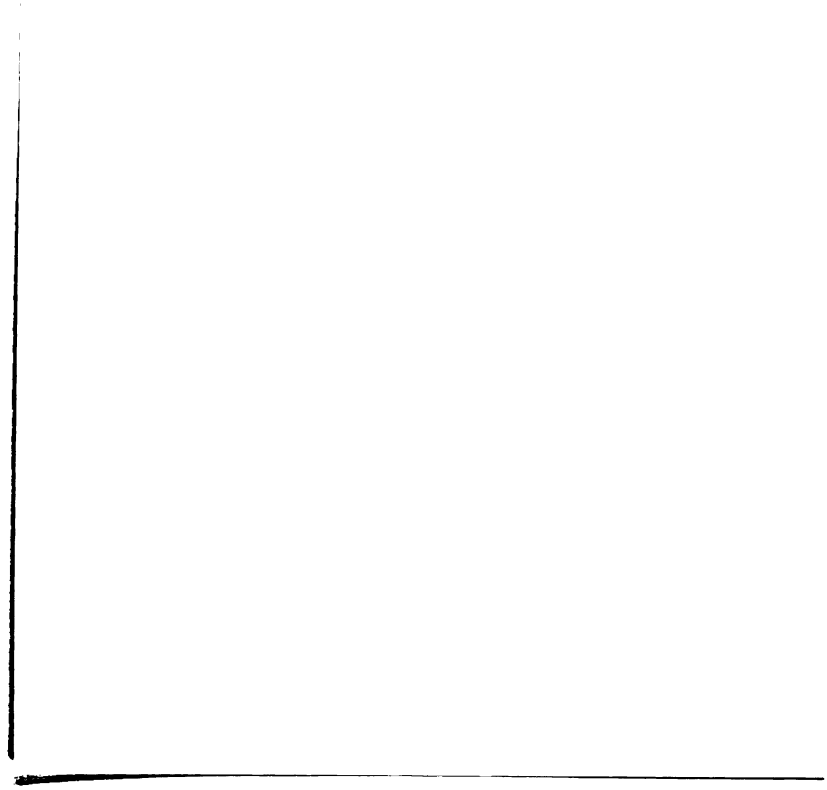
PART I
FREE RADICAL REACTIONS OF SOME α, β-EPOXY KETONES
PART II
CONFIGURATIONS AND REARRANGEMENTS OF THE DIASTEREOISOMERIC PULEGONE OXIDES
PART III
PHOTOCHEMICAL REARRANGEMENTS OF SOME α, β-EPOXY KETONES

Thesis for the Degree of Ph. D.
MICHIGAN STATE UNIVERSITY

Calvin Keith Johnson

1963



ABSTRACT

PART I

FREE RADICAL REACTIONS OF SOME α, β-EPOXY KETONES

PART II

CONFIGURATIONS AND REARRANGEMENTS OF THE DIASTEREOISOMERIC PULEGONE OXIDES

PART III

PHOTOCHEMICAL REARRANGEMENTS OF SOME α, β-EPOXY KETONES

by Calvin Keith Johnson

Free radical rearrangements are quite rare in contrast to the many carbonium ion rearrangements known. A study of the thermal and free radical chain reactions of a number of α, β-epoxy ketones was undertaken in the hope that the strained three membered ring would open and the resulting reactions would yield valuable information about radical rearrangements. Also, the photochemical reactions of some α, β-epoxy ketones were studied in order to compare the thermal and photochemical transformations of carbonyl compounds and to gain information about the mechanisms of photochemical rearrangements.

When trisubstituted α, β-epoxy ketones were refluxed in air or heated at 180-235° in Pyrex vials with radical initiators, they were converted to mixtures of α-diketones, monoketones and carbon monoxide. For example, isophorone oxide yielded a 3:1 mixture of 1, 5, 5-trimethyl-2-hydroxycyclohexene-3-one and 2, 4, 4-trimethyl-cyclopentanone. The latter compound is thought to result from a 1, 2-shift of an acyl radical, and is the first known rearrangement of

this type in thermochemistry. The most efficient initiator was 2-formyl-2,4,4-trimethylcyclopentanone, which was shown to undergo a first order decarbonylation in dilute decalin solutions at 215-255° and to produce free radicals.

In order to study the thermal rearrangements of a tetrasubstituted α,β-epoxy ketone, the diastereoisomeric pulegone oxides were prepared. The two diastereoisomers were isolated as crystalline solids and configurations were assigned to them on the basis of their n.m.r. spectra, optical rotatory dispersion curves, thermal isomerization at 200° and a consideration of the possible conformations. Neat degassed samples of the pulegone oxide isomers underwent concurrent isomerization, rearrangement and fragmentation reactions when heated at 200° in Pyrex vials. The two major products (75%) were identified as the diastereomers of 2-acetyl-2,5-dimethylcyclohexanone and their configurations assigned. Oxygen slowed both the rate of rearrangement and isomerization suggesting that both reactions occur via a triplet intermediate. Support for this postulate was obtained by trapping the intermediate with radical scavengers. A radical cleavage recombination mechanism involving a novel 1,2-shift of a methyl radical was proposed.

The $n \rightarrow \pi^*$ excitation of the carbonyl group of α,β-epoxy ketones resulted in the formation of α-diketones produced by 1,2- shifts of β-alkyl groups. Thus, either neat samples or solutions of 4-methyl-3,4-epoxy-2-pentanone gave methyl acetylacetone. The tendency of a group to migrate decreased in the following order: neopentyl, methyl, phenyl. This order, which is inconsistent with an ionic mechanism, was rationalized in terms of a radical cleavage recombination mechanism. The rearrangement may occur via a triplet state since mercury sensitized the rearrangement of 4-methyl-3,4-epoxy-2-pentanone to methyl acetylacetone. The photolysis products and the proposed mechanism are analogous to those suggested for the thermal rearrangement of pulegone oxide.

PART I

FREE RADICAL REACTIONS OF SOME α, β-EPOXY KETONES

PART II

CONFIGURATIONS AND REARRANGEMENTS OF THE DIASTEREOISOMERIC PULEGONE OXIDES

PART III

PHOTOCHEMICAL REARRANGEMENTS OF SOME α, β-EPOXY KETONES

By

Calvin Keith Johnson

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1963

ACKNOWLEDGMENTS

The author wishes to express his sincere appreciation to Professor William H. Reusch for his encouragement and guidance throughout the course of this investigation.

Grateful acknowledgment is extended to the National Institute of Health for a special graduate research assistantship from June, 1961 through June, 1962. Appreciation is also extended to the National Science Foundation whose fellowship program provided personal financial assistance from June, 1962 through June, 1963 and to the Dow Chemical Company for a summer scholarship in 1963.

****

TABLE OF CONTENTS

TABLE OF CONTENTS - Continued

TABLE OF CONTENTS - Continued

TABLE OF CONTENTS - Continued

TABLE OF CONTENTS - Continued

PART III

PHOTOCHEMICAL REARRANGEMENTS OF SOME α, β-EPOXY KETONES

TABLE OF CONTENTS - Continued

TABLE OF CONTENTS - Continued

TABLE OF CONTENTS - Continued

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES - Continued

FIGURE Page

PART I

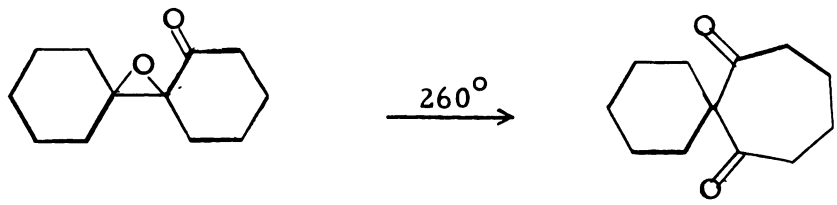
FREE RADICAL REACTIONS OF SOME α, β-EPOXY KETONES

INTRODUCTION AND HISTORICAL

Originally, we planned to study the mechanism and synthetic utility of base catalyzed rearrangements of α,β-epoxy ketones. In order to study the reactions of an acyclic epoxy ketone with base, 4-methyl-3,4-epoxy-2-pentanone was prepared. When it was distilled at atmospheric pressure, b.p.-156°, a bright yellow liquid was obtained. This surprising observation implied that either a thermal or a free radical decomposition of the epoxy ketone was taking place. We decided to undertake a study of this reaction for several reasons.

Thermal reactions which may be formally viewed as proceeding through six membered cyclic transition states are quite common in organic chemistry. Examples of this type of reaction are ester pyrolysis, the Diels-Alder reaction and the Cope rearrangement. Recently, a number of thermal rearrangements of organic molecules in which formal 1,2-shifts occur have been reported (1-6). Very little is known about the mechanism of these rearrangements aside from the fact that the structures are often strained. Since the epoxide ring is strained, it is a potential site for bond rupture upon thermal excitation. The resulting reactions should yield valuable information about intramolecular thermal reactions.

The thermal conversion of epoxides to aldehydes and ketones has been known for some time (7,8). A few cases of thermal rearrangements of α,β-epoxy ketones have been reported, but they are usually effected at higher temperatures than the boiling point of 4-methyl-3,4-epoxy-2-pentanone. Reese (9) and more recently House and Wasson (10) have reported that 2-cyclohexylidenecyclohexanone oxide is converted to spira [5.6]-dodecane-7,12-dione when heated at 260°.



(1)

Pulegone oxide reportedly is converted to an isomer of uncertain structure when heated at 200° (11, 12); however, nothing is known about the mechanism of these transformations.

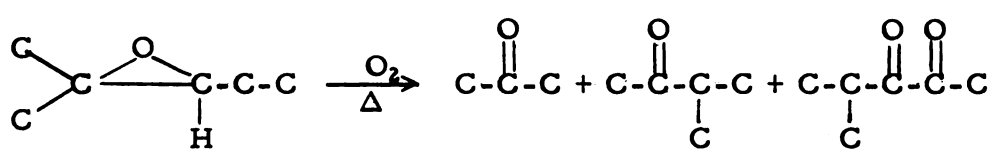
The possibility that a free radical reaction was taking place was intriguing. No reports of free radical reactions of epoxides were in the literature when the rearrangement of 4-methyl-3,4-epoxy-2-pentanone was first observed. However, the facile abstraction of the α-hydrogens of ethers by radicals is well-known (16), and Walling (17) has recently shown that the oxygen of an epoxide similarly facilitates the abstraction of oxirane hydrogens by electrophilic radicals. At the low temperature employed (0°), the oxirane radical did not rearrange prior to subsequent reaction. At the boiling point of 4-methyl-3,4-epoxy-2-pentanone, however, an oxirane free radical was expected to undergo some interesting intramolecular rearrangements. Intramolecular rearrangements to radical centers are quite rare in contrast to the many carbonium ion rearrangements known, and usually require high activation energies (13, 14). Gritter and Wallace (15) have recently shown that the radical formed from propylene oxide by abstraction of the oxirane hydrogen isomerized to a keto-radical at 150°; this keto-radical attacked both a double bond and the epoxide ring.

RESULTS AND DISCUSSION

I. Autoxidation of α, β-Epoxy Ketones

When 4-methyl-3, 4-epoxy-2-pentanone (I), b.p. 156°, was distilled at atmospheric pressure, the product was yellow and contained three low boiling impurities. Redistillation at atmospheric pressure only produced more of the impurities.

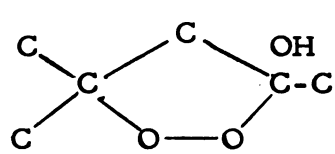
This reaction was studied by refluxing I (containing peroxide) while slowly passing air through it. The low boiling products distilled from the reaction mixture and were collected. The yields were always low and the reaction mixtures became very tarry. Acetone (II) and methyl isopropyl ketone (III) were identified by their v.p.c. retention times and the mixed melting points of their derivatives with authentic samples. The third product was shown to be 4-methyl-2, 3-pentanedione (IV) by comparison with an authentic sample formed by the acid catalyzed rearrangement of I.



(2)

I II III IV

The crude epoxide, prepared by treatment of mesityl oxide with base and hydrogen peroxide, contains a cyclic peroxide, 3-hydroxy-3, 5, 5-trimethyl-1, 2-dioxacyclopentane, which boils only slightly higher than I (18).

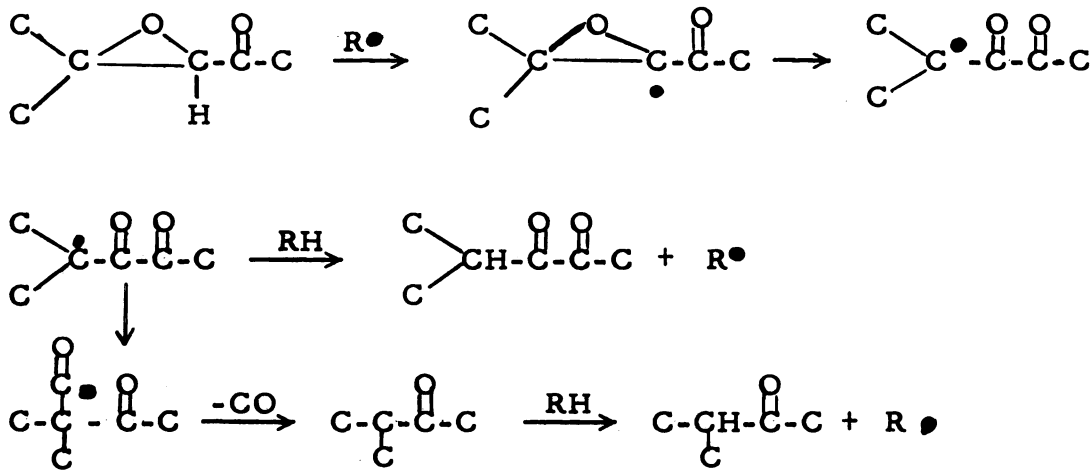


(3)

When I (containing peroxide) was distilled at reduced pressure no rearrangement occurred; furthermore, it did not rearrange when heated at 160° in the absence of air. Peroxide free I did not rearrange when refluxed in air for 16 hours; however, the reaction began as soon as a trace of tert-butyl hydroperoxide was added. These results show that oxygen, an initiator and a relatively high temperature are all necessary for the reaction to occur.

These results rule out a thermal rearrangement and suggest a free radical chain reaction such as the one shown in Chart I. The oxirane hydrogen is abstracted and the resulting radical isomerizes to a keto radical. The keto radical may abstract a hydrogen to give IV or undergo an acyl radical migration with subsequent decarbonylation and hydrogen abstraction to give III.

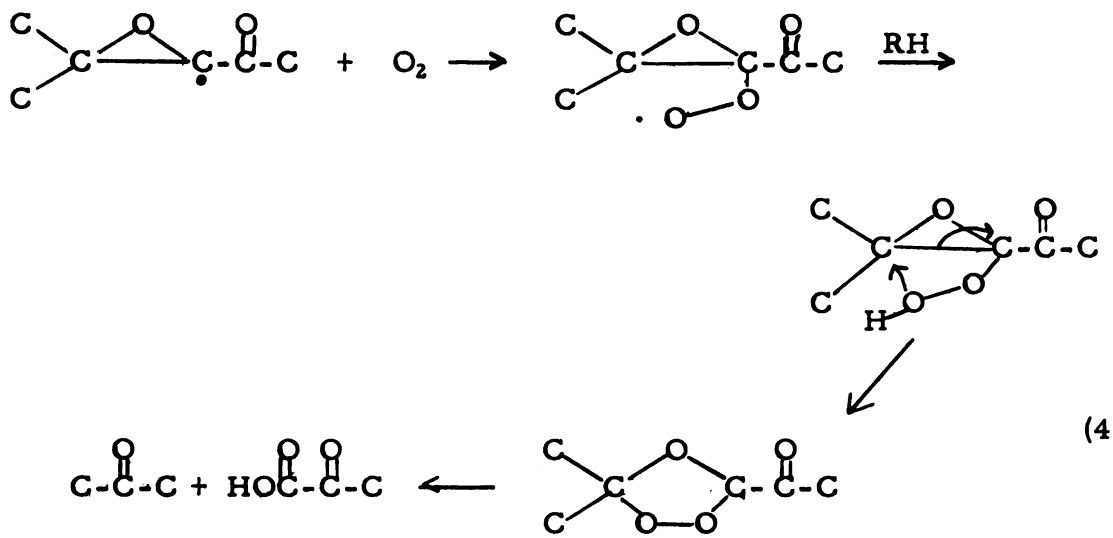
Chart I



It is readily seen that this mechanism does not require the presence of oxygen, as demanded by previous experiments. Inspection of the data in Table 1 shows that small amounts of peroxide initiators cause only slight reaction at 160°. This may be due to the inefficiency of the peroxide initiators or the shortness of the radical chain at this temperature.

When I is refluxed in air, relatively large amounts of peroxides may be formed, which could initiate many chain reactions and thus produce fair yields of the products.

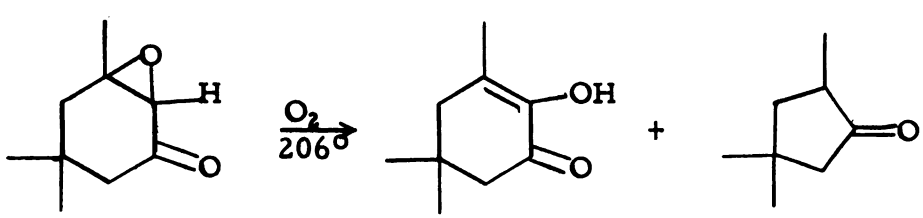
The formation of acetone is difficult to explain. A possible rationale is that the hydroperoxide formed by coupling of the oxirane radical with oxygen might rearrange to an ozonide. The ozonide could then decompose to yield acetone.



(4)

However, acetone is also formed in the radical chain reactions in the absence of oxygen and no satisfactory rationale for its formation has been found.

Peroxide free isophorone oxide (V) was converted into 1, 5, 5-trimethyl-2-hydroxycyclohexene-3-one (VI) and 2, 4, 4-trimethylcyclopentanone (VII) when refluxed in air. VI and VII were formed in 13% and 2% yields respectively after a period of 12 hours.



V VI VII

(5)

No reaction occurred when V was refluxed under nitrogen; furthermore, traces of free radical inhibitors (e.g., N-methylaniline and hydroquinone) were found to prevent the reaction.

These results are best interpreted by a radical chain mechanism such as that shown in Chart II. At the high temperature employed (206°) oxygen might initiate the reaction by directly abstracting the oxirane hydrogen or by forming peroxides which would decompose to radical fragments.

II. Free Radical Rearrangements

Since the autoxidation reactions produced so much tar, a detailed study of these reactions was undertaken using degassed samples in carefully cleaned Pyrex vials.

When 4-methyl-3,4-epoxy-2-pentanone (I) was heated with free radical initiators, it was transformed into a mixture of acetone (II), methyl isopropyl ketone (III) and 4-methyl-2,3-pentanedione (IV). Similarly, isophorone oxide (V) was converted to a mixture of 1,5,5-trimethyl-2-hydroxycyclohexene-3-one (IV) and 2,4,4-trimethylcyclopentanone (VII). The gas formed from I was not analyzed, but carbon monoxide was identified as the gas formed in the free radical reactions of isophorone oxide (V). The main product was always the diosphenol (VI), but the relative amount of cyclopentanone (VII) increased with temperature as shown in Table 3.

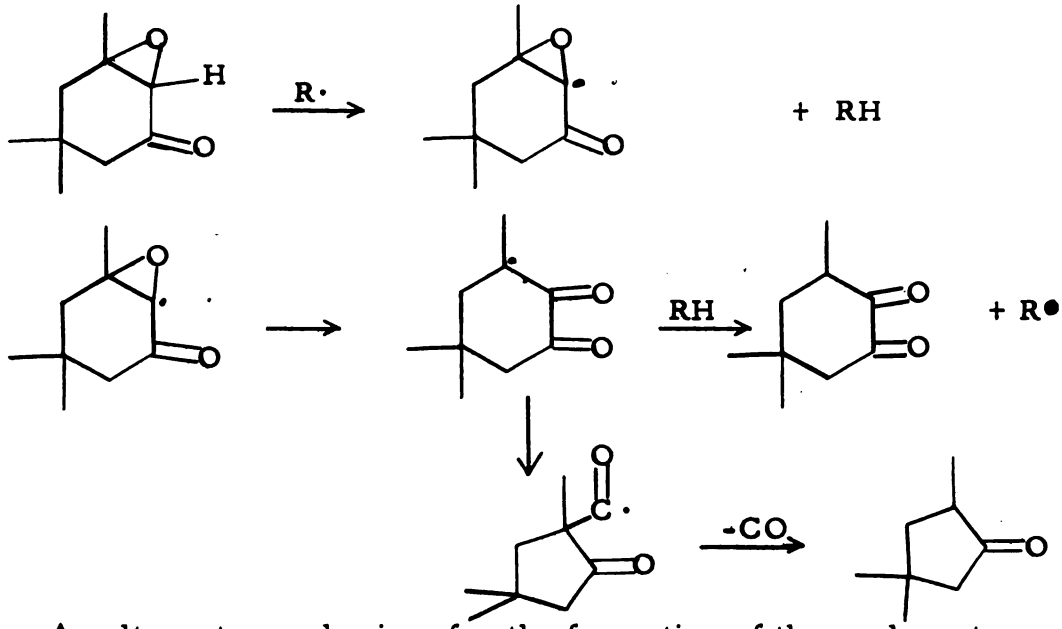
The cyclopentanone (VII) is not a secondary product formed from (VI), inasmuch as prolonged heating of (VI) in the presence or absence of initiators produced no change. Likewise, the α-diketone (IV) was not transformed into (III).

