of 19 was used with 2 g (0.029 mole) 2-methyl-2-butene, 2 ml (0.09 mole) 98% hydrogen peroxide and 2.85 g (0.03 mole) of 18 in 30 ml ether. Iodometric titration of an aliquot showed 50% hydroperoxide present.

The dried ethereal solution was added to a stirred slurry of 0.76 g (0.02 mole) of lithium aluminium hydride in 25 ml ether. The mixture was heated under reflux for one hour and subsequently decomposed with a 15% potassium hydroxide solution. The organic layer was decanted and the precipitate slurried several times with ether. The combined organic solutions were dried and concentrated. Analysis by g.l.c. (hallcomid 180-L, 115°) showed 2 products in 4:1 ratio. Both products were collected from the effluent stream of the g.l.c.. The infrared spectrum (CCl_4) of the major product 29, showed absorption bands at 3580 and 3200-3500 cm^{-1}. The n.m.r. spectrum (CCl_4) of 29 showed peaks at τ 6.05 (q, J = 7 c.p.s.), τ 7.85 (s), τ 8.48 (d, J = 7 c.p.s), and τ 8.72 (s) in the ratio 1 : 1 : 3.36 : 5.90, required 1 : 1 : 3 : 6. The infrared spectrum of the minor product, 30, showed absorption bands at 3575 and 3300-3500 cm^{-1}. The n.m.r. spectrum (CCl_4) showed peaks at τ6.31 (q, J= 7 c.p.s.), τ 7.09 (s), τ8.46 (d, J= 2 c.p.s.), τ8.79 (d, J= 7 c.p.s.) in the ratio 1.08 : 1.0 : 5.92 : 3.0, required 1 : 1 : 6 : 3.

3-Chloro-2-methyl-2-butanol (29):

This was prepared according to the method of Detoeuf (86). A solution of 17.5 g (0.25 mole) of 2-methyl-2-butene, 23.5 g (0.25 mole) N-chloroacetamide, 5 ml of acetic acid in 100 ml water was shaken for 24 hours. The reaction mixture was extracted with ether. The ethereal solution was dried and concentrated. Distillation of the residue gave 1.5 g (11%) of 29, b.p. 135-138°, n_D^{26} = 1.4345. Reported (86) b.p. 141°. The infrared and n.m.r. spectra were identical to those of the collected major product, 29, above.

3-Chloro-3-methyl-2-butanone (31):

A method described by Buchman and Richardson (90) was adapted for the preparation of 31. A solution of 43 g (0.5 mole) methyl iso-propyl ketone in 50 ml dry benzene was stirred in a three-necked flask equipped with a mechanical stirrer, condenser and dropping funnel. Sulfuryl chloride (63 g, 0.5 mole) was added in 20 minutes under exclusion of moisture. The temperature was kept at 20° by cooling with a dry ice/acetone bath. The reaction mixture was left overnight and then fractionated to give 28 g (46%) of 31, b.p. 52-55° (32-34 mm), n_D^{27} = 1.4193. Reported (103) b.p. 145-146°, η_D^{20} = 1.4390. The n.m.r. spectrum showed peaks at τ7.68 (s) and τ8.36 (s) in the ratio 1 : 1.93, required 1 : 2.

3-Chloro-3-methyl-2-butanol (30):

A solution of 10.2 g (0.084 mole) of 31 in 15 ml ether was added to a stirred slurry of 1.12 g (0.03 mole) of lithium aluminium hydride in 25 ml ether. The reaction mixture was refluxed for 30 minutes and subsequently decomposed with 15% potassium hydroxide. The organic layer was decanted and the precipitate slurried several times with ether. The dried organic material was freed of solvent and the residue distilled to give 6 g (58%) of 30, b.p. 77-77.5° (34 mm), η_D^{27} = 1.4385. The infrared and n.m.r. spectra of 30 were identical to those of the collected minor product, 30, above.

2,3-Dimethyl-3-hydroperoxy-butene (2) from 19:

Sixty per cent of the solution of 19 prepared above was added to a solution of 4.0 g sodium hydroxide in 100 ml methanol at 0° and the resulting mixture was stirred for 1 hour. The reaction mixture was then poured into ice-water. This mixture was extracted twice with ether. The combined ether layers were washed several times with water and dried. After careful distillation of ether through a 4 ft Podbielniak column, the residual oil was distilled to yield 3.6 g (48%) of 2, b.p. 56-57° (16 mm), η_D^{25} = 1.4390. Reported (10) b.p. 55° (12 mm), η_D^{20} = 1.4428. The infrared spectrum (CCl_4) showed absorption bands at 3560 and 3300-3500 cm^{-1}.

The n.m.r. spectrum (CCl_4) showed peaks at τ 1.6-1.8 (b), τ 5.1-5.2 (m), τ 8.22 (m) and τ 8.70 (s) in the ratio 1.05 : 1.88 : 3.0 : 5.8, required 1 : 2 : 3 : 6. This material was identical (n.m.r. and infrared spectra) with a sample of 2 prepared by the photosensitized oxidation of tetramethylethylene.

Another solution of 19 prepared as described above from 5.0 g of 1 was shown by iodometric titration to contain a 60% yield of chlorohydroperoxide 19. Four-fifths of this solution was reacted with methanolic base and the product isolated as described above. There was obtained 2.3 g (42% overall, 70% based on 19 formed) of 2, η_D^{25} = 1.4385, identical (infrared and n.m.r. spectra) with authentic 2. G.l.c. analysis of the reaction mixtures containing 2 before distillation indicated only traces of material with the retention time of acetone. No evidence for the formation of any chlorohydrin or oxide was obtained.

2,3-Epoxy-2,3-dimethylbutane (32):

This was prepared according to the method of Eliel (94). An ethereal solution (345 ml) containing 24.1 g (0.14 mole) of m-chloroperoxybenzoic acid was cooled to 0° and 11.0 g (0.13 mole) of 1 was added at such a rate that the temperature did not rise over 30° (30 minutes). The reaction mixture was allowed to stand at 0° for 12 hours. The ethereal solution was washed with 10 per cent sodium hydroxide solution, and with portions of a dilute ferrous sulfate solution until no further color change was observed in the aqueous layer. The ethereal solution was dried and fractionated to yield 4.5 g (34%) of 32, b.p. 88-89.5°, n_D^{25} = 1.3934. Reported (94) b.p. 90-90.5°, n_D^{20} = 1.4010. The n.m.r. spectrum (CCl_4) showed a singlet at τ 8.78.

2,3-Dimethyl-3-hydroperoxy-1-butene from 21:

Four grams of 21 gave 1.8 g (77%) of the allylic hydroperoxide 2, n_D^{25} = 1.4385, when treated with base in the manner described for 19. The product was identical (infrared and n.m.r. spectra) with authentic 2.

2-(Dimethylaminomethyl)-cyclohexanone Hydrochloride (36):

This was prepared according to the procedure of Mannich (95). A mixture of 9 g 37% formaldehyde solution, 9 g dimethylamine hydrochloride, and 48 g cyclohexanone was heated on the steambath. Water (50 ml) was added to the cooled solution and the aqueous layer extracted several times with ether. The aqueous layer was concentrated using a rotary evaporator. The crystals which formed were recrystallized from acetone-alcohol to give 10 g (54%) of salt 36, m.p. 150-151°. Reported (95) m.p. 152°.

2-Methylene-1-methylcyclohexanol (34):

This was prepared from 36 according to the method of Mannich (94). The salt 36 (5 g) was pyrolyzed at 185° under vacuum (0.15 mm). The pyrolysate, containing 2-methylenecyclohexanone, was caught in a trap at -70°, redistilled and stored at -70° until a solution of methylmagnesium iodide made from 0.5 g magnesium and 3 g methyl iodide in 50 ml ether was added. The reaction mixture was allowed to warm to room temperature and then hydrolyzed with water. The ether layer was dried and the solvent removed. The small amount of residual oil had two high boiling components in a 60 : 40 ratio which were isolated by trapping from the effluent of the g.c. (FFAP, 132°). The infrared spectrum (CCl_4) showed absorption bands at 3660 (s) and 3200-3550 (b) cm^{-1}, 1640 (s), 885 and 895 cm^{-1}. The n.m.r. spectrum (CCl_4) showed peaks at τ5.15 (m), τ5.39 (m), τ7.6-8.6 (b) and τ 8.72 (s) in the ratio 0.9 : 0.85 : 9.1 : 3.1, required 1 : 1 : 9 : 3. The second component was not identified.

2-Methylcyclohexenone (38):

The procedure of Warnhoff and Johnson (97) was used for the preparation of this compound. To a solution of 61 g (0.5 mole) of 2-methylcyclohexanone and 250 ml of dry carbon tetrachloride in a 1 litre three-necked flask equipped with a glass stirrer, dropping funnel and tube connected to a gas absorption trap, was added during 1 hour with stirring 75 g (0.55 mole) of sulfuryl chloride in 75 ml of dry carbon tetrachloride. The slightly exothermic reaction was cooled by keeping the flask in a water bath. After the addition was complete, stirring was continued for 2 hours. The yellow reaction mixture was washed with three 75 ml portions of water, two 50 ml portions of saturated sodium bicarbonate solution, one 50 ml portion of saturated sodium chloride and dried with magnesium sulfate. The dried solution was freed of solvent and the residue transferred to a 250 ml three-necked flask equipped with a strong Hershberg stirrer and two efficient condensers. 2,4,6-Collidine (62 g, 0.55 mole) was added and the contents of the flask heated by means of an oil-bath to 150°. A sudden exothermic reaction ensued, and the mixture set to a viscous suspension of collidine hydrochloride. The reaction mixture was cooled and 125 ml of benzene was added through a condenser. The precipitate was filtered off and washed with 75 ml of benzene. The filtrate was washed twice with excess 10% hydrochloric acid in saturated sodium chloride solution, once with saturated sodium bicarbonate and dried. The dried solution was freed of solvent by distillation through a 15 cm Vigreux column. Distillation of the residue gave 16 g (29%) of 38, b.p. 95-100° (75 mm), η_D^{25} = 1.4820. Reported (97) b.p. 98-101° (78 mm), η_D^{25} = 1.4836. The n.m.r. spectrum (CCl_4) showed peaks at τ 3.3-3.6 (m), τ 7.5-8.4 (b) and τ 8.31 (d, J= 1.5 c.p.s.) in the ratio 0.89 : 6.0 : 3.34, required 1 : 6 : 3 .

1,2-Dimethyl-2-cyclohexene-1-ol (35):

2-Methylcyclohexenone (1 g) in 5 ml ether was added to 4 ml of 0.24 M methyllithium at -40° under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and was then hydrolyzed with 10% potassium hydroxide solution. The organic layer was dried, the ether was removed and the residual oil was distilled to give 0.4 g material b.p. 82-85° (25 mm). Reported (104) for 35 b.p. 132° (180 mm). G.l.c. analysis (FFAP, 120°) showed two components in a *ca*. 60 : 40 ratio in addition to a small amount of starting material. The two products were collected from the effluent of the g.c.. The major product, η_D^{26} = 1.4764 (reported (98) for <u>35</u> η_D^{20} = 1.4844) showed absorptions in the infrared spectrum (CCl_4) at 3600, and 3300-3500 cm^{-1}, and at 3160-3120 cm^{-1}. The n.m.r. spectrum (CCl_4) showed peaks at τ4.68 (m), τ7.9-8.6 and τ8.80 (s), in the ratio 0.89:10:3.1, required 1:10:3. The minor product, η_D^{25} = 1.4616, showed hydroxyl absorptions in the infrared spectrum, and had no absorption in the n.m.r. spectrum below τ6. It was not investigated further.

<u>1-Methyl-2-methylenecyclohexanol (34) from 2-Bromo-1,2-dimethylcyclohexyl Hydroperoxide (24):</u>

The ethereal solution of <u>24</u> prepared earlier was added to a solution of 2 g sodium hydroxide in 100 ml methanol at 0°. After stirring for 90 minutes at 0°, the reaction mixture was poured into 200 ml ice-water. The resulting mixture was extracted twice with 100 ml ether and the combined organic layers were washed three times with 100 ml water. The dried solution was then added slowly to a stirred slurry of 1.5 g lithium aluminium hydride in 35 ml ether. The mixture was heated under reflux for 1 hour and then a solution of 15% potassium hydroxide was added dropwise until the organic layer became clear. The organic layer was decanted and the precipitate slurried several times with ether and the combined organic solutions were dried. An aliquot of the solution was analyzed by g.l.c. (FFAP, 120°). There were present 12% 1,2-dimethylcyclohexene, and 76% of product <u>34</u>, based on the hydroperoxide yield. Also present was <u>ca</u>. 2% of a material with the same retention time as the isomeric alcohol, 1,2-dimethyl-2-cyclohexenol (35). Ether was distilled from the solution and the residual oil was distilled to give 0.85 g (42% based on the hydroperoxide content of the starting solution) of 34, b.p. 58-61° (15 mm), n_D^{25} = 1.4799. Reported (95) b.p. 58° (10 mm). The infrared spectrum (neat) showed absorption bands at 3660, 3550-3200 cm^{-1} and at 1640, 895 and 995 cm^{-1}. The n.m.r. spectrum (CCl_4) shows peaks at τ5.15 (m), τ5.39 (m), τ7.6-8.6 (b) and τ8.72 (s), in the ratio 1.0:0.92:9.2:2.84, required 1:1:9:3. This material was identical (g.l.c. retention time, n.m.r. and infrared spectra) with authentic 34. There was no absorption at τ4.68 in the n.m.r. spectrum where the olefinic proton of the isomeric alcohol 35 absorbs.

1-Methyl-2-methylenecyclohexanol (34) from 2-Chloro-1,2-dimethylcyclohexyl Hydroperoxide (23):

The ethereal solution of 23 prepared above was added to 4 g sodium hydroxide in 100 ml methanol at 0° and the resulting mixture was stirred at 0° for 1 hour. To this mixture was added 2.5 g sodium borohydride dissolved in a little methanol. After 1 hour at room temperature the reaction mixture was poured into ice-water. The resulting mixture was extracted twice with ether. The combined ether extracts were washed several times with water and dried. The ether was distilled and the residual oil absorbed on a 2.5 x 30 cm column of basic alumina. The column was washed with 200 ml pentane to remove the unreacted 1,2-dimethylcyclohexene and then the product was eluted with 200 ml ether. The ether was removed and the residual oil distilled to give 1.1 g (19% based on reacted olefin) of 34, $n_D^{25} = 1.4813$. This material was identical (n.m.r. and infrared spectra) with authentic 34. The n.m.r. spectrum showed no absorption at τ 4.68 where the olefinic proton of the isomeric alcohol 35 absorbs. G.l.c. analysis indicated the presence of ca. 1% of a material with the same retention time as the isomeric alcohol 35.

2-Methyl-2-methylenecyclohexanol (34) from Sensitized Oxidation of 1,2-Dimethylcyclohexene:

A solution of 1.1 g 1,2-dimethylcyclohexene and 30 mg of methylene blue in 20 ml methanol was placed in the photolysis cell. The reaction was carried out as described earlier in the preparation of 2. Oxygen uptake became very slow after 1 hour when 250 ml (STP) had been consumed (theoretical 220 ml). This solution was poured into 100 ml ice-water and the resulting mixture extracted twice with 50 ml ether. The combined ether extracts were washed with water and with saturated sodium chloride. The dried solution was added slowly to a slurry of 0.38 g of lithium aluminium hydride in 25 ml ether. The mixture was heated under reflux for 30 minutes and worked up as described in the preparation of 34 from 24. The solution was freed from solvent and the residue distilled to give 0.7 g (59%) of 34, b.p. 60-62° (17 mm), $n_D^{25} = 1.4782$. The product was identical (infrared and n.m.r. spectra) with authentic 34. The n.m.r. spectrum showed no absorption at τ4.68 where the olefinic proton of the isomeric alcohol 35 absorbs. G.l.c. analysis before distillation indicated the presence of *ca*. 3% of a material with the same retention time as 35.

2,3-Diphenyl-3-hydroxybutene (39):

A solution of 3 g (0.014 mole) of *cis*-1,2-dimethylstilbene, and 30 mg methylene blue in 30 ml methanol was placed in the photolysis cell. The reaction was carried out as described earlier in the preparation of 2. Oxygen uptake became very slow after 2 hours when 350 ml (STP) had been consumed (theoretical 310 ml). The solution was poured into 100 ml ice-water and the resulting mixture extracted twice with 50 ml ether. The combined ether extracts were washed with water and with saturated sodium chloride. The dried solution was added slowly to a slurry of 0.5 g of lithium aluminium hydride in 25 ml ether. The mixture was heated under reflux for 30 minutes and worked up as described in the preparation of 34 from 24. The solution was freed of solvent and the residue distilled to give 1.5 g (48%) of 39, b.p. 101-104° (0.1 mm), n_D^{28} = 1.5809. The infrared spectrum ($CHCl_3$) showed absorption bands at 3560, 3300-3500, 3060, 1640 and 905 cm^{-1}. The n.m.r. spectrum (CCl_4) shows peaks at τ2.5-3.2 (m), τ4.55 (d, J=1.5 c.p.s.), τ8.05 (b) and τ8.40 (s), in the ratio 10.4 : 0.94 : 1.0 : 0.90 : 2.80, required 10 : 1 : 1 : 1 : 3. Analysis calculated for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.63; H, 6.00.

2,3-Diphenyl-3-hydroxybutene (39) from *threo*-3-Bromo-2,3-diphenyl-2-butyl Hydroperoxide (28):

An ethereal solution of 28 prepared above was added to a solution of 2 g sodium hydroxide in 75 ml of methanol. The reaction was carried out as described in the preparation of 34 from 24. The resulting dried ethereal solution was reduced with 0.5 g of lithium aluminium hydride and worked up in the usual fashion. Distillation resulted in 1.15 g (60% based on 28 formed) of 39, b.p. 98-100° (0.08 mm), $n_D^{27} = 1.5825$. This product was identical (n.m.r. and infrared spectra) to the one obtained from the sensitized oxidation.

Dye-sensitized Oxygenation of 2-Methyl-2-butene:

A solution of 1 g 2-methyl-2-butene and 30 mg methylene blue in 10 ml ethanol was placed in the photolysis cell. The pump was turned on and the reaction carried out in the usual fashion until 160 ml O_2 had been consumed. The reaction was worked up as described in the preparation of 2 from 1. The dried ethereal solution was reduced with 0.35 g lithium aluminium hydride in the usual manner. Analysis by g.l.c. (hallcomid 180-L, 115°) of the reduced material showed two products present in a 1:1 ratio. One of the products was collected from the effluent of the g.l.c.. The n.m.r. spectrum (CCl_4) showed peaks at τ5.12 (m), τ5.31 (m), τ5.88 (q, J= 7 c.p.s.), τ6.49 (s), τ8.30 (m) and τ8.80 (d, J= 7 c.p.s.), in the ratio 1.0 : 0.91 : 1.0 : 2.91 : 3.18, required 1 : 1 : 1 : 3 : 3. This is in agreement with 3-hydroxy-2-methyl-1-butene as the structure.

Addition-Elimination Reaction on 2-Methyl-2-butene:

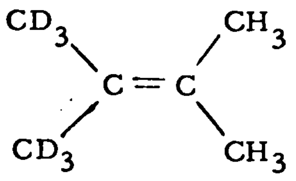
An ethereal solution of chlorohydroperoxides was prepared as described in the preparation of 19, from 2.0 g (0.028 mole) 2-methyl-2-butene, 2.85 g (0.028 mole) N-chloroacetamide and 3.2 g (0.095 mole) 98% sodium hydroxide in 50 ml methanol and stirred at 0^o for 2 hours. A solution of 1.5 g sodium borohydride in water was added and the reaction stirred for 1 hour. The mixture was extracted three times with 50 ml portions of ether. The combined ether solutions were washed with water and dried. The ethereal solution was concentrated and analysed by g.l.c. (hallcomid 180-L). No products with the same retention time, as the products from the dye-sensitized oxidation of 2-methyl-2-butene, were observed.

CHAPTER II

THE MECHANISM OF THE REACTION OF 2-BROMO-2,3-DIMETHYL-3-BUTYL HYDROPEROXIDE WITH BASE.

It was shown in Chapter I that 2-bromo-2,3-dimethyl-3-butyl hydroperoxide (21) could be prepared in high yield from tetramethylethylene (1), hydrogen peroxide and 1,3-dibromo-5,5-dimethylhydatoin. The reaction between 21 and base resulted in a high yield of 2,3-dimethyl-3-hydroperoxy-1-butene (2). Two different mechanisms could account for this observation. The first postulate is the direct elimination of hydrogen bromide and the second possiblitiy is the formation of a perepoxide which opens up to also yield the allylic hydroperoxide.

To aid the investigation of the two possible mechanisms mentioned above, two deuterated 2,3-dimethyl-2-butenes (tetramethylethylenes), 3-methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene (40) and 2,3-*bis*-trideuteriomethyl-2-butene (41), were prepared (olefin 41 can be either *cis*, *trans* or a mixture of these).



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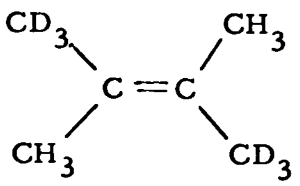


41

Two possible β-bromohydroperoxides can be formed from 40. The reaction between these β-bromohydroperoxides and base results in a mixture of allylic hydroperoxides. A comparison of the ratio of β-bromohydroperoxides and the ratio of allylic hydroperoxides was made and explained in terms of one of the mechanisms mentioned above. An identical ratio before and after the reaction with base would be in favor of straight elimination; different ratios might result if the reaction went through a cyclic peroxide.

The ratio of allylic hydroperoxides formed in the reaction between the β-bromohydroperoxide of 41 and base is expected to be similar to the ratio of allylic hydroperoxides from 40 if a perepoxide is involved. The results from the reactions on 40 and 41 will be presented and discussed in this chapter.

The course of the reaction between 2-bromo-2,3-dimethyl-3-butyl hydroperoxide and base at low temperatures was followed by n.m.r. spectroscopy and will be discussed.

RESULTS

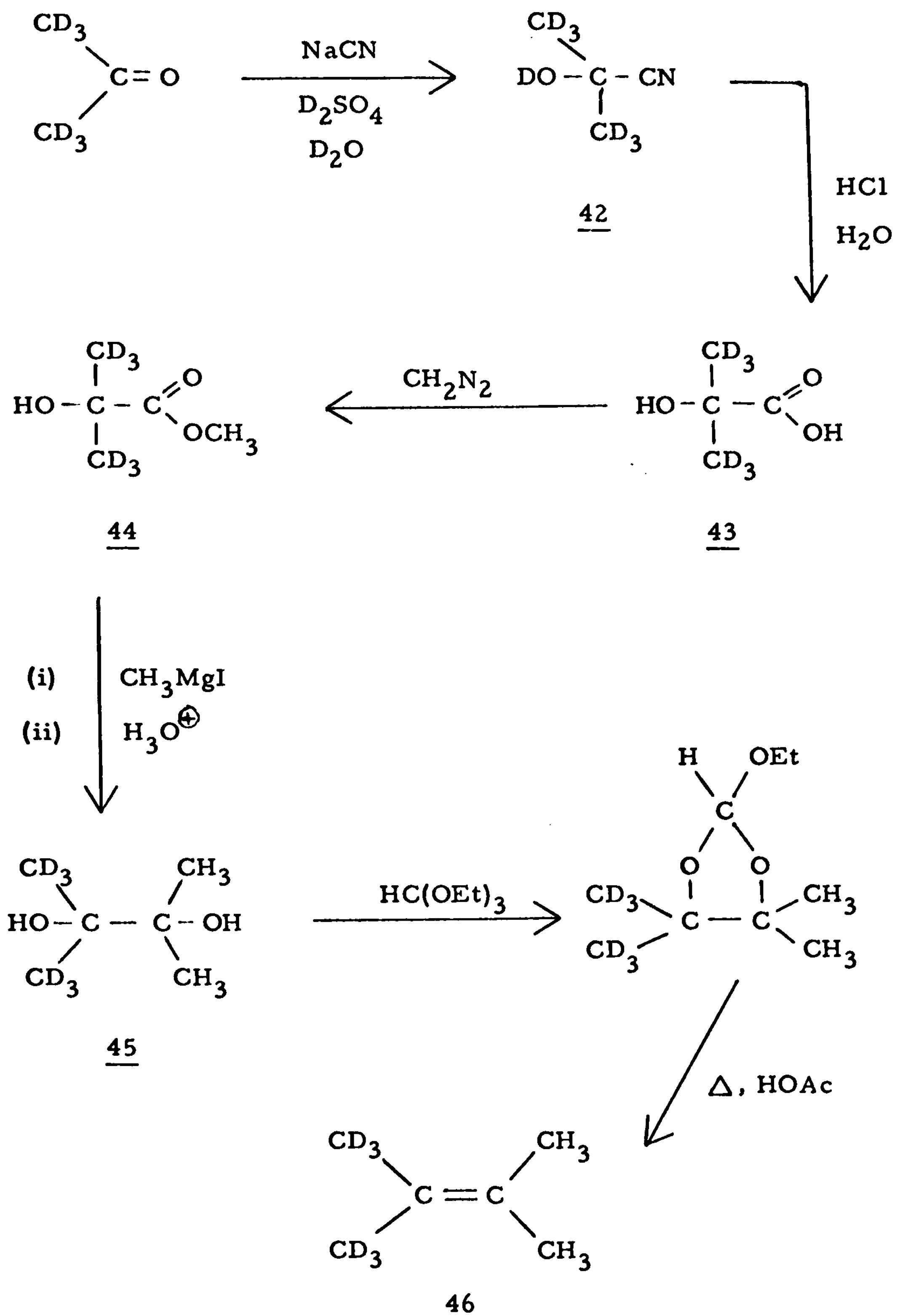
THE SYNTHESIS OF THE DEUTERATED TETRAMETHYLETHYLENES.

3-Methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene (40):

A reaction sequence for the preparation of 40 with excellent isotopic purity was developed. Several attempts to prepare the light tetramethylethylene from derivatives of 2,3-dimethyl-2-butanol under basic conditions were unsuccessful. Reactions of the mesylate or tosylate with base resulted in some tetramethylethylene but mainly in 2,3-dimethyl-1-butene. No acid catalysed dehydrations of 2,3-dimethyl-2-butanol could be carried out because of the danger of isotopic exchange in the case of the heavy alcohol. The sequence of reactions employed successfully for the preparation of 40 is outlined in Scheme 2. Several runs following this scheme were carried out using light materials in order to optimize the yields in the different steps in this sequence.

The reaction between acetone-$\underline{d}_6$, sodium cyanide and deuterated sulfuric acid resulted in a 93% yield of perdeuteroacetone cyanohydrin (42) (104). The infrared spectrum ($CHCl_3$) showed absorption bands at 2400-2700 cm^{-1} for the O-D stretching vibrations and at 2250 cm^{-1} for the -C≡N and C-D stretching vibrations. The n.m.r. spectrum (neat) did not show any absorption, which agrees with compound 42. The n.m.r. spectrum (CCl_4) of the light acetone cyanohydrin showed absorption at τ8.42 (singlet) for the protons

Scheme 2



NaCN
D_2SO_4
D_2O
42
HCl
H_2O
43
CH_2N_2
44
(i) CH_3MgI
(ii) $H_3O^{\oplus}$
45
$HC(OEt)_3$
Δ, HOAc
46

of the *gem*-dimethyl group and at τ 7.81 (singlet) for the hydroxyl proton. Acid hydrolysis of compound 42 produced 3,3,3-trideuterio-2-hydroxy-2-trideuteriomethyl-propanoic acid (43) (105). The acid 43 was characterized by n.m.r. and infrared spectroscopy. The infrared spectrum ($CHCl_3$) showed absorption bands at 2500-3600 cm^{-1} for the monomeric and dimeric O-H stretching vibrations, at 2230 cm^{-1} for the C-D stretching vibration and at 1730 cm^{-1} for the C=O stretching vibration. The n.m.r. spectrum ($CDCl_3$) showed absorption at τ 3.24 (singlet) for the hydroxyl and carboxyl protons. The absence of a singlet at τ 8.50 which was found in the n.m.r. spectrum of the corresponding light acid indicated that 43 contained two fully deuterated methyl groups. The acid 43 was esterified with diazomethane to give methyl 3,3,3-trideuterio-2-hydroxy-2-trideuteriomethyl propionate (44) in 74% yield calculated on starting perdeuteroacetone cyanohydrin. The infrared spectrum ($CHCl_3$) of 44 showed absorption at 3250-3600 cm^{-1} for the free and bonded O-H stretching vibrations and at 2230 and 2100 for the C-D symmetric and antisymmetric stretching vibrations. The n.m.r. spectrum (CCl_4) showed absorption at τ 6.31 (singlet) for the protons of the ester methyl group, and at τ 6.67 (singlet) for the hydroxyl proton. The absence of a singlet at τ 8.67, which is found in the n.m.r. spectrum of the corresponding light ester, indicated that 45 was fully deuterated in the *gem*-dimethyl groups. The ester 44 was allowed to react with a four-fold excess of methylmagnesium iodide to give a 88% yield of 3-methyl-2-trideuteriomethyl-1,1,1-trideuterio-2,3-butanediol (45). The n.m.r. spectrum ($CHCl_3$) of 45 showed absorption at τ 7.23 (singlet) for the hydroxyl protons and at τ 8.82 (singlet) for the protons of the gem-dimethyl group.

All the compounds discussed so far are very water-soluble and care has to be taken in the work-up procedures. It was found that optimum yields were obtained only by continuous ether extraction for two days of all the aqueous reaction mixtures. The deuterated pinacol 45 has to be very dry for the next reaction to proceed in good yield. This was effected by drying an ethereal solution of 45 over molecular sieves for one day, followed by running the solution through a column packed with fresh molecular sieves. If these precautions were not taken, no product was formed in the next step.