Weak acids, such as the diosphenol (VI) and phenol, did not catalyze the rearrangement of (V). Although carboxylic acids catalyze the

rearrangement at 235°, the amount of acid conceivably formed from the oxygen of 1% of t-butylhydroperoxide (e.g., 0.5% acetic acid) induced only one-fourth as much rearrangement as the peroxide. Acid catalysis is further ruled out by the fact that the ratio of IV/VII (5.5) found for acid catalysis differs significantly from that observed (3.3) for the radical reaction at the same temperature, as shown in Table 3.

The data presented in the tables clearly supports a free radical chain mechanism such as the one shown in Chart II. The first two steps, abstraction of the oxirane hydrogen followed by isomerization of the oxirane radical to a keto radical, are completely analogous to those suggested by Gritter (15) to account for the reactions of simple epoxides. Walling (17) has also shown that tert-butoxy radicals will abstract oxirane hydrogens. The keto-radical may either abstract a hydrogen to give VI or acyl group migration may occur followed by decarbonylation and hydrogen abstraction to give VII.

Chart II



An alternate mechanism for the formation of the cyclopentanone (VIII) was suggested by referee, and is shown in Chart III.

Table 1. Free Radical Rearrangements of 4-Methyl-3, 4-epoxy-2-pentanone

Additives	Temp. °C.	Time, hr.	Extent of reaction, %	II, %	III, %	IV, %
$(C_6H_5CO_2)_2$	100	9	0			
----	160	18	0			
tert-$C_4H_9O_2H$ (1%)[a]	160	18	1.0	-	-	1.0
----	180	16	0			
tert-$C_4H_9O_2H$ (1%)	180	6	0			
tert-$C_4H_9O_2H$ (1%)	180	16	4.5	-	-	4.5
tert-$C_4H_9O_2H$ (5%)	180	10	5.0	-	-	5.0
2, 2'-azoisobutane (5%)	180	16	0			
----	200	10	0			
tert-$C_4H_9O_2H$ (5%)	200	10	16.7	2.5	1.2	13.0
----	230	4	0			
tert-$C_4H_9O_2H$ (5%)	230	3	27.6	12.5	2.1	13.0
2, 2'-azoisobutane (5%)	230	3	0			
VIII (5%)[b]	230	3	18.5	8.5	1.0	9.0

[a] It is possible that the action of this initiator is due in part to a decomposition giving molecular oxygen.

[b] 2-formyl-2, 4, 4-trimethylcyclopentanone.

Table 2. Rearrangements of Isophorone Oxide

Additives	Temp. °C.	Time, hr.	Extent of reaction, %
$(C_6H_5CO_2)_2$ (2%)	100	10	0
tert-$(C_4H_9)_2O_2$ (20%)	150	8	1
tert-$C_4H_9O_2H$ (1%)	180	16	0
----	200	16	0
tert-$C_4H_9O_2H$ (1%)	200	16	5
----	235	6	0
tert-$C_4H_9O_2H$ (1%)	235	6	28
tert-$C_4H_9O_2H$ (1%) surface area doubled	235	6	26
$C_6H_5OCH_2C_6H_5$ (1%)	235	6	8
p-C_6H_5-$C_6H_4OCH_2C_6H_5$ (1%)	235	6	18
C_2Cl_6 (1%)	235	6	100[a]
VI (3%)	235	6	0
C_6H_5OH (2%)	235	6	0
CH_3CO_2H (0.5%)	235	6	7
VIII[b] (1%)	235	6	90
iso-$(C_3H_7)_2N_2$ (2%)	235	6	0

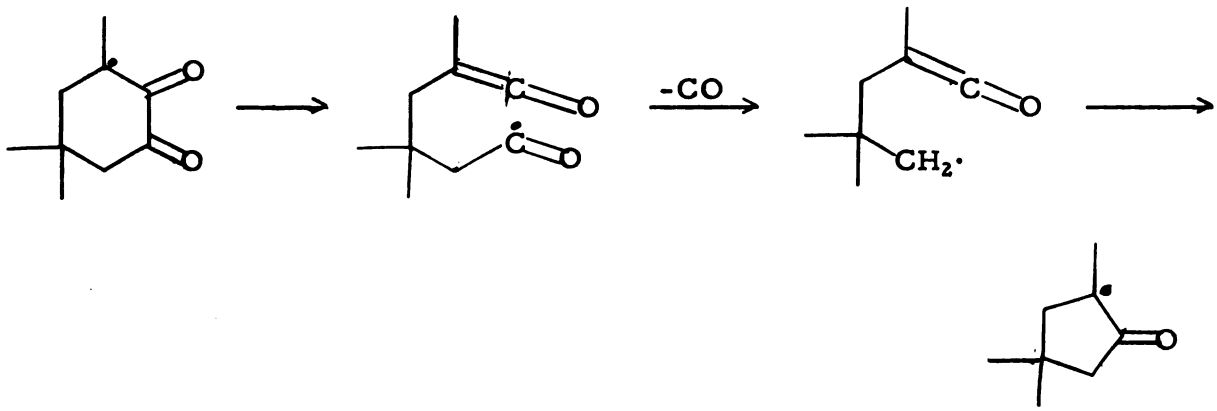
[a] Large amounts of tar are formed.

[b] 2-formyl-2, 4, 4-trimethylcyclopentanone.

Table 3. Effect of temperature on the Rearrangement of Isophorone Oxide

Additives	Temp., °C.	Time, hr.	% VI	% VII	Ratio VI/VII
VIII (1%)	215	6	8	2	4.0
VIII (1%)	235	6	53.8	16.2	3.3
VIII (1%)	255	6	63.5	33.5	1.9
CH_3CO_2H (2%)	235	6	16.2	2.9	5.6
$C_6H_5CO_2H$ (2%)	235	6	14.3	2.7	5.3

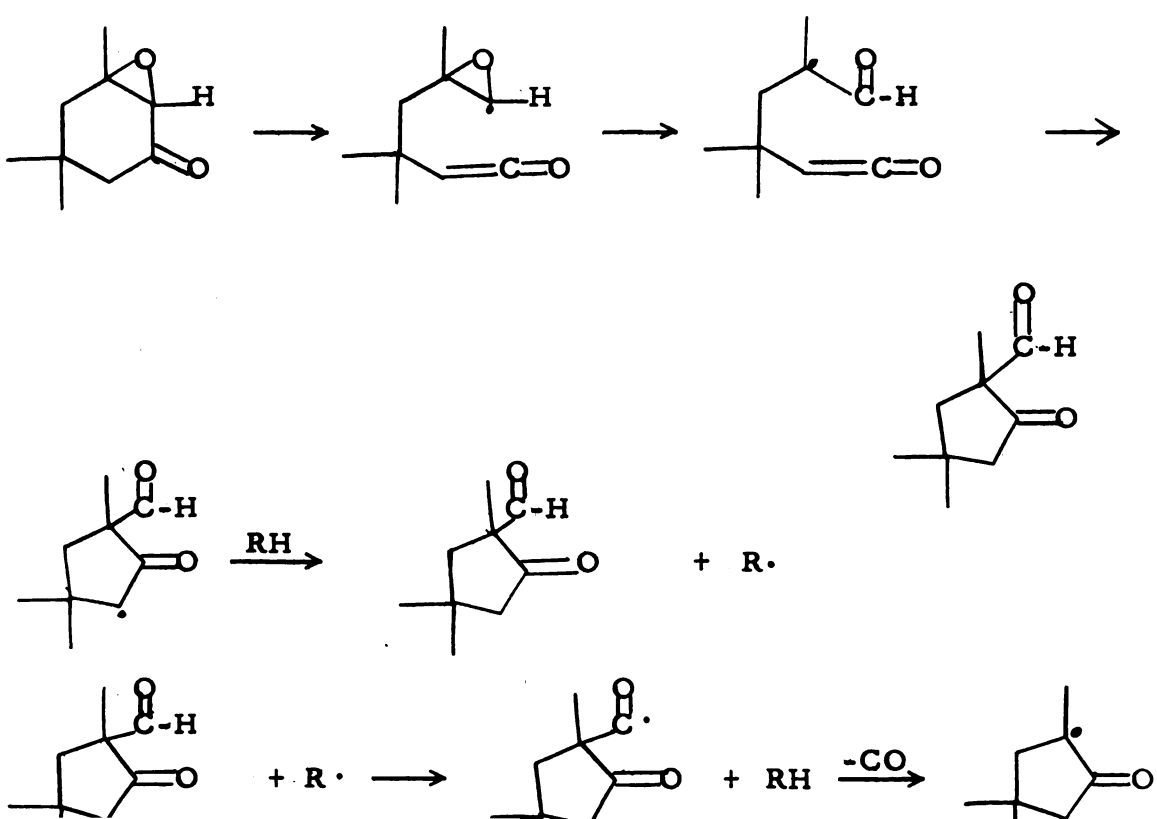
Chart III



Since, a different carbon atom is lost in these two mechanisms it should be possible to distinguish between them by running the rearrangement with C^{14} labeled isophorone oxide. Indeed, Manner and Reusch (19) have recently effected the rearrangement on labeled isophorone oxide and eliminated the latter mechanism.

A third rationale for the formation of the cyclopentanone (VII) is presented in Chart IV.

CHART IV



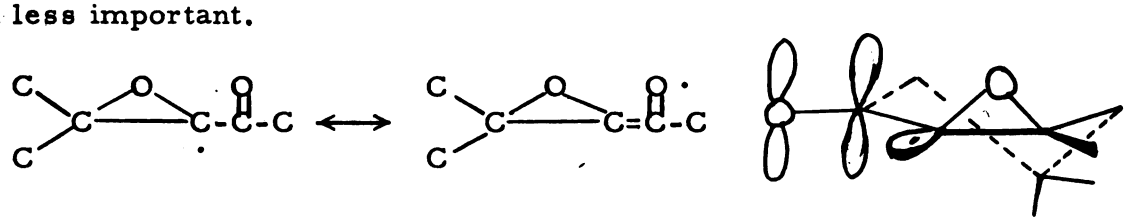
An attempt to trap the postulated ketene intermediate by effecting the radical reaction in the presence of water was unsuccessful. No carboxylic acids could be detected by I. R. or v.p.c. and the ratio of VI/VII remained 3.3, after correcting for the amount of reaction caused by water. However, this negative evidence does not necessarily rule out a mechanism involving a ketene intermediate.

The formation of methyl isopropyl ketone (III) and 4-methyl-2,3-pentanedione (IV) from 4-methyl-3,4-epoxy-2-pentanone (I) may be rationalized in a similar manner. In this case, however, a mechanism utilizing a ketene intermediate in the formation of methyl isopropyl ketone is not attractive since fragmentation of the molecule into a ketene and a radical must occur. In order for the observed product to be formed, the fragments must recombine rapidly within the solvent cage. The mechanism shown in Chart II does not have this drawback provided fragmentation does not occur in the rearrangement step. The formation of acetone is difficult to rationalize and a satisfactory explanation is yet to be found.

Relatively high temperatures are required for reaction. This is probably due to the difficulty in abstracting the oxirane hydrogen and/or the high activation energies required for radical rearrangements. Gritter and Wallace (15) have shown that the reactivity of the ether hydrogens to radical abstraction decreases with rith ring size in the following order: $5 \approx 6 >> 4 > 3$. A similar order was found for cycloalkanes by Gordon and Smith (20). This order is due to the enhanced bond strength of the C-H bonds in small ring compounds. These results also indicate that the reactivity of simple epoxides is similar to that of benzene.

As can be seen from the tables, 4-methyl-3,4-epoxy-2-pentanone (I) is more reactive than isophorone oxide (V). Abstraction of the oxirane hydrogen from I should be facilitated by resonance stabilization

of the oxirane radical, while in the latter the C-H bond is orthogonal to the pi electrons of the carbonyl group making resonance stabilization much less important.



It is interesting to note that neither the isopropyl nor the tert-butyl radical initiated the reaction, while electrophilic radicals such as $t\text{-}C_4H_9O\cdot$ and $Cl_3C\cdot$ were quite effective. Since the ether oxygen may release electrons in the transition state, the oxirane hydrogen should be more easily abstracted by electrophilic than by nycleophilic radicals. Waters (21) has shown that alkyl radicals are nucleophilic in character; thus, they should be inefficient initiators, as was observed.

In general, it is desirable to use initiators which have half-lifes of the same order as the expected reaction time. Only a limited number of radical initiators useful in the temperature range studied are known. Some of these and their half-lifes are recorded in Table 4. A few of the initiators used deserve comment. Benzyl phenyl ether gives benzyl and phenoxy radicals near 250° (22). Since phenol did not catalyze the rearrangement, the phenoxy radical or the less electrophilic benzyl radical must be functioning as the initiator in this case. Hexachloroethane has been used to initiate the polymerization of isobutyric acid ethene at 238-250° (23). The most effective initiator was found to be 2-formyl-2, 4, 4-trimethylcyclopentanone (VIII) which has been shown to produce free radicals at 215-255°.

It is believed that these are the first known examples of intramolecular, free radical, acyl group migrations in thermochemistry. In previous reports of thermal rearrangements of α, β-epoxy ketones, no evidence for a radical mechanism was presented and acid catalysis

Table 4. Half-lifes of Some Free Radical Initiators

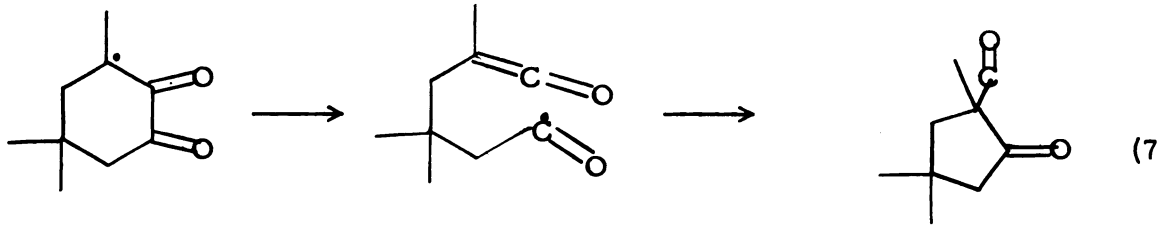
Initiator	Temp., °C.	Half-life, hr.	Ref.
$(C_6H_5CO_2)_2$	100	0.5	(40)
$(tert\text{-}C_4H_9O)_2$	160	0.4	(40)
$tert\text{-}C_4H_9O_2H$[a]	180	16.0	(41)
2, 2'-azoisobutane	210	2.1	(42)
2, 2'-azobispropane	250	4.6	(26)
VIII[b]	235	7.0	

[a]The rate constant varies greatly with concentration and solvent, and the value reported is for a dilute octane solution.

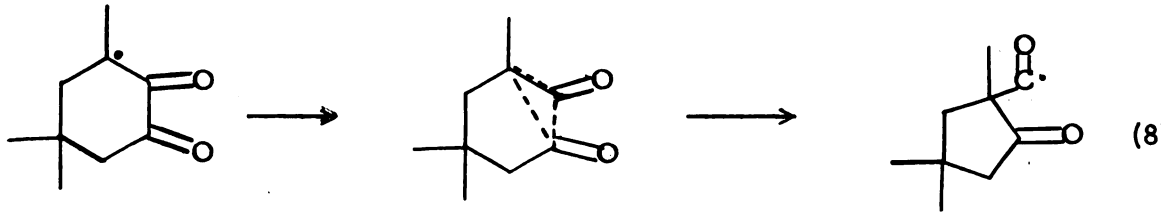
[b]2-Formyl-2, 4, 4-trimethylcyclopentanone.

was not ruled out. Barton (24) has recently reported a Wagner-Meerwein type acyl radical rearrangement in the photolytic reactions of steroid 11-hydroxy-17-keto nitrite esters.

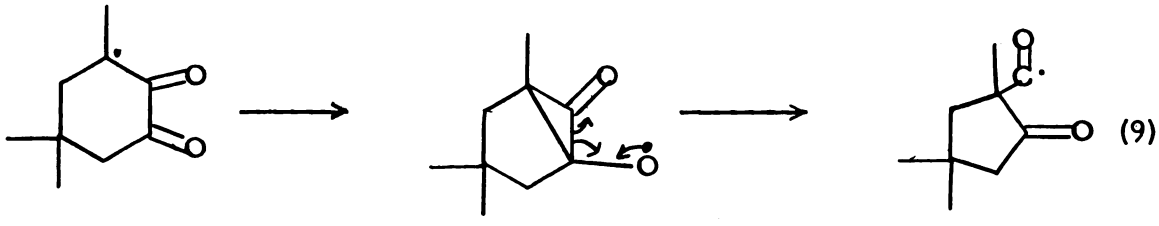
The exact nature of the acyl 1,2-shift is debatable. A two step cleavage recombination mechanism such as that shown in equation (7) is conceivable. Although acyl radicals are known to decarbonylate quite rapidly at the temperature employed, they should have a long enough life time to undergo a 1,2-shift. Tucker (25) has recently shown that the trifluroacetyl radical formed by photolysis exists long enough to be traped with bromine at 250°. However, this mechanism is somewhat unattractive since it would lead to molecular fragmentation in the case of 4-methyl-3,4-epoxy-2-pentanone. A second possibility is a one step process (8) involving some type of bonding force between the migrating groups in the transition state. A third and very attractive two step mechanism (9) involves the formation and opening of a cyclopropanone intermediate.



(7)



(8)



(9)

III. Thermal Rearrangement of Isophorone Oxide

Pure isophorone oxide (V) remains unchanged after heating at 235° in the absence of oxygen for six hours. Consequently, we were quite surprised to find that a neat degassed sample was completely converted to a 3:1 mixture of VI and VII, when heated at 235° for 12 hours. In this capricious reaction, the yields varied between 0 and 100% from one batch of epoxide to the next. The reaction was completely inhibited by N-methylaniline and tetrahydrothiophene and partially inhibited by nitrobenzene and m-dinitrobenzene. These results, which are summarized in Table 5, suggested that a very slow thermal process was producing species capable of initiating the radical chain reaction.

In order to study the thermal rearrangement of V without interference from the chain reaction, dilute decalin solutions were heated at 270°. The rate of rearrangement was followed by measuring the rate of disappearance of the 5.85μ band in the infrared. Although the points tended to scatter, fairly good first order plots were obtained in all cases. The first order rate constants are summarized in Table 6. The difference in rate constants between duplicate runs was about ten percent.

In the runs inhibited with N-methylaniline the only product formed was 2,4,4-trimethylcyclopentanone (VII) while in the uninhibited cases a small amount of the diosphenol (VI) is also formed. The rate constants for the uninhibited runs were greater than those of the inhibited. Evidently, some radical induced decomposition is occurring in the former case.

Basic catalysis by the N-methylaniline was ruled out since the rate of reaction decreases as its concentration increases. Furthermore, the base catalyzed rearrangement of V has been studied by House (27) and the cyclopentanone (VII) was not one of the products.

Table 5. Thermal Rearrangement of Isophorone Oxide

Additives	Temp. °C.	Time, hr.	Extent of Reaction	Number of Runs
----	235	6	0	3
----	235	$7\frac{1}{2}$	5	1
----	235	12	100	4
$C_6H_5NHCH_3$ (1%)	235	12	0	2
$(CH_2)_4S$ (1%)	235	12	0	2
$C_6H_5NO_2$ (1%)	235	12	19	2
m-C_6H_4 $(NO_2)_2$ (1%)	235	12	14	2
p-$C_6H_4(OH)_2$ (1%)	235	12	100	2
p-$C_6H_4O_2$ (1%)	235	12	100	2
10^2 increase in surface area[a]	235	6	80	1

[a]Powdered Pyrex glass added.

Table 6. Rate Constants for the Rearrangement of Isophorone Oxide in Decalin

Isophorone Oxide Molar conc.	M-Methyl aniline Molar conc.	T/°C	k x 10^3/ $min.^{-1}$	Glass Batch Number[b]
0.0278	------	270	1.40	1
0.0308	0.0309	270	0.959	1
0.0315	0.1905	270	0.383	1
0.0315	0.1905	270	0.892[a]	1
0.0313	------	270	0.892	2
0.0308	0.2000	270	0.169	2
0.0157	0.2000	280	0.127	3
0.0308	0.2000	280	0.138	3

[a] 72% increase in surface area.

[b] Refers to vials prepared at the same time.

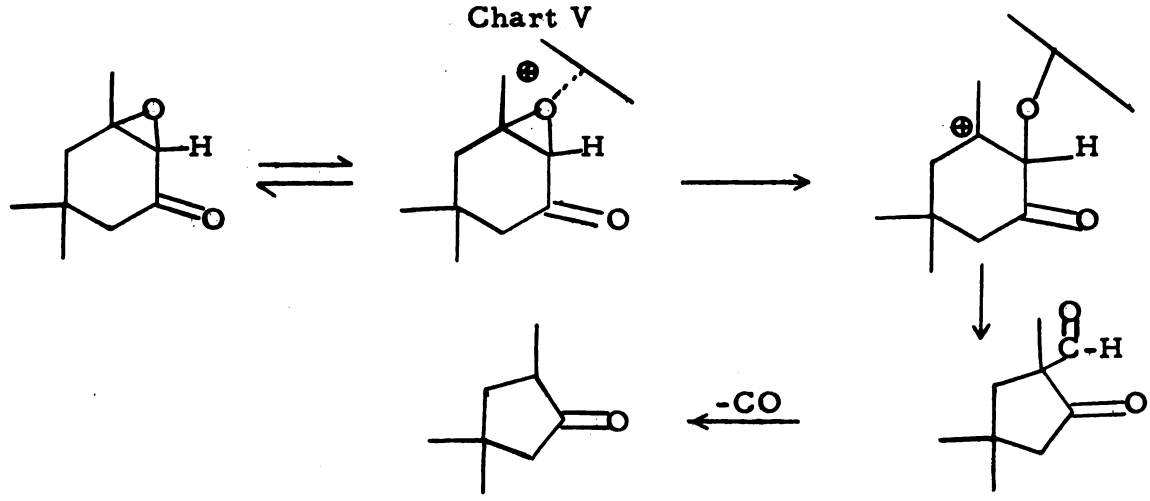
The reaction is surface catalyzed. The apparent first order rate constants were reproducible only as long as the same batch of Pyrex vials was used. When the surface area was increased 72% by adding Pyrex tubes, the rate was increased by 115%. Also, the addition of powdered Pyrex glass to a neat sample of V greatly accelerated its decomposition.

Pyrex glass contains silica, boric oxide and alumina and should have Lewis acid sites on its surface. Recently, Rondestvedt (28) has demonstrated the catalytic decomposition of 1, 3-dioxanes by acidic sites on silica gel. House (29) has shown that the boron trifluoride etherate catalyzed rearrangement of isophorone oxide gives almost exclusively 2-formyl-2, 4, 4-trimethylcyclopentanone (VIII). A similar transformation would be expected to occur at the acid sites on the Pyrex surface. Decarbonylation of the resulting keto aldehyde would then give the observed product VII.

In order to test this theory the keto aldehyde (VIII) was synthesized and was found to decarbonylate rapidly at 270°. It was also found to be a very effective initiator of the radical chain reaction, thus accounting for the observed induced decomposition occurring in the decalin solutions and in the neat samples of isophorone oxide.

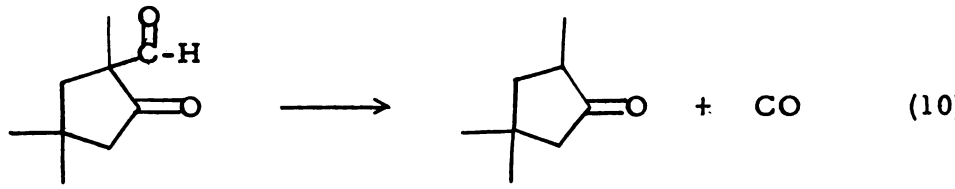
A schematic representation of the proposed acid catalyzed surface rearrangement is presented in Chart V.

Chart V



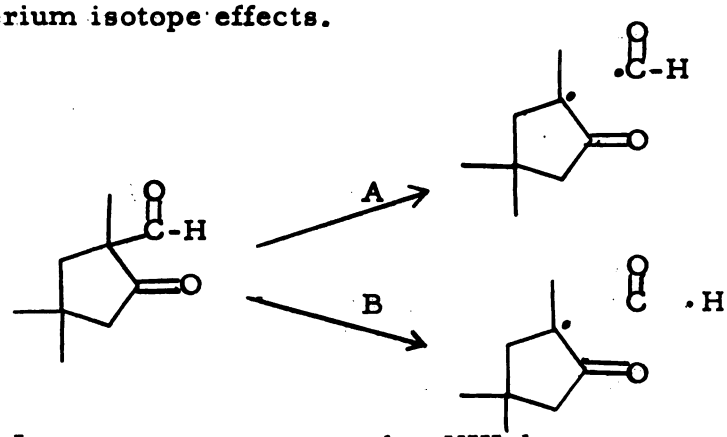
IV. Thermal Decomposition of 2-Formyl-2,4,4-trimethylcyclopentanone

When pure 2-formyl-2,4,4-trimethylcyclopentanone (VIII) was heated in dilute decalin solutions, it underwent a first order decomposition to 2,4,4-trimethylcyclopentanone (VII) and carbon monoxide. The first order rate constants are recorded in Table 7.



(10)

The energy of activation (Ea) for the decomposition of VIII was calculated from the available data and found to be 35.2 ± 7 Kcal./mole. This value is low in comparison with other compounds which decompose unimolecularly in the same temperature range. For example, 2,2-azoisobutane, which decomposes at a lower temperature than VIII, has an activation energy of 42.8 Kcal./mole (42). A detailed kinetic study is needed to determine an accurate value of Ea and to learn whether a one bond cleavage (A) or a two bond cleavage (B) is occurring in the rate determining step. These two processes may be distinguished by deuterium isotope effects.



(11)

In an attempt to prove that VIII decomposes to radicals, a ten percent solution of VIII in pure toluene was degassed and heated at 235°

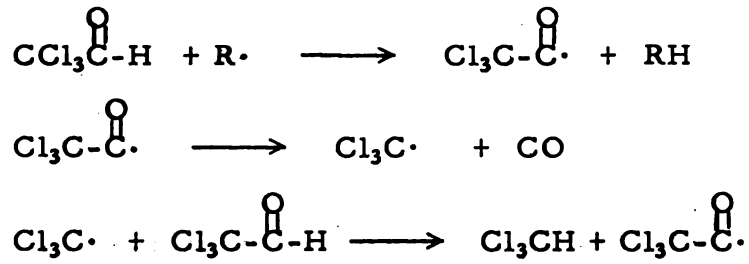
Table 7. Rate Constants for the Decomposition of 2-Formyl-2,4,4-trimethylcyclopentanone in Decalin

T/°C	Moles/liter	K x 10^3 minutes^{-1}
225	.0219	0.79
235	.0219	1.62
235	.0435	1.53

for ten hours. It was hoped that benzyl radicals would form and dimerize, however, no bibenzyl was formed. Likewise, bicumyl was not produced when cumene was used as the solvent.

The radical initiated decarbonylation of aldehydes is well-known (30). The decarbonylation of n-heptaldehyde at 230° using VIII as the initiator produced only a two percent yield of hexane, a fifty percent yield of high boiling products and an immiscible liquid, presumably water. A neat sample under the same conditions gave a fifty percent yield of high boiling products and water but no hexane. A thermal aldol condensation followed by dehydration is probably occurring, The α, β -unsaturated carbonyl compounds thus formed should be effective inhibitors of the radical chain reaction. Consequently, little hexane is produced.

The decarbonylation of chloral, a nonenolizable aldehyde, was then investigated.



(12)

Chloroform, the expected product, was not formed, but a fifty-two percent yield of tar was obtained. 2, 2'-Azoisobutane, a known free radical initiator, caused a similar reaction, whereas oxygen, acetic acid and heat were ineffective thus suggesting that VIII produces radicals at 230°.

The rearrangement of isophorone oxide is initiated by VIII giving the same ratio of products as obtained with other free radical initiators. If traces of acid, formed by autoxidation of VIII, were catalyzing the reaction, the reaction would be slower and would give a different product ratio than observed, as shown in Table 3.

It has been shown that the β-keto aldehyde (VIII) undergoes a first order decomposition between 215-255° to produce radicals capable of initiating chain reactions. Other β-keto aldehydes and β-diketones should decompose in a similar manner thus offering a whole new class of radical initiators.

EXPERIMENTAL

I. General Procedures

A. Apparatus

All routine infrared spectra were obtained on a Perkin-Elmer, Model 21, recording spectrophotometer, using sodium chloride cells. The band positions were recorded in microns. The ultraviolet spectra were determined in 1-cm. quartz cells using a Beckman DK-2 or a Cary, Model 11, spectrophotometer.

Proton magnetic resonance spectra were determined in carbon tetrachloride solution using a Varian, A-60, high resolution spectrometer. All spectra were obtained at 60 Mc using tetramethylsilane as an internal standard.

Vapor phase chromatography analysis were made using a $\frac{1}{4}$ inch, 6 foot column of 30% silicon on chromosorb.

B. Melting Points

Melting points were determined on a Kofler hot-stage and are uncorrected.

C. Microanalysis

All microanalysis were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

D. Furnace

The sample vials were heated in an aluminum block furnace, whose temperature was maintained within $\pm 2^{\circ}$ of the reported value.

E. Preparation of Pyrex Vials

For all sealed tube reactions, the tubes were prepared in the following way. Pyrex tubing was cut to the desired length, and the sections placed in a large cylinder, covered with conc. nitric acid, and heated on a steam bath for 24 hours. The acid was removed and the tubes rinsed thoroughly with distilled water. Concentrated ammonium hydroxide was added and the tubes allowed to stand 30 minutes; the ammonium hydroxide was removed and the tubes thoroughly rinsed with distilled water, and baked in an oven at 200° for 24 hours. The tubes were converted to vials, which were heated for several hours at 200°, and then stored in a desiccator over drierite.

F. Nitrogen

Oil pump nitrogen was purified by passing it through Fieser's solution (31).

G. Purification of Decalin

C. p. grade decalin was washed with concentrated sulfuric acid until the acid layer no longer turned yellow. It was then washed with water, dried over anhydrous sodium sulfate, and passed through a column of silica gel. Finally, it was distilled at reduced pressure and stored over sodium.

H. Purification of N-methylaniline

Reagent grade N-methyl aniline was distilled twice from potassium hydroxide pellets through a 16 inch vacuum jacked Vigreux column and used immediately.

II. Preparation of α, β-Epoxy Ketones

A. Preparation of 4-Methyl-3, 4-epoxy-2-pentanone

1. Preparation of Crude 4-Methyl-3, 4-epoxy-2-pentanone

To a 1 l. flask equipped with stirrer, thermometer and dropping funnel were added 49 g. (0.5 mole) of freshly distilled mesity oxide, b.p. 126-8°, and 100 ml. of dry methanol. The flask was placed in an ice salt bath, and a mixture of 61 ml. (0.6 mole) of 30% hydrogen peroxide and 33.6 g. (0.6 mole) of potassium hydroxide in 100 ml. of methanol added to the stirred solution over a period of 1½ hours with the temperature maintained between 0° and -5°. The solution was stirred an additional hour and then poured into 300 ml. of brine and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and the ether removed by distillation. The residue was distilled at atmospheric pressure to give 25.8 g. of a yellow mixture, b.p. 135-145°, which consisted of 85% 4-methyl-3, 4-epoxy-2-pentanone, 5% starting material and three low boiling components according to v.p.c. analysis. The mixture was carefully redistilled through a 16 inch, vacuum jacketed, tantalum spiral column but all fractions were yellow and contained the three low boiling components.

2. Preparation of Pure 4-Methyl-3, 4-epoxy-2-pentanone

This compound was prepared according to the procedure of Payne (18). One mole (98 g.) of mesityl oxide in methanol was converted to the epoxide on treatment with sodium hydroxide (0.05 mole) and 139 g. (1.25 moles) of 30% hydrogen peroxide. Distillation of the product gave 90 g., 79% yield, of epoxide boiling 63-65°/20 mm., n_D^{20} -1.4234, $\lambda_{max}^{95\% \text{ ethanol}}$ 200 mμ (ε = 1869) and 287 mμ (ε = 28.9), (lit. value (18), b.p. 61-62°/20 mm., n_D^{20} -.4235). The infrared

spectrum exhibited bands at 5.86μ, 7.67μ and 10.91μ. V.p.c. analysis showed the compound to be pure but it gave a positive ferrous sulfate test. The n.m.r. spectrum exhibited unsplit peaks at 8.73τ, 8.59τ, 7.87τ and 6.79τ in the ratio of 3:3:3:1.

3. Preparation of Peroxide Free 4-Methyl-3,4-epoxy-2-pentanone

The method of Payne (18) as described above was used to prepare the epoxide. The fraction boiling 60-65°/20 mm. was taken up in ether and washed with a saturated ferrous sulfate solution until the aqueous layer no longer turned red. The ether layer was washed twice with water, dried over anhydrous magnesium sulfate and the ether removed on a rotary evaporator. Distillation had a 39.5% yield, based on mesityl oxide, boiling 63-64°/20 mm., n_D^{20} -1.4236.

B. Preparation of Isophorone Oxide

This compound was prepared by the method of House (32). Freshly distilled isophorone, 110.4 g. (0.8 mole), was dissolved in 230 ml. (2.4 moles) of 30% hydrogen peroxide and 800 ml. of methanol, and converted to the epoxide upon addition of 66 ml. (0.4 mole) of 6N sodium hydroxide. A yield of 90.5 g. (73%) was obtained boiling 72-74°/5 mm., n_D^{25} - 1.4504, $\lambda_{max}^{95\% \text{ ethanol}}$ 291 mμ (ε = 42), $\nu_{max}^{CCl_4}$ 5.85μ and 11.0μ, (lit. value (32), b.p. 70-73°/5 mm., n_D^{25} -1.4500-1.4510).

III. Autoxidation of α,β-Epoxy Ketones

A. Autoxidation of 4-Methyl-3,4-epoxy-2-pentanone

1. Autoxidation of 4-Methyl-3,4-epoxy-2-pentanone (containing peroxide)

To a 25 ml. three necked flask fitted with a gas inlet tube and a short vigreux column was added 12 g. of 4-methyl-3,4-epoxy-2-pentanone

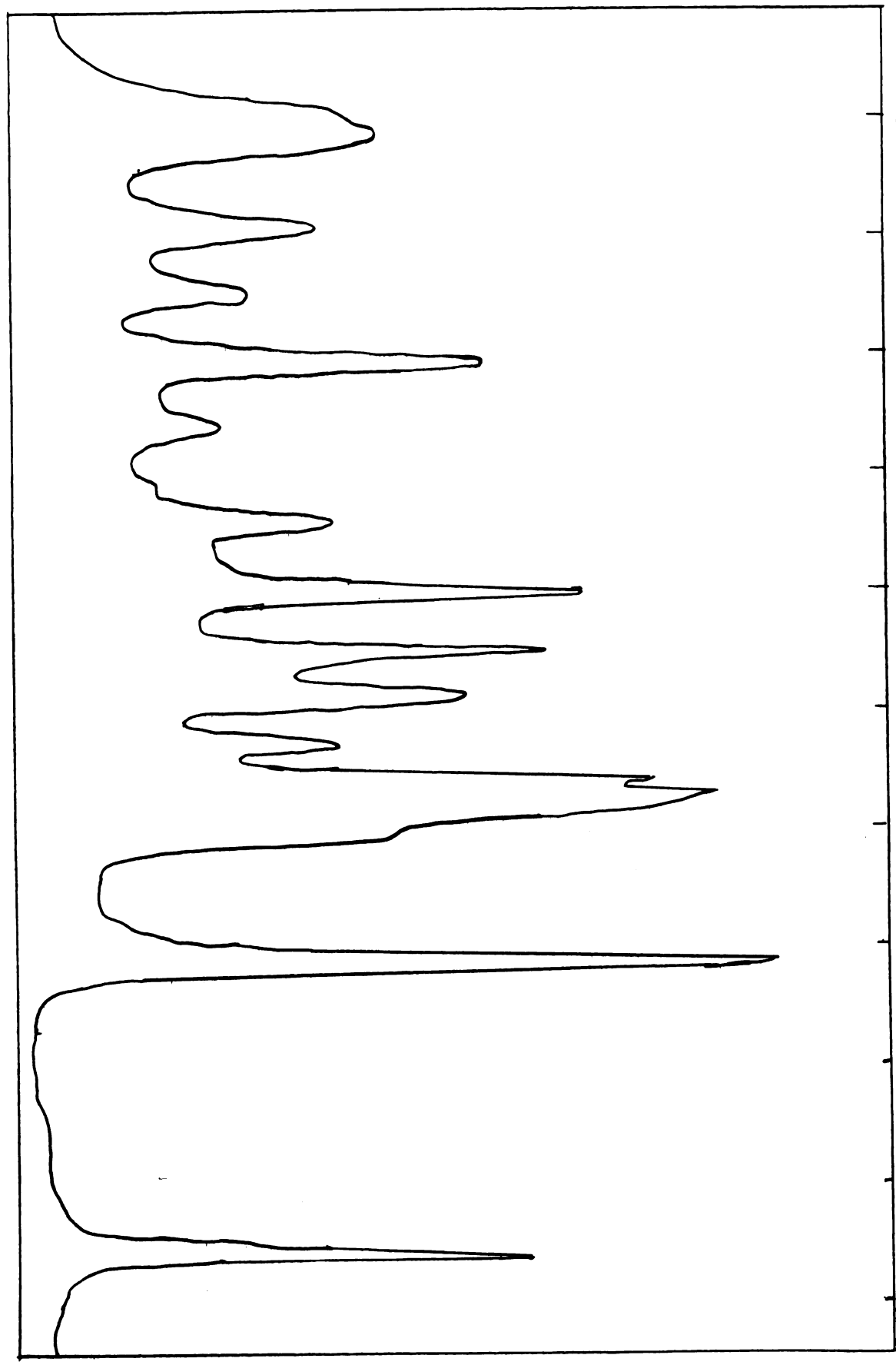


Figure 1. Infrared spectrum of 4-methyl-3,4-epoxy-2-pentanone.

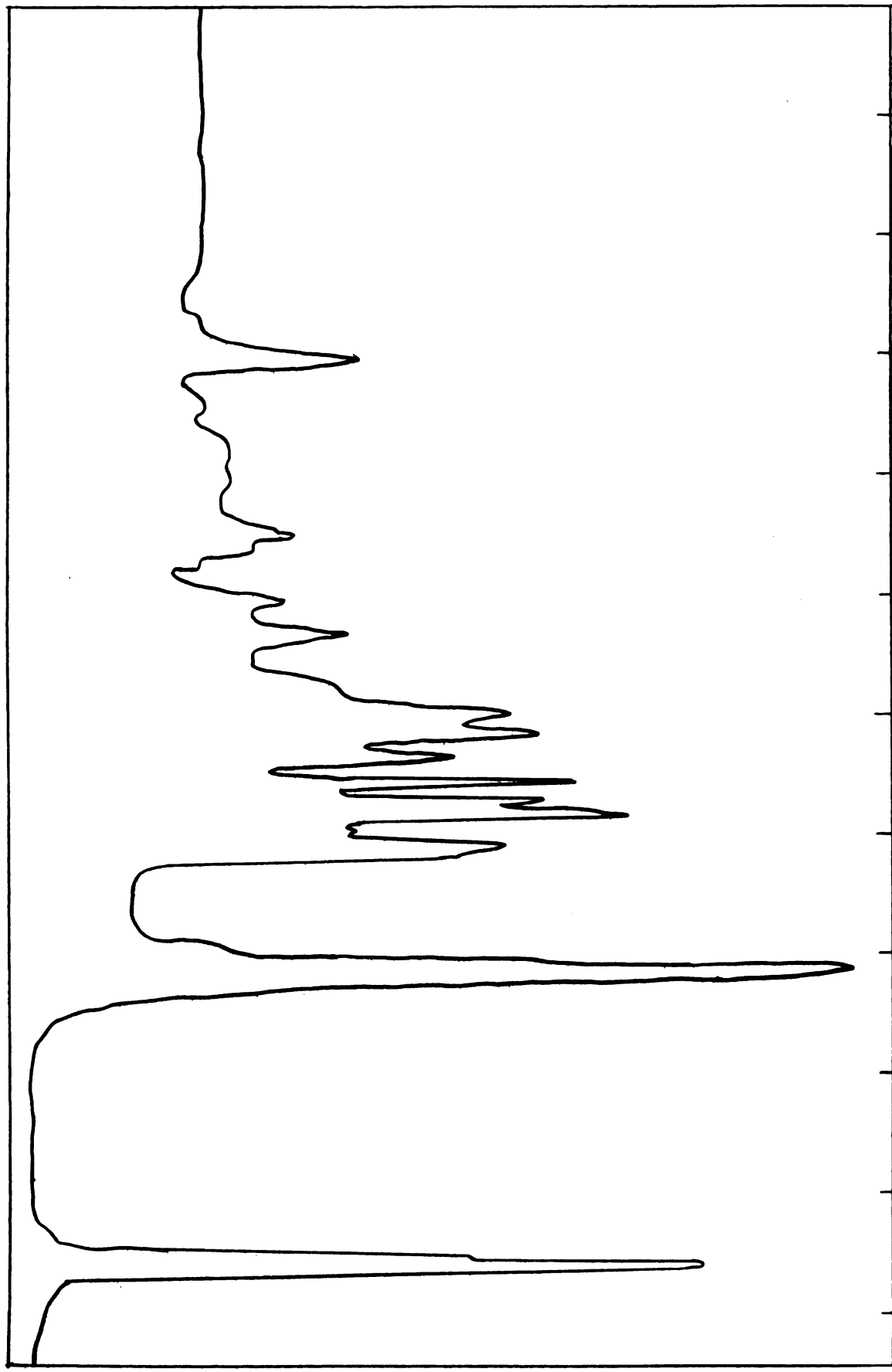


Figure 2. Infrared spectrum of isophorone oxide in carbon tetrachloride.

containing peroxide. The flask was heated in an oil bath at 170°, and air slowly passed through the solution. A yellow liquid began to distill through the column within 1 hour. After 36 hours the pot was very tarry and the reaction was stopped. The product, 1.2 g., was composed of acetone (20%), methyl isopropyl ketone (30%) and 4-methyl-2,3-pentanedione (50%) according to v.p.c. analysis.

2. Autoxidation of Peroxide Free 4-Methyl-3,4-epoxy-2-pentanone

To a 25 ml. three necked flask fitted with a gas inlet tube and a short vigreux column was added 8 g. of 4-methyl-3,4-epoxy-2-pentanone. The flask was heated in an oil bath at 170°, and air slowly passed through the solution. After 16 hours, no reaction had occurred so 0.05 g. (0.6%) of tert-butyl hydroperoxide was added. A yellow liquid then began to distill through the column. After 32 additional hours, the reaction was stopped and 0.7 g. of product, composed of acetone (30%), methyl isopropyl ketone (30%) and 4-methyl-2,3-pentandione (40%) by v.p.c. analysis, was collected.