Compound 45 was allowed to react with ethyl orthoformate as outlined in the preparation of 1 (80). The resulting 1,3-dioxolane was not isolated but pyrolysed directly to give a 54% yield of 3-methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene (46). The infrared spectrum ($CHCl_3$) showed absorption bands at 2250, 2180, 2120 and 2060 cm^{-1} for the C-D symmetrical and antisymmetrical stretching vibrations. The n.m.r. spectrum (CCl_4) showed a singlet at τ 8.40. The mass spectral analysis carried out according to the method of Biemann (106) at 12 ev showed the parent peak at m/e 90 and indicated that the product contained at least 99.3 per cent of deuterium in the two trideuteriomethyl groups. The mass spectrum at 70 ev of 46 (see figure 1) is very similar in its

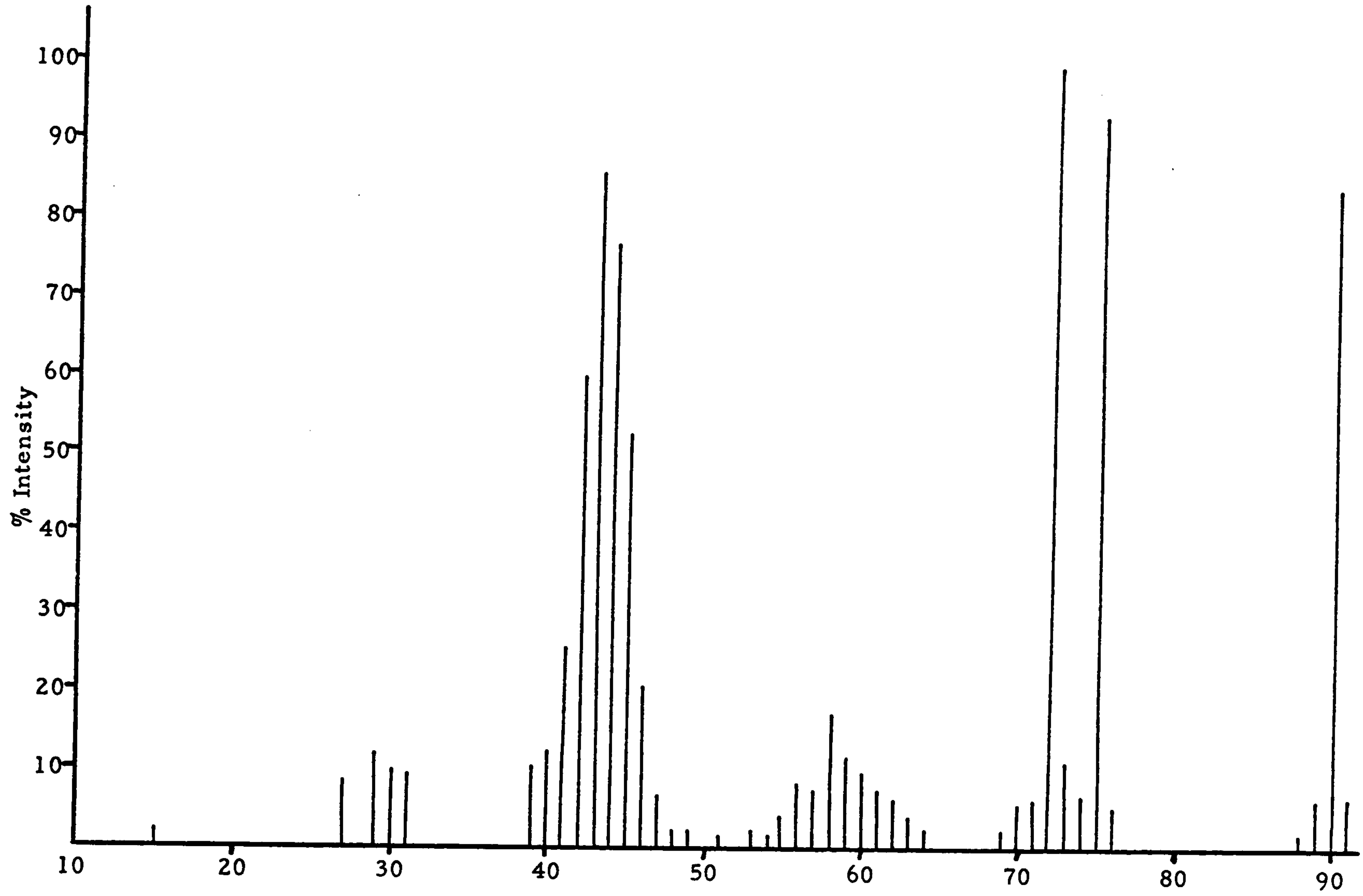


Figure 1. Mass spectrum (70 ev) of 3-methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene.

cracking pattern to the mass spectrum of light tetramethylethylene (see figure 2). The first time this reaction sequence for the preparation of <u>46</u> was carried out, no deuterated sulfuric acid was used in the first reaction step. An exchange took place between the sulfuric acid and the acetone-$\underline{d}_6$ before the latter reacted to form the acetone cyanohydrin. The low energy mass spectral analysis of the final product obtained in this run showed the product <u>46</u> to contain only 80.65 per cent of deuterium in the two trideuteriomethyl groups.

2,3-Bis-trideuteriomethyl-2-butene (41):

A simple two step sequence to form compound <u>41</u> would be the reaction between 2,3-butanedione-$\underline{d}_6$ and methylmagnesium iodide, followed by Cranck's (80) reaction with the resulting pinacol. It was found that the α-hydrogens of acetophenone could be exchanged effectively by running a pentane solution of acetophenone through a column packed with alumina treated with deuterium oxide (see Chapter III). Several attempts to exchange 2,3-butanedione in this manner were unsucessful. This compound is known to be very unstable and polymerized on basic as well as acidic alumina. The second method which was investigated was a sequence as outlined in Scheme 3. The first step, benzylation of acetoin, occurred on carbon instead of on the desired oxygen. This reaction is discussed in more detail in Chapter IV.

A simple, inexpensive way of preparing methyl iodide-$\underline{d}_3$ was known (107). This could be used in the Grignard reaction on

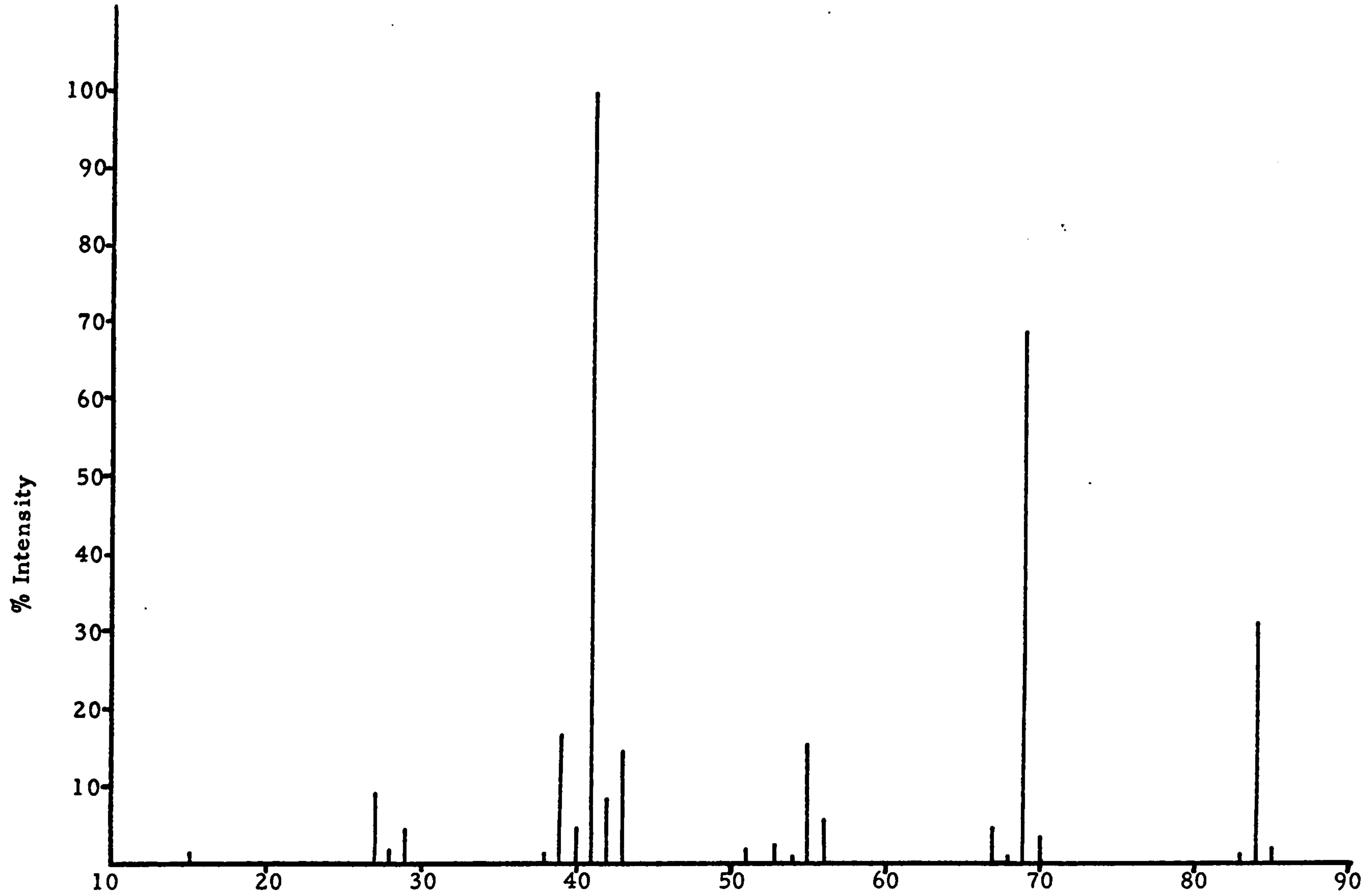
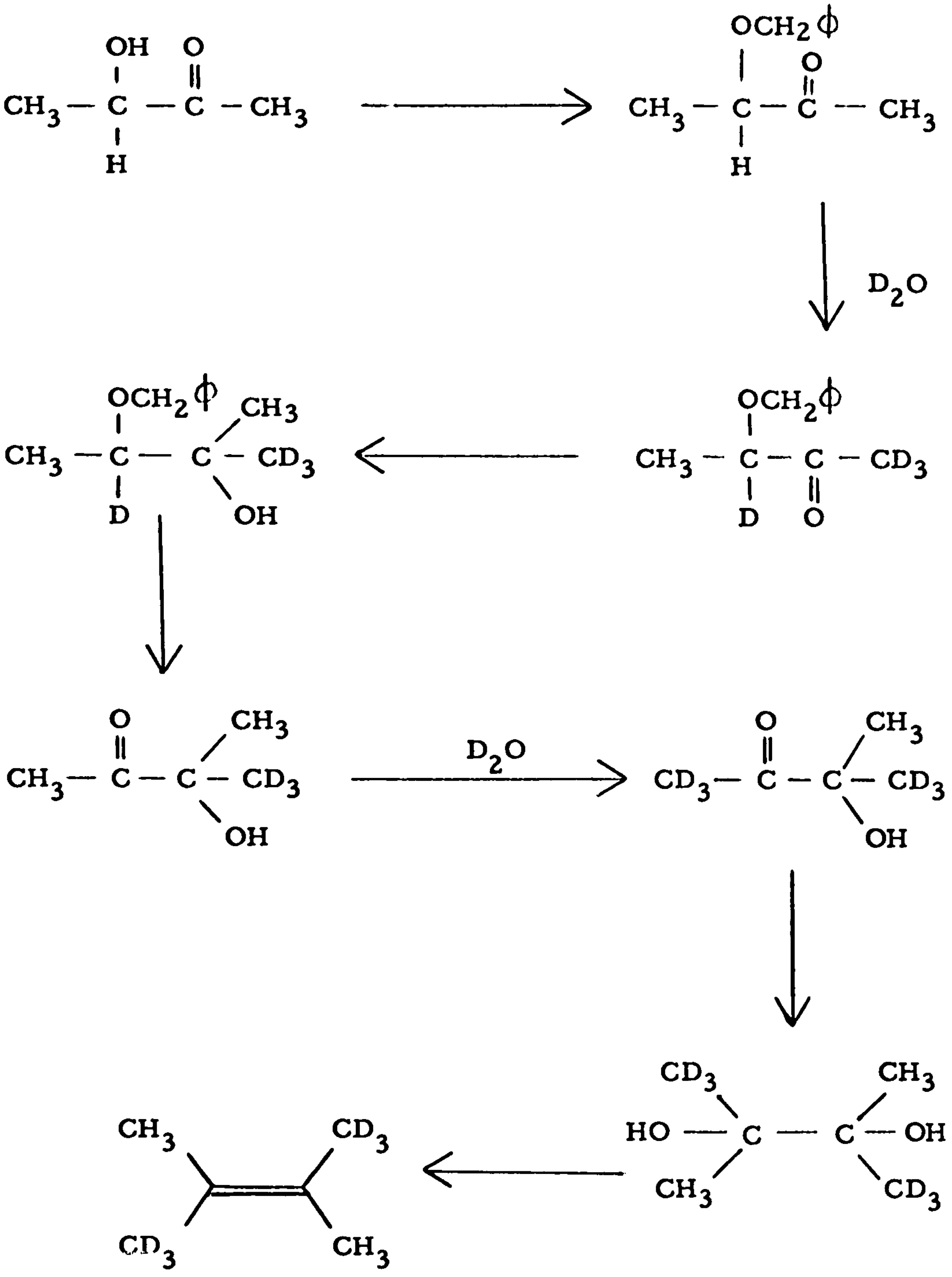


Figure 2. Mass spectrum (70 ev) of 2,3-dimethyl-2-butene.

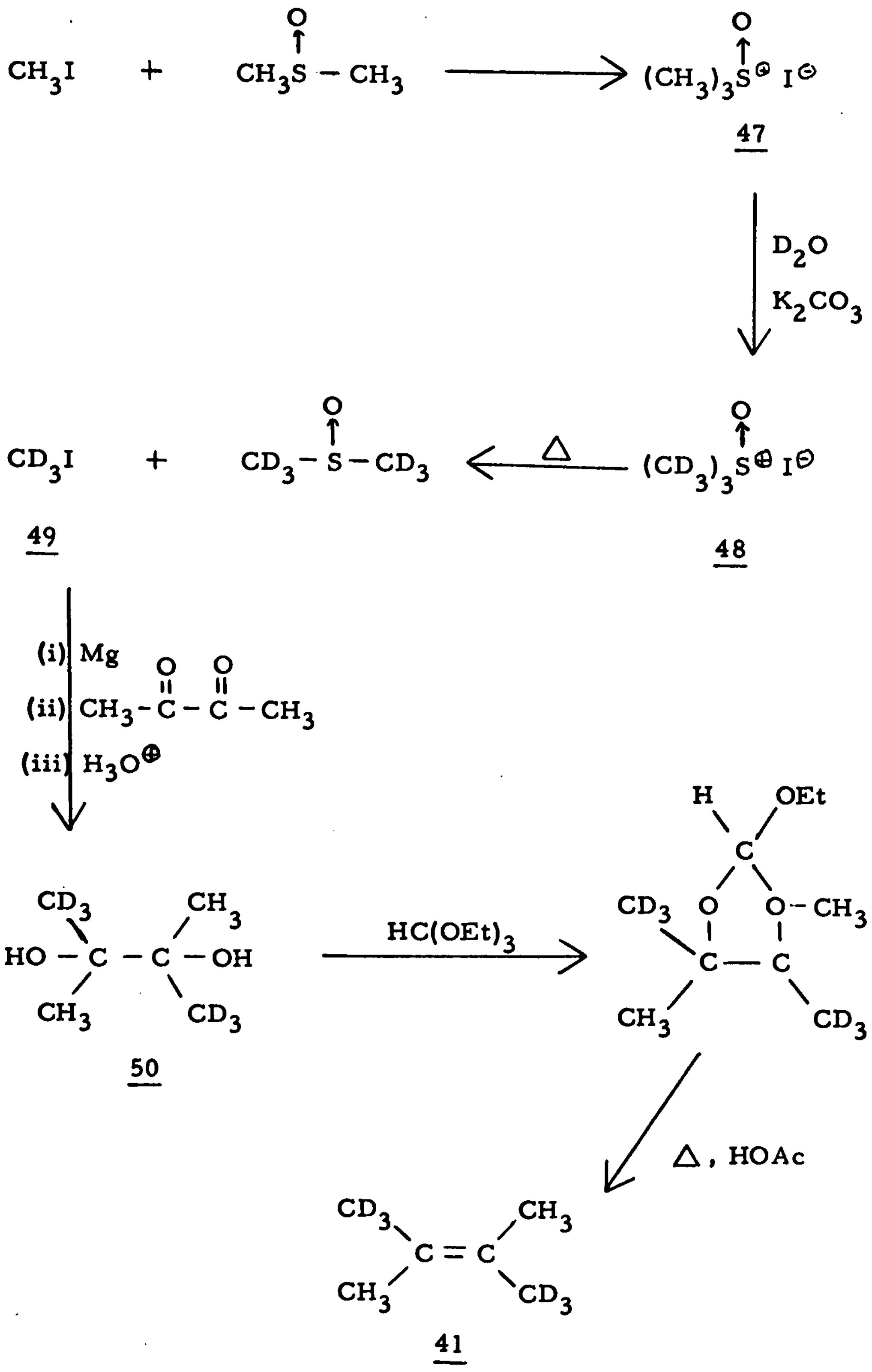
Scheme 3



2,3-butanedione to yield the hexadeuterated pinacol which can be readily converted to the corresponding tetramethylethylene 41. However, the yield in the reaction between methylmagnesium iodide or methyllithium and 2,3-butanedione, carried out in the usual fashion, was lower than 35%. The use of a high speed stirrer in this reaction increased the yield to 79% and it was decided to use this process to prepare compound 41, as outlined in Scheme 4. The reaction between methyl iodide and dimethyl sulphoxide results in a 35.5% of trimethyloxosulphonium iodide (47) (108). The salt 47 was exchanged four times with deuterium oxide in the presence of potassium carbonate to give trimethyloxosulphonium iodide-d_9 (48) in 75% yield. Pyrolysis of 48 under reduced pressure resulted in a 73.6% yield of methyl iodide-d_3 (49). The mass spectral analysis of 49 at 11 ev indicated that the product contained at least 96.4 percent deuterium. The reaction between 2,3-butanedione and methylmagnesium iodide-d_3, using the high speed stirrer technique, resulted in a 79% yield of 2,3-*bis*-trideuteriomethyl-2,3-butanediol (50). This material was isolated and dried according to the method described for the symmetrically deuterated analog 45. The n.m.r. spectrum ($CDCl_3$) showed absorption at τ 6.49 (singlet) for the hydroxylic protons and at τ 8.78 (singlet) for the protons of the methyl groups.

The reaction between the pinacol 50 and ethyl orthoformate was carried out in the usual fashion and the resulting dioxolane pyrolysed to give a 56% yield of the desired olefin 41. The infrared

Scheme 4

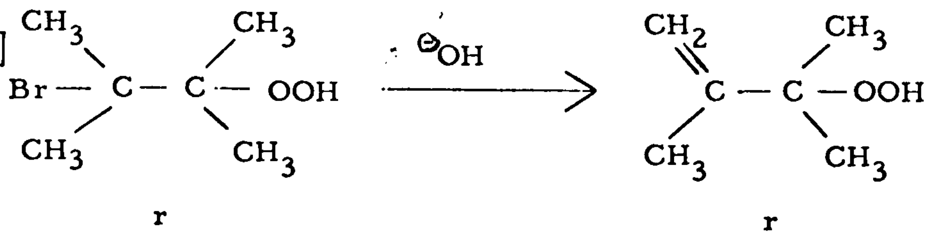

CH3I
CH3S – CH3
(CH3)3S⊕ I⊖
47
D2O
K2CO3
CD3I
CD3 – S – CD3
Δ
(CD3)3S⊕ I⊖
49
48
(i) Mg
(ii) CH3 – C – C – CH3
(iii) H3O⊕
HO – C – C – OH
50
HC(OEt)3
H
OEt
O – CH3
Δ, HOAc
C = C
41

spectrum (CCl_4) showed absorption bands at 2235, 2180, 2130 and 2060 cm^{-1} for the C-D symmetrical and antisymmetrical stretching vibrations. The n.m.r. spectrum (CCl_4) showed one singlet at τ 8.41. The mass spectral analysis of 41 at 9.5 ev indicated that the product contained 95.31 per cent deuterium in the two deuterated methyl groups. The mass spectrum at 70 ev (see figure 3) showed a similar cracking pattern to those of the analogs 40 and 1.

Isotope Effects in the Formation of 2-Bromo-2,3-dimethyl-3-butyl Hydroperoxide and in its Reaction with Base:

As was seen in Chapter I,the reaction between 2-bromo-2,3-dimethyl-3-butyl hydroperoxide and base gave an excellent yield of 2,3-dimethyl-3-hydroperoxy-1-butene (2). The material balance of this reaction was investigated before any work was started with the two deuterated tetramethylethylenes. A simple method for determination of the extent of elimination in this reaction consists of carrying out the elimination in a sealed n.m.r. tube in the presence of an internal standard. The reactions were carried out in methanol using benzene as an internal standard.

[19]



The ratio of the sum of the two signals of the starting material, 2r, over the signal of the internal standard benzene, s, is 2r/s.

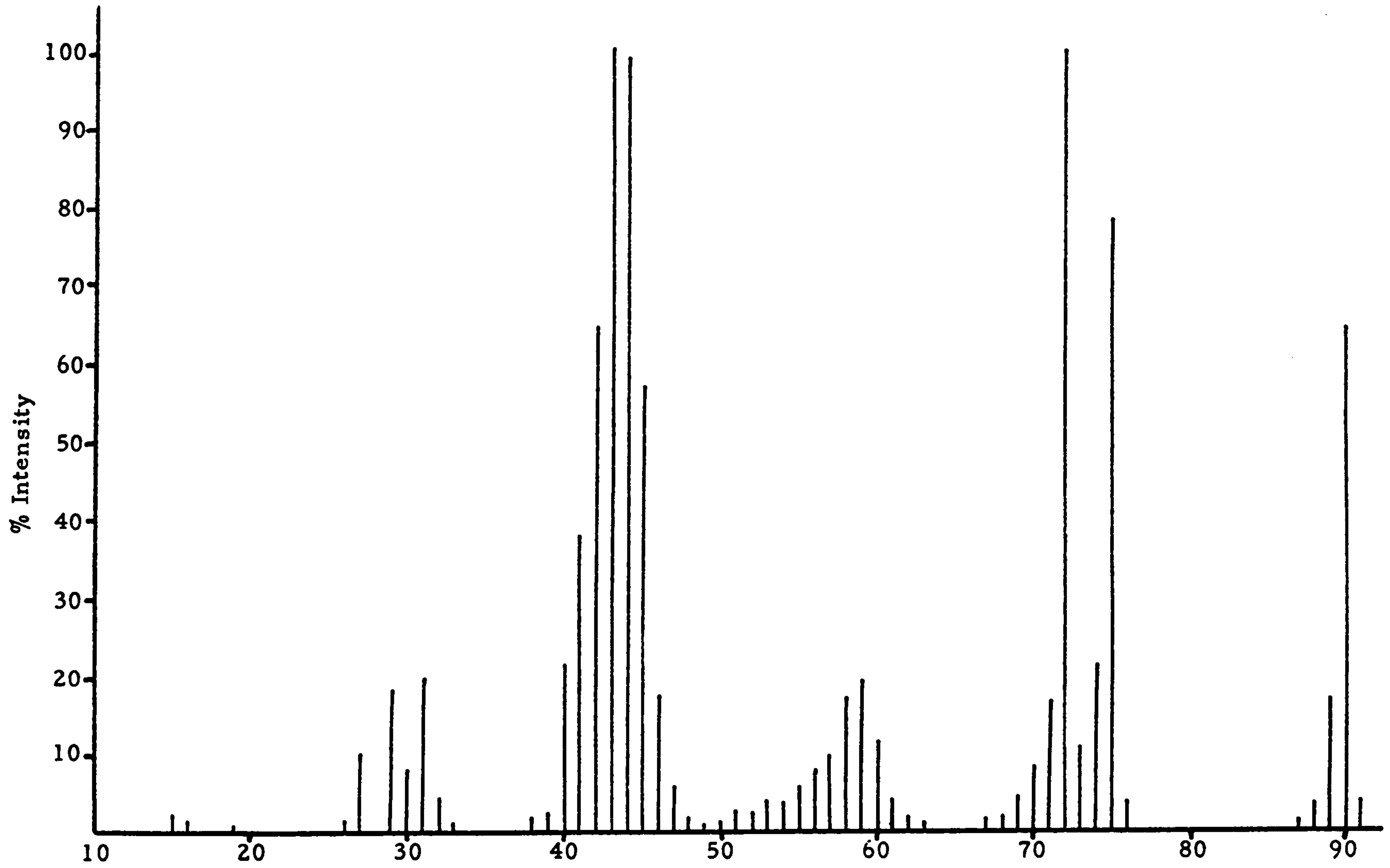


Figure 3. Mass spectrum (70 ev) of 2,3-bis-trideuteriomethyl-2-butene.

Similarly, the sum of the gem-dimethyl signal (r) and twice the allylic methyl signal r/2 of the product divided by the internal standard signal is 2r/s. If the reaction goes completely to the allylic hydroperoxide, the ratios 2r/s before and after the reaction should be equal. The results are shown in Table III.

TABLE III

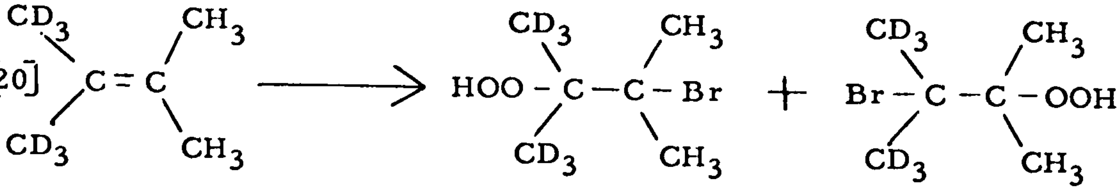
Material Balance in the Reaction of 21 [0.13 M] With Base [0.81 M].

Run	Start	Run 1	Run 2	Run 3
Temperature	25°	25°	2°	-19°
2r/s	1.45	1.44	1.51	1.45

The results from Table III show that a quantitative conversion to allylic hydroperoxide takes place when 21 is reacted with excess base.

The unsymmetrically deuterated tetramethylethylene 40 which contained 80.65% deuterium in the deuterated methyl groups was converted into the corresponding β-bromohydroperoxides, equation [20].

[20]



40

51 (100 - x)

52 x

The ratio of the two products can be calculated from the n.m.r. integration values. It had been shown in Chapter I that the protons of the gem-dimethyl group on the carbon bearing the bromine absorb at τ 8.65 (compound 51) and the protons of the gem-dimethyl group on the carbon bearing the hydroperoxy group absorb at τ 8.19 (compound 52). It was seen immediately from the n.m.r. spectrum that unequal amounts of 51 and 52 are formed. To account for the ca. 20% hydrogen in the deuterated methyl groups, the following equations can be set up:

[21] $$\text{Integration at } \tau\ 8.6 = 1.2\,(100 - x) + 6x = 120 + 4.8x$$

[22] $$\text{Integration at } \tau\ 8.2 = 6\,(100 - x) + 1.2x = 600 - 4.8x$$

[23] $$\frac{[21]}{[22]} = \frac{\text{Integration at } \tau\ 8.6}{\text{Integration at } \tau\ 8.2} = \frac{120 + 4.8x}{600 - 4.8x} = \frac{25 + x}{125 - x}$$

The results are shown in Table IV. The triple integration values are given in this table to show the accuracy of the product determination in the n.m.r. spectra.

The mixture of β-bromohydroperoxides, prepared above, was allowed to react with base at 0° in the usual manner to give, after distillation, a 42% yield of a mixture of allylic hydroperoxides, equation [24].

TABLE IV

Deuterium Isotope Effects in the Formation of β-Bromohydroperoxides from <u>40</u> (80.65% Deuterium).