3. Heating of 4-Methyl-3,4-epoxy-2-pentanone under Nitrogen

A small sample of 4-methyl-3,4-epoxy-2-pentanone, containing peroxide, was placed in a Pyrex tube, flushed with nitrogen and the tube sealed. It was then heated at 160° for 18 hours. V.p.c. analysis of the colorless liquid showed only the presence of starting material.

B. Autoxidation of Isophorone Oxide

1. Autoxidation of Isophorone Oxide

To a 5 ml. flask was added 1 g. of isophorone oxide, b.p. 206°, and the sample refluxed in air for 3½ hours. V.p.c. analysis showed

the presence of 5% of a new compound, which gave a purple ferric chloride test. On standing overnight, crystals formed which were removed by filtration and recrystallized from petroleum ether, m.p. 91-92°, $\nu_{max}^{CCl_4}$ 2.9μ, 5.96μ and 6.05μ. The values reported (29) for 1,5,5-trimethyl-2-hydroxycyclohexene-3-one are m.p. 92-92.5°, $\nu_{max}^{CCl_4}$ 2.9μ, 5.95μ and 6.05μ and $\lambda_{max}^{95\% \text{ ethanol}}$ 274 (ϵ = 9,400). When a 1 g. sample was refluxed in air for 12 hours, 2,4,4-trimethylcyclopentanone (1.5%) and 1,5,5-trimethyl-2-hydroxycyclohexene-3-one (13.5%) were formed according to v.p.c. analysis.

2. Autoxidation of Isophrone Oxide in the Presence of Inhibitors

To a 5 ml. flask was added 1 g. of isophorone oxide and 0.02 g. of either hydroquinone or N-methyl aniline and the mixture refluxed in the presence of air for 3½ hours. In both cases, v.p.c. analysis showed that no reaction had taken place.

3. Refluxing Isophorone Oxide under Nitrogen

To a 5 ml. flask was added 1 g. of isophorone oxide and the air removed by alternately evacuating and flushing the flask with nitrogen four times. The sample was then refluxed under nitrogen for 3½ hours. V.p.c. analysis showed that no reaction had occurred.

IV. Free Radical Rearrangements of α,β-Epoxy Ketones

A. Experimental Techniques

All samples were degassed and sealed in carefully cleaned Pyrex tubes under nitrogen. These tubes were heated at various temperatures and lengths of time in an aluminum block furnace. The reaction mixtures were analyzed by v.p.c.

B. Results

The results of the rearrangements of 4-methyl-3,4-epoxy-2-pentanone are summarized in Table 1, and those of isophorone oxide in Tables 2 and 3.

C. Products from the Rearrangement of 4-Methyl-3,4-epoxy-2-pentanone

To a large combustion tube were added, 19 g. (0.167 mole) of 4-methyl-3,4-epoxy-2-pentanone and 0.5 g. (0.0056 mole of tert-butyl hydroperoxide. The tube was sealed under nitrogen and heated at 190° for 25 hours. V.p.c. analysis of the mixture gave acetone (12%), methyl isopropyl ketone (6%), 4-methyl-2,3-pentanedione (22%), and epoxide. Pure samples of each component were obtained by preparative g.l.c. using a Beckman Megachrom.

1. Acetone

A 2,4-dinitrophenylhydrazone of the peak which corresponded to acetone was prepared melting 123-125°, (lit. value, m.p. -126°). There was no depression of a mixed melting point with an authentic sample.

2. Methyl Isopropyl Ketone

A 2,4-dinitrophenylhydrazone of the peak which corresponded to methyl isopropyl ketone was prepared, which melted at 115-117°, (lit. value, m.p. -117°). There was no depression of a mixed melting point with an authentic sample.

3. 4-Methyl-2,3-pentanedione

This yellow compound boiling 114.5°, $\nu_{max}^{CCl_4}$ 5.85μ, $\lambda_{max}^{95\%\ \text{ethanol}}$ 427mμ (ϵ = 18), (lit. value (33), b.p. 115-116°) formed a di-2,4-dinitrophenylhydrazone melting at 239-240°.

Anal. Calc'd for $C_{18}H_{18}N_8O_8$: C, 48.58; N, 23.62; H, 3.82
Found: C, 45.65; N, 23.63; H, 3.74

4-Methyl-2,3-pentanedione was synthesized by the acid catalyzed rearrangement of 4-methyl-3,4-epoxy-2-pentanone and found to have the same v.p.c. retention time and I.R. spectrum as the product from the free radical rearrangement.

D. Acid Catalyzed Rearrangement of 4-Methyl-3,4-epoxy-2-pentanone

To a 5 ml. flask were added 0.8 g. of 4-methyl-3,4-epoxy-2-pentanone and 0.05 g. of p-toluenesulfonic acid. The flask was heated at 100° for 1 hour and the mixture distilled to give 0.055 g. (9%) of methyl isopropyl ketone and 0.31 g. (39%) of 4-methyl-2,3-pentanedione boiling 115°.

E. Products from the Rearrangement of Isophorone Oxide

To a large combustion tube were added 15 g. of isophorone oxide and 0.5 ml. of tert-butyl hydroperoxide and the tube was sealed under nitrogen. The tube was heated at 240° for 24 hours, and then cooled in liquid nitrogen and opened. V.p.c. analysis of the crude mixture showed the presence of two major components of 22% and 73%, which corresponded to 2,4,4-trimethylcyclopentanone and 1,5,5-trimethyl-2-hydroxycyclohexene-3-one, respectively. On standing overnight, crystals formed, which were removed by filtration and recrystallized from petroleum ether to give 4.5 g. (30%) of 1,5,5-trimethyl-2-hydroxycyclohexene-3-one melting at 91-92°, $\lambda_{max}^{95\% \text{ ethanol}}$ 274 mμ (ϵ = 9,011), $\nu_{max}^{CCl_4}$ 2.92μ, 5.96μ and 6.06μ, (lit. value (29), m.p. 92-92.5°, λ max 274 mμ (ϵ = 9,400), $\nu_{max}^{CCl_4}$ 2.90μ, 5.95μ and 6.05μ).

The filtrate was distilled to give 1.5 g. (12%) of 2,4,4-trimethylcyclopentanone boiling 85-90°/80 mm., $\nu_{max}^{CCl_4}$ 5.75μ, which formed

a 2,4-dinitrophenylhydrazone melting 159-160° (lit. value (29), m.p. -160.5-161°). There was no depression of a mixed melting point with an authentic sample. This product and 2,4,4-trimethylcyclopentanone were found to have identical v.p.c. retention times.

F. Analysis of the Gas Formed in the Rearrangement of Isophorone Oxide

The gas formed in the rearrangement of 0.5 g. of isophorone oxide was collected, and analyzed by v.p.c. at 30° using a molecular sieve column. A peak having the same retention time (9.5 minutes) as carbon monoxide was found. An I.R. of the gas exhibited a band at 4.64μ (reported value, 4.66μ). The carbon monoxide used for comparison was synthesized by the action of concentrated sulfuric acid on formic acid (34).

G. Rearrangement in the Presence of Water

To a small vial was added 0.4 g. (0.0026 mole) of isophorone oxide and 0.0234 g. (0.0013 mole) of water; the tube degassed and sealed under nitrogen. The sample was heated at 235° for seven hours and analyzed by v.p.c. It was composed of epoxide (83%), 2,4,4-trimethylcyclopentane (2.6%) and 1,5,5-trimethyl-2-hydroxy-cyclohexene-3-one (14.4%).

H. Rearrangement in the Presence of Water with Initiator Added

To a small Pyrex vial was added 0.4 g. (0.0026 mole) of isophorone oxide, 0.0236 g. (0.0013 mole) of water and 0.004 g. of 2-formyl-2,4,4-trimethylcyclopentanone. The tube was degassed, sealed under nitrogen and then heated at 235° for seven hours. V.p.c. analysis gave 2,4,4-trimethylcyclopentanone (16%),

1,5,5-trimethyl-2-hydroxycyclohexene-3-one (60%) and epoxide (26%). No other compounds were detected by v.p.c. or I.R.

I. Synthesis of 2,4,4-Trimethylcyclopentanone

This compound was prepared by the cleavage of 2-formyl-2,4,4-trimethylcyclopentanone with sodium hydroxide according to the procedure of House (29). The product gave a 2,4-dinitrophenylhydrazone melting at 159-160°, (lit. value (29), m.p. 160.5-161°).

V. Preparation of Initiators

A. Synthesis of 2-Formyl-2,4,4-trimethylcyclopentanone

This compound was synthesized by the method of House (29). A boron trifluoride etherate catalyzed rearrangement of 20 g. (0.13 mole) of isophorone oxide yielded 14.57 g. (73%) of 2-formyl-2,4,4-trimethylcyclopentanone boiling 50-51°/2 mm., n_D^{25} -1.4497, $\nu_{max}^{CCl_4}$ 3.68μ, 5.72μ and 5.80μ, (lit. values (29), b.p. 49-50°/2 mm., n_D^{25} -1.4495).

B. Synthesis of 2,2'-Azobispropane

2,2'-Azobispropane was synthesized by the procedure of Renaud and Leitch (35). Isopropylideneazine was obtained in 74% yield from the reaction of acetone with hydrazine. It was reduced to 1,2-diisopropylhydrazine by means of lithium aluminum hydride, which was in turn oxidized to 2,2'-azobispropane in 48% yield with mercuric oxide, b.p. 88-89°, n_D^{20} -1.3896, (lit. values (35), b.p. 88.5°, n_D^{20} -1.3899).

C. Synthesis of 2,2'-Azoisobutane

N-bromo-t-butylamine was prepared by the treatment of t-butylamine with bromine and potassium hydroxide (36). A silver oxide oxidation of the crude N-bromo-t-butylamine, by Farenhorst's method

(37), gave 2,2'-azoisobutane in 19% yield, b.p. 109-110°, (lit. value (37), b.p. 108-109°). The n.m.r. spectra exhibited only one unsplit peak at 8.88τ.

D. Synthesis of Benzyl Phenyl Ether

Benzyl phenyl ether was prepared by the method of Adams (38). Treatment of a mixture of 31.5 g. (0.25 mole) of benzyl chloride and 26.25 g. (0.25 mole) of phenol with potassium carbonate in acetone gave 31.33 g. (64.5%) of benzyl phenyl ether melting 40°, (lit. value (38), m.p. 39°).

E. Synthesis of 4-Biphenylyl Benzyl Ether

4-Biphenylyl benzyl ether was prepared according to the procedure of Adams (38). Treatment of a mixture of 31.5 g. (0.25 mole) of benzyl chloride and 43.1 g. (0.25 mole) of p-phenylphenol with 34.5 g. of potassium carbonate in acetone produced 46 g. (67%) of p-phenylyl benzyl ether melting at 136°, (lit. value (39), m.p. 136°).

F. Purification of Hexachloroethane

Technical grade hexachloroethane was purified by sublimation, m.p. 185-7°, (lit. value 187°). No C-H bonds were present in the I.R. spectrum of this compound.

VI. Thermal Rearrangements of α,β-Epoxy Ketones

A. Thermal Rearrangement of Isophorone Oxide

1. Rearrangement of Isophorone Oxide in Decalin

A small sample, 0.8 ml., of a 0.0278 M solution of isophorone oxide in decalin was placed in a Pyrex tube, and the tube degassed and

sealed under nitrogen. The sample was heated at 280° for 4½ hours. An I.R. spectrum of the solution exhibited new peaks at 5.75μ and 6.05μ. The approximate composition of the sample based on the heights of the I.R. peaks is epoxide (50%), 2,4,4-trimethylcyclopentanone (45%), and 1,5,5-trimethyl-2-hydroxycyclohexene-3-one (5%). The solution gave a weak purple ferric chloride test.

2. Thermal Rearrangement of Isophorone Oxide in the Presence of N-Methylaniline

To a Pyrex tube was added 1 ml. of a decalin solution, which was 0.0408 M in isophorone oxide and 0.193 M in N-methylaniline. The tube was degassed and sealed under nitrogen, and then heated at 280-285° for 68 hours. V.p.c. analysis showed that 50% of the epoxide had decomposed, to give 2,4,4-trimethylcyclopentanone. Neither, 3,3-dimethylcyclopentanone nor 1,5,5-trimethyl-2-hydroxycyclohenene-3-one could be detected.

3. Kinetics of the Thermal Rearrangement

The rate of thermal rearrangement of isophorone oxide was followed by measuring the rate of disappearance of the 5.85μ band via a Perkin Elmer, Model 21, or a Beckman, I.R. 7, recording infrared spectrophotometer.

All tubes were the same length and had a volume of about 3 ml. In order to study surface catalysis, small Pyrex tubes of known dimensions were placed in the vials and the rate of rearrangement determined.

The following experimental procedure was used: Solutions of known concentration were prepared in 25 ml. volumetric flasks. Eight tenths of a ml. of solution was introduced into each vial with a hypodermic syringe. The samples were degassed and sealed under

nitrogen with an oxygen-gas torch. They were placed in an aluminum block furnace controlled to $\pm$ 0.5°. A period of five minutes was allowed for the samples to reach the temperature of the furnace; zero time was thus assumed to be five minutes after the samples were placed in the furnace. At various time intervals, samples were removed from the furnace and immediately quenched in water at room temperature. The vials were marked and stored at 0° in a refrigerator until completion of the run.

The log of the concentration versus time was plotted and the rate constant calculated from the slope of the line.

Different rate constants were obtained with each batch of tubes. Considerable random scattering of points occurred and reproducibility was poor due to surface catalysis. The estimated error in the rate constants is 10%.

VII. Thermal Decomposition of 2-Formyl-2,4,4-trimethylcyclopentanone

A. Neat Sample

A pure sample of 2-formyl-2,4,4-trimethylcyclopentanone was degassed and sealed in a Pyrex tube under nitrogen. The tube was then heated at 235° for 3 hours. V.p.c. analysis indicated that fifteen percent decomposition to 2,4,4-trimethylcyclopentanone has occurred.

B. Attempted Decarbonylation of n-Heptaldehyde

A 2% solution of 2-formyl-2,4,4-trimethylcyclopentanone in pure n-heptaldehyde was placed in a Pyrex tube, degassed, sealed under nitrogen, and heated at 230° for six hours. On cooling, an immissible layer, presumably water, formed. V.p.c. analysis showed that 50% of the aldehyde had been converted to high boiling products;

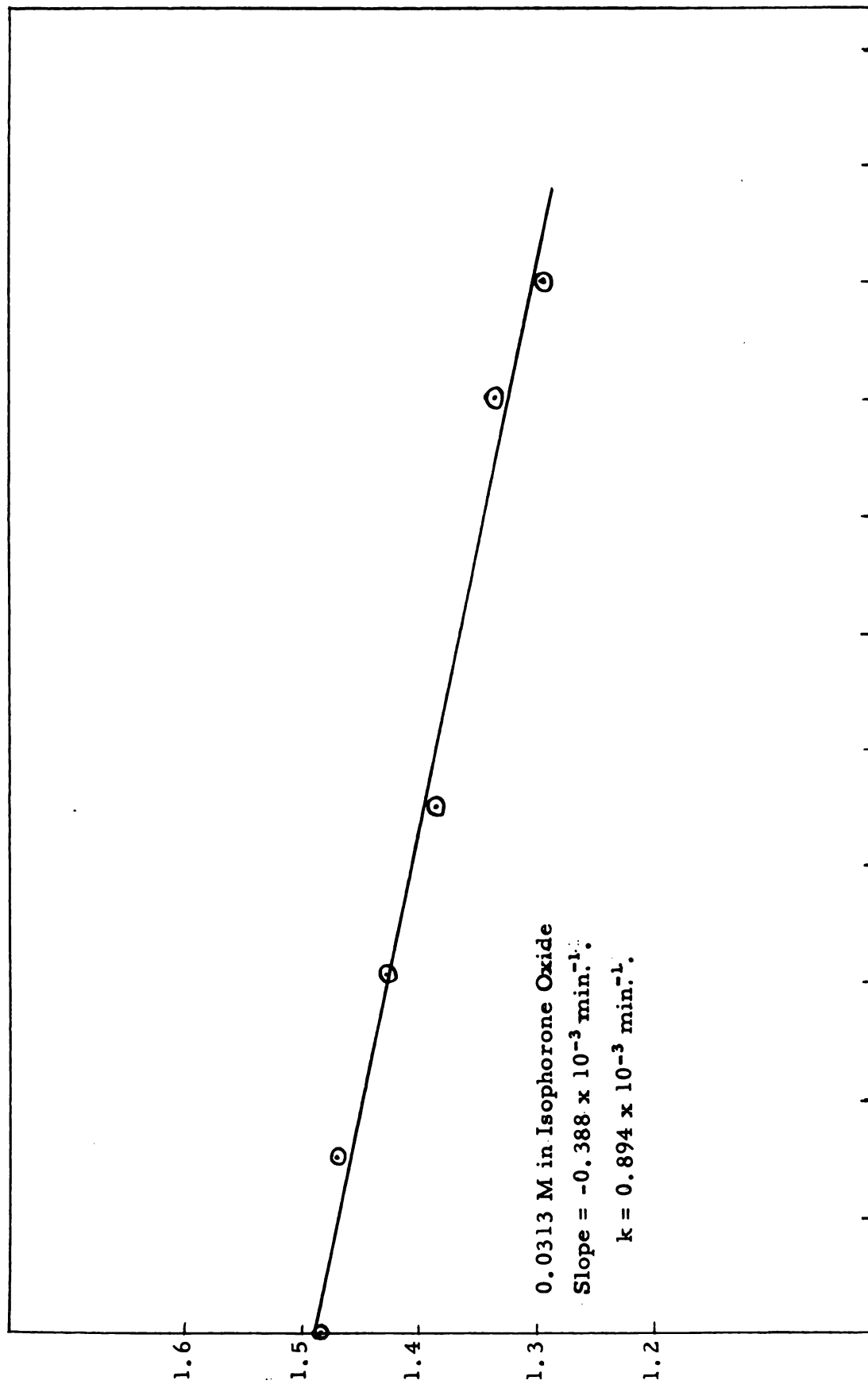


Figure 3. First order plot for the rearrangement of Isophorone oxide at 270° in decalin.

however, a peak whose r etention time matched that of hexane was present in 2% yield. A neat sample of n-heptaldehyde, under the same conditions, also produced 50% high boiling products but no hexane peak was observed.

C. Decarbonylation of Chloral

A 3% solution of 2-formyl-2, 4, 4-trimethylcyclopentanone in freshly distilled chloral was placed in a Pyrex tube. The tube was degassed, sealed under nitrogen, and heated at 230° for 3 hours. The product mixture was very tarry. Fifty-two percent of the chloral was converted to high boiling products but neither chloroform nor carbon tetrachloride were formed. Chloral is stable under the conditions of the reaction and neither air nor acetic acid cause such a transformation; however, 3% of 2, 2'-azoisobutane causes a similar reaction, with the formation of 21% tar in 3 hours.

D. Kinetics of Decomposition

The rate of thermal decomposition of 2-formyl-2, 4, 4-trimethylcyclopentanone was followed by measuring the rate of disappearance of the 5.80μ band via a Perkin Elmer, Model 21, recording infrared spectrophotometer.

The same experimental techniques as already outlined for the thermal rearrangement of isophorone oxide were used.

The only product was identified as 2, 4, 4-trimethylcyclopentanone by v.p.c. retention time and the appearance of a band at 5.75μ in the I.R. No peak having the same retention time as 3, 3-dimethylcyclopentanone was formed.

E. Decomposition of 2-Formyl-2, 4, 4-trimethylcyclopentanone in Toluene

To a Pyrex vial was added 0.1 g. of 2-formyl-2, 4, 4-trimethylcyclopentanone and 0.9 g. of pure toluene. The sample was degassed, sealed under nitrogen, and then heated at 255° for 10 hours. No bibenzyl could be detected by v.p.c. analysis of the resulting mixture.

F. Determination of the Energy of Activation

The energy of activation, Ea, was calculated using equation (1) where k is the first

$$k = se^{-Ea/RT} \qquad (1)$$

order rate constant, Ea is the experimental activation energy in calories, R is the gas constant per mole (1.987 calories 1°K), and s is the frequency factor. Conversion of equation (1) into a more convenient form gives equation (2).

$$\log k = \log s + Ea/2.303RT \qquad (2)$$

The energy of activation was obtained by plotting log k versus 1/T and multiplying the slope of the line by -2.303R.

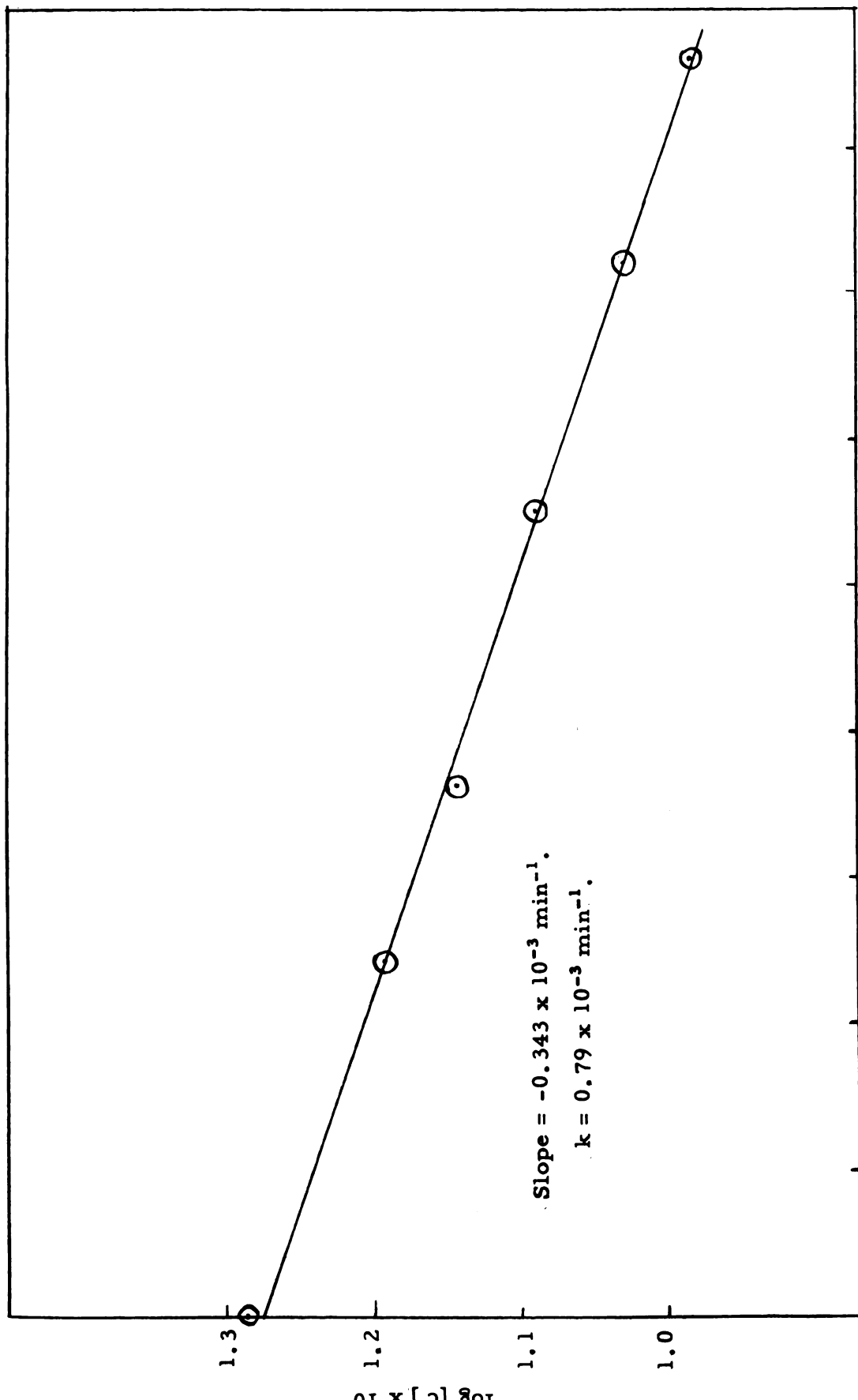


Figure 4. First order plot for the decomposition of 2-formyl-2,4,4-trimethylcyclopentanone at 225°

SUMMARY

1. The autoxidation of several α,β-epoxy ketones was studied. When 4-methyl-3,4-epoxy-2-pentanone (containing peroxide) was refluxed in air, it was converted to acetone, methyl isopropyl ketone, 4-methyl-2,3-pentanedione and considerable tar. Isophorone oxide, b.p. 206°, gave 2,4,4-trimethylcyclopentanone and 1,5,5-trimethyl-2-hydroxycyclohexene-3-one in low yield when refluxed in air. These must be radical chain reactions since no reaction occurred in the absence of oxygen or in the presence of radical inhibitors.

2. Degassed samples of these epoxides rearranged to the above mentioned products when heated in the presence of small amounts of radical initiators. Although carboxylic acids catalyzed the rearrangement, the product ratio was different and the rate of reaction too slow to account for the results. These free radical rearrangements have high activation energies since little reaction occurred below 200°. Possible mechanisms for these transformations are discussed. The formation of 2,4,4-trimethylcyclopentanone from 4-methyl-3,4-epoxy-2-pentanone are thought to be the result of novel 1,2-shifts of acyl groups.

3. Dilute decalin solutions of isophorone oxide containing an excess of methylaniline were shown to undergo apparent first order decomposition at 270° to give 2,4,4-trimethylcyclopentanone as the sole product. The initial product of this surface catalyzed rearrangement is probably 2-formyl-2,4,4-trimethylcyclopentanone, which was shown to undergo first order decarbonylation at this temperature to yield 2,4,4-trimethylcyclopentanone and species capable of initiating free radical reactions.

PART II

CONFIGURATIONS AND REARRANGEMENTS OF THE DIASTEREOISOMERIC PULEGONE OXIDES

INTRODUCTION AND HISTORICAL

The thermal and radical chain reactions of trisubstituted α, β-epoxy ketones were discussed in Part I of this thesis. In order to study the thermal rearrangements without interference from radical chain reactions, a tetrasubstituted α, β-epoxy ketone, pulegone oxide, was prepared. This compound was chosen for study because of the availability of pulegone and because it reportedly rearranges to products of uncertain structure when heated at 200°. We planned to determine the structures of the products, and investigate the mechanism of this thermal reaction.

In 1927, Prilejaeff (11) first prepared pulegone oxide, m.p. 43-44°, $[\alpha]_D = 0$, by the oxidation of pulegone with perbenzoic acid. He observed that the oxide was converted into a liquid isomer of unknown structure when heated at 200°. A similar transformation reportedly occurred on prolonged standing at room temperature.

Treibs (43) has also prepared pulegone oxide, m.p. 40°, $[\alpha]_D = +6.6°$, by the action of hydrogen peroxide on pulegone in the presence of alkali.

Recently, Pigulevski and Mironova (12) have reinvestigated the work of Prilejaeff. They heated pulegone oxide, m.p. 43-45°, $[\alpha]_D = +10.28°$, at 200° under nitrogen and followed the change in specific rotation with time. The oxide was converted to a more strongly dextrorotatory liquid modification whose Raman spectra was quite similar to that of the original epoxide after 8 hours of heating. Pigulevski and Mironova therefore concluded that only epimerization of the epoxide ring was occurring. This conclusion is dubious, as no products were isolated.

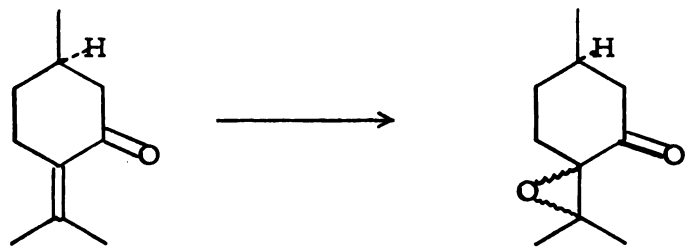
The specific rotations reported for pulegone oxide by the various investigators are all different. This suggested that they were working with optically impure epoxide. Indeed, neither synthetic method would be expected to be stereospecific, and a mixture of the two possible isomers of pulegone oxide should be formed. The first problem therefore was to isolate and establish the absolute configurations of the isomeric pulegone epoxides.

(1)

RESULTS AND DISCUSSION

I. Isolation and Configurations of the Pulegone Oxides

Pulegone oxide mixtures were prepared in good yield from (+)-pulegone either by perbenzoic acid oxidation or by reaction with alkaline hydrogen peroxide.



These mixtures consisted of 34% Ia and 66% IIa in the former reaction and 32% Ia and 68% IIa in the latter according to vapor phase chromatography analysis. Epimerization did not occur under the conditions of these reactions. Both of these reactions must be kinetically controlled inasmuch as the least stable isomer (IIa) is the major product.

A crystalline compound was readily isolated which exhibited physical properties (m.p. 42-43°, $[\alpha]_D^{25}$ + 15.2) identical to those previously reported for one of the diastereomers (12). However, vapor phase chromatography analysis showed this compound to be an equimolar mixture of the two isomers. The isomers were separated by careful distillation at reduced pressure followed by crystallization from petroleum ether. The physical properties of the isomers are given in Table 8.

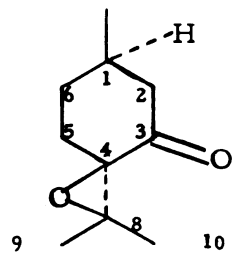
The configuration of isomers I and II were assigned on the basis of four arguments. The first argument is based on the similarity of

Table 8. Physical Properties of the Pulegone Oxide Isomers

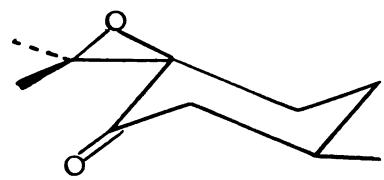
Isomer	m.p.	$\lambda_{max}^{heptane}$ ϵ	CCl_4 max	$[\alpha]_D^{C_2H_5OH}$
Ia	59	209mμ(225) 303mμ(31)	1727 cm^{-1}	+ 48.0
IIa	55	209mμ(221) 303mμ(31)	1728 cm^{-1}	- 19.6

the ultraviolet spectra and the carbonyl absorption in the infrared spectra of the two isomers. These observations suggest that the principle conformers in each case have almost identical configurations in the carbonyl regions of the molecules. A bathochromic shift of the $n \rightarrow \pi^*$ transitions of both isomers with respect to menthone, $\lambda_{max}^{heptane}$ 296mμ (ϵ = 21), indicates that the oxirane oxygen is oriented either above or below the plane of the carbonyl group, since polar axial substituents α to the carbonyl group of cyclohexanones are known to cause such shifts (44).

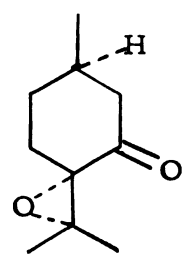
A careful examination of Dreiding Models has led us to conclude that the chair conformation Ib is the most important contributor to isomer Ia; while the twist boat conformation IIb is the major contributor to isomer IIa. These conformations readily account for the observed spectra and have the fewest non-bonded interactions.



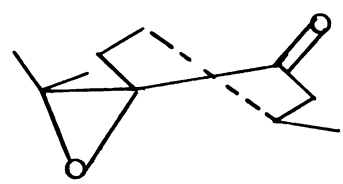
Ia



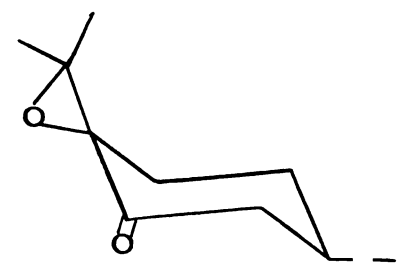
Ib



IIa



IIb



IIc

The following unfavorable steric interactions were measured using Dreiding Models.

I_b: C_9-C_5 1.9 Å, C_{10}-Carbonyl Oxygen 1.6 Å

II_b: C_9-C_5 2.0 Å, C_{10}-Carbonyl Oxygen 1.7 Å

These measurements are not accurate to more than ± 0.05 Å and refer to the distance of maximum steric interaction. Other conformations, such as the chair conformer IIc, must also be considered. However, this conformation is not only destabilized by steric compressions, but also suffers from electrostatic repulsion resulting from the eclipsed oxygen carbon bonds at C_3 and C_4.

Secondly, significant differences are found in the n.m.r. spectra of the two diastereomers, which are shown in Figure 5. These differences are readily explained in terms of conformations I_b and II_b. The spectrum of isomer Ia exhibits a pair of doublets at 7.44 τ and 7.58 τ, Jvic. = 2.2 c.p.s., J = gem. 9.0 c.p.s. Examination of conformations Ib shows that the equatorial hydrogen at C_2 is almost eclipsed by the adjacent carbonyl group, and is therefore deshielded with respect to the axial C_2 hydrogen, which is located above the plane of the carbonyl group (45). These hydrogens should be split by the tertiary C_1 hydrogen to give an ABC resonance pattern, of which only the low field portion was observed because of the other multiplets present. The area of these doublets is only one-fourth that of the methyl group at 8.63 τ, however, the latter peak apparently overlaps some parts of other multiplets.

In contrast, the lowest field absorption of isomer II_a is a doublet at 7.68 τ, J = 2 c.p.s. the observed spectrum is reasonable if II_b is the main contributor to II_a. In this conformation, the carbonyl group bisects the H-C_2-H bond angle; therefore, both hydrogens will have similar chemical shifts. The tertiary hydrogen at C_1 should split the C_2 hydrogens into a doublet as observed. If the boat conformation II_c was predominant, an ABC resonance pattern would have been observed.

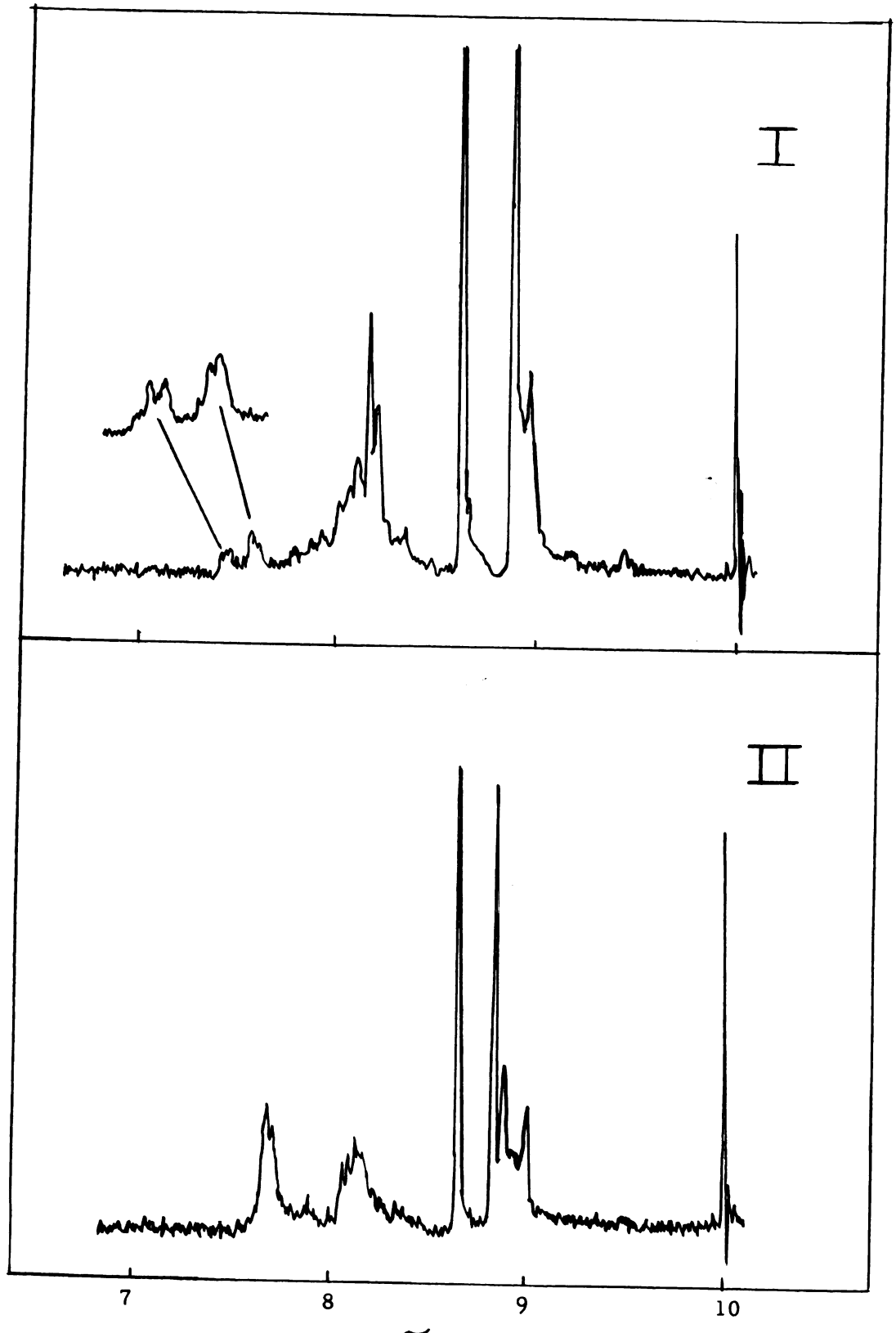
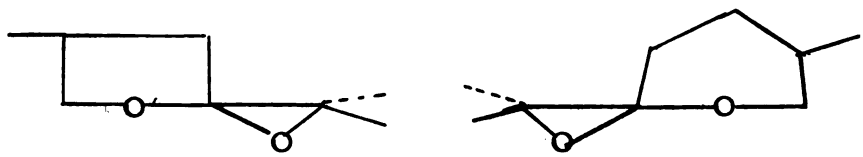


Figure 5. N.M.R. spectra of the pulegone oxide isomers

However, the area of the doublet is greater than expected, since the ratio of the doublet to the methyl group at 8.55 τ was 2.5/3. This interpretation seems to be reasonable in spite of this difficulty.

The third argument supporting our assignments is based on optical rotatory dispersion measurements. As shown in Table 8, the isomers have specific rotations of opposite sign. This difference is the result of opposite Cotton effects near 300 mμ. Isomers Ia and IIa gave positive and negative rotatory dispersion curves respectively, which are shown in Figure 6. Application of the Octant Rule (46) to conformations Ib and IIb predicts these results as illustrated with formulas Ic and IId.



Ic IId

Alternately, the axially oriented oxygen of the epoxide ring and the adjacent carbonyl group may be considered to be an inherently dissymmetric chromophore, similar to those which gave rise to the "axial haloketone rule" (47). In this case the configuration of the dissymmetric chromophore determines the sign of the anomolous dispersion curve. The application of this principle to conformers Ib and IIb also predicts the observed Cotton effects.

Epimerization of the diastereoisomeric pulegone oxides occurs when they are heated in a nitrogen atmosphere at 200° as previously suggested (12). However, considerable fragmentation and rearrangement take place simultaneously to give at least eight other products. The ratio of I/II was found to approach a limit of approximately 3.5.

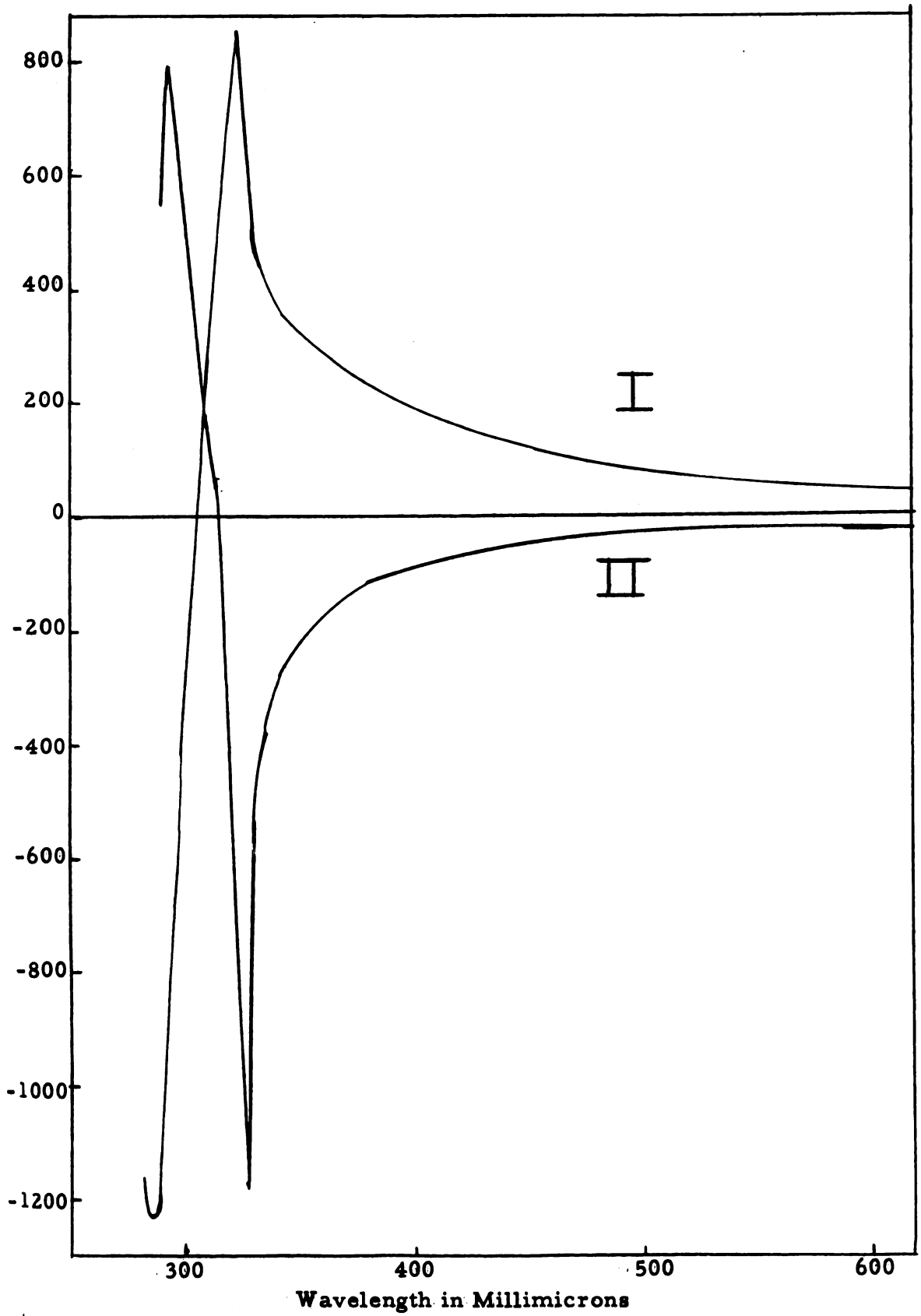
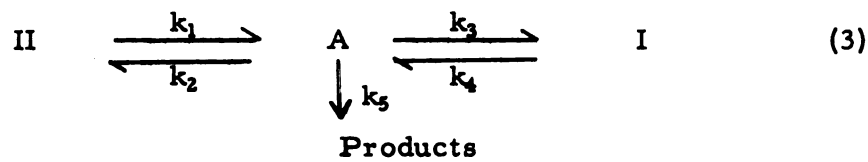


Figure 6. Optical rotatory dispersion curves of the pulegone oxide isomers.