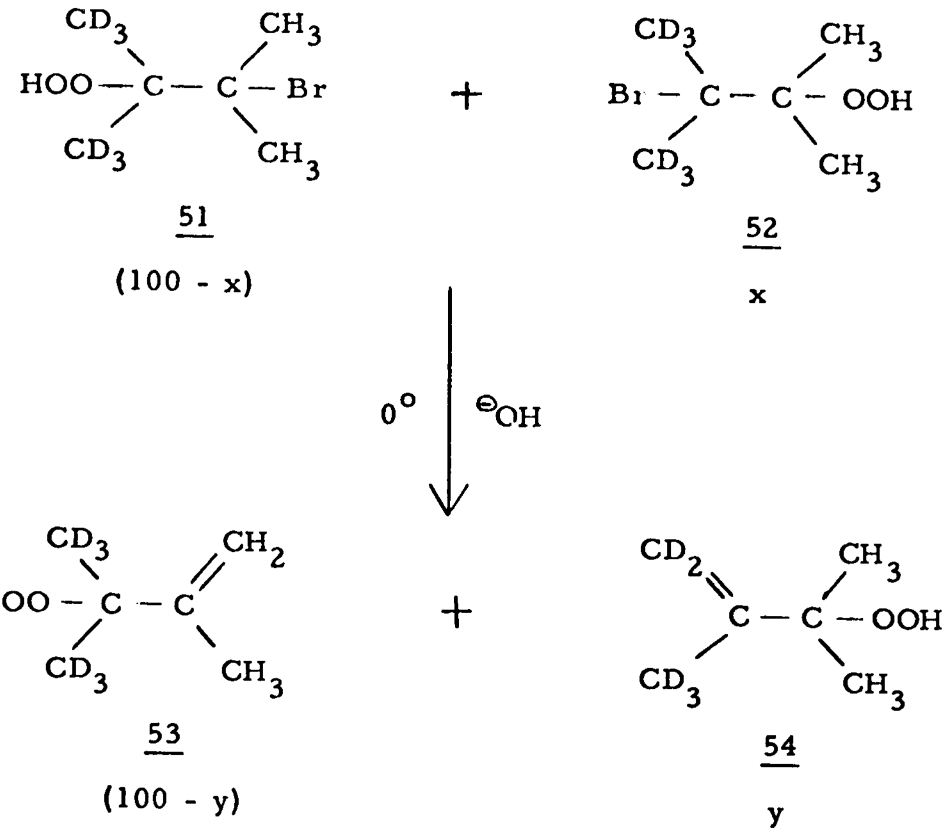
Run	Intensity at τ8.6	Intensity at τ 8.2	% <u>52</u>	$\frac{k_H}{k_D}$ obs	$\frac{k_H}{k_D}$ per D[a]	Average $\frac{k_H}{k_D}$ per D
	83.2	65.0	59.2	1.45	1.08	
1	83.3	65.0	59.3	1.46	1.08	1.08 ± 0.01
	83.6	66.0	58.8	1.43	1.08	
	57.0	45.5	58.4	1.40	1.07	
2	58.0	45.5	59.1	1.44	1.08	1.08 ± 0.01
	58.0	45.5	59.1	1.44	1.08	

[a] The isotope effect per deuterium was calculated using the following expression (109):

$$\frac{k_H}{k_D} \text{ per D} = \left(\frac{k_H}{k_D} \text{ obs}\right)^{\frac{1.0}{6.z}}$$

where z is the fraction of deuterium in compound <u>50</u>.

[24]



The ratio of two products can be obtained from the n.m.r. spectrum. The following equations are set up to account for the ca. 20% hydrogen in the two deuterated methyl groups.

[25] Integration gem-dimethyl group at τ 8.7

$$= 6y + 1.2(100 - y) = 120 - 4.8y$$

[26] Integration allylic methyl group at τ 8.2

$$= 3(100 - y) + 0.6y = 300 - 2.4y$$

[27] $$\frac{[25]}{[26]} = \frac{\text{Integration at } \tau\, 8.7}{\text{Integration at } \tau\, 8.2} = \frac{120 + 4.8y}{300 - 2.4y} = \frac{50 + 2y}{125 - y}$$

The values for y and k_H/k_D are shown in Table V.

TABLE V

Deuterium Isotope Effects in the Reaction Between Base [0.66 M] and β-Bromohydroperoxides [0.28 M] from 40 (80.65% Deuterium) in Methanol at 0°

Run	% 54	$\frac{k_H}{k_D}$	$\frac{k_H}{k_D}$ corr.[a]
1	36.48	1.74	2.12

[a] Correction to 100% isotopic purity using the following expression:

$$\frac{k_H}{k_H(1 - z) + k_D(z)} = \frac{k_H}{k_D} \text{ observed}$$

where z is the fraction of deuterium compound.

Similar experiments were carried out on the 99.3% deuterated 3-methyl-2-trideuterio methyl -1,1,1-trideuterio-2-butene (40). This compound was converted in 75% yield into the corresponding β-bromohydroperoxides. The mixture of β-bromohydroperoxides contained 97% of the theoretical amount of active oxygen as determined by iodometric titration. The infrared spectrum (CCl_4) showed absorption bands at 3550 and 3200-3500 cm^{-1} for the -OOH stretching vibrations and at 2245 and 2125 for the C-D symmetric and antisymmetric stretching vibrations.

The isotope effects in the reaction with base were determined in the presence of benzene as an internal standard in methanol-$\underline{d}_4$ as a solvent using sealed n.m.r. tubes as described earlier. The check for material balance was carried out as described earlier. The equations [23] and [27] can be simplified here, because no correction had to be made for the presence of hydrogen in the deuterated methyl groups, and can be written as:

$$[28] \quad \frac{\text{Integration at } \tau\, 8.6}{\text{Integration at } \tau\, 8.2} = \frac{6\,x}{6\,(100 - x)} = \frac{x}{(100 - x)}$$

$$[29] \quad \frac{\text{Integration at } \tau\, 8.7}{\text{Integration at } \tau\, 8.2} = \frac{6\,y}{3\,(100 - y)} = \frac{2\,y}{(100 - y)}$$

The results are shown in Table VI. The sum of the integrals at τ8.2 and τ8.6 is $6\,x + 6\,(100 - x) = 600$ and the sum of the integral at τ 8.7 plus 2 times the integral at τ 8.2 in the product is $6\,y + 6\,(100 - y) = 600$ and they can be both compared with the internal standard as shown in column two of Table VI. The comparison of the ratios of product over internal standard showed that a quantitative conversion had taken place. The values in Tables V and VI show that an inversion took place. In the starting material most of the hydroperoxy group (61%) is on the carbon bearing the light methyl groups. In the product, however, the hydroperoxy group is mainly (69%) on the carbon bearing the heavy (deuterated) methyl groups. The migration of the hydroperoxy group in the elimination reactions is evidence for the formation of a

TABLE VI

Deuterium Isotope Effects in the Reaction Between Base [0.55 M] and β-Bromohydroperoxides from 40 (99.3% Deuterated) in Methanol-d_4 at 0°.

Run	Integral Product / Integral Standard	% 52	% 54	$\frac{k_H}{k_D}$	$\frac{k_H}{k_D}$ per D	Average $\frac{k_H}{k_D}$
Start	2.0	61.0		1.56	1.08	
	2.0	61.1		1.57	1.08	1.08 ± 0.001[a]
	2.1	61.5		1.60	1.08	
I	1.9		31.0	2.23	2.24	
	2.0		30.9	2.24	2.26	2.22 ± 0.05[b]
	1.9		31.8	2.14	2.15	
II	2.0		32.1	2.12	2.13	
	2.2		31.7	2.15	2.17	2.19 ± 0.06[b]
	2.1		30.8	2.25	2.27	

[a] corrected as in Table IV

[b] corrected as in Table V

cyclic peroxide. The magnitude of the isotope effect in the elimination reaction ($k_H/k_D = 2.2$) is of the order for a primary deuterium isotope effect.

A close look was taken at the respective rates of reaction of <u>51</u> and <u>52</u> with base. Mixtures of these two compounds prepared from <u>40</u> were reacted for 6 hours with different amounts of base, insufficient for complete reaction to take place. The ratios of starting material left, <u>52</u>/<u>51</u>, were determined by n.m.r. spectroscopy. The absorptions in the n.m.r. spectra for the <u>gem</u>-dimethyl group at τ8.19 in the starting material and for the allylic methyl group in the product at τ8.22 are too close to obtain an accurate integration. Therefore, the peak height method was used for the analysis. Benzene was used as an internal standard and the results are shown in Table VII. The results showed that the ratio <u>52</u>/<u>51</u> stayed constant during the elimination, which means that <u>52</u> and <u>51</u> reacted with base at the same rate. This observation would be very unlikely if direct elimination of hydrogen bromide took place, but is consistent with the formation of a cyclic peroxide. The ratio of products <u>54</u>/<u>53</u> is different in runs II and III and also different from the ratios in the previous runs (Tables V and VI). This seems to indicate that the ratio of products <u>54</u>/<u>53</u> formed in the reaction of β-bromohydroperoxides <u>51</u> and <u>52</u> with base is dependent on the base concentration.

A check was made whether the observed isotope effect in the formation of β-bromohydroperoxides <u>51</u> and <u>52</u> from <u>40</u> would be

TABLE VII

Ratio of Starting Materials Left During the Reaction of β-Bromohydroperoxides from 40 and Insufficient Base in Methanol at 0°.

Run	Starting Material[a] / Benzene	% Conversion	% 52[a] / 54	% 54
Start	1.29	0	1.45	-
I	1.10	15	1.42	
II	0.89	31	1.46	58.8 ± 1.0
III	0.56	57	1.43	62.7 ± 0.4
Start	1.27	-	1.45	

[a] Calcualted using peak heights

the same if another nucleophile was used in the reaction with 40 and 1,3-dibromo-5,5-dimethylhydantoin. The reaction between tetramethylethylene, 1,3-dibromo-5,5-dimethylhydantoin and methanol results in a 63% yield of 2-bromo-2,3-dimethyl-3-methoxybutane (55). The n.m.r. spectrum (CCl_4) showed absorption at τ6.79 (singlet) for the methoxy protons, and at τ 8.26 (singlet) and τ8.67 (singlet) for the protons of the *gem*-dimethyl groups. In analogy to the interpretation of the n.m.r. spectrum of 2-bromo-2,3-dimethyl-3-butylhydroperoxide, the signal at τ 8.26 was assigned to the protons of the *gem*-dimethyl group on the carbon bearing the bromine and the signal at τ 8.67 was assigned to the protons of the methyl groups on the carbon bearing the methoxy group.

The same reaction was carried out on the 99.3% deuterated 40 and the isotope effect was determined by n.m.r. in the same way as it was determined in the case of the β-bromohydroperoxides of compound 40. The results are shown in Table VIII. The isotope effect found here is very close to the one observed in the formation of the β-bromohydroperoxides from 40. The ratio of twice the integral for the methoxy protons over the sum of the integrals for the *gem*-dimethyl groups' protons should equal one. It is shown in the internal check column. The error found in this experiment is larger than in any of the previous ones.

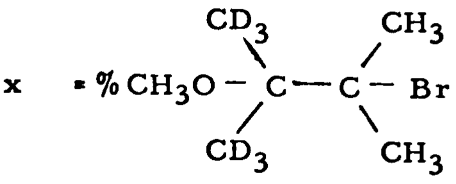
The symmetrically deuterated tetramethylethylene 41 was converted into the β-bromohydroperoxide 56 in 79% yield. The infrared spectrum (CCl_4) showed absorption bands at 3550 and 3200-

TABLE VIII

Deuterium Isotope Effects in the Formation of β-Methoxybromides from 40 (99.3% Deuterated).

Run	x^{a}	$\frac{k_H}{k_D}$	$\frac{k_H}{k_D}$ per D [b]	Average $\frac{k_H}{k_D}$ per D	Internal Check [c]
I	40.6	1.47	1.07		1.07
200 cycl sweep-width	40.5	1.47	1.07	1.07 ± 0.01	1.08
	40.3	1.48	1.07		1.09
I	39.8	1.52	1.07		1.09
500 cycles sweep-width	40.1	1.50	1.07	1.07 ± 0.01	1.09
	39.7	1.52	1.07		1.08

[a]



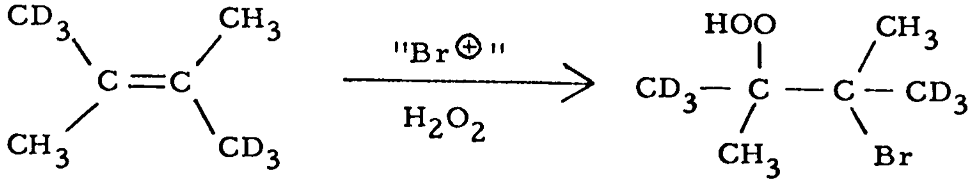
$$x = \%\,CH_3O-C(CD_3)_2-C(CH_3)_2-Br$$

[b] Calculated as indicated in Table IV

[c] $$\frac{2 \times OCH_3 \text{ integration}}{\text{sum of } \underline{\text{gem}}\text{-dimethyl integrations}}$$

3500 cm^{-1} for the free and bonded -OOH stretching vibrations and at 2245 and 2150 cm^{-1} for the C-D symmetric and antisymmetric stretching vibrations. Iodometric titration indicated 96.5% of the theoretical amount of active oxygen. Equation [30] shows that only a symmetrical bromohydroperoxide can be formed from compound 41 (either the threo or erythro configuration, or a mixture of them is formed).

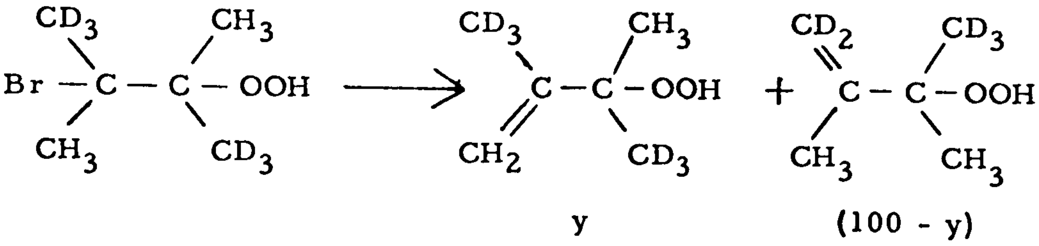
[30]



56

The β-bromohydroperoxide was allowed to react with base in the usual fashion at 0° and the reaction was analyzed by n.m.r. spectroscopy. The formation of the two allylic hydroperoxides from the bromohydroperoxide of 41 can be represented as in equation [31].

[31]



To account for only 95.3% D:

[32] Integration at τ 8.7 (gem-dimethyl) =

$$3\,(100 - y) + 0.1407\,(100 - y) + 3\,y + 0.1407\,y = 314.07$$

[33] Integration at $\tau 8.2$ (allylic methyl) =

$$3\,(100 - y) + 0.1407\,y = 300 - 2.86\,y$$

[34] $$\frac{[32]}{[33]} = \frac{\text{Integral } \tau 8.7}{\text{Integral } \tau 8.2} = \frac{314.07}{(300 - 2.86\,y)}$$

The results of these experiments are shown in Table IX. The internal standard analysis showed again that a quantitative reaction took place. The major product in these experiments is the one formed by loss of hydrogen bromide instead of deuterium bromide. The results show that a very similar isotope effect is obtained in this reaction as was in the reaction of β-bromohydroperoxides of 40 with base. A cyclic peroxide intermediate, formed in either the reaction of 51 and 52 with base or in the reaction of 56 with base, which opens up to the allylic hydroperoxide would explain the similar isotope effects observed in the two reactions.

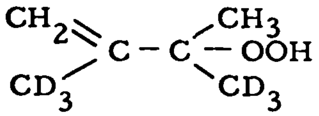
Some kinetic experiments in the reaction between 21 and base were carried out at low temperatures by following the course of the elimination by n.m.r. spectroscopy. Besides the peaks for starting material and product, a new peak appeared at $\tau 8.67$ during the elimination. This absorption was not present after the reaction mixture was allowed to warm up to room temperature and scanned in the n.m.r.. This new peak could be an absorption for the protons of a cyclic peroxide or for the protons of the anion of 21. A cyclic peroxide should give rise to a twelve proton absorption, and the hydroperoxy anion to two six proton signals. The protons of

TABLE IX

Deuterium Isotope Effects in the Reaction Between Base [0.55 M] and 2-Bromo-2,3-*bis*-trideuteriomethyl-3-butyl Hydroperoxide [0.12 M] in Methanol-d_4 at 0°.

Run	Integral Product / Integral Standard	% y[a]	$\frac{k_H}{k_D}$	$\frac{k_H}{k_D}$ per D[b]	Average $\frac{k_H}{k_D}$ per D
Start	1.24				
	1.19				
	1.16				
I	1.19	66.3	1.97	2.07	2.13 ± 0.1
60 Mc	1.24	68.0	2.12	2.24	
	1.24	67.2	2.05	2.16	
100 Mc		66.9	2.02	2.13	
		67.0	2.03	2.14	
		66.3	1.96	2.06	
II	1.18	65.5	1.90	1.99	2.10 ± 0.1
60 Mc	1.15	66.2	1.96	2.06	
	1.19	66.2	1.96	2.06	
100 Mc		68.3	2.16	2.29	
		67.1	2.04	2.15	
		66.0	1.94	2.04	

[a] y is



[b] calculated as in Table V

the methyl groups on the carbon bearing the hydroperoxy anion could be expected to have a different chemical shift from the protons of the methyl groups in the starting material 21. The protons of the other methyl group (on the carbon bearing bromine) of the anion should have the same chemical shift as in 21. If the new absorption in the n.m.r. is for the anion, it should be a six proton signal. Using tetramethylsilane as an internal standard, a run was made at -17.5° to decide whether the new peak was a twelve proton or six proton absorption. The results are shown in Table X. As the results indicate only a product balance is obtained for a twelve proton intermediate. The figures for a six proton absorption are too high and also no presence of the other six proton signal of the possible anion could be detected.

The reaction between 2-bromo-2,3-dimethyl-3-butyl hydroperoxide and base was followed at -17.5°, -27.5° and -37.5°. The results are shown in Tables XI, XII and XIII.

The reaction did not fit first order kinetics, but good agreements were found for second order kinetics. The rate constants for the second order reaction between 21 and base were calculated using the formula in equation [35].

$$[35] \quad \frac{1}{a - b} \ln \frac{b\,(a - x)}{a\,(b - x)} = k_2 \cdot t \qquad (110)$$

By plotting the left side of equation [35] versus the time, a straight line was obtained whose slope gives the rate constant k_2. An

TABLE X

Determination of Weight of the Intermediate in the Reaction Between 21 and Base with Tetramethylsilane as Internal Standard in Methanol at -17.5°.

time in sec.	$\frac{\text{moles of } (21 + \text{products})}{\text{moles of standard}}$ for 12 proton intermediate	$\frac{\text{moles of } (21 + \text{products})}{\text{moles of standard}}$ for 6 proton intermediate
0	1.78	1.78
930	1.79	1.95
1800	1.81	1.98
2460	1.78	1.97
3120	1.80	2.01
3810	1.82	2.10
4590	1.86	2.11
5100	1.88	2.11

TABLE XI

Rate of Reaction of 2-Bromo-2,3-dimethyl-3-butyl Hydroperoxide [0.216 M] at -37.5° with Sodium Hydroxide [0.83 M] in Methanol.

time (sec)	[21]	[Intermediate]	[2]	k_2 (graphical) liter/mole sec
300	0.155	0.017	0.044	1.0×10^{-4}
570	0.15	0.019	0.048	
1320	0.14	0.021	0.059	
2280	0.13	0.022	0.066	
3180	0.12	0.021	0.072	

TABLE XII

Rate of Reaction of 2-Bromo-2,3-dimethyl-3-butyl Hydroperoxide [0.15 M] at -27.5° with Sodium Hydroxide [0.817 M] in Methanol.

time (sec)	[21]	[Intermediate]	[2]	k_2 (graphical) liter/mole sec
720	0.124	0.0135	0.0127	1.7×10^{-4}
1110	0.116	0.0141	0.0194	
1500	0.111	0.0149	0.0246	
2640	0.096	0.0159	0.0385	
3240	0.088	0.0167	0.0456	
3780	0.084	0.017	0.0497	
4470	0.077	0.0176	0.056	

TABLE XIII

Rate of Reaction of 2-Bromo-2,3-dimethyl-3-butyl Hydroperoxide [0.232 M] at -17.5° with Sodium Hydroxide [0.575 M] in Methanol.

time (sec)	[21]	[Intermediate]	[2]	K	k_2 (graphical) liter/mole sec
930	0.177	0.020	0.035	8.8	
1800	0.157	0.022	0.053	7.5	
2460	0.139	0.025	0.068	6.1	
3120	0.125	0.026	0.080	5.5	3.5×10^{-4}
3810	0.108	0.027	0.097	4.7	
4590	0.090	0.0285	0.114	3.9	
5100	0.085	0.029	0.120	3.7	

example of this is shown for the run at -27.5°, figure 4. A plot of the concentrations of starting material, intermediate and product against time is shown for the run at -17.5° in figure 5.

The formation of product 2 from the reaction between 21 and base can be considered as a two step process. Firstly, the bimolecular formation of the cyclic peroxide, followed by unimolecular or bimolecualr decomposition of the cyclic peroxide to the allylic hydroperoxides.

McMillan (111) had derived an expression for the ratio of the rate constants, κ, for competitive consecutive second order reactions. This expression was used to calculate the κ's shown in Table XIII. A variation of over 100% was found in the κ during the reaction. The explanation for this observation could be the fact that a unimolecular and bimolecular reaction operate at the same time.

From the rate constants found in the kinetic experiments the activation parameters were calculated using the text book (112) methods. The activation energy was found to be $E_a = 7.6 \pm 1.0$ kcal and the entropy $\Delta S^{\#} = -46 \pm 5$ e.u..

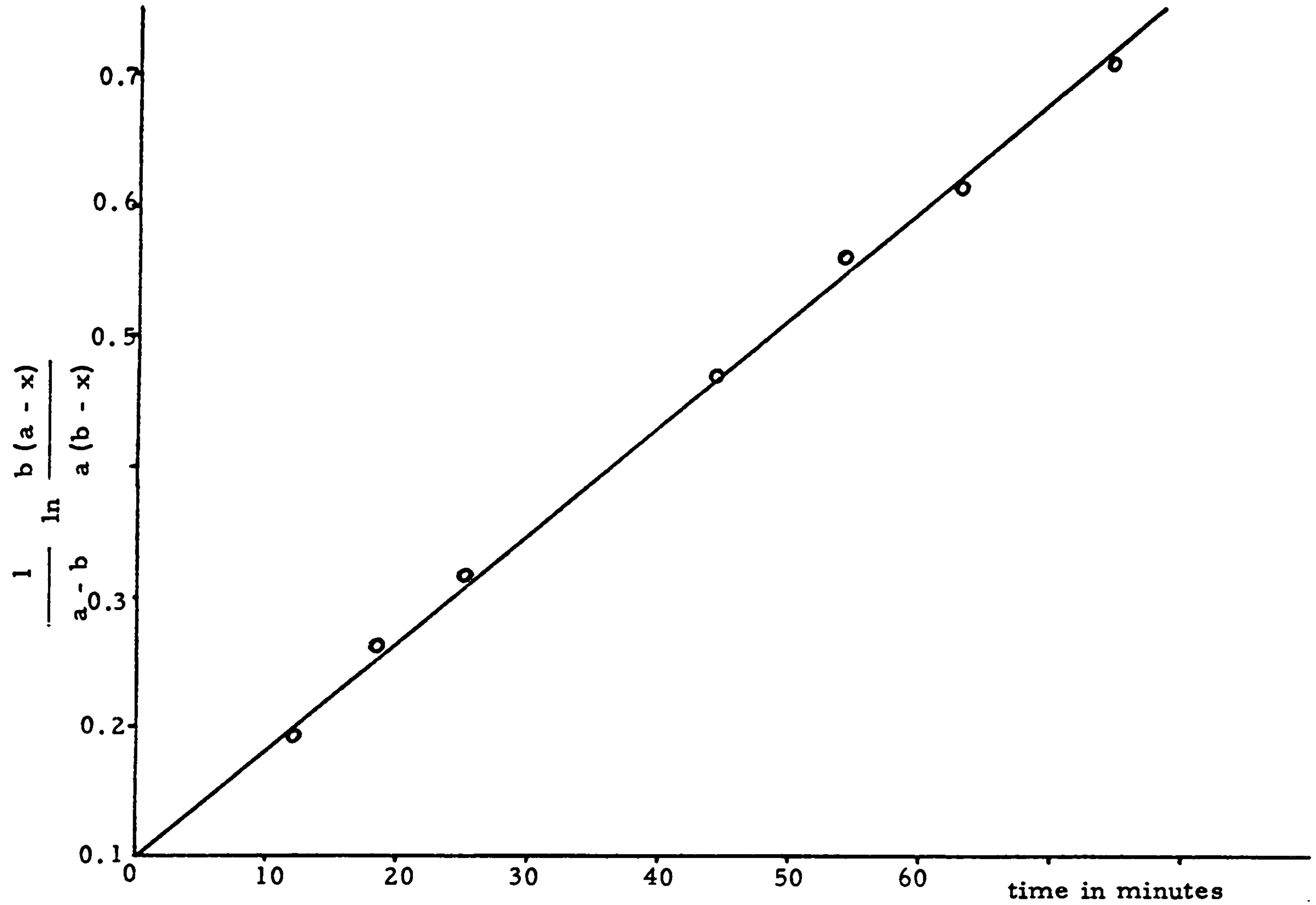


Figure 4. The reaction between 2-bromo-2,3-dimethyl-3-butyl hydroperoxide and base at -27.5°

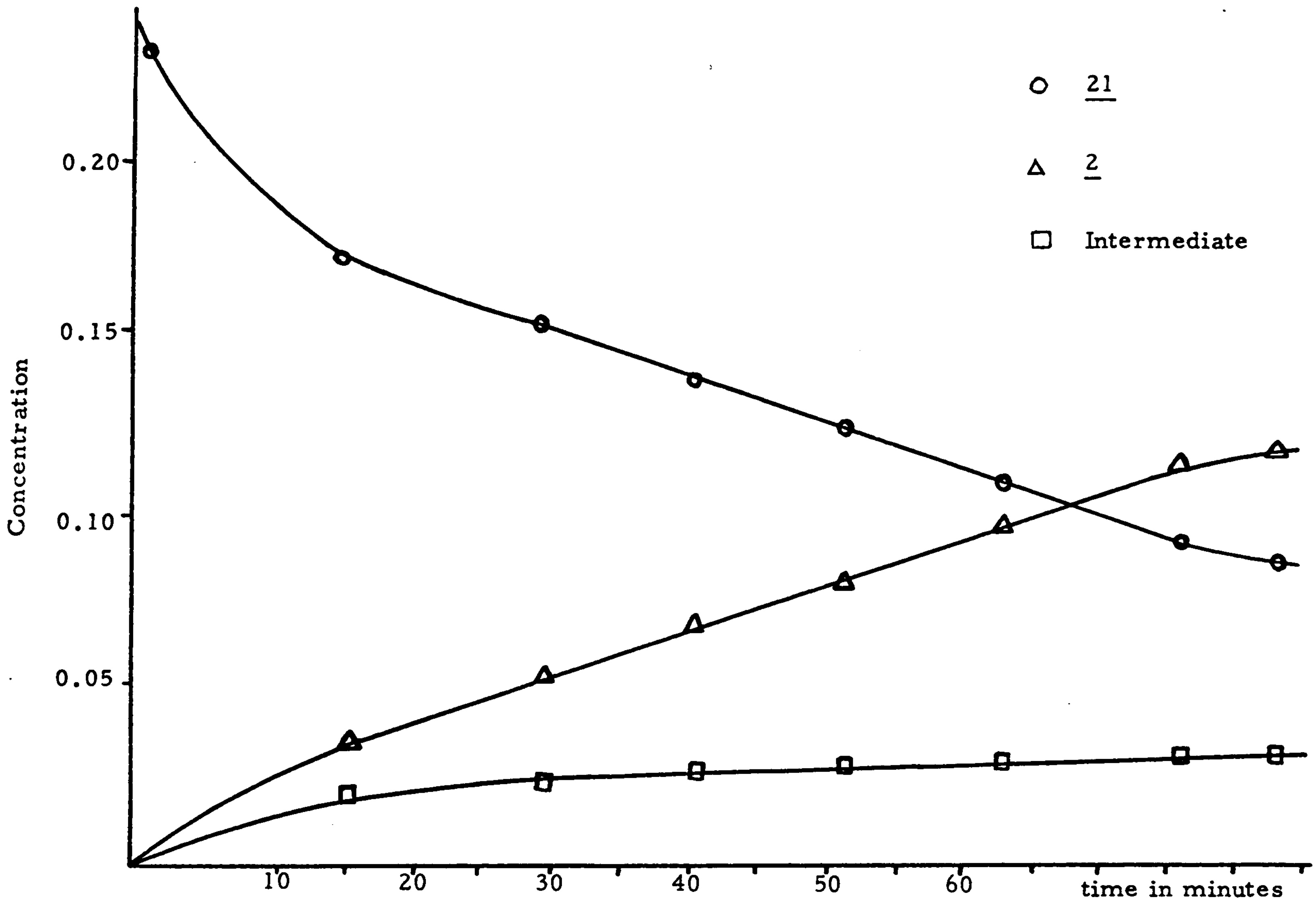


Figure 5. The reaction between 2-bromo-2,3-dimethyl-3-butyl hydroperoxide and base at -17.5°.

DISCUSSION

Before rationalizing the observed deuterium isotope effects in the formation of β-bromohydroperoxides from the deuterated tetramethylethylene <u>40</u> and in the reaction of the β-bromohydroperoxides from <u>40</u> and <u>41</u> with base, a brief survey will be given of some observed primary and secondary deuterium isotope effects.

<u>Primary Deuterium Kinetic Isotope Effects:</u>

Several authors (113, 114, 115) have reviewed the subject of deuterium isotope effects as applied to organic reactions involving C-H bond breaking. It was predicted that hydrogen and deuterium compounds should react at different rates, because of the difference in the zero-point energy for the C-H and C-D bonds which will result in a difference in the height of the potential barrier for the reaction. The difference in zero-point energy for the C-H and C-D bonds is $1/2\ h\nu_H - 1/2\ h\nu_D = 1.15$ kcal/mole. In the transition state, the stretching vibration of the C-H or C-D bond becomes a degree of translational freedom and is lost. Therefore $1/2\ h\nu_H{}^* - 1/2\ h\nu_D{}^* = 0$, where $\nu_H{}^*$ and $\nu_D{}^*$ represent the stretching vibrations of the C-H and C-D bonds in the transition state. The activation energy difference for the reaction is then equal to the zero-point energy difference of the reactants, which is 1.15 kcal/mole. This difference in the energy corresponds to a factor of seven in the rate at 25° (115). However, in many cases the isotope effect observed is less than calculated. Westheimer (115) pointed out that only in a symmetrical transition state the maximum isotope effect of $k_H/k_D = 7$ is to be found. If the transition state is not symmetrical and the hydrogen or deuterium atom still has some motion, a different zero-point energy of hydrogen from deuterium is present in the transition state. This difference will decrease the contribution of the zero-point energy to the activation energies for the reaction of the hydrogen compound or deuterium compound. Consequently, the isotope effect may be small. Wiberg (114) predicted, on the basis of a similar explanation as Westheimer's, that the minimum primary kinetic isotope effect that might be expected is 1.4 (k_H/k_D).