This ratio does not necessarily represent the equilibrium constant, because of the simultaneous rearrangement and fragmentation reactions.

The equilibrium constant of approximately 3.5 is in agreement with the suggestion that Ib and IIb are the major conformers of isomers I and II, respectively. Isomer I should predominate over isomer II at equilibrium, as was observed, since a chair conformation is more stable than a twist boat conformation. A study of models shows that there are only slight differences in the non-bonded interactions present in Ib and IIb. Consequently, the main energy difference must be due to the torsional strain present in the twist boat conformation IIb which is absent in the chair conformation Ib. The equilibrium value of about 3.5 is in agreement with other measurements (48, 49) and calculations (50) which show that the standard free energy difference between the twist boat and the chair conformations of cyclohexane is about 3 Kcal./ mole at 200°.

It is thought that both the rearrangement and isomerization reactions have a common diradical intermediate (A) which will be discussed in detail later. These transformations are conveniently summarized in equation 3.



(3)

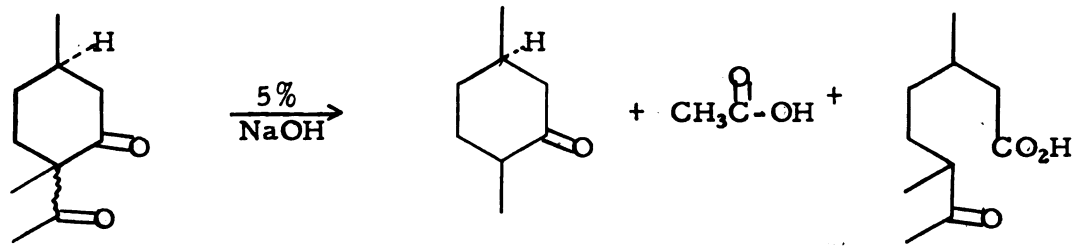
Although none of the rate constants were determined, it is evident from the data in Table 9 that all of the rate constants are of the same order of magnitude.

II. Products from the Rearrangement of Pulegone Oxide

Both pulegone oxide isomers underwent rearrangement and fragmentation reactions as well as epimerization, when heated at 200° in small Pyrex vials. In order to isolate the rearrangement products, 15 g. of a mixture of pulegone oxide isomers was placed in a large tube, degassed, and heated for 18 hours at 200°. Two major products III and IV were formed in 50_ and 25% yield, respectively, along with 20% of six minor products. The main products were separated from the six low boiling products and the starting material by distillation. Pure samples of III and IV were obtained by preparative v.p.c.

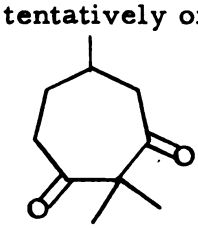
Elemental analysis showed that III was an isomer of pulegone oxide. This compound exhibited the following properties: $\nu_{max}^{CCl_4}$ 5.87μ and $\lambda_{max}^{95\% \text{ ethanol}}$ 198 mμ (ϵ = 9,640) and 286 mμ (ϵ = 71). The infrared and ultraviolet spectra indicate that the molecule contains two unconjugated carbonyl groups. The strong end absorption in the ultraviolet was thought to be due to the presence of a tetrasubstituted double bond, because the compound lacked double bond absorption in the I.R. The n.m.r. spectrum showed the presence of three methyl groups; one was a doublet at 9.01 τ, J = 6.5 c.p.s. and two were singlets at 8.77 τ and 7.98 τ. Since the latter peak is characteristic of methyl ketones (51), it was not surprising that III gave a positive iodoform test. A very good clue to the structure of III was the observation that it reacted on basic alumina to give a number of products, one of which formed a 2,4-dinitrophenylhydrazone having the same melting point as that reported for the 2,4-dinitrophenylhydrazone of 2,5-dimethylcyclohexanone. This reaction was catalyzed by base, since no reaction occurred on acid washed alumina. Basic cleavage

of III led to a mixture of acetic acid, 2,5-dimethylcyclohexanone (50%) and 3,6-dimethyl-7-keto-octanoic acid (50%); therefore, it must be 2,5-dimethyl-2-acetylcyclohexanone. The strong end absorption in the ultraviolet must be the result of interactions between the carbonyl groups inasmuch as no double bonds are present.

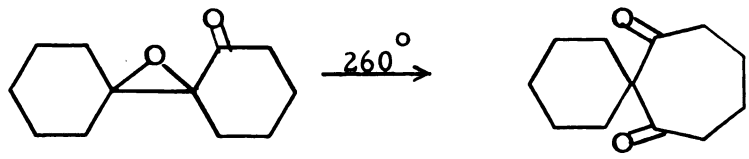


(4)

IV was also found to be an isomer of pulegone oxide. This compound had the following properties: m.p. 25°, $\nu_{max}^{CCl_4}$ 5.88μ and a doublet at 7.25μ and 7.33μ, $\lambda_{max}^{95\%\ ethanol}$ 209 mμ (ϵ = 705) and 291 mμ (ϵ = 73). This spectral data suggested that the molecule contained two unconjugated carbonyl groups. This was confirmed by the preparation of a disemicarbazone, m.p. 222-223°. The doublet at 7.25μ and 7.33μ in the I.R. is characteristic of gem dimethyl groups and the band at 209 mμ in the ultraviolet is similar to that reported (52) for the non-enolizable β-diketone, 1,1,4,4-tetramethyl-2,6-cyclohexanedione, $\lambda_{max}^{ethanol}$ 207 mμ ($\epsilon \cong$ 1,100). The n.m.r. spectrum exhibited three methyl groups; a doublet at 9.00 τ, J = 6 c.p.s. and two singlets at 8.85 τ and 8.02 τ. In contrast to III, this compound was thermally stable at 200° and inert to basic alumina suggesting that III and IV are not just sterio isomers. The following structure, which satisfies all of the previous points, was tentatively offered for IV.

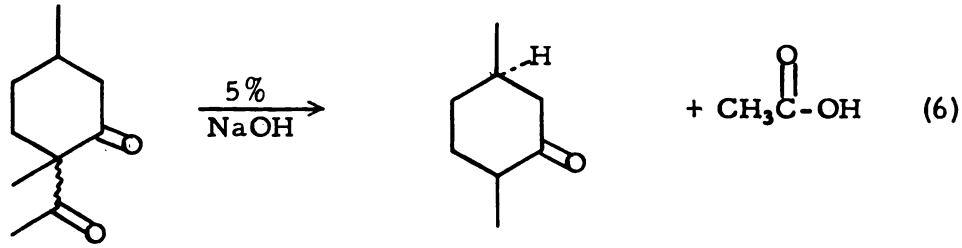


An analogous compound is reportedly formed in the thermal rearrangement of 2-cyclohexylidenecyclohexanone oxide (10).



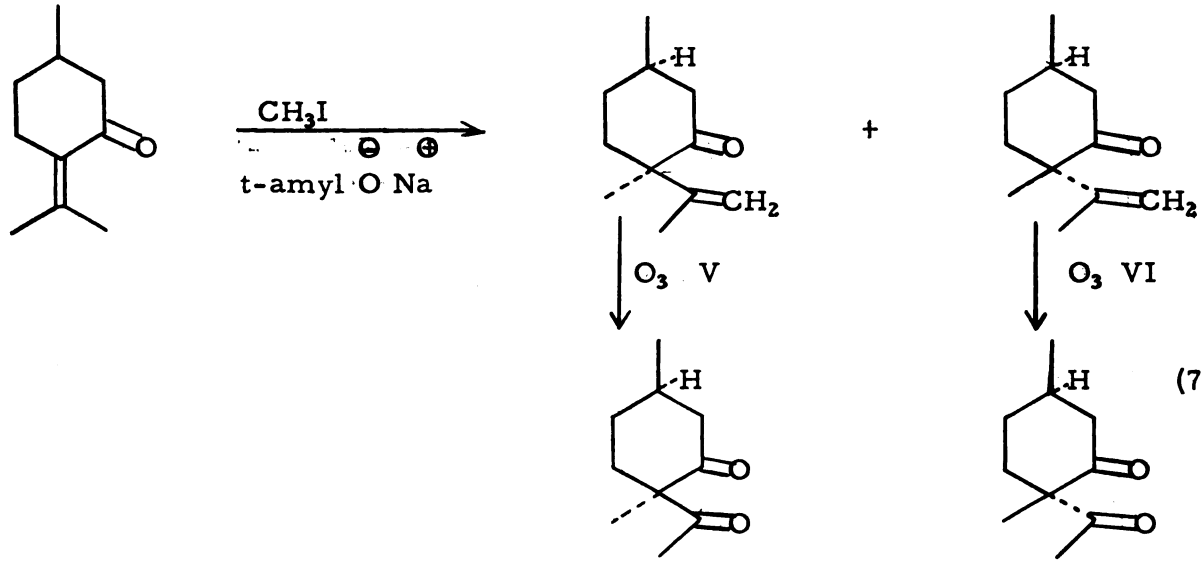
(5)

A number of attempts to prove that IV was the seven membered ring β-diketone were unsuccessful and IV was finally subjected to cleavage with sodium hydroxide. The only products formed were acetic acid and 2,5-dimethylcyclohexanone, thus showing that IV is indeed the other stereo isomer of 2,5-dimethyl-2-acetylcyclohexanone. It is interesting to note that no 3,6-dimethyl-7-keto-octanoic acid was formed from this isomer whereas a 50% yield was obtained from III.



(6)

The configurations of the 2,5-dimethyl-2-acetylcyclohexanone isomers III and IV were determined by an unequivocal synthesis of each. A mixture of 4-methylisopulegone isomers V and VI was prepared by methylation of (+)-pulegone by the method of Djerassi (53). These workers obtained a 83/17 ratio of V/VI and assigned the configurations shown in equation (7). We obtained a mixture of 76% V and 24% VI, which on ozonalysis gave a 75/25 mixture of III and IV, respectively. Since epimerization can not occur during ozonalysis, III and V must have identical configurations at C_4.



III IV

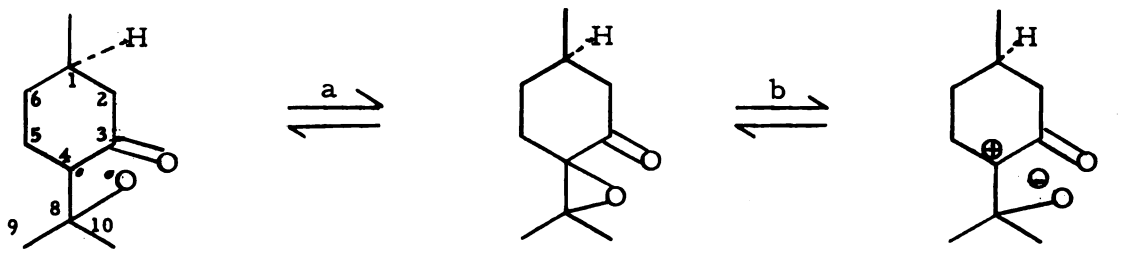
Of the six low boiling products formed, only two have been identified. The lowest boiling component was shown to be acetone by comparison of its v.p.c. retention times on both polar and nonpolar columns and its infrared spectrum with those of an authentic sample. 2,5-Dimethylcyclohexanone was shown to be present in a similar fashion. A small amount (3%) of acetic acid was also formed when the rearrangement was carried out in the presence of air.

We have confirmed Pigulevske and Mironova's (12) observation that samples of pulegone oxide become more dextrorotatory when heated at 200°. For example, the specific rotation of a 1:1 mixture of epoxide isomers I and II increased from +15.2° to +36.78° in 8 1/3 hours. However, their conclusion that only epimerization was occurring is erroneous.

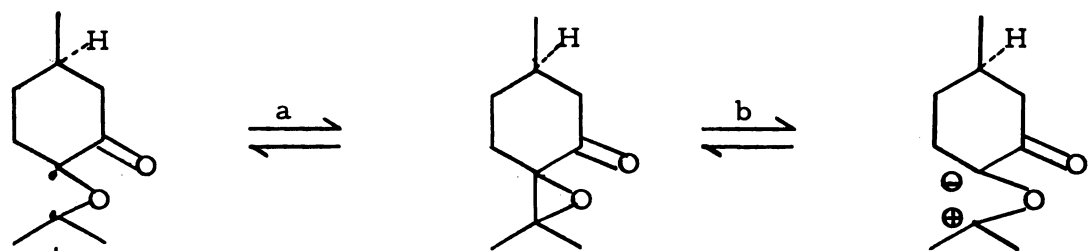
III. Mechanism of the Epimerization and Rearrangement of Pulegone Oxide

There are a number of paths by which the isomerization and rearrangement of pulegone oxide could conceivably occur. Homolytic or

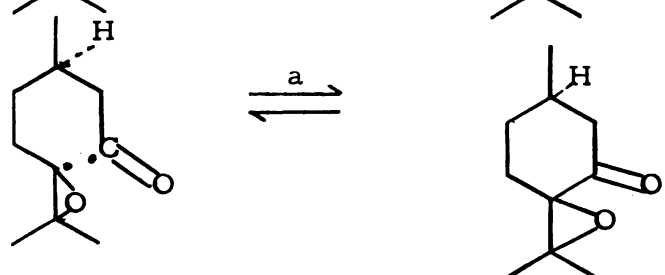
heterolytic cleavage of either the C_4 oxygen bond or the C_4-C_8 carbon bond followed by rotation and recombination would result in the epimerization of the epoxide isomers. Alternately, the C_3-C_4 bond might break upon thermal excitation. Inversion of the oxirane radical and coupling of the radicals would account for the isomerization.



(8)



(9)



(10)

The paths illustrated in equations 8 and 9 are quite attractive since bond cleavage leads to the formation of tertiary resonance stabilized radicals or ions. Furthermore, the strain energy of about 13 kcal./mole (54) present in the three membered ring would lower the activation energy in both cases. The latter possibility (10) is not particularly attractive because it involves the breaking of a strong bond and the formation of radicals which are not especially stable. We were unable to determine if the reactions shown in equation 9 were taking place. However, cleavage of the C_4 oxygen bond must occur followed by a

1,2-methyl shift in order for the observed products to be formed. The C_4-oxygen bond would be expected to break in preference to the other bonds inasmuch as the carbon oxygen bonds of ethers usually have lower bond dissociation energies than carbon carbon bonds (55).

The heterolytic cleavage of the C_4-oxygen bond (8b) is an unlikely possibility, since it leads to the formation of a carbonium ion adjacent to the positive carbonyl carbon. The acid catalyzed openings of many α,β-epoxy ketones are known to result in the formation of a positive site at the β carbon (29). Thermal heterolysis of an α,β-epoxy ketone likewise should give a carbonium ion at the β-carbon but such a reaction would not lead to isomerization of pulegone oxide.

These transformations are not acid catalyzed since the addition of benzoic acid had no effect on the reaction, while the addition of powdered Pyrex glass slowed the reaction indicating that acid sites on the Pyrex surface were not causing the reaction. Although, p-toluene sulfonic acid catalyzed a rearrangement of pulegone oxide, none of the products of the thermal reaction were formed.

As shown in Table 9, traces of initiators and inhibitors had no effect on the reaction, and the addition of 5% of tert-butyl hydroperoxide actually slowed both the rates of isomerization and rearrangement. Although 2,2'-azoisobutane initiated a rearrangement of pulegone oxide, entirely different products were formed. These facts certainly do not support a radical chain mechanism. Indeed, it is difficult to rationalize the isomerization and rearrangement of pulegone oxide by a free radical chain mechanism.

The observation that oxygen slowed both the rate of rearrangement and epimerization, without the formation of tars or other new products, was very significant. This fact is readily explained only in terms of a diradical intermediate (8a). The singlet diradical initially formed may rearrange, collapse to epoxide, or be transformed into

Table 9. Thermal Rearrangement of Pulegone Oxide at 200°

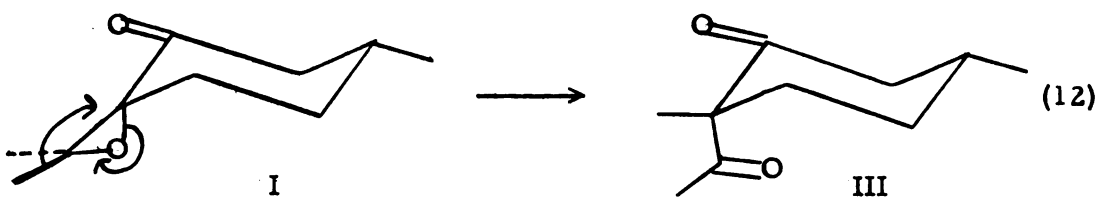
Isomer	Time, hr.	Additives, mole %	% Low boilers	III, %	IV, %	Ratio III/IV	I, %	II, %	Ratio I/II
I	3	----	4	17.0	7.5	2.3	63.5	8.0	7.9
I	5	----	6	24.0	11.0	2.2	45.5	13.5	3.4
I	10	----	14	27.2	15.5	1.8	34.5	8.8	3.9
II	5	----	10	28.6	16.0	1.8	17.3	27.7	.6
II	7	----	13.1	42.0	21.3	2.0	16.7	10.0	1.7
II	$8\frac{1}{2}$	----	12.2	47.2	23.2	2.0	14.3	6.5	2.2
II	10	----	15.0	50.0	25.0	2.0	7.5	2.5	3.0
II	5	100% increase in surface[d]	9.0	19.0	11.0	1.7	5.0	55.0	.09
II	5	air	14.0	13.0	10.0	1.3	5.0	56.0	.10
II	5	t-$C_4H_9O_2H$ (.05%)	10.0	29.0	14.4	2.0	16.6	30.0	.55
II	5	t-$C_4H_9O_2H$ (5%)	15.0	5.0	6.0	.83	3.0	70.0	.04
II	5	m-$C_6H_4(NO_2)_2$[e] (51%)	7.0	29.0	22.0	1.3	3.0	13.0	.23
II	5	m-$C_6H_4(NO_2)_2$ (1%)	10.0	25.6	15.6	1.65	17.4	31.4	.55
II	5	p-$C_6H_4O_2$[f] (54%)	1.5	18.0	22.0	.82	0	0	----
II	5	p-$C_6H_4(OH)_2$[g]	7.6	35.0	22.7	1.55	0	1.0	----
II	5	$C_6H_5CO_2H$ (5%)	12.0	29.0	16.0	1.8	16.0	27.0	.59
II	5	p-$C_6H_4O_2$ (1%)	9.0	29.0	16.0	1.8	17.0	29.0	.59
II[h]	$\frac{1}{4}$	----	26.9	35.3	21.4	1.65	7.3	9.1	.8
II[h]	$\frac{1}{4}$	air	30.4	32.6	19.4	1.67	6.4	13.0	.49

[a] Samples were degassed unless otherwise indicated.
[b] Acetophenone was used as an internal standard in most cases.
[c] Percentages reported are the average of at least two runs.
[d] Powdered Pyrex glass was added.
[e] 26% of high boiling residues were formed.
[f] 57.5% high boiling products formed.
[g] 29.4% high boiling products formed.
[h] Heated at 260°.

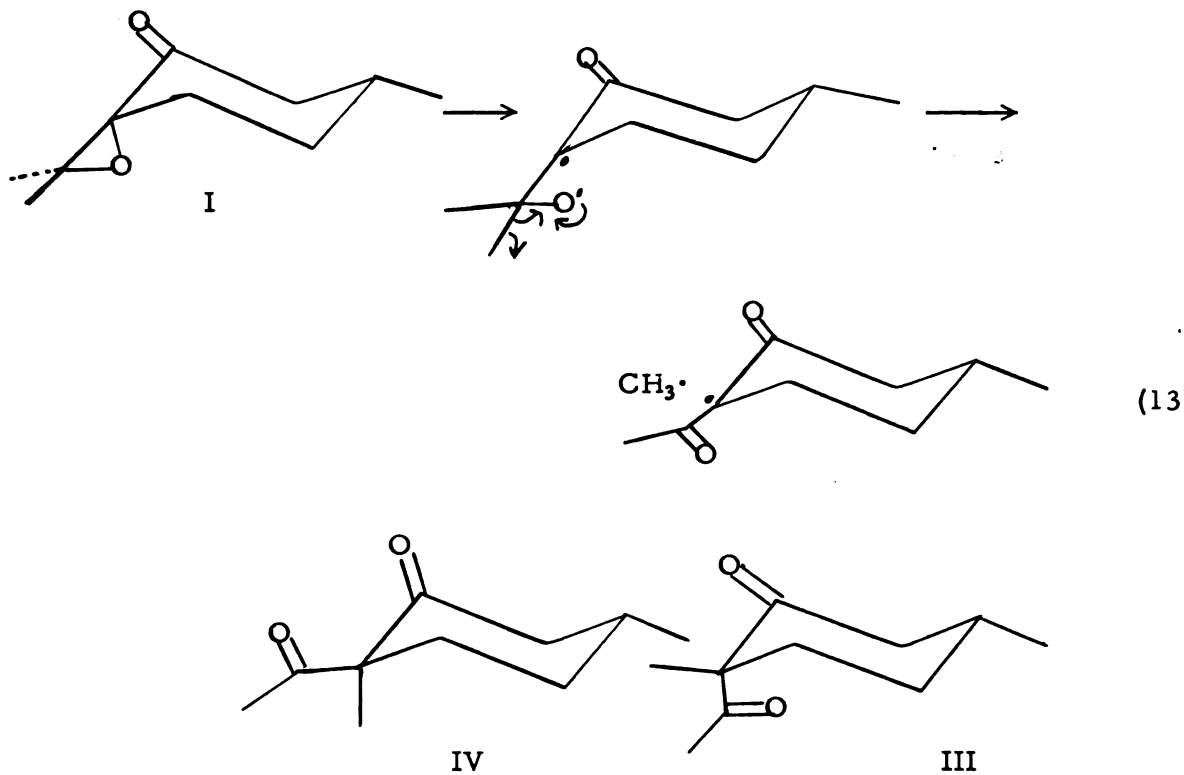
a triplet. The triplet may in turn rearrange or decay to starting material. This triplet would be deactivated by oxygen or other paramagnetic species in the same fashion as triplets produced photochemically are deactivated to their ground states by oxygen (56). Thus, the concentration of the diradical intermediate is lowered, and consequently, the rates of isomerization and rearrangement are decreased. The same argument may be used to explain the inhibitory effect of tert-butyl hydroperoxide since Vaughan (41) has shown that oxygen is formed in the thermal decomposition of this hydroperoxide.

The diradical intermediates must have a long enough lifetime for the occurrence of a rotation about a single bond; therefore, it should exist long enough to be trapped by radical scavengers. This was confirmed by carrying out the reaction in the presence of radical inhibitors such as m-dinitrobenzene, benzoquinone and hydroquinone. Between 26% and 58% of the epoxide was trapped when heated with equimolar amounts of the above compounds.

The rearrangement of the pulegone oxide isomers I and II to the 2,5-dimethyl-2-acetylcyclohexanone isomers III and IV may formally occur by either a concerted process (12) or a radical cleavage recombination mechanism (13).



I III (12)

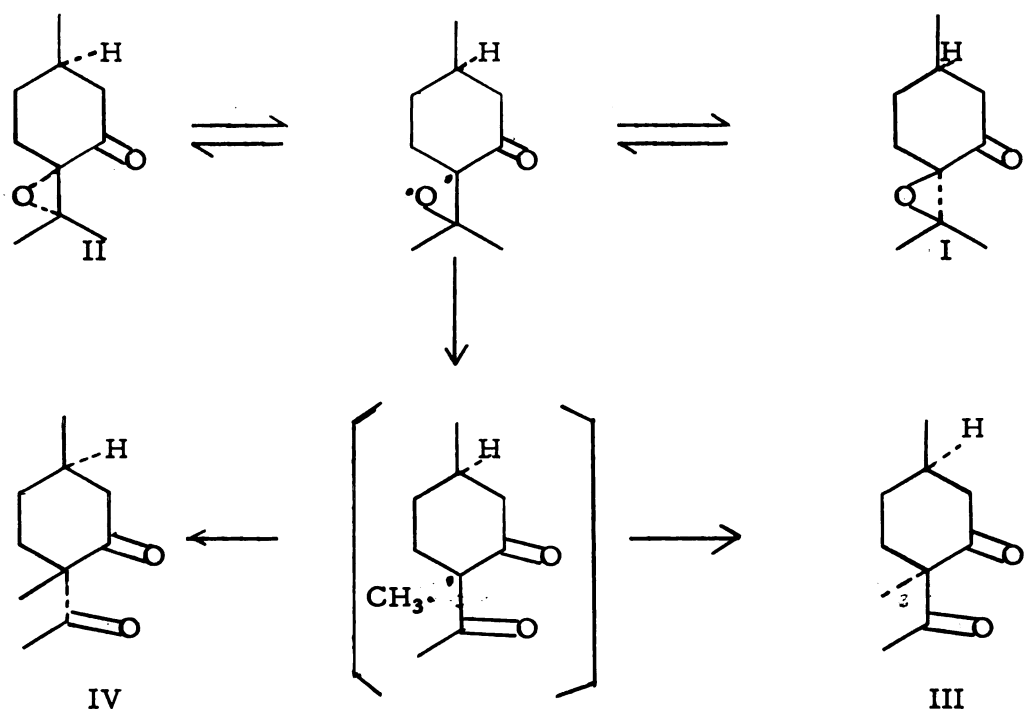


(13)

One distinguishing characteristic of the concerted mechanism is that it is stereospecific. Thus, epoxide isomer I would rearrange exclusively to isomer III while oxide isomer II would give only IV. The ratio of II/IV should therefore depend upon which epoxide isomer is used and the extent of reaction unless a rapid pre-equilibrium of the epoxide isomers I and II is established. Inspection of the data in Table 9 shows that a constant ratio of III/IV of about 2 was obtained starting with either isomer of pulegon oxide and that a rapid equilibrium is not established between I and II, thus eliminating any concerted mechanism. Furthermore, a concerted mechanism can not account for the change in the rate of rearrangement or the change in the ratio of III/IV when the reaction was carried out in the presence of oxygen or radical scavengers.

The constant ratio of products and the effects of oxygen and inhibitors are readily rationalized by a mechanism employing a common diradical intermediate. A schematic representation of such a mechanism is shown in Chart I. The diradical intermediate may revert to epoxide or decompose with the formation of two free radicals which could couple within the solvent cage to give the observed products. In this 1,2-methyl radical migration, the methyl radical is written as a discrete intermediate because Zimmerman's calculations have shown that there is no bonding in the transition state of a 1,2-alkyl shift to a radical center (57).

Chart I



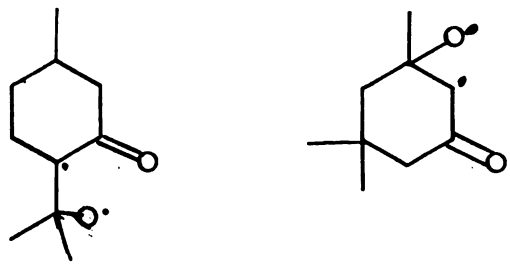
The manner in which the minor products are formed is uncertain. A degassed sample of 2,5-dimethyl-2-acetylcyclohexanone isomer III was found to decompose slowly at 200° to give 2,5-dimethylcyclohexanone and one other product which was also formed in the thermal

rearrangement of pulegone oxide. However, the rate of decomposition was too slow to account for all of the 2,5-dimethylcyclohexanone formed in the thermal reaction of pulegone oxide. Possibly these products are the result of free radical reactions initiated by methyl or β-diketo-radicals which escaped from the solvent cage. The fact that the amount of the low boiling products formed decreases when inhibitors are present, lends credence to this postulate.

Pulegone oxide, isomer II, rearranged to three new compounds of unknown structure when heated in the gas phase at 200°. A similar transformation occurred with a 0.057 M solution of pulegone oxide isomer II in decalin; whereas both thermal reactions occurred simultaneously in a 10% solution of isomer II in decalin. Evidently the thermal rearrangement of pulegone oxide to 2,5-dimethyl-2-acetylcyclohexanone is very sensitive to changes in the dielectric constant of the solvent. This result was surprising but in no way refutes a mechanism employing a diradical intermediate. In actuality, it may be an interesting example of the well documented polar character of free radical reactions (58, 21).

It is interesting to compare the thermal rearrangement of pulegone oxide with those of other α,β-epoxy ketones. House (10) and Reeves (9) have reported that neat 2-cyclohexylidenecyclohexanone oxide is converted to spiro [5.6] -dodecane-7, 12-dione when heated at 260° (see equation 5). This rearrangement as well as that of isophorone oxide, described in Part I of this thesis, formally require 1,2-shifts of acyl groups, whereas a 1,2-shift of a methyl radical occurs with neat pulegone oxide. This disparity in reaction paths is not the result of the temperature differential since pulegone oxide gave the usual products when heated at 260°. The difference may be due to the solvent effects previously discussed. Also, pulegone oxide is more thermally labile than isophorone oxide. This reflects not only the fact that the

former gives a tertiary radical and the latter a secondary radical upon cleavage of the α-carbon oxygen bond, but also that considerable entropy is gained upon cleavage in the case of pulegone oxide, whereas little is gained with isophorone oxide.



(14)

EXPERIMENTAL

I. Apparatus and Reagents

A. Apparatus

The equipment described in Part I of this thesis was also used in this work. Vapor phase chromatography analysis were made with a Aerograph, A-90-P, gas chromatograph using a 5 foot, $\frac{1}{4}$ inch column of 5% P.D.E.A.S. (phenyldiethanolaminesuccinate) on chromosorb W.

B. Optical Rotatory Dispersion Measurements

Optical rotatory dispersion measurements were kindly made at Wayne State University by Mr. Fredrick Karkowski, Dr. Margaret DaRooge and Dr. Norman L. Allinger.

C. Pulegone

Pulegone was obtained from K and K Laboratories and carefully distilled under nitrogen prior to use. It was isolated from pennyroyal oil, which was obtained from Fritzsche Brothers Inc., by careful distillation under nitrogen.

II. Preparation of Pulegone Oxide

A. Preparation with Base and Hydrogen Peroxide

To a 500 ml. three necked flask equipped with a stirrer, a dropping funnel and a thermometer were added 30 g. (0.179 mole) of

pulegone, 160 ml. of methanol and 34.4 g. (0.304 mole) of 30% hydrogen peroxide. The mixture was cooled to 15° in an ice bath and 1 g. (0.025 mole) of sodium hydroxide in 10 ml. of water was added dropwise with stirring over a period of fifteen minutes. Stirring was continued for 4 hours with the temperature being maintained at 20-25°. The solution was then poured into 400 ml. of saturated salt solution and extracted with three 200 ml. portions of benzene. The combined benzene extracts were washed with 100 ml. of water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was analyzed by vapor phase chromatography. The crude product, which consisted of 32% I and 68% II, was distilled to give 20 g. (67%) of a mixture of diastereoisomeric pulegone oxides boiling at 95-102°/5 mm. A similar yield was obtained when ether was used as the extraction solvent.

B. Preparation Using Perbenzoic Acid

A 0.48 M benzene solution of perbenzoic acid was prepared by the method of Koltoff (59). To 15 ml. of this solution was added 1 g. of pulegone, and the reaction mixture was kept at 5-10° for 24 hours with occasional stirring. The benzene solution was washed with 10% sodium hydroxide, followed by water, and then dried over anhydrous magnesium sulfate. The solvent was removed by distillation and the residue shown to be a mixture of 34% I and 66% II by v.p.c. analysis. Distillation over a short path at 5 mm. pressure gives an 86% yield of the pulegone oxides. Benzoic acid was shown not to isomerize the pulegone oxides under the reaction conditions.

III. Isolation and Properties of the Pulegone Oxide Isomers

A. Isolation of a Molecular Compound

Repeated recrystallizations of the crude epoxide mixture described in the previous section from chilled pentane gave a crystalline solid, which exhibited physical properties (m.p. 42-43°, $[\alpha]_D^{25}$ + 15.2 (c = 5.445 in 95% ethanol) identical to those previously attributed to one of the diastereoisomeric pulegone oxides. However, vapor phase chromatography analysis proved these crystals to consist of an equimolar mixture of isomers I and II.

Anal. Calc'd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59.
Found: C, 71.69; H, 9.60.

B. Isolation of Isomers I and II

Isolation of the pure diastereoisomers was accomplished by careful distillation of the epoxide mixture through a 16 inch, vacuum jacketed tantalum spiral column. The fraction boiling 95-97°/5 mm. was crystallized twice from pentane to give II, m.p. 55-56°, $\lambda_{max}^{heptane}$ 209 mμ (ϵ = 221) and 303 mμ (ϵ = 31), $\nu_{max}^{CCl_4}$ 1728 cm^{-1}. Rotatory dispersion in 95% ethanol (c, 0.028), 25°; $[\alpha]_{700}$ -24.9, $[\alpha]_{589}$ -14.2, $[\alpha]_{327}$ -1177.9, $[\alpha]_{293}$ 786.5, $[\alpha]_{290}$ 562.3. The n.m.r. and I.R. spectra of this isomer are shown in Figures 5 and 7, respectively.

Anal. Calc'd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59.
Found: C, 71.60; H, 9.58.

The fraction boiling at 100-102°/5 mm. was redistilled and the high boiling fraction was crystallized from petroleum ether (60-110°) to give I, m.p. 59°, $\lambda_{max}^{heptane}$ 209 (ϵ = 225) and 303 mμ (ϵ = 31), $\nu_{max}^{CCl_4}$ 1727 cm^{-1}. Rotatory dispersion in 95% ethanol (c, 0.040), 25°; $[\alpha]_{700}$ 32.2, $[\alpha]_{589}$ 50.0, $[\alpha]_{324}$ 853.9, $[\alpha]_{285}$ -1242.5, $[\alpha]_{283}$ -1203. The

n.m.r. and I.R. spectra of this isomer are shown in Figures 5 and 8, respectively. The rotatory dispersion curves of both isomers are plotted in Figure 6.

IV. Thermal Rearrangements

A. Experimental Techniques

The same experimental techniques outlined in detail in Part I of this thesis were used. All samples were degassed and sealed under nitrogen in carefully cleaned Pyrex tubes. They were then heated at $200 \pm 2^{\circ}$ for the desired length of time in an aluminum block furnace. The resulting mixtures were analyzed by vapor phase chromatography using a $\frac{1}{4}$ inch, 5 foot P.D.E.A.S. column at 135°.

The results are summarized in Table 8. The reproducibility, $\pm$ 3%, is not good and all percentages reported are average values of at least two runs. Acetophenone, which was found to be stable under the conditions of these reactions, was added as an internal standard in most cases. It was thus shown that no high boiling products or tars were formed from neat samples of pulegone oxide. It also allowed us to determine the amount of high boiling products formed when additives were present.

V. Isomerization

A. Proof of Isomerization

When either pure isomer I or II was heated at 200°, a compound was formed, which had the same v.p.c. retention time as the other isomer. In each case, a sample of this new compound was isolated by vapor phase chromatography. The infrared spectra of each sample

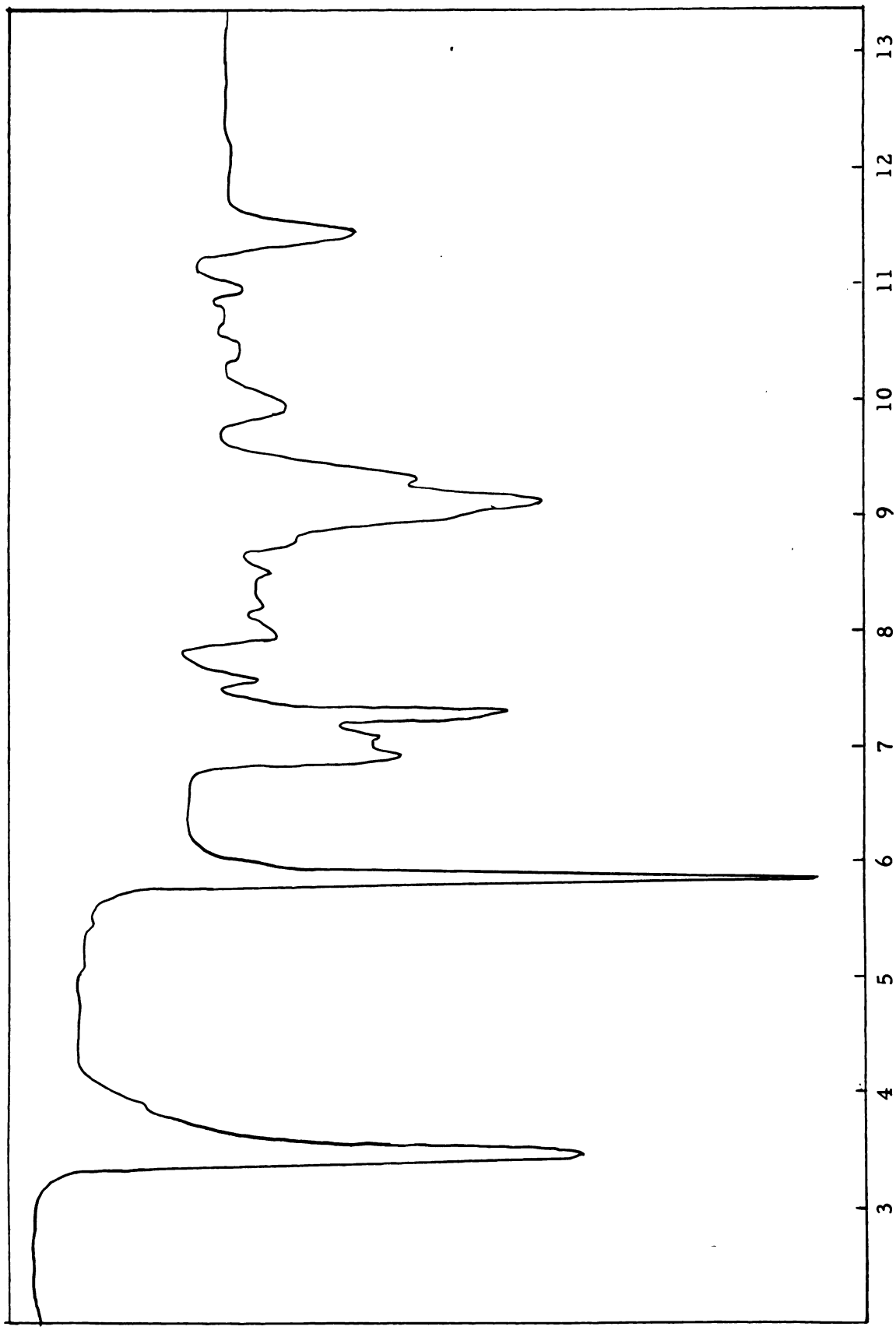


Figure 7. Infrared spectrum of pulegone oxide, isomer II.

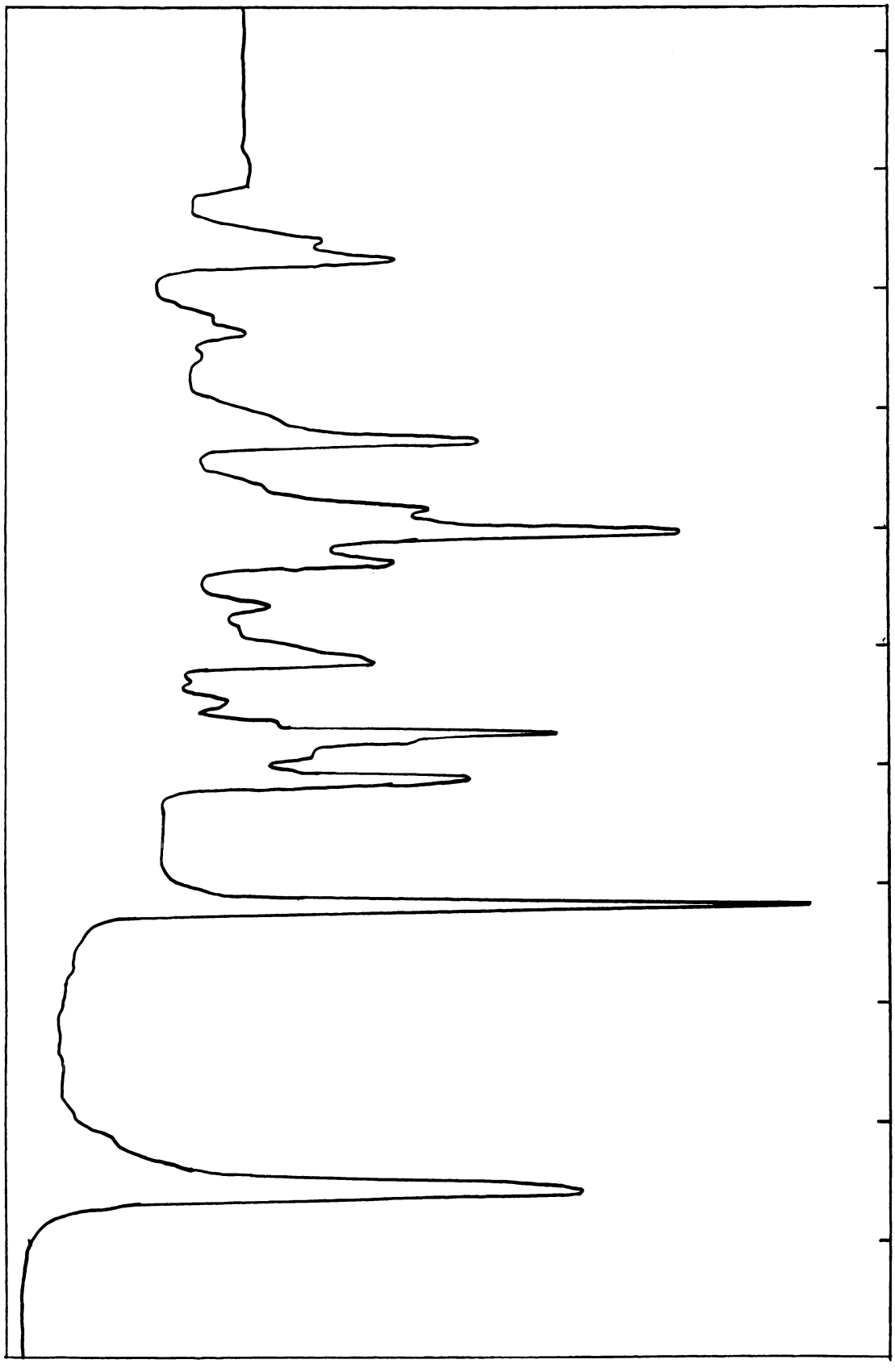


Figure 8. Infrared spectrum of pulegone oxide, isomer I.

was obtained and found to be identical to that of the corresponding pulegone oxide isomer. A constant ratio of I/II could be approached from either isomer. The results of these epimerization experiments are summarized in Table 9.