Secondary Deuterium Isotope Effects:

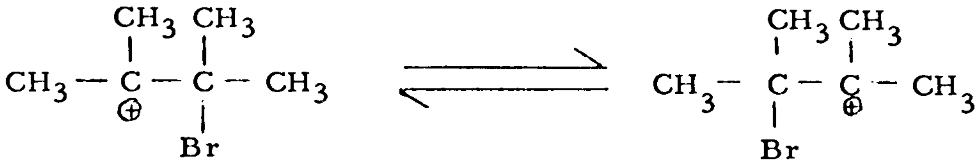
Several reviews on the subject have appeared in the literature (118, 119, 120). Secondary isotope effects are divided into two main types; (i) secondary deuterium isotope effects of the 'first kind' or α-deuterium isotope effects, in which the deuterium atom is substituted on a carbon atom which undergoes a change in hybridization as the reaction proceeds; and (ii) those of the 'second kind' or β-deuterium isotope effects, in which the deuterium is substituted on a carbon atom β to the reaction center. Secondary α-deuterium isotope effects will not be discussed here. In the β-deuterium isotope effects the β-carbon atom does not undergo re-orientation during the reaction. The effects of the 'second kind' have been attributed to hyperconjugative (121) and inductive effects (120) and recently to steric effects (122, 123, 124). The maximum

β-deuterium isotope effect observed is ca. 12% per deuterium (121).

Secondary Deuterium Isotope Effects in the Addition Reaction:

Bromonium ion formation in certain electrophilic additions of bromine to olefins is the accepted explanation for the complete stereospecifity observed (125, 126). It has been suggested that rapidly equilibrating ions, as seen in equation [36], could also lead to stereospecifity (127).

[36]



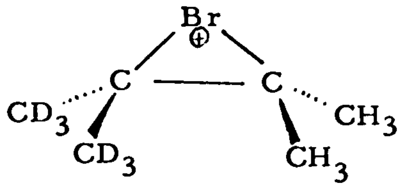
$$CH_3-\overset{CH_3}{\underset{\oplus}{C}}-\overset{CH_3}{\underset{Br}{C}}-CH_3 \rightleftharpoons CH_3-\overset{CH_3}{\underset{Br}{C}}-\overset{CH_3}{\underset{\oplus}{C}}-CH_3$$

Similarly, from results of rate measurements and stereochemistry, bromine has been suggested as a good neighboring group, participating to give the same type of bridged bromonium ions as suggested for bromination of olefins (128, 129).

N-Haloacetamides, like 1,3-dibromo-5,5-dimethylhydantoin, are known to be positive halogen donors (130) and react in electrophilic additions to olefinic materials. The stereoselectivity in a related reaction was shown by Winstein and Lucas (128) in the formation of threo-3-bromo-2-butanol from cis-2-butene. The formation of 2-bromo-2,3-dimethyl-3-butyl hydroperoxide from tetramethylethylene could be expressed as a two step process. First the electrophilic addition of a "$Br^{\oplus}$" to the double bond to give a bromonium ion or a rapidly equilibrating pair of ions as in equation [36], which is followed by attack of the nucleophilic hydrogen peroxide.

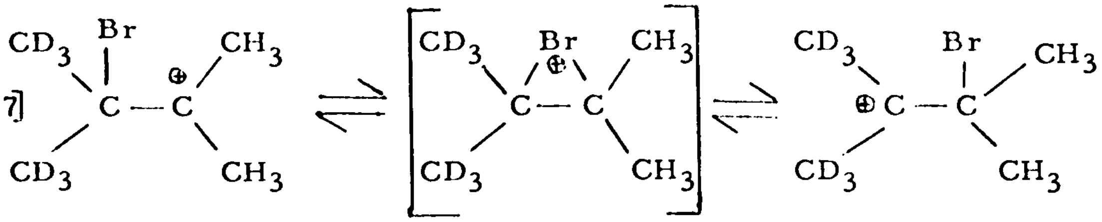
The ratio of products in the formation of β-bromohydroperoxides or β-bromomethoxides from 3-methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene, 40 (Tables IV, VI and VIII) will be discussed in terms of the mechanism outlined above.

The bromonium ion from the electrophilic addition of "Br$^{\oplus}$" to olefin 40 is shown below.



Brown and coworkers (123, 124) had shown that there is an inverse isotope effect in the reaction of 2,6-dimethyl-$\underline{d}_6$-pyridine with methyl iodide. Their explanation of this observation was based on the smaller steric requirements of a methyl-$\underline{d}_3$ group compared to a methyl group. If a symmetrical bromonium ion in the reaction of 40 is formed, the only determining factor in the isotope effect is the steric requirements of either the methyl groups or the methyl-$\underline{d}_3$ groups. The methyl-$\underline{d}_3$ groups are smaller and hydrogen peroxide attack should be favored on the carbon bearing the methyl-$\underline{d}_3$ groups. The opposite is observed however, and a symmetrical bromonium ion can be ruled out as the intermediate on which nucleophilic attack occurs.

The observed results can be explained through a pair of equilibrating carbonium ions, equation [37].



[37]

The most favoured explanation of β-secondary deuterium isotope effect until recently was hyperconjugation (120, 121). The replacement of hydrogen in a hyperconjugating position by a deuterium atom generally leads to a dimunition in the rate of carbonium ion type reactions. Shiner (131) observed an intermolecular deuterium kinetic isotope effect of $k_H/k_D = 1.77$ in the solvolysis of *t*-amyl-d_6-chloride in aqueous alcohol.

Bartell (122) and Brown (123) feel that steric effects can be responsible for deuterium kinetic isotope effects in solvolysis reactions. Non-bonded repulsions, averaged over the atomic vibrations, are greater for hydrogen atoms than for deuterium atoms. There are more non-bonded repulsions in a tetrahedral reactant than in a trigonal product or carbonium ion transition state. Accordingly, the relief of non-bonded repulsions associated with the transformation from a tetrahedral to a trigonal form is greater in molecules containing hydrogens than it is in those containing deuterium.

The intramolecular isotope effects observed in the formation of β-bromohydroperoxides and β-bromomethoxides from 40 were 1.58 and 1.49 respectively and are representative of β-secondary deuterium isotope effects. The fast quenching of the intermediate by the nucleophile is a reflection of the structure of this intermediate. The open ion with a positive charge on the carbon bearing the light methyl groups is expected to be favored over the other ion by the following reasons. Hyperconjugation, as explained by Shiner (121), plays a more important role when hydrogen atoms are in a hyperconjugating position than when deuterium atoms are. The backstrain will also be less in the open ion with the positive charge on the carbon bearing the methyl groups. The adjacent tetrahedral carbon bears the methyl-$\underline{d}_3$ groups which have less non-bonded interactions than the methyl groups on a tetrahedral carbon. Both explanations, hyperconjugation or backstrain, will favor the same open ion and the product formed this way. No distinction can be made between the relative contributions of either hyperconjugation or relief of backstrain.

The decreased acidity of formic-$\underline{d}$-acid is ascribed to the inductive effect of deuterium (119). Inductive effects cannot explain the observed secondary deuterium isotope effects in the formation of $\underline{51}$ and $\underline{52}$ from $\underline{40}$. Deuterium has an enhanced ability to donate electrons over hydrogen and consequently would favor the carbonium ion on the carbon bearing the methyl-$\underline{d}_3$ groups which is the opposite from what is observed.

A symmetrical bromonium ion could not explain the observed results in the addition reaction. However, a bromonium ion (unsymmetrical) where the carbon bearing the methyl groups has more partial charge than the carbon bearing the methyl-$\underline{d}_3$ groups could explain the observed ratios of $\underline{51}$ and $\underline{52}$. Attack of the nucleophile on the carbon with most partial charge will give the predominance of 52 over 51.

Deuterium Isotope Effects in the Elimination Reaction:

The reaction between 3-bromo-2,3-dimethyl-2-butyl hydroperoxide and base to give 2,3-dimethyl-3-hydroperoxy-1-butene is quantitative as the results in Table III indicated. No side reactions take place to any extent detectable by n.m.r. spectroscopy.

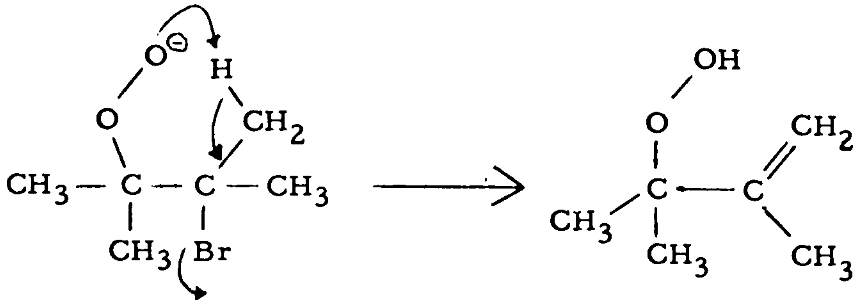
It was shown in the results section that there was evidence for the formation of a cyclic peroxide in the reaction of 21 with base, which will be discussed in four parts.

1. The evidence found in the low temperature n.m.r. runs.

An extra twelve proton signal at τ 8.67 was present during the reaction. This signal disappeared upon warming up and was assigned to the protons of the methyl groups of a cyclic peroxide.

2. The evidence found in the tracer studies with 40:

When the two β-bromohydroperoxides prepared from 40 were reacted with base, a different ratio of products 53 and 54 compared to the ratio of starting compounds 51 and 52 was formed. If a straight bimolecular elimination of the elements of hydrogen bromide by base had taken place, the ratio of products (53 and 54) would have been expected to be the same as the ratio of starting materials (51 and 52). An elimination involving a six membered concerted mechanism would not change the ratio either, equation [38].

[38] 

Not only has the ratio changed but it has also inverted from 40:60 to 69:31. The hydroperoxy group in the starting material was mainly on the carbon bearing the light methyl groups (52), while after reaction with base the hydroperoxy group,is mainly on the carbon bearing the methyl-$\underline{d}_3$ groups (54). In other words, the product which is expected to be the minor one via straight elimination from the minor starting material 51, is the major product.

The mechanism which can account for such an observation is the formation of a cyclic peroxide (57) which can then show an isotope effect in the formation of products 53 and 54, Scheme 5. However, the formation of products via a cyclic peroxide and formation of products from direct elimination could take place simultaneously.

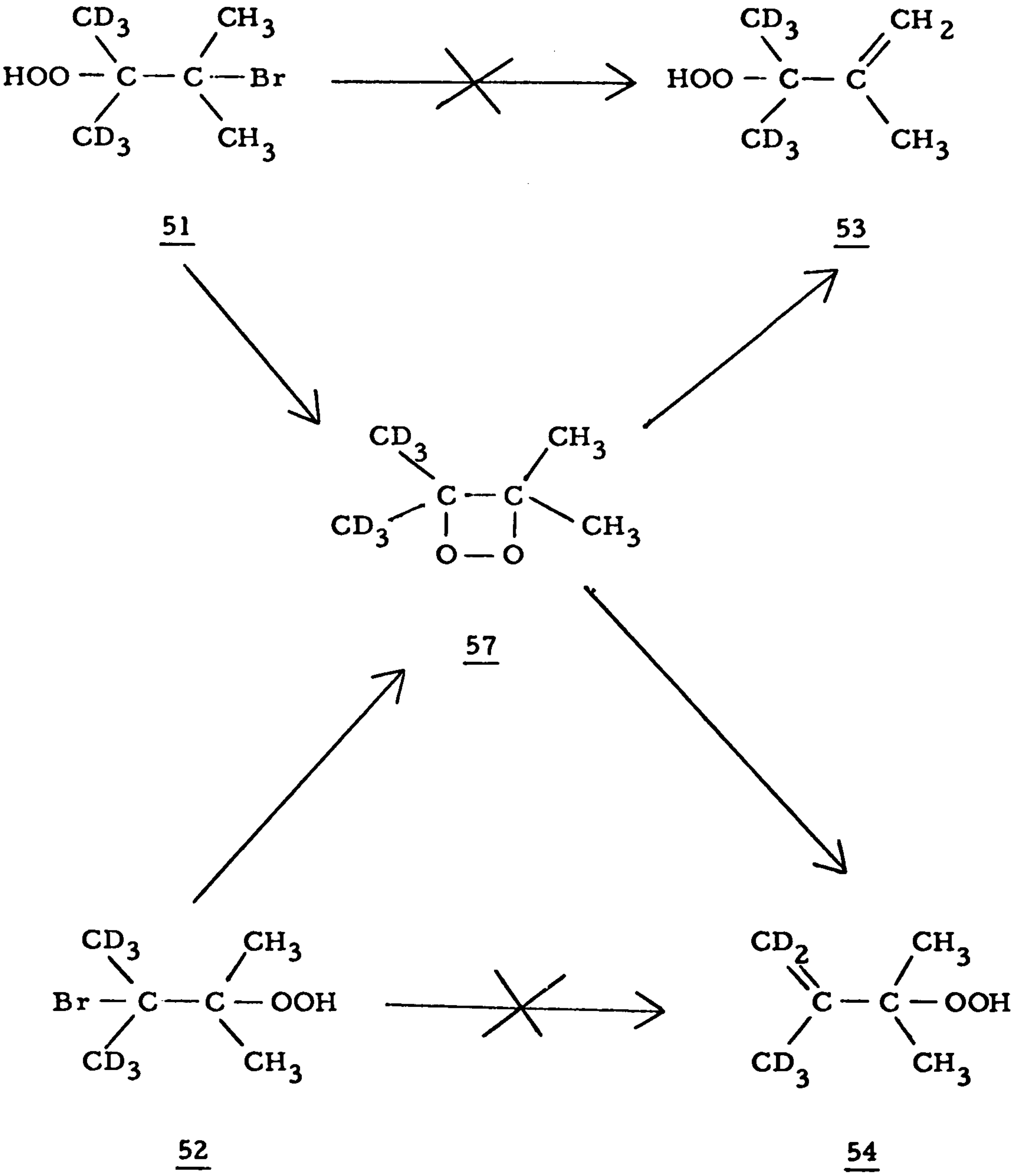
3. The evidence that the β-bromohydroperoxides 51 and 52 from 40 react at the same rate:

In reactions of 51 and 52 with insufficient amounts of base, no change in the ratio of β-bromohydroperoxides left 52/51 was observed as is shown in Table VII. The rate of formation of cyclic peroxide 57 from either 51 or 52 is expected to be about the same.

4. The evidence found in tracer studies with 41:

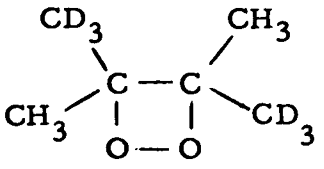
The primary isotope effect, corrected to 100% deuterium

Scheme 5



purity, from the reaction of cyclic peroxide 57, containing 80.65% D or 99.3% D, to products 53 and 54, were found to be 2.12 and 2.20 (Tables V and VI) respectively. Those values are representative for a primary isotope effect.

The cyclic peroxide (58) from 3-bromo-2,3-bis-trideuteriomethyl - 2-butyl hyroperoxide (56) would be expected to give the same isotope effect in the reaction with base as the cyclic peroxide 57.



58

As was shown in Table XI, the isotope effect in the reaction of 56 with base is 2.12, very similar to the one observed in the case of the unsymmetrical β-bromohydroperoxides. From the observation that the isotope effects in the reaction of base with the β-bromohydroperoxides from 40 and 41 are nearly the same, it can be concluded that the reactions go via a perepoxide.

The evidence outlined in the four points above shows very clearly that a cyclic peroxide is formed in the reaction of 21 with base. The eliminations using insufficient base ruled out a direct elimination taking place at the same time as the formation of cyclic peroxide. In a direct elimination compound 51 should react faster than compound 52 (elimination of HBr versus DBr) and consequently the ratio of starting materials left should change during the reaction which was not observed.

Two ways of formation of product from the cyclic peroxide will be discussed: a thermal decomposition and a base catalyzed reaction. A thermal decomposition appeared unlikely since Mumford (132) found that the thermal decomposition of perepoxide of 2-methyl-2-butene yields acetone and formaldehyde quantitatively. However, the reactions between 51 and 52 with insufficient amounts of base showed a different ratio of products 54/53 during the reaction which was also different from the ratios in the previous runs. This indicates that a thermal reaction may take place at the same time as the base catalyzed reaction, and the ratio 54/53 is dependent on the base concentration. If only a base catalyzed reaction of the cyclic peroxide took place, the reaction of 21 with base should follow competitive consecutive second order kinetics. The ratio of second order rate constants γ, calculated using McMillan's (111) expression, varied during the elimination reaction. This is also an indication that, besides a base catalyzed reaction, another decomposition reaction (thermal) of the cyclic peroxide takes place. Good fits for the second order disappearance of 21 were found, Tables XI, XII and XIII.

In the isotope studies (Tables V and VI), a large (five fold) excess of base was used and it is felt that the thermal reaction will be minimal under those conditions. Therefore, the ratio of products obtained in the reaction of the mixture 54 and 53 with base and in the reaction of 56 with base illustrates the isotope effect in the reaction of cyclic peroxide 57 or 58 with base.

Mumford's cyclic peroxide does not yield allylic hydroperoxides upon reaction with base. A remarkable difference is observed in the behaviour of the tetrasubstituted and trisubstituted perepoxides. The tetrasubstituted cyclic peroxide reacts with base or thermally to yield allylic hydroperoxides only.

Several attempts to prepare the perepoxide of tetramethylethylene were unsuccessful. A slow reaction took place between 21 and silver tetrafluoroborate but no evidence for a cyclic peroxide was found in the n.m.r. spectrum of the reaction mixture. Kirschke (74)found the presence of acetone by g.l.c. in the reaction product from reaction between 21 and silver perchlorate. It was impossible to repeat Kirschke's experiment since it was impossible to stop benzene from freezing at -10°. Kirschke's claim of the cyclic peroxide, formed in the reaction of 21 with silver perchlorate, which decomposes to acetone appears doubtful, since Mumford (132) found that 21 itself decomposes in the g.l.c. to give acetone. Mumford was able to prepare his cyclic peroxide since it is fairly stable towards base, which is clearly not the case in the perepoxide of tetramethylethylene.

EXPERIMENTAL

All the experiments described below for the deuterated materials were first carried out on the corresponding light compounds. The reaction conditions were adjusted to obtain optimum yields for the different reactions.

Perdeuteracetone Cyanohydrin (42):

This compound was prepared according to the procedure of Organic Synthesis (104) for the normal compound. In a 500 ml three-necked flask was placed 25 g (0.39 mole) of acetone-$\underline{d}_6$, 22 g (0.45 mole) sodium cyanide and 48 ml of deuterium oxide. The flask was cooled in an ice bath and the contents stirred with a mechanical stirrer. A solution of 28 ml concentrated sulphuric acid-$\underline{d}_2$ in 79 ml of deuterium oxide was added at such a rate to keep the temperature of the mixture below 15° (3 hours). After the addition was completed, the solution was stirred for another 15 minutes. The reaction mixture was once extracted with 100 ml of ether and the aqueous solution was subsequently continuously extracted with ether for 36 hours. The combined dried ether extracts were freed of solvent and the residue distilled to give 33 g (93%) of 42, b.p. 78-80° (17 mm), $\eta_D^{25} = 1.3966$. Reported for the light compound (104) b.p. 78-82° (15 mm), $\eta_D^{19} = 1.4002$. The infrared spectrum ($CHCl_3$) showed absorption bands at 2400-2700 and 2250 cm^{-1}. The n.m.r. spectrum (neat) did not show any absorption.

Methyl-3,3,3-trideuterio-2-hydroxy-2-trideuteriomethyl Propionate (44):

The method of Young, Dillon and Lucas (105) was used with slight modification for the hydrolysis of 42 to the corresponding acid 43. A solution of 32.5 g (0.35 mole) of 42 and 35 g of concentrated hydrochloric acid in 14 ml of water was heated at 95° for 2 hours. During this time a white precipitate appeared. Sodium sulfate (12 g) was added and the mixture cooled to -15°. The precipitate was filtered off and the filtrate as well as the precipitate was extracted continuously with ether for 2 days. The combined ethereal solutions of the acid 43 were used as such for the methylation. A small sample of acid was isolated from the ethereal solution and characterized, m.p. 75-76°, reported for the light compound (133) 79°. The infrared spectrum ($CHCl_3$) showed absorption bands at 2500-3600 cm^{-1}, and 2230 and 1730 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) showed one singlet at τ 3.24.

The ethereal solution of 43 was treated with diazomethane at 0°. Diazomethane was prepared from N-nitrosomethylurea following the procedure of Organic Synthesis (134). The ethereal solution after the reaction was dried and freed of solvent. Distillation of the residue gave 33.0 g (74%) of 44, b.p. 133-134°, η_D^{25} = 1.4069. Reported for the normal compound (135) b.p. 137°. The infrared spectrum ($CHCl_3$) showed abosrption bands at 3250-3600 cm^{-1}, and 2230, 2210 and 1745 cm^{-1}. The n.m.r. spectrum (CCl_4) showed peaks at τ 6.31 (s) and τ 6.67 (s), in the ratio 3.10:1.0, required 3:1.

3-Methyl-2-trideuteriomethyl-1,1,1-trideuterio-2,3-butanediol (45):

A solution of methylmagnesium iodide in ether was prepared from 26.4 g (1.1 mole) of magnesium and 200 g (1.45 mole) methyl iodide. The ethereal solution was stirred in a three-necked flask, fitted with a reflux condenser, dropping funnel and mechanical stirrer, and 33 g (0.27 mole) of 44 in 150 ml ether added at such a rate as to maintain a reflux of the ether. After the additicn was completed, the mixture was stirred for four hours. The reaction mixture was decomposed by pouring it into a beaker containing ice and hydrochloric acid. The amount of acid was regulated to effect a neutral solution after decomposition. The ethereal layer was separated and the aqueous solution extracted continuously with ether for two days.

A separate experiment indicated that only 10% of pinacol was recovered from an aqueous pinacol solution by five extractions with ether. However, recovery of 95% pinacol was made after two days continuous liquid-liquid extraction.

The product of the reaction has to be very dry in order for the next step to proceed in the desired way. The combined ethereal extracts were dried over magnesium sulfate, then allowed to stand for 24 hours over molecular sieves (4A). The ethereal solution was then poured through a column containing molecular sieves. The ethereal solution was freed of solvent and the residue distilled to give 29 g (88%)of 45, b.p. 164-167°. Reported (136) b.p. 172°.

The n.m.r. spectrum (CCl_4) showed peaks at τ 7.23 (s) and τ 8.82 (s), in the ratio 1.0 : 3.05, required 1 : 3.

2-Methyl-3-trideuteriomethyl-1,1,1-trideuterio-2-butene (40):

A mixture of 27 g (0.218 mole) 45 and 32.2 g (0.218 mole) ethyl orthoformate was allowed to react in the manner outlined in the preparation of 1. Final distillation of the product gave 10.9 g (54%) of 40, b.p. 69.5-70.5°. Reported for the normal compound b.p. 73°. The infrared spectrum (CCl_4) showed absorption bands at 2250, 2180, 2120 and 2060 cm^{-1}. The n.m.r. spectrum (CCl_4) showed one peak at τ 8.40 (s). The mass spectral analysis at 12 ev indicated that the product consisted of 0.51 mole % of $\underline{d}_3$-, 0.10 mole % of $\underline{d}_4$-, 2.5 mole % of $\underline{d}_5$- and 96.88 mole % of $\underline{d}_6$-2,3-dimethyl-2-butene. This indicates that the two gem-dimethyl groups are 99.4% deuterated.

Methyl Iodide-$\underline{d}_3$ (49):

Trimethyloxosulphonium iodide (47) was prepared in 35.5% following the procedure of Kuhn and Trischmann (108). The salt 47 (350 g) was exchanged four times with deuterium oxide containing potassium carbonate in the manner described by Nelson and co-workers (107) to yield 250 g (75%) of trimethyloxosulphonium iodide-$\underline{d}_9$ (48). The pyrolysis of 48 was carried out at 200°/ 20 mm following Nelson's procedure (107). The crude methyl iodide-$\underline{d}_3$ was washed with saturated sodium thiosulfate, ice water and dried over calcium chloride. The liquid was distilled to give 120 g (73.6%) of

49, b.p. 40-41°. Reported (107) b.p. 41°. The mass spectral analysis at 12 ev indicated that the product consisted of 0.84 mole % of $\underline{d}_1$-, 9.04 mole % of $\underline{d}_2$- and 90.05 mole % of $\underline{d}_3$-methyl iodides. Calculated from these mole per cents, compound 46 is 96.4 per cent deuterated.

2,3-*Bis*-trideuteriomethyl-2,3-butanediol (50):

Methylmagnesium iodide-$\underline{d}_3$ was prepared under nitrogen from 120 g (0.83 mole) 49 and 18 g (0.75 mole) magnesium in 700 ml ether. The solution was transferred under nitrogen through a glass wool plug into a 2 l three-necked Morton flask which had been flushed with nitrogen and filled with 800 ml anhydrous ether. The three-necked flask was fitted with a high speed stirrer, reflux condenser and dropping funnel. A solution of 28 g (0.325 mole) of freshly distilled (b.p. 86-87°) and dried (magnesium sulfate) 2,3-butanedione in 200 ml ether was added at such a rate to maintain a mild reflux of the ether. High speed stirring was used throughout the addition and for 8 hours after the addition was completed. The work-up procedure and drying were identical to those described in the preparation of 45. The residue after removal of the ether was distilled to give 34 g (79%) of 50, b.p. 163-168°. Reported for the light pinacol (136) b.p. 172°. The n.m.r. spectrum showed peaks at τ 6.49 (s) and τ 8.78 (s) in the ratio 1.0 : 3.04, required 1 : 3.

2,3-*Bis*-trideuteriomethyl-2-butene (41):

A mixture of 34 g (0.28 mole) 50 and 41 g (0.28 mole) ethyl orthoformate were reacted in the manner outlined in the preparation of 1. Final distillation of the product gave 14 g (56%) of 41, b.p. 69-70.5°. The infrared spectrum (CCl_4) showed absorption bands at 2235, 2180, 2130 and 2060 cm^{-1}. The n.m.r. spectrum showed one peak at τ 8.41 (s). The mass spectral analysis at 9.5 ev indicated that the product consisted of 0.31 mole % d_2-, 0.77 mole % of d_3-, 3.09 mole % of d_4-, 18.4 mole % of d_5- and 77.43 mole % of d_6- tetramethylethylene. This indicates that the two methyl groups are 95.31 % deuterated.

Material Balance in Elimination Reaction of 21:

A solution of 0.7672 g 21 and 0.201 g benzene in 10.0 ml methanol was prepared. A solution of 0.489 g sodium hydroxide in 10.0 ml methanol was prepared in the same way. Three n.m.r. tubes were filled with 0.20 ml of substrate solution and 0.40 ml of base solution each and sealed at -70°. The reactions were carried out at 25°, 2° and -19°. The n.m.r. tubes were kept at the respective temperatures for 28 hours, long enough for complete reaction to occur at -19°. The n.m.r. analysis of the reaction mixture showed only allylic hydroperoxide (2) present. The results are shown in Table III.

β-Bromohydroperoxides from 3-Methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene (40) (80.65% D):

The reaction was carried out as described in the preparation of 21, from 5.3 g (0.06 mole) 40, 8.52 g (0.03 mole) 20 and 10 g

(0.3 mole) 98% hydrogen peroxide. Crystallization from pentane gave 8.5 g (76%) of the corresponding β-bromohydroperoxides, m.p. 90-92°. The ratio of the two products was determined by n.m.r. and the results are shown in Table IV.

Allylic Hydroperoxides from the β-Bromohydroperoxides of 40 (80.65% D):

The reaction between 8.5 g (0.042 mole) of the mixture of β-bromohydroperoxides from 40 and 4 g (0.1 mole) sodium hydroxide in 150 ml methanol was carried out in the usual fashion at 0°. Distillation of the residue gave 1.9 g (42%) of the allylic hydroperoxides, b.p. 55-59° (17 mm). The ratio was determined by n.m.r. and the results are shown in Table V.

The Addition-Elimination Reaction of 3-Methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene (40) (99.3% D):

The mixture of β-bromohydroperoxides of 40 was prepared as described above. A solution of 0.0697 g mixture 51 and 52 and 0.0179 g benzene in 1.0 ml methanol-d_4 was prepared. Similarly a solution of 0.038 g sodium and 0.0463 g deuterium oxide in 2.0 ml methanol-d_4 was prepared. N.m.r. sample tubes, filled with 0.15 ml substrate solution and 0.30 ml base solution at -70°, were kept in an ice-water bath for 6 hours and analyzed by n.m.r.. The results are shown in Table VI.

2-Bromo-2,3-dimethyl-3-methoxybutane (55):

The procedure described for the preparation of 21 was used to prepare a solution of 55 from 5 g (0.059 mole) 1, 9.6 g (0.3 mole) of methanol and 8.1 g (0.029 mole) of 1,3-dibromo-5,5-dimethylhydantoin (20) in 50 ml ether. The solution was freed of solvent and residue distilled to give 9.2 g (79%) of 55, b.p. 75-77° (15 mm) which crystallized on standing. Recrystallization from methanol gave 7.3 g (63%) of 55, m.p. 71-73°. The n.m.r. spectrum (CCl_4) showed peaks at τ 6.70 (s), τ 8.26 (s) and τ 8.67 (s) in the ratio 1.0 : 2.0 : 2.04, required 1 : 2 : 2. Due to the high vapour pressure no satisfactory analysis could be obtained.

Mixture of β-Bromomethoxides from 40 (99.3% D):

The procedure described above for the preparation of 55 was used with 0.15 g (0.0016 mole) 40, 0.23 g (0.0008 mole) of 20 and 0.26 g (0.008 mole) methanol in 5 ml ether. After work-up, short path distillation gave 0.095 g of a mixture of β-bromomethoxides which was analysed by n.m.r. spectroscopy, see Table VIII.

2-Bromo-2,3-bis-trideuteriomethyl-3-butyl Hydroperoxide (56):

This compound was prepared in the usual fashion from 3 g (0.033 mole) 41, 4.8 g (0.017 mole) 20 and 5 g (0.15 mole) 98% hydrogen peroxide. After work-up, recrystallization from pentane gave 5 g (75%) of β-bromo-2,3-bis-trideuteriomethyl-3-butyl hydroperoxide, m.p. 90-92°. The infrared spectrum (CCl_4) showed absorption bands at 3550, 3200-3500, 2250 and 2160 cm^{-1}. The n.m.r. spectrum (CCl_4) showed peaks at τ 8.2 (s) and τ 8.6 (s) in the ratio 0.96 : 1.0, required 1 : 1.

Reaction between 2-Bromo-2,3-*bis*-trideuteriomethyl-3-butyl Hydroperoxide and Base:

A solution of 0.0733 g 56 and 0.0184 g benzene in 1.0 ml methanol-d_4 was prepared. An aliquot (0.15 ml) of this solution was added to 0.30 ml of base solution used in the eliminations above and the mixture sealed in a n.m.r. tube at -70°. The mixture was reacted at 0° for 6 hours and analyzed by n.m.r. spectroscopy. The results are shown in Table IX.

Reaction Rates of 2-Bromo-2,3-dimethyl-3-butyl Hydroperoxide with Base:

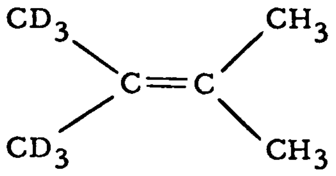
Volumetric solutions of 21 and base in methanol were prepared. Aliquots of these solutions were transferred to an n.m.r. tube at -78° and the n.m.r. tube transferred to the probe of a HR-100 varian analytical spectrophotometer. The reactions were followed by repetitive scanning, the results are shown in Tables XI, XII, XIII, XIV, XV.

CHAPTER III

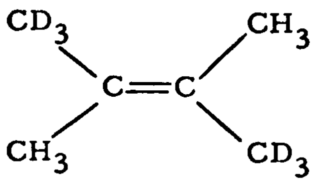
DEUTERIUM ISOTOPE EFFECTS IN REACTIONS WITH SINGLET OXYGEN.

The object of the work discussed in this chapter is to find more information concerning the mechanism of the reaction between singlet oxygen and olefins. Two different mechanisms have been proposed for this reaction. Sharp (27) and later Kopecky (28) suggested a two-step reaction. First an intermediate with ionic character is formed, followed by a hydrogen transfer to yield an allylic hydroperoxide. Foote (33) suggested a concerted mechanism similar to the one of the "ene" reaction (137). An attempt was made to distinguish between the two proposed mechanisms by means of tracer studies.

Intramolecular deuterium isotope effects were determined in the reactions of singlet oxygen with the two deuterated tetramethylethylenes 40 and 41.



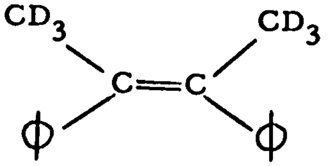
40



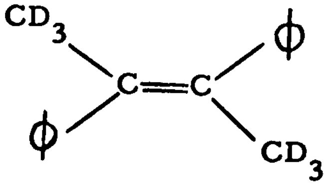
41

Singlet oxygen was generated in three different ways: by dye-sensitization, by the reaction between alkaline hypochlorite and hydrogen peroxide and by decomposition of a triphenyl phosphite-ozone complex.

The cis- and trans-dimethyl-$\underset{=}{d}_6$-stilbenes (59 and 60) were prepared and the intermolecular deuterium isotope effects were determined in the dye-sensitized photooxidation reaction.



59



60

RESULTS

Preparation of the Deuterated Dimethylstilbenes:

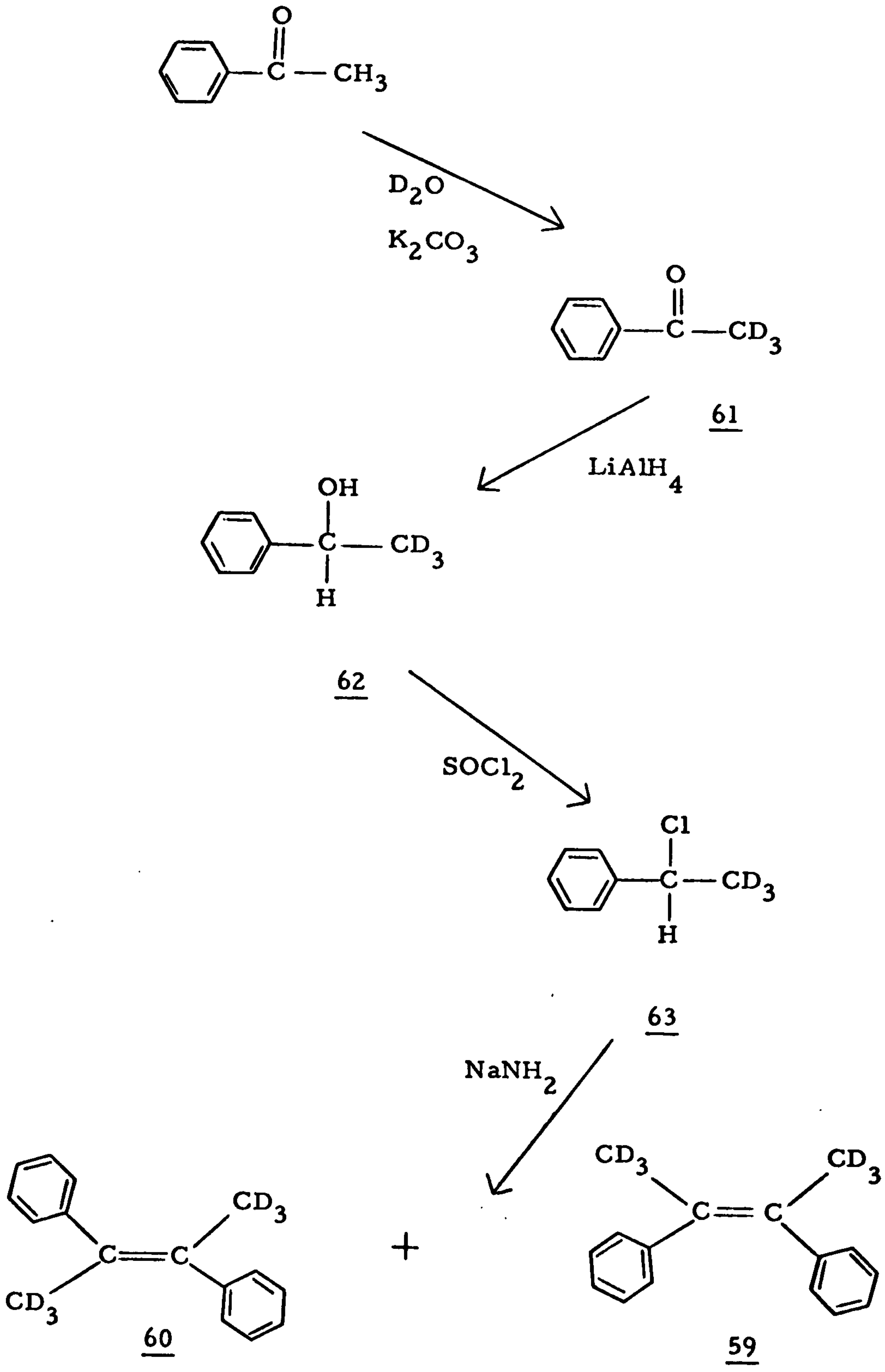
It has been established that hydrogens on a carbon α to a carbonyl group are exchangeable by deuterium. The normal process of exchange is by reaction of the compound to be exchanged with deuterium oxide containing a trace of base. This process has to be repeated numerous times with new deuterium oxide baths to achieve a high deuterium content. Besides being expensive, difficulties may be encountered in separating the compound to be exchanged from the heavy water.

Mislow and coworkers (138) found that compounds containing enolizable hydrogens could be exchanged by passing them through a column with alumina pretreated with deuterium oxide. However, only 100 mg of ketone on 25 g of pretreated alumina could be exchanged this way. It was found that a higher ratio of carbonyl compound to alumina could be exchanged if the alumina was treated with 10 per cent potassium carbonate in deuterium oxide.

Acetophenone was exchanged this way using basic alumina made to activity V with deuterium oxide containing 10% potassium carbonate. Before the alumina was made up to activity V, it was exchanged four times with deuterium oxide. After each exchange, the heavy water was driven off and analyzed by n.m.r. for the water content. After the fourth exchange, the water content of the driven-off deuterium oxide was less than one per cent and the alumina was deactivated to activity V as mentioned above. Acetophenone-$\underline{d}_3$ (61) was recovered by this exchange procedure in 67% yield. The n.m.r. spectrum (CCl_4) showed that 92.5% of the methyl group was deuterated. This procedure for exchange is not too expensive, fast, and does not give any isolation problems.

Compound 61 was converted in a three step process into a mixture of cis- and trans-dimethyl-$\underline{d}_6$-stilbenes, see Scheme 6. The reduction of acetophenone-$\underline{d}_3$ with lithium aluminium hydride gave a 91.5% yield of 1-phenylethanol-2,2,2-$\underline{d}_3$ (62). The infrared spectrum (CCl_4) of 62 showed absorption bands at 3600 and 3200-3550 cm^{-1} for the free and bonded -OH stretching vibrations, and at 2220 cm^{-1} for the C-D stretching vibrations. The absence of a doublet τ8.75 and the change of a quartet to a singlet at τ 5.40 in the n.m.r. spectrum (CCl_4) showed that the compound 62 was extensively deuterated in the 2-position. Reaction of compound 62 with thionyl chloride resulted in a 90% yield of 1-phenylethylchloride-2,2,2-$\underline{d}_3$ (63). The infrared spectrum showed absorption bands at 2225 and 2120 cm^{-1} for the C-D symmetric and antisymmetric stretching vibrations. The absence of a doublet at τ8.39 and the change of a quartet to a singlet at τ4.89 in the n.m.r. spectrum showed that the 2-position of 63 was completely deuterated. The coupling reaction with sodium amide (88) was carried out to give an 87% yield of a 65:35 mixture of cis- and trans-dimethyl-$\underline{d}_6$-stilbenes. The two stilbenes were separated by fractional crystallization. G.l.c. analysis showed each isomer to be free of the other one.

Scheme 6



The infrared spectrum (CCl_4) of 59 showed abosrption bands at 2240, 2200, 2115 and 2060 for the C-D symmetric and antisymmetric stretching vibrations. The n.m.r. of this compound shows a singlet at τ 3.09 for the aromatic protons. The absence of a singlet at τ 7.87 which is present in the n.m.r. spectrum of the corresponding light compound indicates that two methyl groups are highly deuterated. The mass spectral analysis at 9.5 ev indicated that 59 contained at least 91.96 per cent deuterium in the two methyl groups. The cracking pattern in the mass spectrum at 70 ev (figure 6) is similar to the one in the mass spectrum of the light *cis*-dimethylstilbene (figure 7). The infrared spectrum (CCl_4) of 60 showed absorption bands at 2230, 2200, 2110 and 2060 cm^{-1} for the C-D symmetric and antisymmetric stretching vibrations. The n.m.r. spectrum (CCl_4) of the compound shows a singlet at τ 2.40 for the aromatic protons. The absence of a singlet τ 8.15 which was found in the n.m.r. spectrum of the corresponding light compound indicated that 60 was extensively deuterated in the two methyl groups. The cracking pattern in the mass spectrum at 70 ev (figure 8) is similar to the one in the mass spectrum of the light *trans*-dimethylstilbene (figure 9).

Intramolecular Deuterium Isotope Effects in the Reaction of Deuterated Tetramethylethylenes with Singlet Oxygen:

Singlet oxygen was suggested (33) to be the reactive species in either the dye-sensitized photooxygenation of olefins or

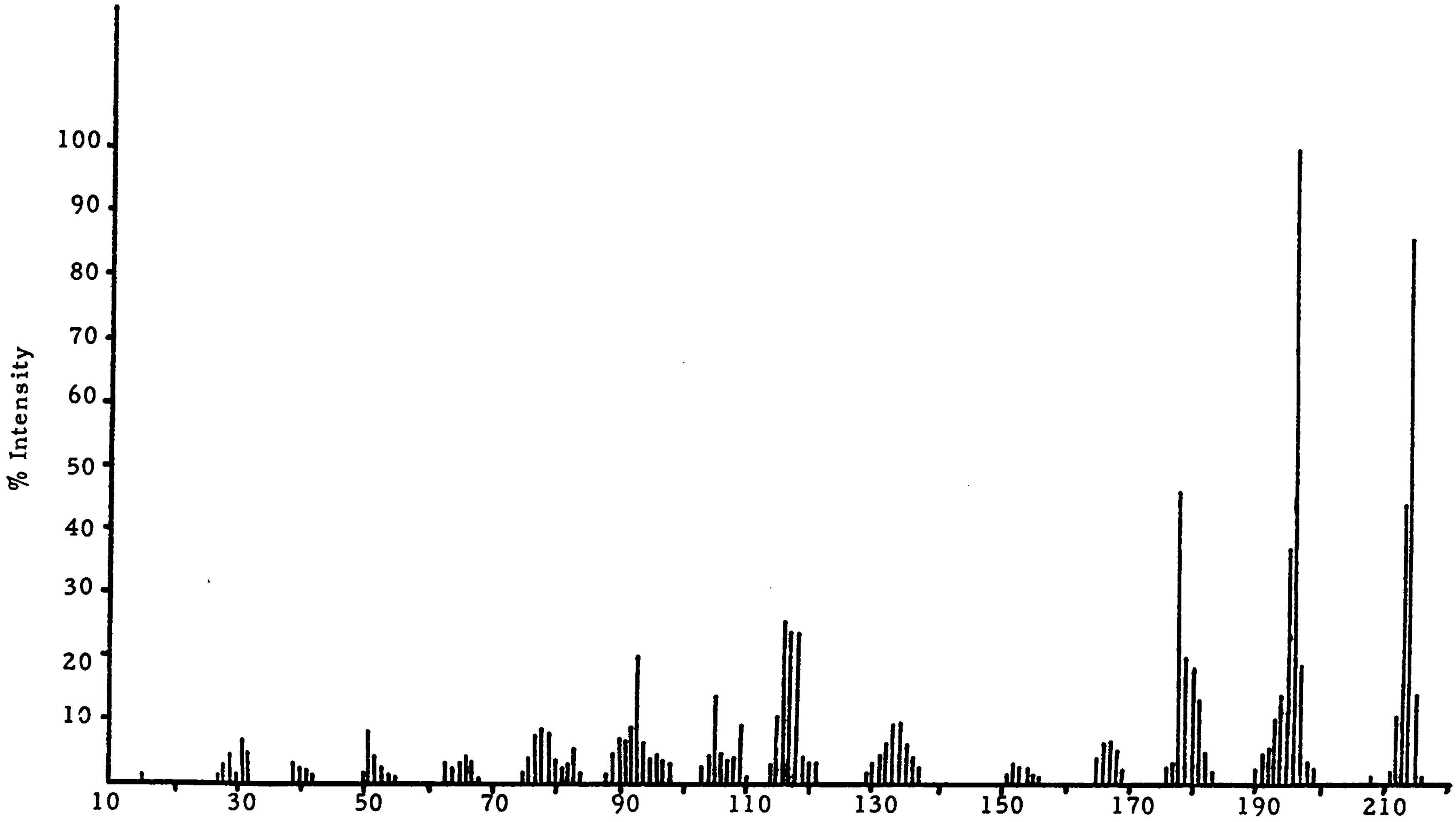


Figure 6. Mass spectrum (70 ev) of cis-dimethyl-d_6-stilbene (59).

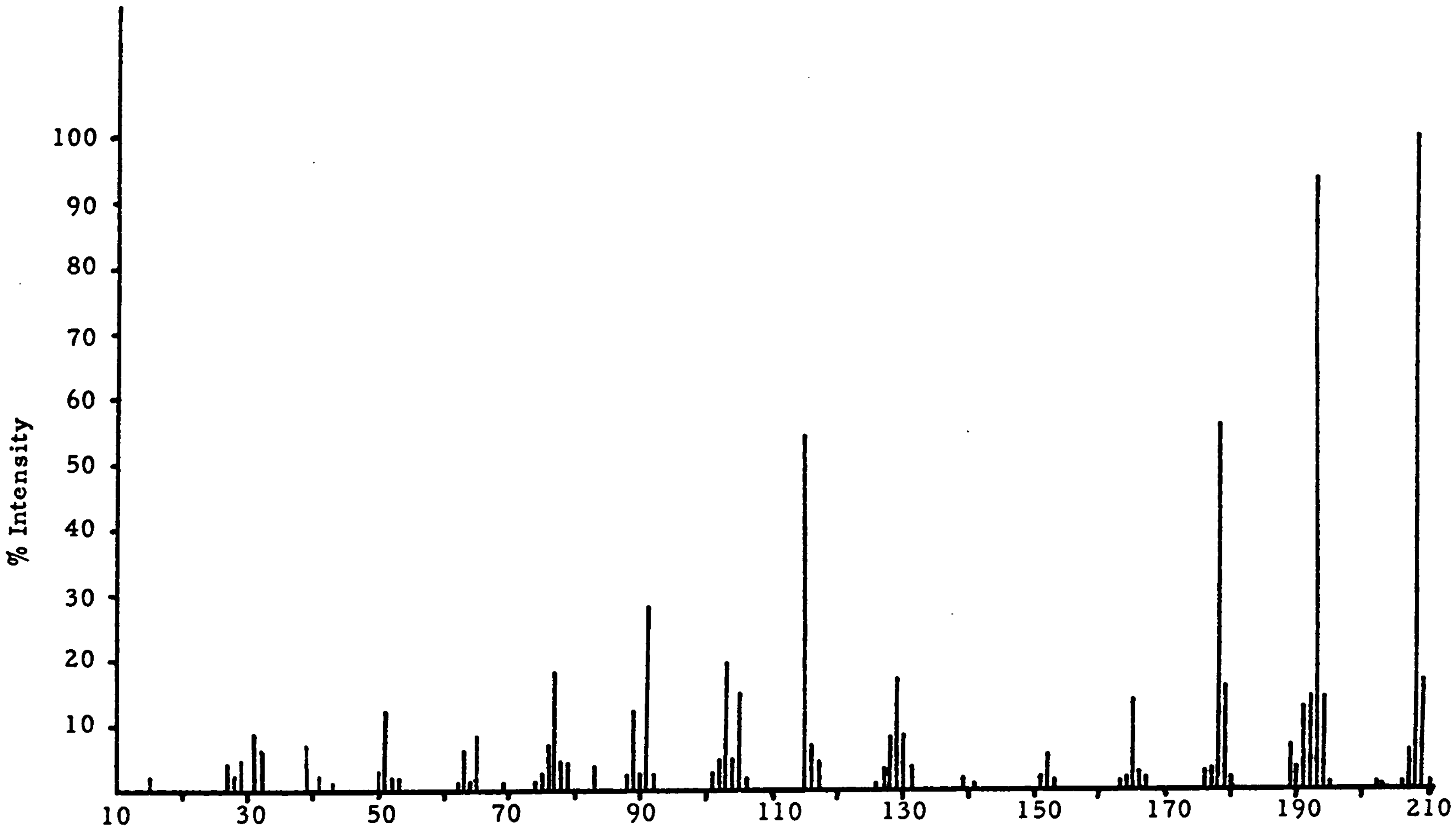


Figure 7. Mass spectrum (70 ev) of cis-Dimethylstilbere (25).

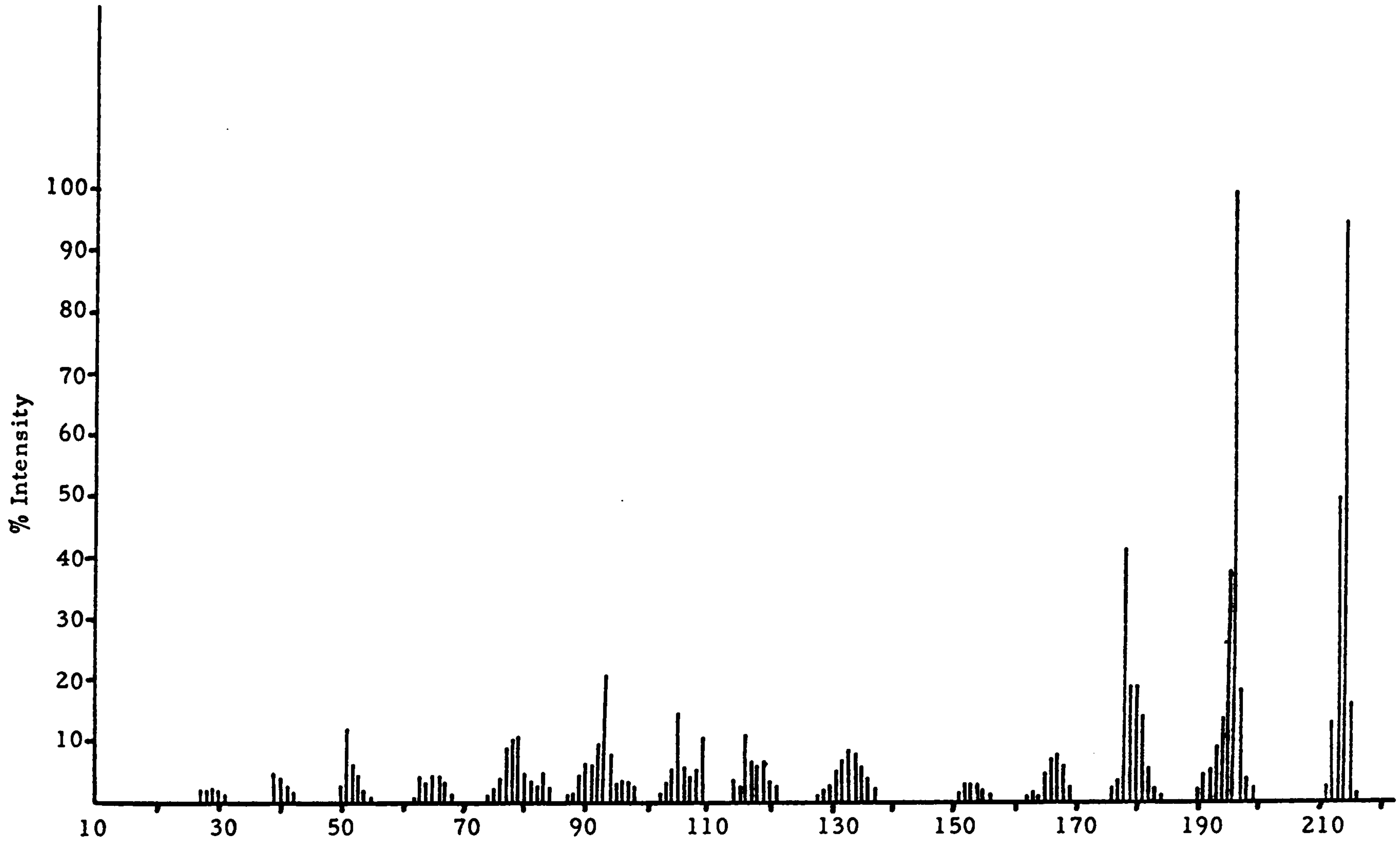


Figure 8. Mass spectrum (70 ev) of trans-Dimethyl-d_6-stilbene (60).

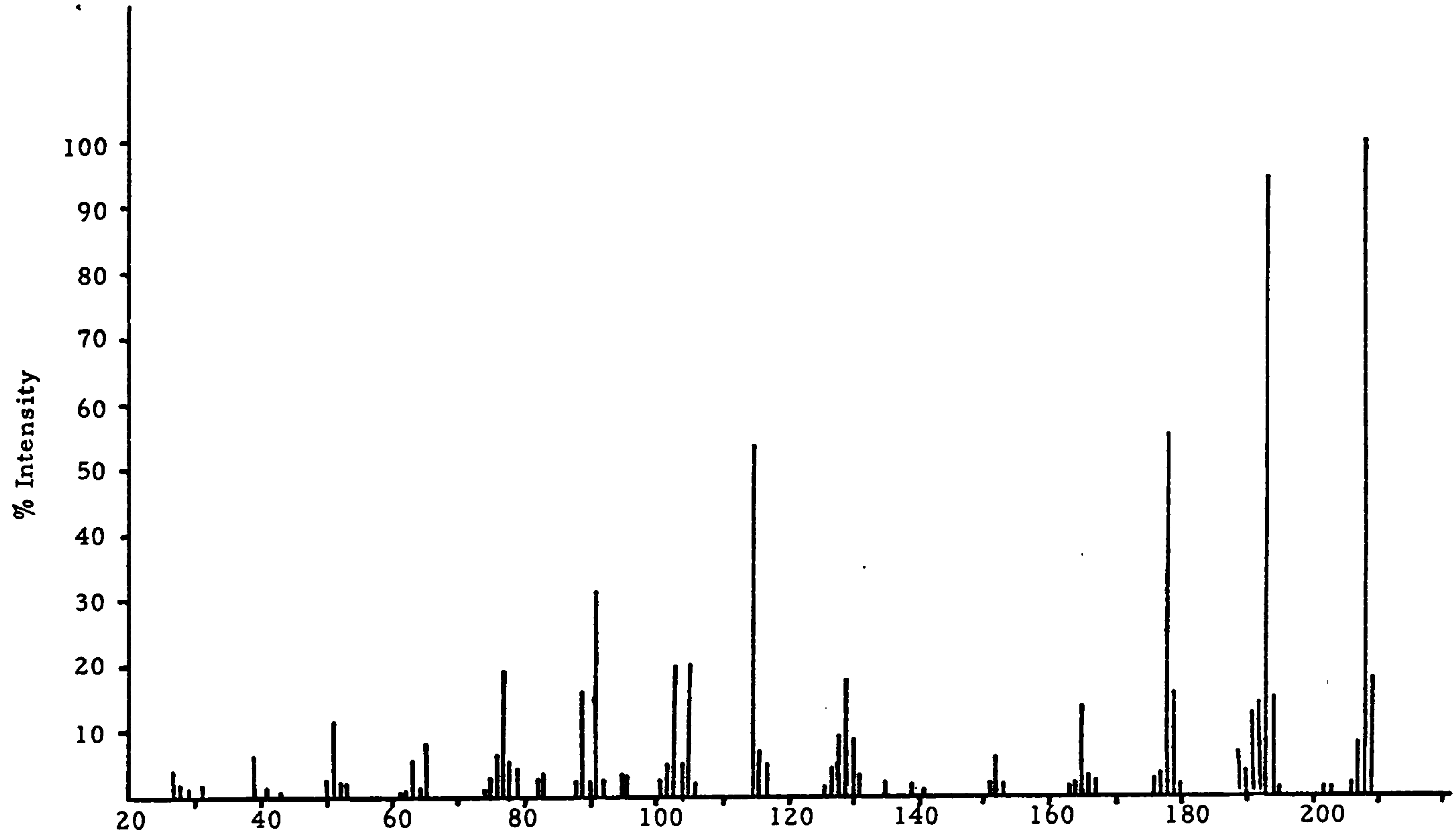


Figure 9. Mass spectrum (70 ev) of trans-Dimethylstilbene (26).

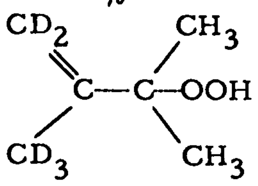
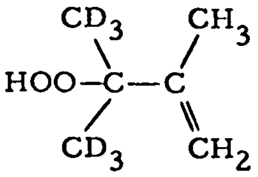
the hypochlorite-hydrogen peroxide oxidation of olefins. A comparison of the deuterium isotope effects in the two reactions with 40 was expected to give a confirmation of the singlet oxygen intermediacy in these allylic oxidations.

Compound 40 was oxygenated with methylene blue as a sensitizer and a mixture of the allylic hydroperoxides 53 and 54 was isolated 48.4% yield. The n.m.r. spectrum showed that the ratio 53/54 was different from one. The results are shown in Table XIV. The runs given in this table and the following tables were triple integrated and the three sets of numbers calculated from these integrals. The product composition in this experiment and the following ones with 40 are calculated using the expressions of equations [27] and [29]. A small isotope effect was obtained in this reaction. The olefin 40 was also subjected to hypochlorite-hydrogen peroxide oxygenation and the mixture of allylic hydroperoxides (53 and 54) isolated in a 28% yield. The ratios of the two products are shown in Table XV. The isotope effect is a small one, similar to the one observed in the photooxygenation. The similar isotope effects in the chemical oxygenation and in the dye-sensitized photooxygenation would indicate that a similar oxidizing species, singlet oxygen, is present in both reactions.

Dilute solutions of 40 (0.045 molar) were subjected to the dye-sensitized photooxygenations using different sensitizers. The reactions were carried out using methanol as a solvent. The methanolic reaction mixtures were poured into water and were

TABLE XIV

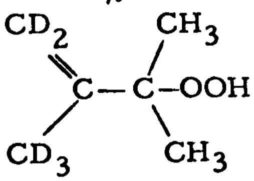
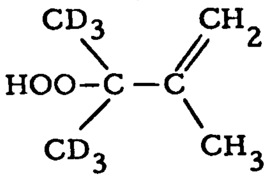
Methylene Blue Sensitized Photooxidation of 3-Methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene [0.44 M] in Methanol at 14°C.

% D	% 	% 	$\frac{k_H}{k_D}$	$\frac{k_H}{k_D}$ corrected[a]
80.65	43.3	56.7	1.31	1.42
	43.7	56.3	1.29	1.38
	43.3	56.7	1.31	1.42
			$\frac{k_H}{k_D}$ average =	1.41± 0.02
99.3	42.3	57.7	1.36	1.36
	42.9	57.1	1.33	1.33
	42.6	57.4	1.35	1.35
			$\frac{k_H}{k_D}$ average =	1.35± 0.01

[a] corrected as in Table V

TABLE XV

Hypochlorite-Hydrogen Peroxide Oxygenation of 3-Methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene in Methanol/Water at 0°.

% D	% 	% 	$\frac{k_H}{k_D}$	$\frac{k_H}{k_D}$ corrected
80.65	43.7	56.3	1.29	1.39
99.3	40.4	59.6	1.46	1.46
	40.3	59.7	1.48	1.48
	40.4	59.6	1.46	1.46

$\frac{k_H}{k_D}$ average = 1.47 ± 0.01

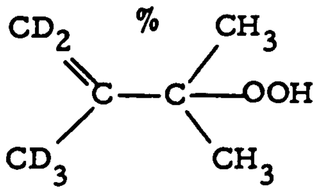
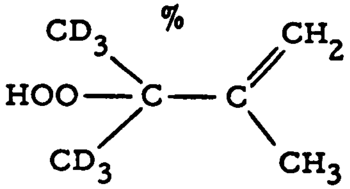
extracted with ether and the combined ether extracts dried. The ether was removed by means of rotary evaporation in the presence of carbon tetrachloride. The carbon tetrachloride solutions of 53 and 54 were analyzed by n.m.r. spectroscopy. The results are shown in Table XVI. The results showed a slight variation in isotope effect when different sensitizers were used. No relationship was present, however, between the isotope effect and the triplet state energy of the sensitizer. The variations of the deuterium isotope effect are very small and could well be considered to be within experimental error. Dye-sensitized photooxygenations, using methylene blue and eosin-y as sensitizers, were carried out on 40 in methanol at -52°. The results are shown in Table XVII. The results show that the isotope effects observed in these reactions were slightly higher than those of the previous runs at 14°.

Recently Murray and coworkers (41) found that the decomposition of a triphenyl phophite-ozone complex gave triphenylphosphite and oxygen in the singlet state. It was found that tetramethylethylene was oxidized using Murray's procedure to the allylic hydroperoxide at -28° (carbon tetrachloride slurry) in 60% yield. The same reaction was carried out on 40 to 49% yield of the mixture of allylic hydroperoxides. The isotope effect was calculated from the n.m.r. spectrum and the results are shown in Table XVIII. The deuterium isotope effect is very similar to the ones observed in the chemical (hydrogen peroxide-hypochlorite) and photochemical oxygenation reactions. This is a good indication that a similar

TABLE XVI

The Effect in the
Variation of Sensitizer in Photooxygenation of 3-Methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene

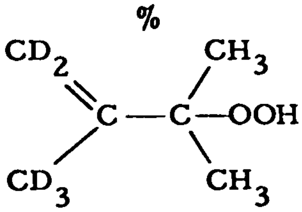
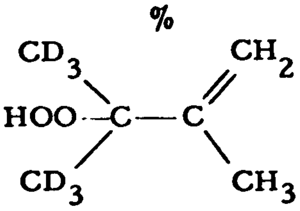
0.0446 in Methanol at 14°.

Sensitizer E_t in Kcal	Methylene blue 34	Rose Bengal 44	Fluorescein 51	Eosin-y 47
% 	43.0	41.9	42.0	41.4
	43.5	42.9	43.1	41.4
	43.3	41.4	42.9	41.5
% 	57.0	58.1	58.0	58.6
	56.5	57.1	56.9	58.6
	56.7	58.6	58.0	58.5
$\frac{k_H}{k_D}$	1.33	1.39	1.38	1.41
	1.30	1.33	1.32	1.42
	1.31	1.42	1.38	1.41
Average $\frac{k_H}{k_D}$	1.31±0.01	1.38±0.04	1.36±0.03	1.41±0.01

$\frac{k_H}{k_D}$ average = 1.37± 0.04

TABLE XVII

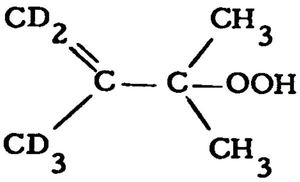
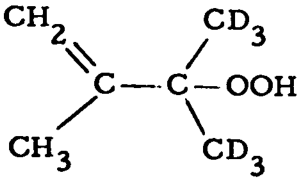
Dye-sensitized Photooxygenation of 3-Methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene (0.0456 mole/liter) in Methanol at -52°.

Sensitizer	Methylene Blue	Eosin-y
% 	42.1	41.0
	42.6	41.3
	43.1	40.5
% 	57.9	59.0
	57.4	58.7
	56.9	59.5
$\frac{k_H}{k_D}$	1.38	1.44
	1.35	1.42
	1.32	1.47
$\frac{k_H}{k_D}$ average	1.35± 0.02	1.44± 0.02

$\frac{k_H}{k_D}$ average = 1.40± 0.05

TABLE XVIII

Deuterium Isotope Effects in the Reaction of 3-Methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene with a triphenyl phosphite-ozone Complex at -28° in Methylene Chloride.

% 	% 	$\frac{k_H}{k_D}$	$\frac{k_H}{k_D}$ average
40.8	59.2	1.45	
40.9	59.1	1.44	1.45± 0.01
40.7	59.3	1.46	

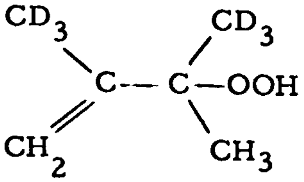
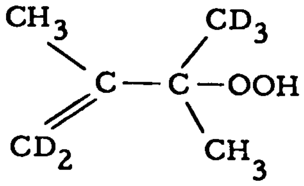
reactive oxygen species, singlet oxygen, is involved in all three reactions.

The isotope effects determined above do not give much information about the manner in which singlet oxygen is transferred to tetramethylethylene to yield the allylic hydroperoxide. In an attempt to find more information about the oxygen transfer, the deuterium isotope effects were studied in the oxygenation reaction of 2,3-*bis*-trideuteriomethyl-2-butene (41). In a two-step mechanism, the first step is the formation of an intermediate with ionic character. In the intermediate of compound 40, a charge can be localized on either the carbon bearing the methyl groups or on the carbon bearing the methyl-d_3 groups. A charge localized on the carbon bearing the methyl groups is favored and an isotope effect of the second kind is to be expected in going from the ground state of 40 to the intermediate in the two-step reaction. In the reaction of 41, however, the localized charge can be on only a carbon bearing a methyl group and a methyl-d_3 group, since the compound 41 is symmetrically deuterated. No isotope effect of the second kind is therefore expected in the oxygenation of 41 and the total deuterium isotope effect is expected to be somewhat smaller in the reaction of singlet oxygen with 41 than in the reaction with 40, if a two-step mechanism is operating in these reactions.

Compound 41 was subjected to dye-sensitized photooxidation and the deuterium isotope effects were calculated using the expression of equation [34]. The results are shown in Table XIX.

TABLE XIX

Methylene Blue Sensitized Photooxidation of 2,3-Bis-trideuteriomethyl-2-butene [0.444 M] in Methanol at 14°.

		$\frac{k_H}{k_D}$	$\frac{k_H}{k_D}$ corrected
56.5	43.5	1.30	1.32
56.7	43.3	1.31	1.33
55.6	44.4	1.25	1.27
57.1	42.9	1.33	1.35

Average $\frac{k_H}{k_D}$ = 1.32 ± 0.03

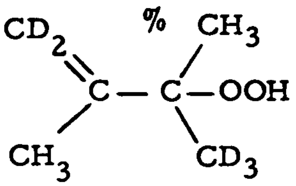
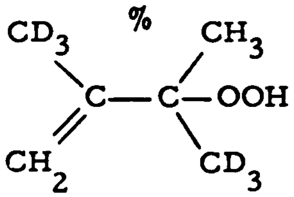
The results show that the isotope effect is very similar in this reaction to the one observed in the dye-sensitized photooxidation of 40. This is an indication that the reaction between singlet oxygen and olefins is unlikely to be a two-step process. Compound 41 was also reacted with a variety of sensitizers in methanol at 14°. The results are shown in Table XX. Again a slight variation was shown in the isotope effect with a change in sensitizer. The change of isotope effect with change of sensitizer has no direct correlation with the energy of the sensitizer.

A sensitized oxygenation at low temperature, -52°, was carried out with compound 41. The results are shown in Table XXI. The results show that the isotope effects are slightly higher at this temperature, similar to what was observed in the sensitized reaction of 40 at low temperature. Compound 41 was also reacted with the triphenyl phosphite-ozone complex in methylene chloride at -28°. The results are shown in Table XXII. The isotope effects observed are slightly lower than those of the photosensitized reactions, but this difference found is not considered to be significant.

In the previous chapter, it was shown that the cyclic peroxide of tetramethylethylene reacts with base to give allylic hydroperoxide. In the reactions of the cyclic peroxides of 40 and 41 with sodium hydroxide, the observed isotope effect k_H/k_D was ca. 2.15. Also evidence of a thermal decomposition of the cyclic peroxide was shown which has a smaller isotope effect. The formation of a cyclic peroxide, which decomposes thermally, could be involved in the

TABLE XX

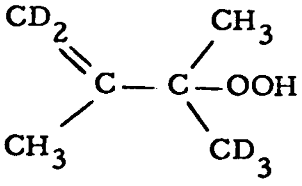
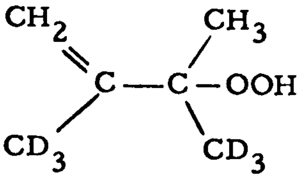
The Effect in the
Variation of Sensitizer in Photooxygenation of 2,3-Bis-trideuteriomethyl-2-butene [0.0453] in Methanol at 14°.

Sensitizer E_t in Kcal	Methylene Blue 34	Rose Bengal 44	Fluorescein 51	Eosin-y 47
% 	40.6	42.3	43.5	42.6
	42.3	42.0	44.3	45.3
	42.4	43.3	41.6	45.0
% 	59.4	57.7	56.5	57.4
	57.7	58.0	55.7	54.7
	57.6	56.7	58.4	55.0
$\frac{k_H}{k_D}$	1.46 1.36 1.36	1.36 1.38 1.31	1.30 1.26 1.40	1.35 1.21 1.22
$\frac{k_H}{k_D}$ corrected	1.49 1.38 1.38	1.38 1.41 1.33	1.32 1.28 1.43	1.37 1.23 1.24
Average $\frac{k_H}{k_D}$	1.42±0.05	1.37±0.03	1.34±0.06	1.28±0.06

$\frac{k_H}{k_D}$ average = 1.35±0.07

TABLE XXI

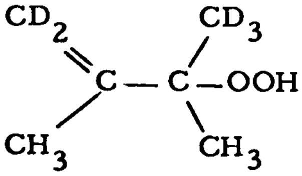
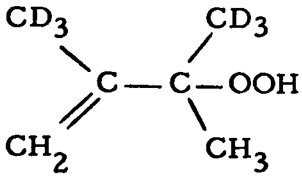
Dye-Sensitized Photooxygenation of 2,3-Bis-trideuterio-2-butene [0.0466 M] in Methanol at -52°.

Sensitizer	Methylene Blue	Eosin-y
% 	40.8 40.8 38.6	42.1 40.1 41.4
% 	59.2 59.2 61.4	57.9 59.9 58.6
$\frac{k_H}{k_D}$	1.45 1.45 1.59	1.38 1.49 1.41
$\frac{k_H}{k_D}$ Corrected	1.48 1.48 1.63	1.41 1.52 1.44
Average $\frac{k_H}{k_D}$	1.53 ± 0.07	1.46 ± 0.05

Average $\frac{k_H}{k_D} = 1.50 \pm 0.07$

TABLE XXII

Deuterium Isotope Effects in the Reaction of 2,3-*Bis*-trideuterio-methyl-2-butene with a Triphenyl Phosphite-ozone Complex at -28° in Methylene Chloride.

% 	% 	$\frac{k_H}{k_D}$	$\frac{k_H}{k_D}$ corr.	$\frac{k_H}{k_D}$ average
44.5	55.5	1.25	1.27	1.27
44.5	55.5	1.25	1.27	
44.5	55.5	1.25	1.27	

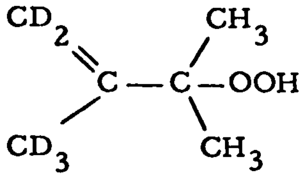
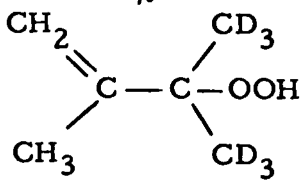
reaction of tetramethylethylene with singlet oxygen. The presence of base should change the isotope effect considerably (to a higher value) in the dye-sensitized reaction if this goes through a cyclic peroxide. Methylene blue could not be used as a sensitizer since it is sensitive to base. An eosin-y sensitized oxygenation of 40 in the presence of sodium hydroxide was carried out at -52°. The reaction mixture was allowed to stand at -65° for 1.5 hours after the reaction was finished and then slowly warmed to 0° (2 hours). This was done in order to give a possible cyclic peroxide the time to react with base and not decompose thermally. The results are shown in Table XXIII. From the results, it can be seen that the isotope effect is slightly lower than normal. If the cyclic peroxide would have been involved, a higher isotope effect would have been expected in the presence of base, hence this possibility can be ruled out.

Schenck (139) had reported that *cis*-dimethylstilbene (25) reacted faster than the *trans* isomer (26) and that no isomerization took place in the dye-sensitized photooxidation. A mixture of 25 and 26 was subjected to a methylene blue sensitized photooxidation and the starting materials left at times determined by g.l.c. (S.F. 96) with bibenzyl as an internal standard. The relative rates for the *cis* and *trans* compound were calculated using an expression derived by Foote (33), equation [39].

$$[39] \quad \frac{k_{cis}}{k_{trans}} = \frac{\log(\text{cis}_t / \text{cis}_0)}{\log(\text{trans}_t / \text{trans}_0)}$$

TABLE XXIII

Deuterium Isotope Effects in the Eosin-y Sensitized Reaction of 3-Methyl-2-trideuteriomethyl-1,1,1-trideuterio-2-butene [0.089 M] in the Presence of Sodium Hydroxide [0.825 M] in Methanol at -52°.

% 	% 	$\frac{k_H}{k_D}$	$\frac{k_H}{k_D}$ average
43.5	56.5	1.30	
43.5	56.5	1.30	1.30
43.5	56.5	1.30	

The amounts of starting materials left were also determined by n.m.r. spectroscopy. Aliquots of the reaction mixture were extracted with ether and the dried ethereal solutions reduced by lithium aluminium hydride. The starting materials and the internal standard were separated from the reaction mixture by column chromatography and analyzed by n.m.r.. The results of these experiments are shown in Table XXIV. The results show that there is quite a variation in the rate ratios determined by g.l.c.. Since there is a large difference in rates, the error in the determination of starting materials left is fairly large. The relative rates determined in this experiment are in agreement with Schenck's observation that $\underline{25}$ reacts faster than $\underline{26}$.

Intermolecular deuterium isotope effects were determined in the photooxidation of the deuterated dimethylstilbenes. The isotope effects were calculated following the procedure given below.

A mixture of $\underline{\text{cis}}$-dimethylstilbene ($\underline{25}$) and $\underline{\text{cis}}$-dimethyl-$\underline{d}_6$-stilbene ($\underline{59}$) was prepared and analyzed by low energy (9.5 ev) mass spectroscopy. If it is assumed that there were originally N moles of dimethylstilbenes, it can be calculated from the mass spectra that there were:

$\frac{55.34}{100}$ N moles of hydrogen compound $\underline{25}$ and

$\frac{44.66}{100}$ N moles of deuterium compound $\underline{59}$.

This mixture was oxygenated with eosin-y as a sensitizer. The

TABLE XXIV

Relative Rates of Oxidation of cis- and trans-Dimethylstilbene (25 and 26) in the Methylene Blue Sensitized Photooxidation at 14° in Methanol.

t in min.	G.l.c. mmoles 25	G.l.c. mmoles 26	G.l.c. $\frac{k_{cis}}{k_{trans}}$	N.m.r. mmoles 25	N.m.r. mmoles 26	N.m.r. $\frac{k_{cis}}{k_{trans}}$
0	1.21	1.19	-	1.39	1.43	-
25	0.11	0.92	9.3	0.13	0.97	6.1
30	0.06	0.90	11.5	0.09	0.96	7.1
35	0.02	0.88	13.2	0.06	0.94	7.6

average $\frac{k_{cis}}{k_{trans}} = 11.4 \pm 1.6$

average $\frac{k_{cis}}{k_{trans}} = 6.9 \pm 0.6$

reaction was stopped when 73% of the normal compound had reacted as determined by n.m.r. spectroscopy. This indicates that 0.73 x 55.34/100 N = 17.02/100 N moles of starting material were left. The reaction mixture was extracted with ether and the dried ether solution reduced with lithium aluminium hydride. The starting material was separated from the reaction mixture by column chromatography and was analyzed by low energy mass spectrometry. The ratio of 25:59 was found to be 52.64 : 47.36. The amount of deuterated starting material left is calculated to be:

$$\frac{47.36}{52.64} \times \frac{17.02}{100} N = 15.31 \text{ N moles.}$$

Knowing the amounts of starting materials after 73% reaction and before reaction, the isotope effect can be calculated using equation [40]:

$$[40] \quad \frac{k_H}{k_D} = \frac{\log (17.02\ N/\ 55.34\ N)}{\log (15.31\ N/44.66\ N)} = 1.10$$

The results of the experiments on the dimethylstilbenes are shown in Table XXV. The results show that the isotope effects are small and similar for the cis and trans compounds.

TABLE XXV

Deuterium Isotope Effects in the Dye-sensitized Photooxidation of Dimethylstilbenes in Methanol at 14°.

Compound	Sensitizer	Starting ratio		% Reaction of		Produced ratio		
		$\frac{\mathbf{25}}{\mathbf{59}}$	$\frac{\mathbf{26}}{\mathbf{60}}$	**25**	**26**	$\frac{\mathbf{25}}{\mathbf{59}}$	$\frac{\mathbf{26}}{\mathbf{60}}$	$\frac{k_H}{k_D}$
cis	Methylene Blue	1.24	-	73	-	1.14	-	1.07
cis	Eosine-y	1.24	-	69	-	1.11	-	1.10
trans	Methylene Blue	-	1.29	-	49	-	1.20	1.10

DISCUSSION

For a long time the mechanism of the dye-sensitized photooxidation was subject to several interpretations as outlined in the introduction. The elegant work by Foote and coworkers (29, 30, 32, 33, 38) showed that the same results were obtained, whether the olefins were reacted in the photooxidation or in the chemical oxidation. From Foote's results and interpretations, the singlet oxygen mechanism has been widely accepted as the mechanism for the dye-sensitized photooxidation as well as for the hypochlorite-hydrogen peroxide oxidation.

Similar deuterium isotope effects were observed in either the photosensitized or hypochlorite-hydrogen peroxide oxidation of compound 40. A very similar isotope effect was also observed in the reaction of 40 with a triphenyl phosphite-ozone complex. The latter reactions has also been suggested to go via the intermediacy of singlet oxygen (31, 41). The similarity in the deuterium isotope effects of the three different reactions above is in agreement with the singlet oxygen mechanism.

A "mole" oxygen complex between sensitizer and oxygen, as proposed by Schönberg (21), was expected to be sensitive to the sensitizer used. If this mechanism is operating, different isotope effects could be expected in the reactions of 40 and 41 with a change in sensitizer. Small differences in isotope effects are found between the various sensitizers. All the values are within 10 per cent of the average isotope effect and are random. No correlation could be found between the triplet-state energy of the sensitizer and the observed k_H/k_D's. Tetramethylethylene reacts very quickly in the photosensitized oxidation and is expected to have a low activation energy for this reaction. This means that if a change in isotope effect occurred by changing the sensitizer, this change is expected to be small and might well be within the experimental error of the experiments. Kopecky (28) and Wilson (35) found, however, that in reactions, which probably have significant activation energy, no change occurred in the relative rates of oxidation of several olefins by changing the sensitizer.

The intermediacy of a cyclic peroxide, in the reaction between singlet oxygen and tetramethylethylene, was disproven. If a cyclic peroxide would have been formed, the isotope effect should increase in the sensitized oxygenation reaction of <u>40</u> in the presence of base, since a base catalyzed reaction of the cyclic peroxide of <u>40</u> was shown in Chapter II to have an isotope effect of 2.15. The actual observed value of $k_H/k_D = 1.3$ in the dye-sensitized photooxidation of <u>40</u> in the presence of base ruled out a cyclic peroxide in this reaction.

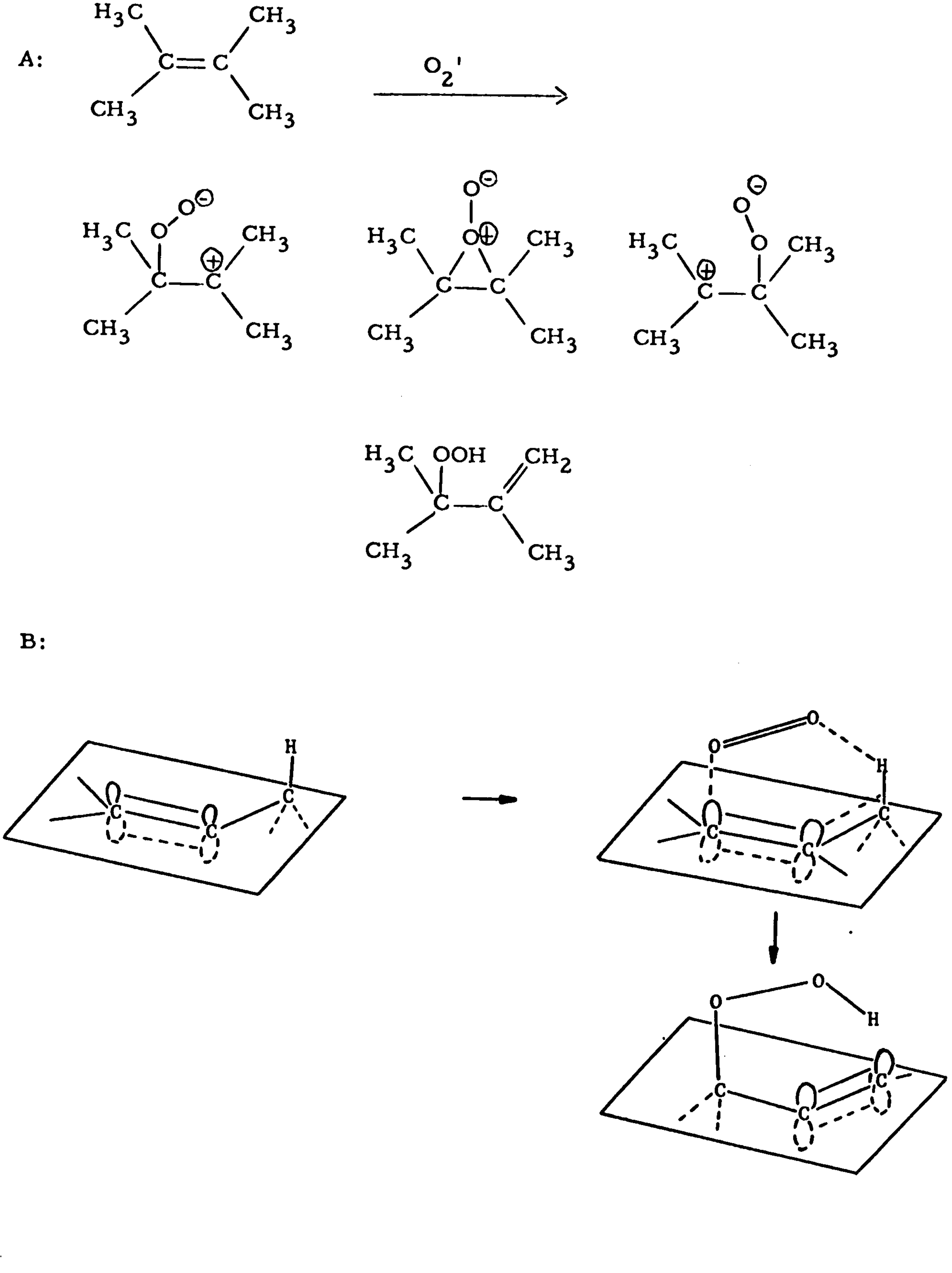
The two possible mechanism for the reaction between singlet oxygen and tetramethylethylene are:

A. The two-step mechanism

B. Concerted mechanism

Both mechanisms are shown in Scheme 7. The deuterium isotope effect in the reactions of <u>40</u> and <u>41</u> with singlet oxygen are expected

Scheme 7



to be small if mechanism A is operating. The abstraction of a hydrogen (or deuterium) from the methyl group, which is attached to a carbon atom with a positive charge, by a hydroperoxy anion is expected to be very fast. As was explained in the results section of this chapter, a small difference in isotope effects in the oxidations of 40 and 41 is expected if the reaction goes via mechanism A. The concerted mechanism, B, could have larger isotope effects in the reactions of 40 and 41 with singlet oxygen. In a primary isotope effect, which is expected for mechanism B, the important factor is the C-H versus the C-D cleavage regardless of whether the methyl-d_3 groups are geminal (40) or vicinal (41) and a similar isotope effect is expected for the oxydation of 40 and 41.

The observed isotope effects in the reactions of singlet oxygen with either 40 or 41 are similar and small (Tables XIV and XIX). Small isotope effects can, however, be explained for a concerted mechanism. Scheme 7 shows, that in the transition state of the concerted mechanism, the relationship between the oxygen, hydrogen and carbon is nonlinear. Lewis and coworkers (116, 117) have pointed out that in such reactions, it may more nearly be said that a bending rather than a stretching vibration is converted to translational motion (115). Assuming a carbon-hydrogen bending frequency of 1400 cm^{-1}, the zero-point energy is about 2 kcal/mole. The correspoinding carbon-deuterium frequency, ν_D, is about 1000 cm^{-1} and the zero-point energy about 1.45 kcal/mole. The difforence in zero-point energies is $1/2\ h\nu_H - 1/2\ h\nu_D = 0.55$ kcal/mole. In a symmetrical transition state where the bending vibration becomes translational motion, this difference is lost and the net difference in activation energy for the reaction of C-H or C-D is just 0.55 kcal/mole. This corresponds to a factor of 3.3 in rate at 25°, which is the maximum possible isotope effect for such a process.

Bigeleisen (140) and Westheimer (115) pointed out that if the transition state is not symmetrical, very small primary isotope effects (theoretically even inverse) could be observed. In linear transition states, the value of the primary isotope effect can be as low as 1.4 (115). In a nonlinear transition state, as in mechanism B, even lower primary isotope effects could be expected.

Since it is not known how much difference is expected in the isotope effects, for the reactions of <u>40</u> or <u>41</u> with singlet oxygen if mechanism A is operative, this mechanism can not be ruled out on the basis of the observed isotope effects.

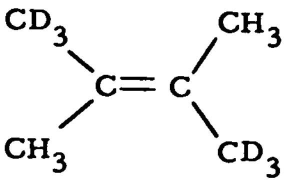
No Markovnikoff-type directing effects were observed in the photooxygenations of trisubstituted olefins (2). Foote (141) found no change in the ratio of products by changing substituents on the phenyl ring of trimethyl styrene which is an indication that little charge is localized in the transition state. Both observations show that no charge is localized in the dye-sensitized oxidation, and they are in disagreement with mechanism A.

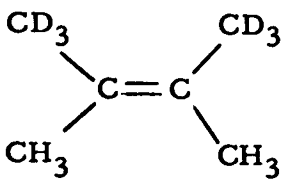
Nickon (61, 62, 63) found that in cyclic olefins the allylic hydrogen has to be in an axial or pseudo-axial position for reaction with singlet oxygen to occur. This observation can not be explained in terms of a two step mechanism. The first step, formation of an intermediate with ionic character should occur regardless whether the allylic hydrogens are axial or equatorial. The next step, abstraction of a hydrogen, should not have the stringent steric requirement as was found by Nickon. If the abstraction of a hydrogen in the second step would be impossible due to steric reasons, it means that a reversible addition of oxygen to a cyclic olefin without axial (or pseudo-axial) hydrogens takes place, which is unlikely.

On the grounds of the evidence presented above, mechanism A can be ruled out. The observed deuterium isotope effects in the reaction of 40 and 41 with singlet oxygen are in agreement with a concerted mechanism.

In the oxygenation of compound 40, an added steric effect could be expected since the oxygen can approach the carbon bearing the methyl-$\underline{d}_3$ groups easier because of the smaller steric requirements of these compared to the methyl group. Therefore, the observed isotope effect is somewhat larger than the true isotope effect.

Steric effects also play a role in the singlet oxygen reaction of 41. Compound 41 can exist in the *trans* and the *cis* form.



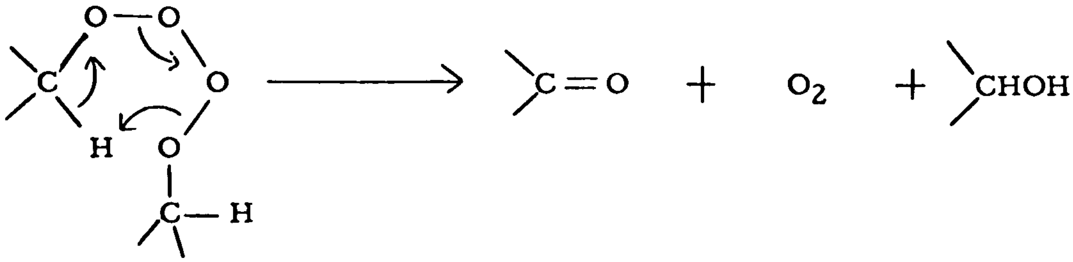


The oxygen will approach from that side of the double bond where the allylic hydrogen (or deuterium) to be abstracted is located. In the trans-41, the oxygen can approach the carbon easier from the methyl-d_3 side and the observed isotope effect will be larger than the true isotope effect. In the cis-41, the oxygen can approach again easier from the methyl-d_3 side but must then abstract a deuterium and the observed isotope effect will be smaller than the true one. Assuming a 50 : 50 ratio of cis : trans, the observed isotope effect will be equal to the true isotope effect on the basis of steric effects.

In the isotope studies carried out, an added α-deuterium isotope effect is introduced. The methyl group, from which the deuterium is abstracted, has two deuterium atoms and an isotope effect is expected in going from a sp^3 hybridized carbon to a sp^2 hybridized one (119). These isotope effects are normal ($k_H/k_D > 1$) and in the experiments carried out will cause an observed isotope effect higher than the true isotope effect.

In compound 40, a steric effect as well as an α-deuterium isotope effect will make the observed isotope effect higher than the true primary isotope effect. In compound 41, only the α-deuterium isotope effect will make the observed isotope effect larger than the true primary isotope effect. A small isotope effect would be expected if the transition state lies close to starting material or close to product. Since the reaction of singlet oxygen with tetramethylethylene is fast, a low activation energy is expected for these reactions. This would indicate that the transition state in the reaction of tetramethylethylene with singlet oxygen lies close to starting material.

A similar small primary isotope effect of $k_H/k_D = 1.37$ was observed by Ingold (142) in the chain termination reaction of secondary peroxy radicals. This reaction is thought to go through a tetroxide as depicted in the Russell mechanism (143) below.



A nonlinear relationship between the carbon, hydrogen and oxygen is found in this mechanism, similar to the concerted mechanism of singlet oxygen with olefins.

Small isotope effects are observed in the oxygenations of the deuterated dimethylstilbenes. In these reactions, the transition state probably lies again close to the starting materials. A differentiation between a two step and a one step mechanism cannot be made on the basis of the isotope effects observed.

EXPERIMENTAL

Acetophenone-$\underline{d}_3$ (61):

Basic alumina (Harshaw Chemical Co.) (380 g) was heated in a porcelain dish for 2 hours and subsequently it was cooled in a desicator containing calcium chloride. After the alumina was cooled down to room temperature, a solution of anhydrous potassium carbonate (5.7 g) in 57 g deuterium oxide was added and the mixture shaken for 24 hours. The alumina activity V (in D_2O) was put in two 5 ft x 17 mm chromatography columns and a solution of freshly distilled acetophenone (30 g) in pentane was passed through both columns. Analysis by n.m.r. showed that 67% of the hydrogens of the methyl group were replaced by deuterium. The pentane solution was passed through freshly prepared 250 g of alumina activity V in deuterium oxide after which analysis bv n.m.r. showed that 75% of the methyl group was deuterated. Alumina with a very high deuterium content in the deuterium oxide was prepared according to Mislow's (138) procedure. Alumina (300 g) was shaken over-night with 18 ml of deuterium oxide. Then the deuterium oxide was removed at 200° and 0.1 mm pressure and collected in a Dry Ice trap. This process was repeated three more times. The pumped-off water was analyzed by n.m.r. for protium oxide content, of which the results are shown in Table XXVI.

TABLE XXVI

Amount of Water in the Deuterium Oxide after Exchange with Basic Alumina.

% H_2O	Exchange Number
10.2	1
3.85	2
2.80	3
0.4	4

The alumina free of protium oxide in this manner was made up to activity V in deuterium oxide in the manner described above. The pentane solution of acetophenone (75% deuterated) was passed through a column containing the alumina prepared above. The solvent was removed and the residue distilled to give 20 g (67%) <u>61</u>, b.p. 89-90° (15 mm). Reported (144) for the light compound b.p. 91° (16 mm). The analysis by n.m.r. (CCl_4) showed that 92.6% of the hydrogens of the methyl group were replaced by deuterium.

<u>1-Phenylethanol-2,2,2-*d*$_3$ (62):</u>

The procedure described by Rao (145) was followed to react 20 g (0.163 mole) of <u>61</u> with 1.7 g (0.045 mole) of lithium aluminium hydride in 75 ml ether. Distillation of the final product gave 18.6 g (91.5%) <u>62</u>, b.p. 97-98° (18 mm), η_D^{25} = 1.5245.

Reported for the corresponding light compound (146) b.p. 90° (15 mm), N_D^{15} = 1.5260. The infrared spectrum (CCl_4) shows absorption bands at 3600, 3200-3550 and 2220 cm^{-1}. The n.m.r. spectrum (CCl_4) shows peaks at τ 2.7 (s), τ 5.33 (s) and τ 6.23 (s), in the ratio 5.15:1.0:1.0, required 5:1:1.

1-Phenylethylchloride-2,2,2-$\underline{d}_3$ (63):

Thionyl chloride (18.5 g, 0.155 mole) was stirred in a 100 ml three-necked flask which was cooled in an ice-bath. A solution of 18.5 g (0.149 mole) 62 in 20 ml anhydrous (sodium) benzene was added dropwise while the temperature was kept at 0°. After the addition was completed, the reaction was stirred for another hour at 0° and for two hours at 60°. The solvent was removed by distillation and the residue distilled to give 19.2 g (90.0%) 63, b.p. 76-77° (13 mm), η_D^{25} = 1.5235. Reported (146) for the light compound 93° (30 mm).

Cis- and trans-dimethyl-$\underline{d}_6$-stilbene (59 and 60):

The procedure for the preparation of 25 and 26 was followed with 19.2 g (0.14 mole) and 5.7 g (0.145 mole) of sodium amide to yield 13 g (87%) of a 65:35 mixture of 59 and 60. Fractional crystallization gave 59, m.p. 63-64°, reported (102) for the light compound, m.p. 66°; and 60, m.p. 103-104°, reported (102) for the light compound, 107°. Both compounds were free of the other isomer as determined by n.m.r. and g.l.c. (SF-96). The infrared spectrum (CCl_4) of 59 showed absorption bands at 2240, 2200, 2115 and 2060

cm^{-1}. The n.m.r. spectrum (CCl_4) showed one singlet at τ 3.09. The mass spectral analysis at 9.5 ev showed that the product contained 0.17 mole % $\underline{d}_0$-, 0.14 mole % $\underline{d}_1$-, 0.09 mole % $\underline{d}_2$-, 0.9 mole % $\underline{d}_3$-, 6.45 mole % $\underline{d}_4$-, 30.68 mole % $\underline{d}_5$- and 61.6 mole % $\underline{d}_6$-cis-dimethyl stilbenes. Calculated from these numbers, the two methyl groups are 91.96% deuterated. The infrared spectrum (CCl_4) of 60 showed absorption bands at 2230, 2210, 2110 and 2060 cm^{-1}. The n.m.r. spectrum (CCl_4) shows a singlet at τ 2.50. The mass spectral analysis at 9.5 ev showed that the product contained 0.07 mole % $\underline{d}_0$-, 0.03 mole % $\underline{d}_1$-, 0.09 mole % $\underline{d}_2$-, 0.90 mole % $\underline{d}_3$-, 6.65 mole % $\underline{d}_4$-, 30.80 mole % $\underline{d}_5$- and 61.47 mole % $\underline{d}_6$-trans-dimethylstilbenes. Calculated from these numbers, the two methyl groups are 92.05% deuterated.

Methylene Blue Sensitized Photooxidation of 40:

A solution of 1 g 40 (80.65 deuterated or 99.3% deuterated) in 25 ml methanol (0.444 M) and 15 mg methylene blue was oxygenated as described in the preparation of 2. The oxygen uptake in 45 minutes was 300 ml (STP), theoretical 246 ml. The work up procedure was similar as described in the prepartion of 2 and distillation of the residue gave 0.65 g (48.4%) of a mixture of 53 and 54, b.p. 57-59° (17 mm), η_D^{29} = 1.4375. Reported (10) for the light compound b.p. 55° (12 mm), η_D^{20} = 1.4428. The mixture was analyzed by n.m.r. spectroscopy and the results are shown in Table XIV.

Hypochlorite-Hydrogen Peroxide Oxidation of 40:

This reaction was carried out as described in a similar preparation of 2 from 1 g (0.011mole) of 40 (80.65% or 99.3% deuterated), 7.7 ml (0.072 mole) 30% hydrogen peroxide and 78 ml 0.78 N (0.06 mole) sodium hypochlorite. The work-up procedure was identical to the one described in the preparation of 2. Final distillation gave 0.35 g (28%) of a mixture of 53 and 54, b.p. 58-63° (25 mm), η_D^{29} = 1.4345. Reported (10) for the light compound b.p. 55° (12 mm), η_D^{20} = 1.4428. The mixture of products was analyzed by n.m.r. spectroscopy, the results are shown in Table XV.

Photooxygenation with Sensitizer Variation of 40:

Aliquots (25 ml) of a 0.0446 molar solution of 40 in methanol were subjected to photooxidation using different sensitizers. The reaction mixtures, after reaction, were poured into water and were extracted with ether. The ether solution was washed with water and dried. The solvent was removed from the dried ethereal solution by means of a rotary evaporator. Carbon tetrachloride (2 ml) was added and the solutions were analyzed by n.m.r. and the results are shown in Table XVI.

Photooxygenations of 40 at -52°:

Solutions (0.0456 M) of 40 in methanol were oxidized at -52°. The low temperature was maintained by cooling the jacketed test tube with nitrogen which was led through a copper spiral kept in liquid nitrogen. The reactions were worked up and analyzed as described above. The results are shown in Table XVII.

Reaction of Triphenyl Phosphite-Ozone Complex with 1:

A solution of 4.4 g (0.014 mole) freshly distilled triphenyl phosphite in 75 ml dry (phosphorous pentoxide) methylene chloride was stirred in a 250 ml three-necked flask at -75°. Ozone was introduced until a blue color persisted in the solution. Excess ozone was flushed out with nitrogen (5 min) and a solution of 1 g (0.012 mole) 1 in 10 ml methylene chloride was added. The mixture was stirred for 150 minutes at -28° (carbon tetrachloride slurry). After warming up to room temperature, the methylene chloride was removed through a Nestor-Faust annular teflon spinning band column. Distillation of the residue gave 0.86 g (60%) of 2, b.p. 50-54° (15 mm), $^{25}_{D}$ = 1.4395. Reported (10) b.p. 55° (12 mm), $^{20}_{D}$ = 1.4428. The infra-red and n.m.r. spectra were identical to those of 2 prepared in the photosensitized reaction.

Reaction of Triphenyl Phosphite-Ozone Complex with 40:

The triphenyl phosophite-ozone complex was prepared from 2.2 g (0.007 mole) triphenyl phosphite as described above and allowed to react with 0.6 g (0.006 mole) 40 in the same manner as outlined above. Distillation gave 0.36 g (49%) of a mixture of 53 and 54, b.p. 50-56° (12 mm). The mixture was analyzed by n.m.r. spectroscopy and the results are shown in Table XVIII.

Methylene Blue Sensitized Photooxidation of 41:

The reaction was carried out as described earlier in the preparation of 2, with 1 g (0.011 mole) 41. After work-up, distillation yielded 0.7 g (56%) of the mixture of allylic hydroperoxides, b.p. 58-60° (17 mm). The mixture was analyzed by n.m.r. and the results are shown in Table XIX.

Photooxygenation of 41 with Sensitizer Variation:

A 0.0453 M solution of 41 in methanol was oxidized with different sensitizers as outlined in the identical experiment on 40. The work-up procedure was similar as described in that experiment. The results are shown in Table XX.

Photooxygenation of 41 at -52°:

Solutions of 41 (0.0466 M) in methanol were oxidized at -52° in a similar manner as described in the low temperature oxidation of 40. The results are shown in Table XXI.

Reaction of Triphenyl Phosphite-Ozone Complex with 41:

The triphenyl phosphite-ozone complex was prepared from 2.2 g (0.007 mole) triphenyl phosphite as described earlier and reacted with 0.6 g (0.006 mole) 41 in the same manner as outlined above. Distillation gave 0.28 g (40%) of a mixture of allylic hydroperoxides, b.p. 49-54° (15 mm) $n_D^{25} = 1.4395$. The mixture was analyzed by n.m.r. and the results are shown in Table XXII.

Photooxygenation of 40 in the Presence of Base at -52°:

A solution of 40 (0.089 M) and sodium hydroxide (0.825 M) in methanol was oxidized with eosin-y as a sensitizer at -52°. After the reaction was finished, the mixture was kept at -65° for 1.5 hours and then very slowly warmed to 0° (2 hours). The reaction work-up was similar to the ones of the other low temperature runs. The mixture of 53 and 54 was analyzed by n.m.r. spectroscopy. The results are shown in Table XXIII.

Relative Rates of Sensitized Oxidation of cis- and trans-Dimethylstilbene:

A mixture of 0.253 g 25, 0.251 g 26 and 0.204 g bibenzyl was prepared and analyzed by n.m.r. and g.l.c. (S.F. 96, 165°). The response factors of these compounds for the g.l.c. were determined: bibenzyl 100, 25 93.3 and 26 93.8. After the methylene blue sensitized oxidation had started, aliquots were taken out and analyzed by g.l.c.. The aliquots were reduced with lithium aluminium hydride and chromatographed over basic alumina. The hydrocarbons were removed by pentane and were analyzed by n.m.r. spectroscopy. The results are shown in Table XXIV.

Deuterium Isotope Effects in Photooxidation of Dimethylstilbenes:

Mixtures of 25 and 59 and of 26 and 60 were prepared and analyzed by low energy mass spectrometry. The mixtures were subjected to dye-sensitized photooxidation and the reaction was followed by n.m.r.. After the reaction was stopped, the mixtures were reduced with lithium aluminium hydride. The starting materials left were separated from the reaction mixtures by column chromatography over basic alumina. The recovered starting materials were analyzed by low energy mass spectroscopy and the results are shown in Table XXV.

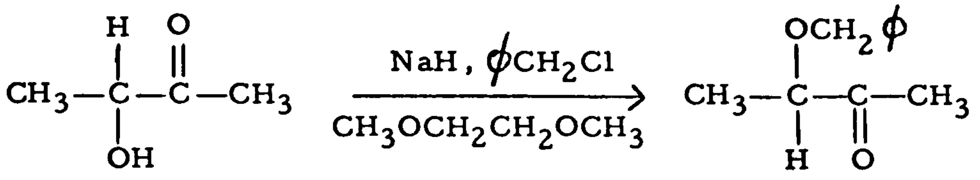
CHAPTER IV

METHYLATION AND BENZYLATION OF SOME α-KETOLS

RESULTS AND DISCUSSION

We showed in Chapter II our interest in protecting the hydroxyl group of 3-hydroxy-2-butanone (acetoin) (64). A convenient methylation procedure of hydroxy compounds was recently reported by Brown, Diner and Sweet (147). These authors add sodium hydride to a solution of the hydroxy compound and methyl iodide in 1,2-dimethoxyethane. A similar procedure has been reported by Tate and Bishop (148) for the preparation of benzyl ethers, using benzyl chloride as solvent.

Using the procedure of Brown (147), an attempt was made to prepare 2-benzyloxy-3-butanone (65) from 2-hydroxy-3-butanone (64).



$$CH_3-CH(OH)-C(=O)-CH_3 \xrightarrow[CH_3OCH_2CH_2OCH_3]{NaH,\ \phi CH_2Cl} CH_3-CH(OCH_2\phi)-C(=O)-CH_3$$

64 65

The product isolated from this reaction in 45% yield, showed absorption bands in the infrared spectrum (CCl_4) at 3480 (-OH stretching vibration) and 1720 cm^{-1} (-C=O stretching vibration). The n.m.r. spectrum (CCl_4) showed a singlet at τ 2.86, a broad singlet at τ 7.13 and two singlets at τ 7.95 and τ 8.76. The absence of a quartet and a doublet in the n.m.r. spectrum, expected for the methine hydrogen and methyl group of compound 65, and the presence of a hydroxyl absorption in the infrared spectrum of the product, indicated that the isolated product was 3-benzyl-3-hydroxy-2-butanone (66). The n.m.r. spectrum corresponds to the compound 66.

Instead of the expected O-alkylation, predominant C-alkylation occurred. The reaction was shown to be general with a series of α-ketols in both a methylation and a benzylation procedure. The results are shown in Table XXVII.

Methylation of 64 gives 3-hydroxy-3-methyl-2-butanone (67) in good yield. The infrared spectrum (CCl_4) of 67 showed an absorption band at 3530 cm^{-1} (-OH stretching vibration). The n.m.r. spectrum (CCl_4) of 67 showed a broad one proton singlet at τ 6.10 and spectrum corresponds to the required compound 67. The physical properties of 67 are identical to the literature values (149).

Benzoin (68) was methylated in high yield to produce methyl-benzoin (69). The infrared spectrum ($CHCl_3$) showed an absorption band at 3440 cm^{-1} (-OH stretching vibration). The n.m.r. spectrum ($CDCl_3$) showed a one proton broad singlet at τ 5.38. Both spectra are in excellent agreement with structure 69. The melting point of 69 is identical with the literature value (150).

The benzylation of benzoin was carried out to yield the expected benzylbenzoin (70). The infrared spectrum ($CHCl_3$) showed absorption bands at 3545 and 3425 cm^{-1} (free and bonded -OH stretching vibration). The n.m.r. spectrum ($CDCl_3$) showed two multiplets

TABLE XXVII

Alkylations of some α-Ketols

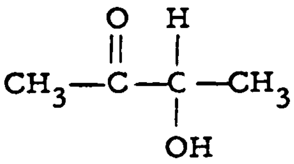
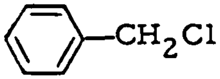
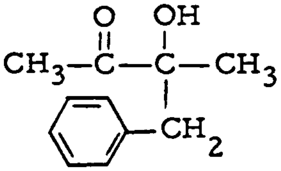
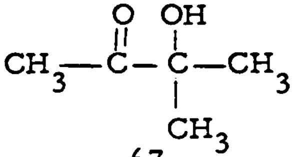
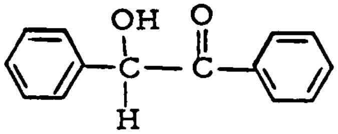
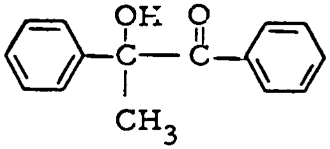
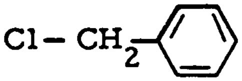
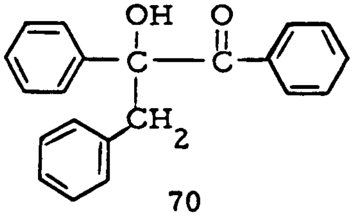
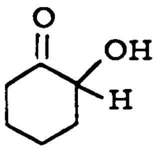
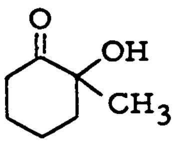
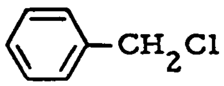
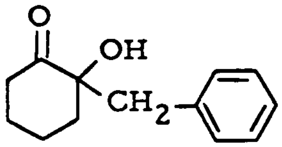
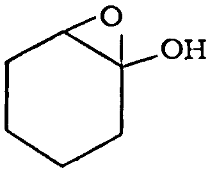
Starting Material	Alkylating Agent	Product	% Yield
 $CH_3-\overset{\overset{O}{\|}}{C}-\underset{\underset{OH}{\|}}{\overset{\overset{H}{\|}}{C}}-CH_3$ 64		 66	45
64	CH_3I	 $CH_3-\overset{\overset{O}{\|}}{C}-\underset{\underset{CH_3}{\|}}{\overset{\overset{OH}{\|}}{C}}-CH_3$ 67	63
 68	CH_3I	 69	67
68		 70	46.5

TABLE XXVII - Continued

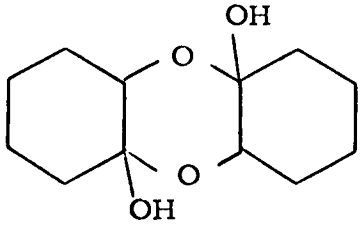
Starting Material	Alkylating Agent	Product	% Yield
 71	CH_3I	 72	41
71		 73	46

centered at τ 2.3 and 2.85, a singlet at τ 6.27 and a pair of doublets centered at τ 6.47 (J = 14 c.p.s.). It has been well established (151) that protons in a compound of the type $X-CH_2-CRST$ are magnetically (and chemically) nonequivalent. The benzylic hydrogens will give rise to an AB type spectrum and the calculated positions of the A and B peaks at τ 6.20 and τ 6.73 (151). The difference between the two calculated positions of the A and B protons, 32 cycles, is not unusually large. It can be calculated from a spectrum of methyl-2,3-dibromo-2-methylpropionate reported by Roberts and Nair (152) that the difference between the calculated position of the A and B peaks is 28.5 cycles. The melting point of compound 70 is identical with the reported value (153).

2-Hydroxycyclohexanone (adipoin) (71) was prepared from cyclohexanone. Chlorination of cyclohexanone in water following the "Organic Synthesis" procedure (154) gave 2-chlorocyclohexanone (74) in 72% yield. The hydrolysis of 2-chlorocyclohexanone was achieved by shaking the compound overnight with an aqueous potassium carbonate solution (155). Recrystallization of the precipitate formed in the hydrolysis reaction gave adipoin, 71, in 49% yield. The compound 71 had a melting point of 112-113°. Melting points anywhere between 90° and 130° have been reported (155-162). The infrared spectrum (nujol mull) shows absorption bands at 3360 cm^{-1} (-OH stretching vibration) and 1725 cm^{-1} (-C=O stretching vibration). The carbonyl absorption band is extremely weak, as was observed by Sheenan (162) and Criegee (163). Bergmann and Gierth (159) showed that the reaction between adipoin (71) and methanol and acid resulted in the formation of two products. The expected product 2-methoxy-cyclohexanone was formed and a compound was present with the same emperical formula but twice the molecular weight of 2-methoxy-cyclohexanone and this compound did not have a carbonyl group present. Bergmann and Gierth (159) suggested that adipoin in the solid state is in the form of lactolide 75 and that the second product found in the reaction above is a dimer of the methyl ether of lactolide 75. Criegie and Schnorrenberg (163) advanced the dimethyl ether of the bimolecular lactolide 76 as the structure of the dimeric methyl ether of adipoin.



75



76

Both structures above explain the very weak carbonyl absorption in the infrared spectrum of adipoin. Structure 75 is not favoured since all α-ketols can have a lactolids structure which is not observed.

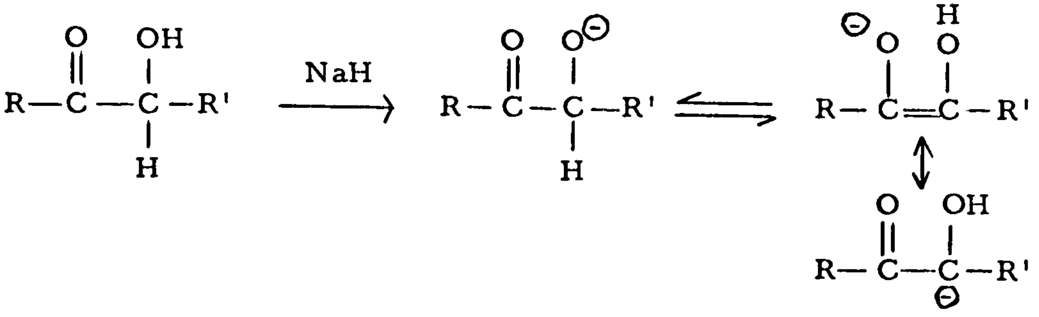
Adipoin was methylated with sodium hydride and methyl iodide to form 2-hydroxy-2-methyl-cyclohexanone (72) in moderate yield. The infrared spectrum (CCl_4) showed an absorption band at 3530 cm^{-1} (-OH stretching vibration). The n.m.r. spectrum (CCl_4) showed a one proton broad singlet at τ 6.13. The spectra and the physical properties correspond to the required compound 72 (164).

Benzylation of 71 was carried out to give 2-benzyl-2-hydroxy-cyclohexanone (73) in good yield. The infrared spectrum

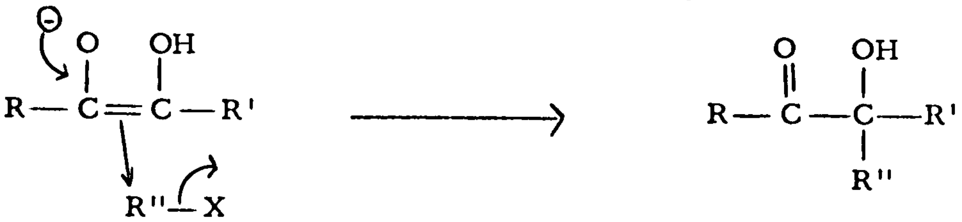
(CCl_4) of 73 showed an absorption band at 3480 cm^{-1} (-OH stretching vibration). The n.m.r. spectrum ($CDCl_3$) showed an one proton broad singlet at τ 6.10. The spectra and the chemical analysis were in excellent agreement with those expected for compound 73.

The reactions discussed above show that in the alkylation of α-ketols C-alkylation is the predominant reaction. The n.m.r. spectrum (CCl_4) of the crude reaction mixture in the preparation of compound 72, showed a strong singlet at τ 6.9. This could be an indication of O-alkylation similar to the observation made by Bergmann and Gierth in the methylation of adipoin (159).

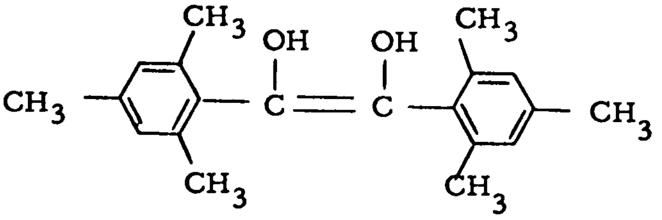
The following mechanism can be proposed to account for the predominant C-alkylation observed. Either the α-hydrogen or the hydroxyl hydrogen can be abstracted followed by equilibration.



Alkylation at carbon can take place readily from the enediol anion.

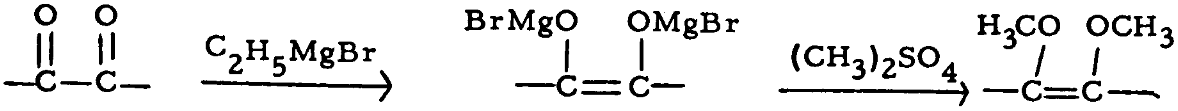


The enediol anion is the more stable anion in the equilibrium and consequently most of the product formed will arise from this anion. Carbon is a better nucleophile than oxygen, which is found in other enolate anions. Hindered enediols, like 1,2-(di-2,4,6-trimethylphenyl)-1,2-ethenediol (77) have been successfully synthesized (165).

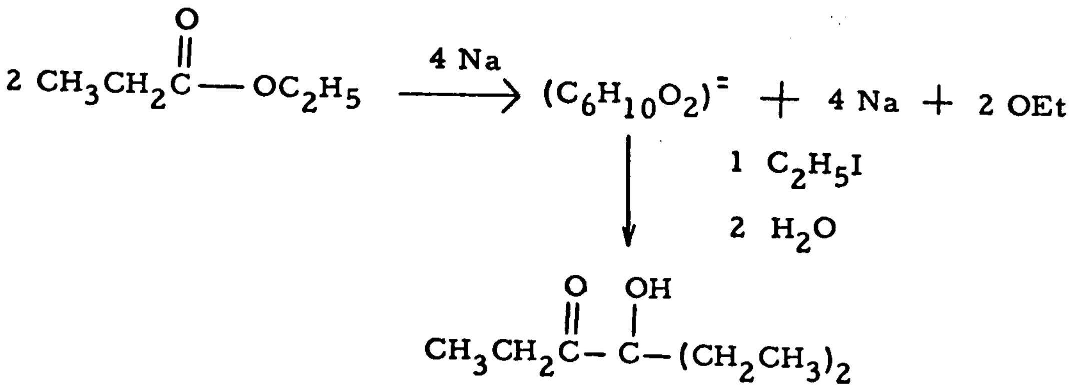


77

Alkylation, however, of stable enediols has been unsuccessful. Reduction of benzils with ethylmagnesium bromide followed by addition of dimethyl sulfate resulted in the formation of the dimethyl ether of the enediol (165).



C-alkylation following the acyloin-condensation had been observed by Speck and Bost (166). When they reacted ethyl propionate with sodium in toluene under acyloin reaction conditions, followed by addition of ethyl iodide before hydrolysis, the product formed was 4-ethyl-4-hydroxy-3-hexanone (78).

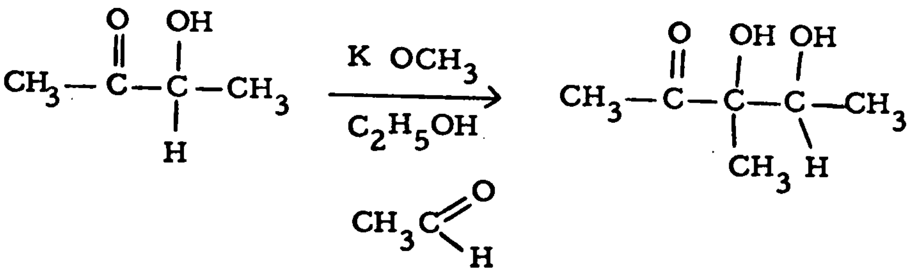


$$2\ CH_3CH_2\overset{\overset{O}{\|}}{C}-OC_2H_5 \xrightarrow{4\ Na} (C_6H_{10}O_2)^{=} + 4\ Na + 2\ OEt \quad \downarrow \begin{smallmatrix} 1\ C_2H_5I \\ 2\ H_2O \end{smallmatrix} \quad CH_3CH_2\overset{\overset{O}{\|}}{C}-\overset{\overset{OH}{|}}{C}-(CH_2CH_3)_2$$

78

However, O-alkylation was found to take place when the acyloin condensation of dibenzyl-ethyl acetate was followed by reaction with ethylbromide (171).

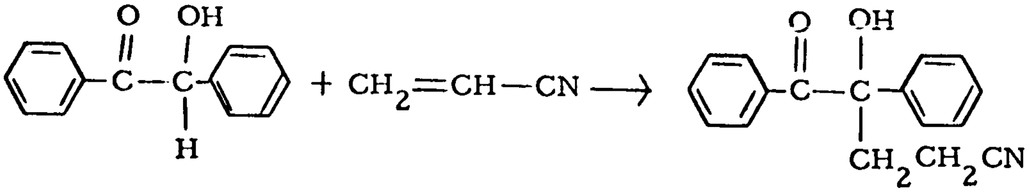
Cologne and coworkers (168, 169, 170) extended on some results found by Szuszkovicz and Bom (167) in the Michael reaction between adipoin and ethyl vinyl ketone. Cologne and Vaginay (170) carried out aldol condensations with α-ketols. When, for example, acetoin was reacted with potassium methoxide and acetaldehyde in ethanol, condensation took place to yield 2,3-dihydroxy-3-methyl-4-pentanone (79).



$$CH_3-\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{|}}{\overset{\overset{OH}{|}}{C}}-CH_3 \xrightarrow[C_2H_5OH,\ CH_3CHO]{K\ OCH_3} CH_3-\overset{\overset{O}{\|}}{C}-\underset{\underset{CH_3}{|}}{\overset{\overset{OH}{|}}{C}}-\underset{\underset{H}{\backslash}}{\overset{\overset{OH}{|}}{C}}-CH_3$$

79

Michael reactions were also carried out with success by Colonge and Vaginay. An example is shown below.



When unsymmetrical α-ketols were subjected to aldolcondensation reactions by Colonge and Vaginay, they claimed that reaction took place on the carbon bearing the hydroxyl group. Their evidence, however, was only based on physical properties such as boiling point and requires more investigation.

After abstraction of a proton, equilibration to the enediol anion is expected to be faster than alkylation. This can be tested by the use of an unsymmetrical α-ketol. Two possible products can be formed if equilibration to the enediol anion occurs prior to alkylation.

It has been shown that the alkylation of α-ketols using sodium hydride as a base is a selective reaction for C-alkylation.

EXPERIMENTAL

1,2-Dimethoxyethane was refluxed over $LiAlH_4$ for two hours and distilled through a 45 cm. Vigreux column. The sodium hydride dispersed on mineral oil was freed from the oil by washing with n-pentane and filtered by suction. The sodium hydride could be stored under nitrogen without serious fire hazard. The sodium hydride was weighed free of the dispersing agent.

3-Benzyl-3-hydroxy-2-butanone (66):

To a solution of freshly distilled 2-hydroxy-3-butanone (8.8 , 0.1 mole) and benzyl chloride (14.7 g, 0.11 mole) in 200 ml of 1,2-dimethoxyethane, all contained in a 500 ml three-necked flask equipped with a dry ice and acetone condenser, drying tube and magnetic stirrer, was added 2.5 g (0.105 mole) of sodium hydride. Vigorous hydrogen evolution took place after addition of each of the portions of the sodium hydride. After the addition was completed (20 minutes), the solution was stirred for two hours at room temperature. The 1,2-dimethoxyethane was removed by distillation at atmospheric pressure. Anhydrous ether (50 ml) was added, whereupon more sodium iodide precipitated. The precipitate was filtered off and the filtrate was distilled at atmospheric pressure to remove the solvent. The residual liquid was distilled under vacuum to obtain 7.9 g (45%) of 66, b.p. 88-91° (0.8 mm), $\eta_D^{27} = 1.5175$. The infrared spectrum (CCl_4) showed absorption bands at 3480, and 1720 cm^{-1}. The n.m.r. spectrum (CCl_4) showed peaks at τ 2.86 (s), τ 7.13 (bs), τ 7.95 (s), τ 8.76 (s), in the ratio 5.0 : 0.93 : 1.85 : 2.84 :

3.24, required 5 : 1 : 2 : 3 : 3.

Analysis calculated for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.24; H, 8.20.

3-Hydroxy-3-methyl-2-butanone (67):

The same procedure as for 66 was followed. Sodium hydride (5.04 g, 0.21 mole) was added in small portions to a solution of 17.6 g (0.20 mole) of 64 and 32.7 g (0.23 mole) of methyl iodide in 125 ml 1,2-dimethoxyethane. The reaction was worked up in the manner described in the preparation of 66, with the exception that a Nestor-Faust annular teflon spinning band distillation column was used to remove solvent. Distillation at atmospheric pressure resulted in 12 g (63%) of 67, b.p. 136-139°, $\eta_D^{27.5} = 1.4096$. Reported (149) b.p. 140-141°, $\eta_D^{21} = 1.415$.

Methylbenzoin (69):

The reaction was carried out as indicated in the preparation of 66. Sodium hydride (1.25 g, 0.052 mole) was added in small portions to a solution of 10.6 g (0.05 mole) of benzoin and 15 g (0.105 mole) of methyl iodide in 300 ml of 1,2-dimethoxyethane. After the reaction was finished, the solution was poured into water. The aqueous solution was extracted three times with 50 ml of chloroform. The combined chloroform extracts were washed twice with water and subsequently dried over $MgSO_4$. The solution was filtered by suction and the filtrate was freed of chloroform by rotary evaporation. The residue was crystallized from *n*-pentane to yield 7.6 g (67%) of 69, m.p. 63-65°. Reported (150) m.p. 65-66°.

The infrared spectrum ($CHCl_3$) showed absorption bands at 3440, and 1640 cm^{-1}. The n.m.r. spectrum showed peaks at τ 2.38 (m), τ 2.72 (m), τ 5.38 (b), and τ 8.17 (s), in the ratio 2.0 : 8.2 : 0.90: 2.74, required 2 : 8 : 1 : 3.

Benzylbenzoin (70):

The benzylation of benzoin was carried out by adding sodium hydride(0.63 g, 0.026 mole) to a solution of 5.3 g (0.025 mole) of benzoin and 3.4 g (0.027 mole) of benzylchloride in 150 ml of 1,2-dimethoxyethane. The work-up procedure was identical to that in the preparation of 69. The product was crystallized to yield 3.5 g (46.5%) of 70, m.p. 113-116°. Reported (153) m.p. 115-118°. The infrared spectrum ($CHCl_3$) showed absorption bands at 3545, 3525 and 1640 cm^{-1}. The n.m.r. spectrum ($CDCl_3$) showed peaks at τ 2.3 (m), τ 2.85 (m), τ 6.27 (s), τ 6.20 (d) (J = 14 cps) and 6.73 (d) (J = 14 cps), in the ratio 2.5 : 13.5 : 1 : 1.9, required 2 : 13 : 1 : 2. The peak at τ 6.27 disappeared on D_2O exchange.

2-Chlorocyclohexanone (74):

This was prepared from cyclohexanone according to the method of Organic Synthesis (154). Chlorine (Ca. 110 g, 3 mole) was passed quickly into a solution of cyclohexanone (150 g, 1.5 mole) in 450 ml of water contained in a 2 l three-necked flask provided with a mechanical stirrer, a gas inlet tube and a gas outlet tube. The gas outlet tube led to the bottom of a measure cylinder filled with six inches of water. The solution was stirred and cooled with an ice-bath during the reaction. The heavier 2-chlorocyclohexanone was separated from the aqueous layer and the latter extracted three times with 100 ml portions of ether. The combined ether extracts and the organic layer were washed with 100 ml of water and 100 ml of saturated sodium chloride solution. The ether solution was filtered through sodium sulfate by gravity and the ether removed by distillation at atmospheric pressure. Distillation of the residue under vacuum yielded 135 g (72%) of 74, b.p. 92-93° (16 mm). Reported (154) b.p. 90-91° (14-15 mm).

2-Hydroxy-cyclohexanone (71):

This was prepared according to the method of Kotz and coworkers (155). A solution of 100 g (0.75 mole) of 74 and 300 g of potassium carbonate in 500 ml of water was shaken overnight. The precipitate formed was filtered and recrystallized from ethanol to yield 42 g (49%) of 71, m.p. 112-113°. Reported (155-162) m.p. anywhere between 90 and 130°. The infrared spectrum (nujol mull) showed absorption bands at 3360, 1725 cm^{-1}. The last absorption was extremely weak. Reported (162) infrared absorptions at 3355 and 1715 cm^{-1} (very weak).

2-Hydroxy-2-methyl-cyclohexanone (72):

The reaction was carried out in the same manner as the preparation of 66. Sodium hydride (2.4 g, 0.1 mole) was added in small portions to a solution of 11.4 g (0.1 mole) of adipoin and 20 g (0.14 mole) of methyl iodide in 250 ml of 1,2-dimethoxyethane.

Work-up of the reaction was identical to that in the preparation of 66. Final distillation under reduced pressure yielded 5.3 g (41%) of 72, b.p. 82-85° (15 mm), $\eta_D^{27} = 1.4605$. Reported (164) b.p. 80-95° (15 mm), $\eta_D^{20} = 1.4644$. The infrared spectrum (CCl_4) showed absorption bands at 3530 and 1735 cm^{-1}. The n.m.r. spectrum (CCl_4) showed peaks at τ 6.13 (s), τ 7.5-8.6 (b) and τ 8.67 (s), ratio 0.85 : 8.8 : 3.08, required 1 : 8 : 3 .

2-Benzyl-2-hydroxy-cyclohexanone (73):

Sodium hydride (2.4 g, 0.1 mole) was added in small portions to a solution of 11.4 g (0.1 mole) of 71 and 12.6 g (0.1 mole) of benzylchloride in 250 ml 1,2-dimethoxyethane. Work-up procedure was identical to that in the preparation of 69. Distillation yielded 9.5 g (46%) of 73, b.p. 115-118° (0.3 mm), $\eta_D^{25} = 1.5438$, which was n.m.r. pure. The viscous liquid was crystallized from n-pentane to yield yellow crystalline 73, m.p. 65-67°. The infrared spectrum (CCl_4) showed peaks at τ 2.76 (s), τ 6.10 (b), τ 6.95 (d) and τ 7.1-8.7 (b), in the ratio 5 : 0.82 : 1.75 : 8.35, required 5 : 1 : 2 : 8.

Analysis calculated for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90.
Found: C, 76.35; H, 8.02.

BIBLIOGRAPHY

1. G. O. Schenck, Angew. Chem., 69, 579 (1957).
2. K. Gollnick and G. O. Schenck, Pure Appl. Chem., 9, 507 (1964).
3. W. Bergmann and M. J. McLean, Chem. Rev., 28,367 (1941).
4. G. O. Schenck and W. Willmundt, reported by R. Criegee in Houben-Weyl, "Methoden der Organischen Chemic", vol. VIII, 4th Ed., E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1952, p. 16.
5. H. H. Wasserman and A. Liberles, J. Am. Chem. Soc., 82, 2086 (1960).
6. R. E. Lutz, W. J. Welstead Jr., R. G. Bass and J. I. Dale, J. Org. Chem., 27, 1111 (1962).
7. A. I. Scott and C. T. Bedford, J. Am. Chem. Soc., 84, 2271 (1962).
8. R. A. Bell and R. E. Ireland, Tetrahedron Letters, 269 (1963).
9. S. Masamune, J. Am. Chem. Soc., 86, 290 (1964).
10. G. O. Schenck and K. H. Schulte-Elte, Ann., 618, 185 (1958).
11. K. Alder and H. von Brachel, Ann., 651, 141 (1962).
12. K. Alder, H. Soll and H. Soll, Ann., 565, 73 (1949).
13. R. L. Livingstone in "Autooxidation and Autooxidants", W. O. Lundberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 249.
14. E. J. Bowen and D. W. Tanner, Trans. Faraday Soc., 51, 475 (1955).

15. C. P. Casey in "Seminars in Organic Chemistry", Massachusetts Institute of Technology, 1964-1965, p. 172.

16. E. J. Bowen in "Advances in Photochemistry", vol. 1, W. A. Noyes, G. S. Hammond, J. N. Pitts Jr., Ed., Interscience Publishers, 1963, p.23.

17. E. J. Bowen, Discussions Faraday Soc., 17, 178 (1954).

18. G. Porter and M. W. Windsor, J. Chem. Phys., 21, 2099 (1953).

19. G. Porter and M. W. Windsor, Discussion Faraday Soc., 17, 178 (1954).

20. E. J. Bowen and A. H. Williams, Trans. Faraday Soc., 35, 765 (1939).

21. A. Schönberg, Ann., 518, 299 (1935).

22. H. Kautzky and H. de Bruin, Naturwiss., 19, 1043 (1931).

23. H. Kautzky, biochem. Z., 291, 271 (1937).

24. H. Kautzky, H. de Bruin, R. Neuwirth and W. Baumeister, Chem. Ber. 66, 1585 (1933).

25. G. Porter and M. R. Wright, J. Chem. Phys., 55, 705 (1958).

26. G. Porter and M. R. Wright, Discussions Faraday Soc., 27, 18 (1959).

27. D. B. Sharp, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960, p. 79P.

28. K. R. Kopecky and H. J. Reich, Can. J. Chem., 43, 2265 (1965).

29. C. S. Foote and S. Wexler, J. Am. Chem Soc., 86, 3879 (1964).

30. C. S. Foote and S. Wexler, J. Am. Chem. Soc., 86, 3880 (1964).

31. E. J. Corey and W. C. Taylor, J. Am. Chem. Soc., 86, 3881 (1964).

32. C. S. Foote, S. Wexler and W. Ando, Tetrahedron Letters, 411, (1965).

33. R. Higgins, C. S. Foote and H. Cheng, "Chemistry of Singlet Oxygen" V, Contribution no. 2112, Department of Chemistry, University of California, Los Angeles, in press.

34. E. Mc Keown and W. A. Waters, J. Chem. Soc., Sect. B, 1040 (1966).

35. T. Wilson, J. Am. Chem. Soc. 88, 2898 (1966).

36. D. R. Kearns, R. A. Hollins, A. U. Khan, R. W. Chambers, P. Radlick, J. Am. Chem. Soc., 89, 5455 (1967).

37. D. R. Kearns, R. A. Hollins, A. U. Khan, P. Radlick, J. Am. Chem. Soc., 89, 5456 (1967).

38. C. S. Foote, S. Wexler, W. Ando and R. Higgens, J. Am. Chem. Soc., 90, 975 (1968).

39. H. H. Wasserman and J. R. Scheffer, J. Am. Chem. Soc., 89, 3073 (1967).

40. K. R. Kopecky and H. J. Reich, unpublished results.

41. R. W. Murray and M. L. Kaplan, J. Am. Chem. Soc., 90, 537 (1968).

42. Q. E. Thompson, J. Am. Chem. Soc., 83, 846)1961).

43. E. McKeown and W. A. Waters, Nature, 203, 1063 (1963).

44. E. J. Corey and W. C. Taylor, J. Am. Chem. Soc., 86, 3882 (1964).

45. J. S. Arnold, R. J. Browne and E. A. Ogryzlo, Photochem. Photobiol., 4, 963 (1965).

46. E. J. Bowen and R. A. Lloyd, Proc. Chem. Soc., 305 (1963).

47. R. J. Brown and E. A. Ogryzlo, Proc. Chem. Soc., 117 (1964).

48. A. R. Khan and M. Kasha, J. Chem. Phys., 39, 2105 (1963).

49. S. J. Arnold, E. A. Ogryzlo and H. Witzke, J. Chem. Phys., 40, 1769 (1964).

50. R. J. Brown and E. A. Ogryzlo, Can. J. Chem., 43, 2195 (1965).

51. G. Herzberg, "Molecular Spectra and Molecular Structure. I. Spectra of Diatomic Molecules", 2nd ed., D. Van Nostrand Co., New York, N. Y. 1950, p. 560.

52. K. B. Wiberg, J. Am. Chem. Soc., 75, 3961 (1953).

53. A. M. Winer and K. D. Bayes, J. Phys. Chem., 70, 302 (1966).

54. A. Vallance-Jones and A. W. Harrison, J. Atmospheric Terrest. Phys., 13, 45 (1958).

55. R. M. Badger, A. C. Wright and R. F. Whitlock, J. Chem. Phys., 43, 4345 (1965).

56. L. W. Bader and E. A. Ogryzlo, Disc, Faraday Soc., 37, 46 (1964).

57. A. M. Falick, B. H. Mahan and R. J. Meyers, J. Chem. Phys., 42, 1837 (1965).

58. H. Gaffron, Biochem. Z., 287, 130 (1936).

59. J. L. Rosenberg and D. J. Shombert, J. Am. Chem. Soc., 82, 3527 (1960).

60. A. Nickon and W. L. Mendelson, J. Am. Chem. Soc., 85, 1894

(1963).

61. A. Nickon and J. F. Bagli, J. Am. Chem. Soc., 81, 6330 (1959).

62. A. Nickon and J. F. Bagli, J. Am. Chem. Soc., 83, 1498 (1961).

63. A. Nickon, N. Schwartz, J. B. DiGiorgio, and D. A. Widdowson, J. Org. Chem., 30, 1711 (1965).

64. A. Nickon and W. L. Mendelson, J. Org. Chem., 30, 2037 (1965).

65. A. Nickon and W. L. Mendelson, J. Am. Chem. Soc., 87, 3921 (1965).

66. A. Nickon and W. L. Mendelson, Can. J. Chem., 43, 1419 (1965).

67. E. Klein and W. Rojahn, Tetrahedron, 21, 2173 (1965).

68. R. L. Kenny and G. S. Fischer, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., September 1960, p. 79P.

69. R. L. Kenny and F. S. Fischer, J. Org. Chem., 28, 3509 (1963).

70. K. Gollnick and G. Schade, Tetrahedron Letters, No. 6, 689 (1968).

71. E. H. White and M. J. C. Harding, J. Am. Chem. Soc., 86, 5686 (1964).

72. F. McCapra and D. F. Richardson, Tetrahedron Letters, No. 43, 3167 (1964).

73. W. H. Richardson, J. W. Peters, W. P. Kinopka, Tetrahedron Letters, No. 45, 5531 (1966).

74. M. Schultz, A. Rieche and K. Kirschke, Chem. Ber., 100, 370 (1967).

75. L. Dulog and W. Vogt, Tetrahedron Letters, No. 42, 5169 (1966).

76. K. R. Kopecky, J. H. van de Sande and C. Mumford, Can. J. Chem., 46, 25 (1968).

77. E. R. Bell, R. H. Dickey, J. H. Riley, F. F. Rust, and W. B. Vaughn, Ind. Eng. Chem., 41, 2597 (1949).

78. A. Rieche, E. Schmitz, and M. Schulz, Z. Chem., 3, 433 (1963).

79. K. Weissermel and M. Lederer, Chem. Ber., 99, 3244 (1966).

80. G. Cranck and F. W. Eastwood, Austr. J. of Chem. 17, 1392 (1964).

81. N. A. Milas, R. L. Puler, Jr., O. O. Mageli, J. Am. Chem. Soc., 76, 2325 (1954).

82. L. S. Silbert, E. Siegel and D. Sivern, J. Org. Chem., 27, 1338 (1962).

83. A.Roedig, in Houben Weyl, "Methoden der Organischen Chemie", vol. 5/4, E. Muller, Ed., George Thieme Verlag, Stuttgart, 1960, p. 139.

84. R. Stroh in Houben Weyl, "Methoden der Organischen Chemie", vol. V/3, E. Muller, Ed., George Thieme Verlag, Stuttgart, 1962, p. 768.

85. K. J. Orton and A. E. Bradfield, J. Chem. Soc., 993, (1927).

86. A. Detoeuf, Bull. Soc. Chim. France 4, 31, 169 (1922).

87. G. L. Goerner and W. G. Hines, J. Am. Chem. Soc., 70, 3511 (1948).

88. W. R. Brasen, S. W. Kantor, P. S. Skell and C. R. Hauser,

J. Am. Chem. Soc., 79, 397 (1957).

89. G. Van Dyke Tiers in "Characteristic Nuclear Magnetic Resonance 'Shielding Values' (spectral positions) for Hydrogen in Organic Structures", Central Research Department, Minnesota Mining and Manufacturing Company, St. Paul, Minnesota, 1958, P. 24 and 27.

90. E. R. Buchman and E. M. Richardson, J. Am. Chem. Soc., 67, 395 (1945).

91. M. Schulz, A. Rieche and K. Kirschke, Chem. Ber., 100, 370 (1967).

92. A. Rieche, M. Schulz and K. Kirschke, Chem. Ber., 99, 3244 (1966).

93. M. S. Kharasch, A. Fono, W. Nudenberg and B. Bischof, J. Org. Chem., 17, 207 (1953).

94. E. L. Eliel and M. N. Rerick, J. Chem. Soc., 4200 (1954).

95. C. Mannich and R. Braun, Chem. Ber., 53, 1874 (1920).

96. E. W. Warnhoff and W. S. Johnson, J. Am. Chem. Soc., 75, 496 (1953).

97. E. W. Warnhoff and W. S. Johnson, J. Am. Chem. Soc., 75, 494 (1953).

98. W. N. Haworth, J. Chem. Soc., 103, 1242 (1913).

99. J. P. Wibaut, H. Hoog, S. L. Langedijk, J. Overhoff and J. Smittenber, Rec. trav. chim., 58, 329 (1939).

100. F. D. Rossini et al. Selected values of chemical thermodynamic

properties. U. S. Government Printing Office, Washington D. C., 1955, p. 55.

101. A. Hantsch and T. E. Dollfus, Chem. Ber. 35, 252 (1902).

102. E. Ott and R. Schroter, Chem. Ber., 61, 2135 (1928).

103. N. Rabjohn and E. R. Rogier, J. Org. Chem., 11, 781 (1946).

104. Organic Synthesis, Coll. vol. II, John Wiley and Sons, Inc., New York, 1963, p. 7.

105. W. G. Young, R. T. Dillon and H. J. Lucas, J. Am. Chem. Soc., 51, 2528 (1939).

106. K. Biemann, "Mass Spectrometry: Organic Chemical Applications", McGraw-Hill, New York, N. Y., 1962, p. 223.

107. F. A. Cotton, J. H. Fassnacht, W. D. Horrocks Jr. and N. A. Nelson, J. Chem. Soc., 4138 (1959).

108. R. Kuhn and H. Trischmann, Ann., 611, 117 (1958).

109. S. E. Scheppele and S. Selzer, J. Am. Chem. Soc., 90, 358 (1968).

110. W. J. Moore in "Physical Chemistry", Longmans, Green and Co. Ltd., London, England, 1957, p. 535.

111. W. G. McMillan, J. Am. Chem. Soc., 79, 4838 (157).

112. A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms", second edition, John Wiley and Sons, Inc., New York, 1961, Chapter 5.

113. L. Melander, "Isotope Effects on Reaction Rates", The Ronald Press Co., N. Y., 1960, Chapter 4.

114. K. B. Wiberg, Chem. Reviews, 55, 713 (1955).

115. F. H. Westheimer, Chem. Reviews, 61, 265 (1961).

116. M. F. Hawthorne and E. S. Lewis, J. Am. Chem. Soc., 80, 4296 (1958).

117. E. S. Lewis and M. C. R. Symons, Quart. Revs., 12, 230 (1958).

118. Reference 113, Chapter 5.

119. E. A. Halevi in Progress in Physical Organic Chemistry, Interscience, N. Y., 1963, Vol. 1, p. 109.

120. A. Streitwiesser, R. H. Jagow, R. C. Fahey and S. Suzuki, J. Am. Chem. Soc., 80, 2326 (1958).

121. V. J. Shiner Jr., Tetrahedron 5, 243 (1959).

122. L. S. Bartell, J. Am. Chem. Soc., 83, 3567 (1961).

123. H. C. Brown and G. J. McDonald, J. Am. Chem. Soc., 88, 2514 (1966).

124. H. C. Brown, M. E. Azzaro, J. G. Koelling, G. J. McDonald, J. Am. Chem. Soc., 88, 2520 (1966).

125. B. Capone, Quart. Rev. (London), 18, 45 (1964).

126. I. Roberts and F. E. Kimball, J. Am. Chem. Soc., 59, 947 (1937).

127. S. Winstein and B. K. Morse, J. Am. Chem. Soc., 74, 1133 (1952).

128. S. Winstein and H. J. Lucas, J. Am. Chem. Soc., 61, 1576 (1939).

129. S. Winstein and H. J. Lucas, J. Am. Chem. Soc., 61, 2845 (1939).

130. D. J. Cram and F. S. Hammond, "Organic Chemistry", McGraw-Hill Book Company Inc., New York, 1959, p. 341.

131. V. J. Shiner, Jr., J. Am. Chem. Soc., 75, 2925 (1953).

132. C. Mumford, unpublished results.

133. L. O. Binder., J. Chem. Ed., 23, 285 (1946).

134. Organic Synthesis, Coll. Vol. II John Wiley and Sons, Inc., New York, 1963, p. 165.

135. H. Meerwein, Ann., 396, 251.

136. J. Ayers, J. Am. Chem. Soc., 60, 2958 (1938).

137. J. A. Berson, R. G. Wall, H. D. Perlmutter, J. Am. Chem. Soc., 88, 187 (1966).

138. K. Mislow, M. A. W. Glass, H. B. Hopes, E. Simon and G. H. Wahl, Jr., J. Am. Chem. Soc., 86, 1710 (1964).

139. K. H. Schulte-Elte, reported by G. O. Schenck and K. Gollnick, Pure Appl. Chem.., 9, 507 (1964).

140. J. Bigeleisen, Pure Appl. Chem., 8, 217 (1964).

141. C. S. Foote, "Photosensitized Oxygenations and the Role of Singlet Oxygen", Contribution no. 2140 from the Department of Chemistry, University of California, Los Angelos, California 90024.

142. J. A. Howard and K. U. Ingold, J. Am. Chem. Soc., 90, 1059 (1968).

143. G. A. Russell, J. Am. Chem. Soc., 79, 3871 (1957).

144. H. Gilman and J. F. Nelson, Rec. trav. chim., 55, 520 (1936).

145. E. S. Rao, Ph. D. Thesis, University of Alberta, 1967.

146. Dictionary of Organic Compounds, Exre and Spottiswoode, Publishers, Ltd., E. & F. N. Spon Ltd., London, 1965.

147. U. E. Diner, F. Sweet and R. K. Brown, Can. J. Chem., 44, 1591 (1966).

148. M. E. Tate and C. T. Bishop, Can. J. Chem., 41, 1801 (1963).

149. P. Freon, Ann. Chim., 11, 453 (1939).

150. R. Roger, J. Chem. Soc., 127, 523 (1925).

151. L. M. Jackman in "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press Limited, Oxford, England, 1959, p. 101.

152. P. M. Nair and J. D. Roberts, J. Am. Chem. Soc., 79, 4565 (1957).

153. G. Schneing and A. Hensle, Ann., 440, 82 (1924).

154. Organic Synthesis Coll. Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 188.

155. A. Kötz, K. Blendermann, R. Rosenbusch and E. Sirringhaus, Ann. 400, 62 (1913).

156. A. Kötz and Grethe, J. prakt. Chimie, [2], 80, 488 (1919).

157. L. Bouveault and F. Chereau, Compt. Rendu 142, 1086 (1906).

158. R. Willstatter and E. Sonnenfeld, Chem. Ber., 46, 2957 (1913).

159. M. Bergmann and M. Gierth, Ann., 488, 48 (1926).

160. A. E. Venus-Danilova, J. Gen. Chem. (U. S. S. R)., 6, 1784 (1936) Chem. Ab., 31, 4279 (1931).

161. A. Kötz and K. Richte, J. prakt. Chemie 2 , 111, 394 (1925).

162. J. C. Sheenan, R. C. O'Neill, M. A. White, J. Am. Chem. Soc., 72, 3376 (1950).

163. R. Criegee and W. Schnorrenberg, Ann., 560, 144 (1948).

164. L. W. Butz, B. L. Davis and A. M. Gaddis, J. Org. Chem., 12, 122 (1947).

165. C. A. Buchler, Chem. Rev., 64, 7, (1964) and references cited.

166. J. C. Speck and R. W. Bast., J. Org. Chem., 11, 788 (1946).

167. J. Szmuszkovicz and H. Bom, J. Am. Chem. Soc., 75, 3350 (1953).

168. J. Colonge and P. Brison, Bull. Soc. Chim. Fr., 96 (1962).

169. J. Colonge and P. Brison, ebid, 175 (1962).

170. J. Colonge and Y. Vaginay, Bull, Soc. Chim. Fr., 3140 (1965).

171. H. Scheibler and R. Emden, Ann., 434, 275 (1923).