VI. Products from the Thermal Rearrangement of Pulegone Oxide

A. Isolation of Products

To a large carefully cleaned Pyrex tube was added 15 g. of a mixture of pulegone oxide isomers. The tube was degassed and sealed under nitrogen. It was then heated at 200° for 18 hours and the crude mixture analyzed by vapor phase chromatography. The mixture was found to consist of 2,5-dimethylcyclohexanone (5%), four other low boiling products of unknown structure (10%), 2,5-dimethyl-2-acetylcyclohexanone isomer IV (25%), 2,5-dimethyl-2-acetylcyclohexanone isomer III (50%), and starting material (5%). The mixture was distilled through a 16 inch, vacuum jacketed, tantalum spiral column in order to separate the low and high boiling components. The two products III and IV could be separated from all other components by distillation, but they could not be completely separated from each even with a spinning band column.

1. Acetone: A low boiling product having the same v.p.c. retention time as acetone was isolated in 2% yield by distillation. It was shown to be acetone by the preparation of a 2,4-dinitrophenylhydrazone, melting 125-126° (reported value, 126°) which did not depress the melting point of an authentic sample. Further, the infrared spectra of the unknown compound and acetone were identical.

2. 2,5-Dimethylcyclohexanone: This product was identified by comparison of its v.p.c. retention times on a 20% silicon column and

a 15% N.P.G.S. (neopentylglycol succinate) column with an authenic sample. The infrared spectrum of a sample collected from the v.p.c. was shown to be identical to that of 2,5-dimethylcyclohexanone.

3. Unknown Products: Nothing is known about the structure of the other four low boiling products. A mixture of these compounds turned dark and tarry on standing so some of them must be sensitive to oxygen and/or light.

4. 2,5-Dimethyl-2-acetylcyclohexanone, Isomer IV: Pure samples of this compound were obtained by vapor phase chromatography on a 5 foot, $\frac{1}{4}$ inch 15% N.P.G.S. column at 155°. This isomer had the following properties: $\nu_{max}^{CCl_4}$ 5.88μ and $\lambda_{max}^{95\% \text{ ethanol}}$ 209 mμ (ϵ = 705) and 291 mμ (ϵ = 73). A disemicarbazone, m.p. 222-223°, $\lambda_{max}^{95\% \text{ ethanol}}$ 232 mμ (ϵ = 21,800) and a mono-2,4-dinitrophenylhydrazone, m.p. 230-231° were formed.

Anal. Calc'd. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.79; N, 16.09.
Found: C, 54.71; H, 6.02; N, 15.78.

The n.m.r. spectrum which is shown in Figure 9 exhibited a doublet at 9.0 τ, J = 6 c.p.s., and singlets at 8.85 τ and 8.02 τ in the ratio of 3:3:3. The compound gave a positive iodoform test and a negative tetranitromethane test. The structural assignment is based on the basic cleavage of IV to 2,5-dimethylcyclohexanone and an unequivocal synthesis which are described later.

5. 2,5-Dimethyl-2-acetylcyclohexanone Isomer III: Pure samples of this isomer, which were obtained by vapor phase chromatography on a 5 foot, $\frac{1}{4}$ inch, 15% N.P.G.S. column at 155°, had the following properties; $\nu_{max}^{CCl_4}$ 5.87μ, $\lambda_{max}^{95\% \text{ ethanol}}$ end absorption 198 mμ (ϵ = 9,640) and 286 mμ (ϵ = 71) and simicarbazone, m.p. 211.5-212.5°. The n.m.r. spectrum which is shown in Figure 11 exhibited a doublet 9.01 τ, J = 6.5 c.p.s., and singlets at 8.77 τ and 7.98 τ in the relative ratio of 3:3:3. The compound gave a positive iodoform test

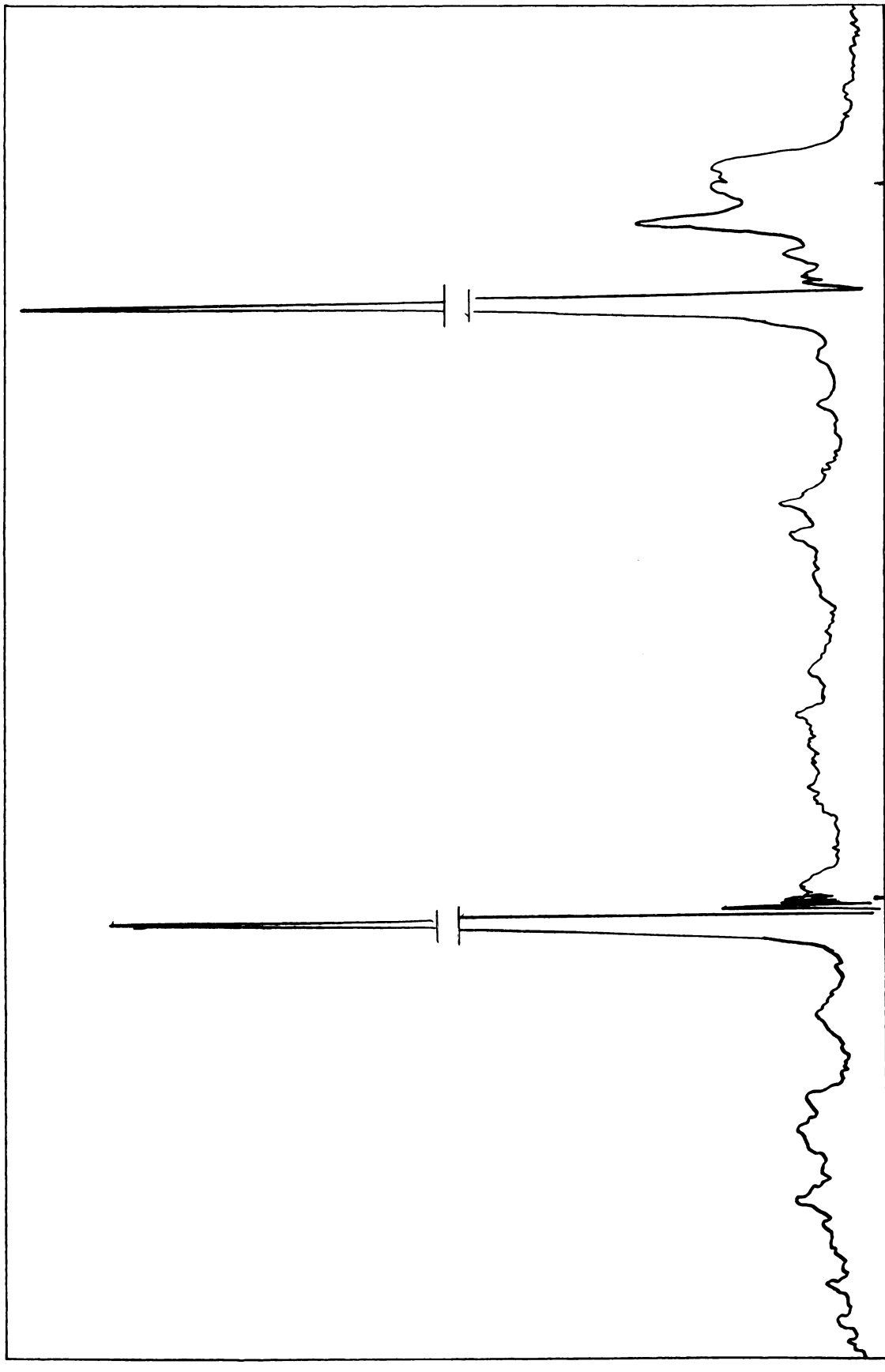


Figure 9. N.m.r. spectrum of 2,5-dimethyl-2-acetylcyclohexanone, isomer IV, in carbon tetrachloride.

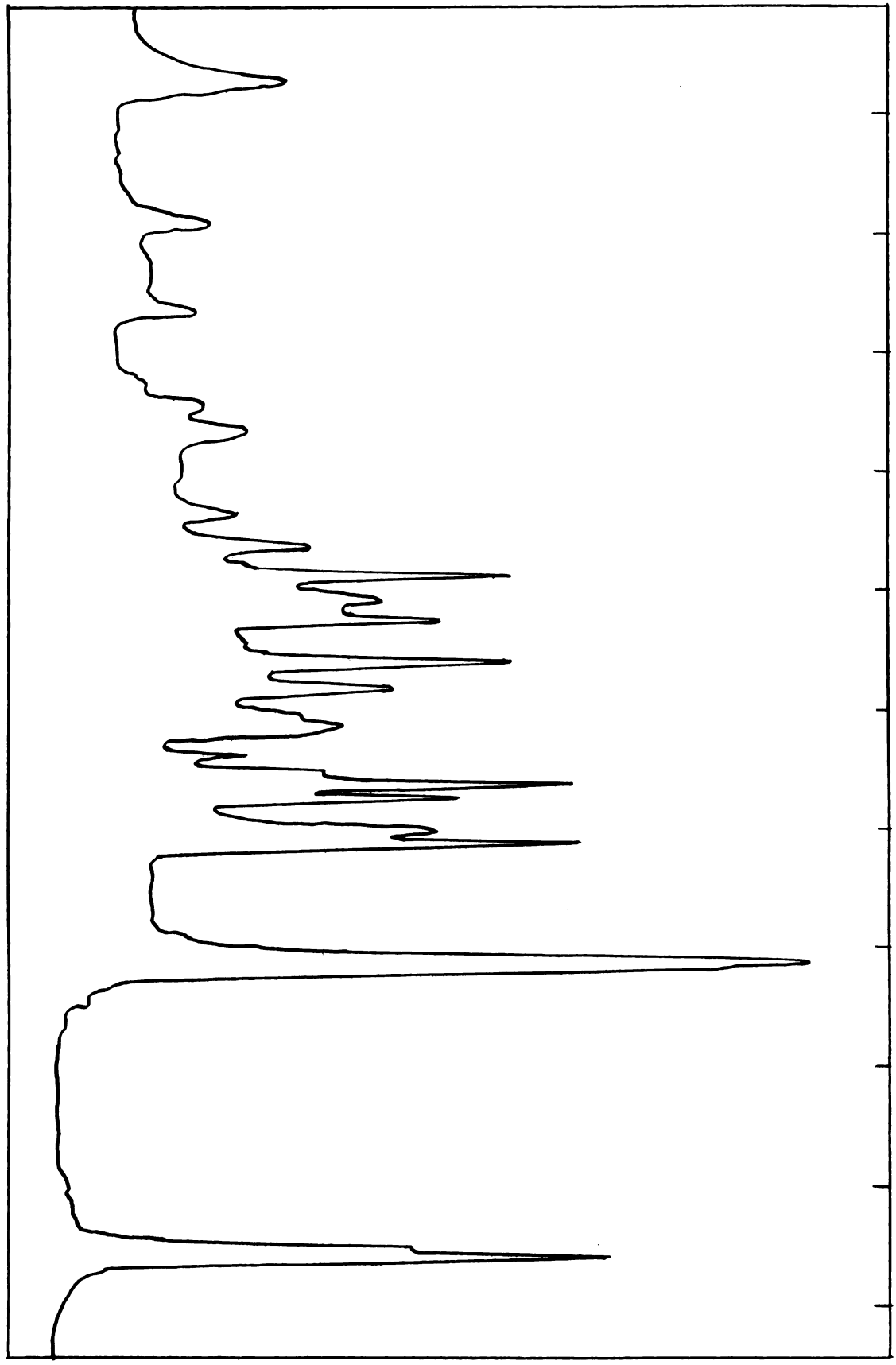


Figure 10. Infrared spectrum of 2,5-dimethyl-2-acetylcyclohexanone, isomer IV.

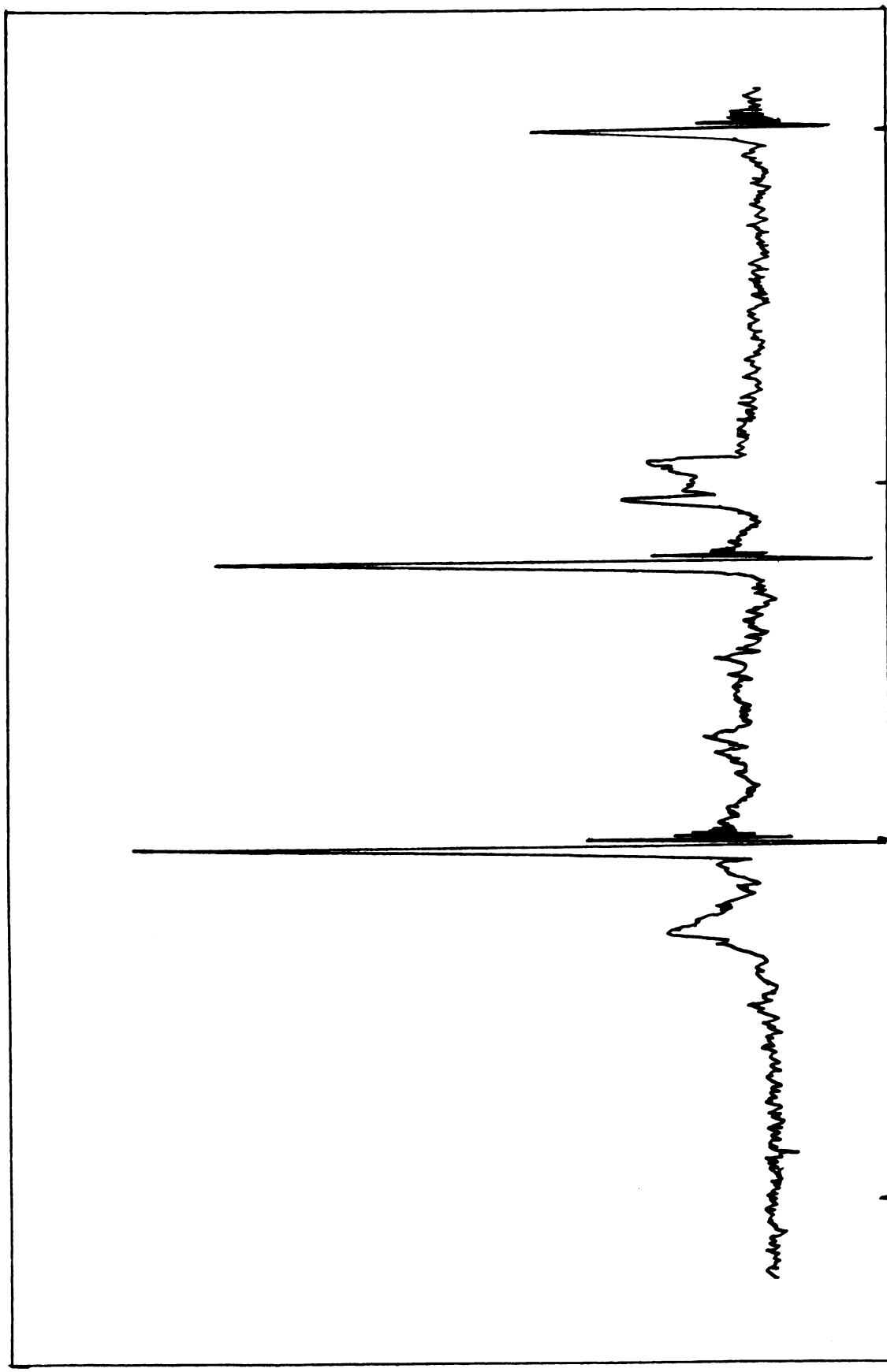


Figure 11. N.m.r. spectrum of 2,5-dimethyl-2-acetylcyclohexanone, isomer III, in carbon tetrachloride.

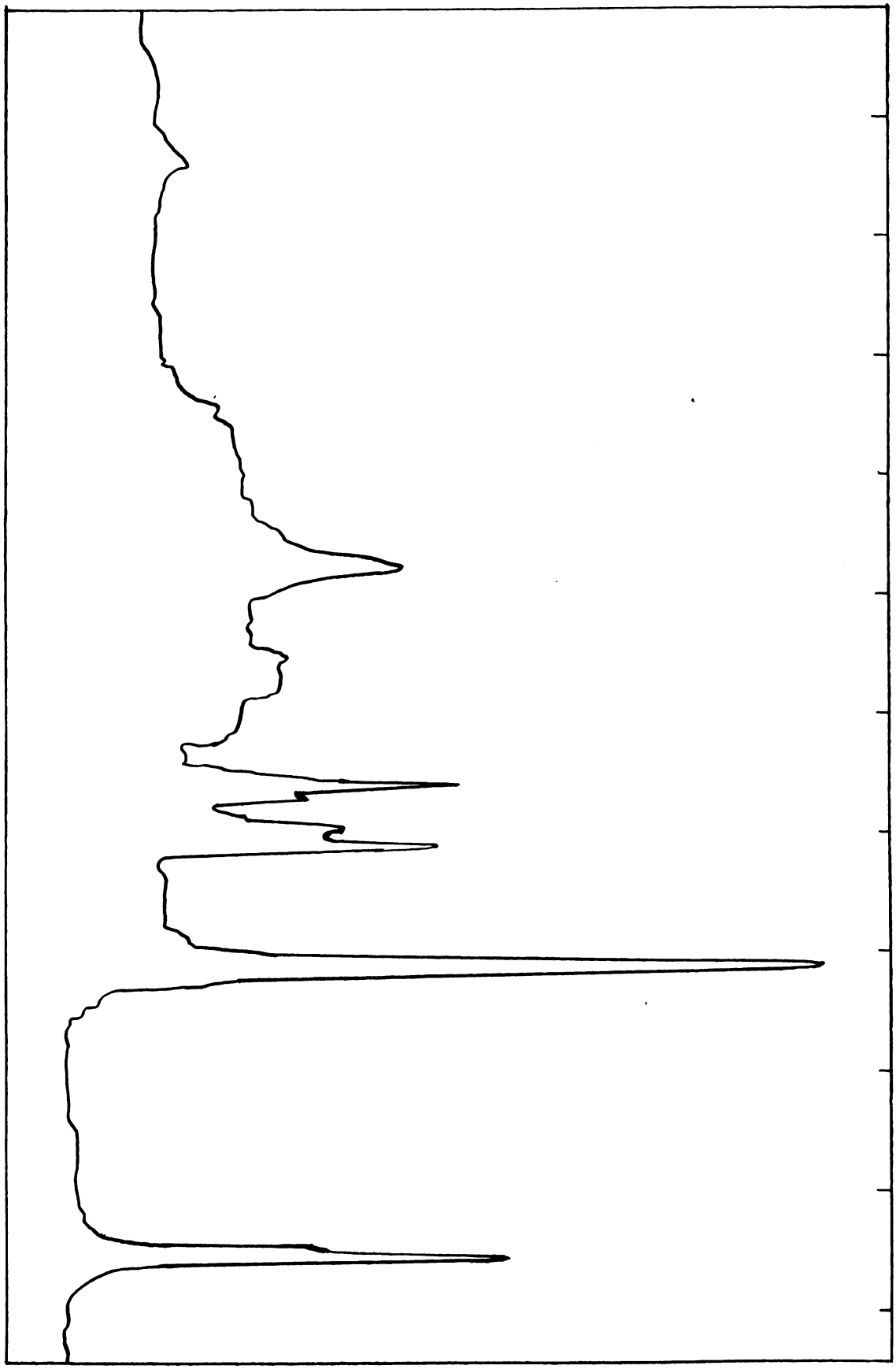


Figure 12. Infrared spectrum of 2,5-dimethyl-2-acetylcyclohexanone, isomer III.

and a negative tetranitromethane test. The structure was determined by unequivocal synthesis and degradation to 2,5-dimethylcyclohexanone as described later.

6. Acetic Acid: Acetic acid formed only when pulegone oxide was heated at 200° in the presence of air. A 3% yield of the acid was isolated by distillation from the rearrangement of 10 g. of pulegone oxide. Identification was accomplished by comparison of the v.p.c. retention time and infrared spectrum of the product with those of authentic acetic acid.

B. Basic Cleavage of the Major Products

1. Cleavage of 2,5-Dimethyl-2-acetylcyclohexanone, Isomer IV, with Sodium Hydroxide

To a 5 ml. flask were added 0.15 g. (0.009 mole) of pure isomer IV, 1.0 ml. of 5% sodium hydroxide and 0.2 ml. of methanol. The mixture was refluxed for 2 hours, cooled and extracted with two 3 ml. portions of ether. The ether layers were combined, washed with water and dried over anhydrous sodium sulfate. The ether was distilled to give 0.11 g. (88%) of the cyclohexanone. The infrared spectrum of the product and its v.p.c. retention times on both a 30% silicon column and a 15% N.P.G.S. column were found to be identical to those of 2,5-dimethylcyclohexanone.

The water layer was acidified with concentrated hydrochloric acid and extracted with two 3 ml. portions of ether. The combined ether layers were dried over anhydrous sodium sulfate and the ether removed by distillation. A single compound, having the same v.p.c. retention time and infrared spectrum as acetic acid, was found.

2. Cleavage of 2,5-Dimethyl-2-acetylcyclohexanone, Isomer III, with Sodium Hydroxide

To a 5 ml. flask were added 0.2 g. (0.0012 mole) of pure isomer III, 1.1 ml. of 5% sodium hydroxide and 0.2 ml. of methanol. The mixture was refluxed for 1½ hours, the solution cooled and extracted with two 3 ml. portions of ether. The ether layers were combined, washed with water and dried over anhydrous sodium sulfate. Most of the ether was removed by distillation and the residue analyzed by v.p.c. A single product was present, which had the same retention time as 2,5-dimethylcyclohexanone on both a 30% silicon column and a 15% N.P.G.S. column. The I.R. spectrum of a sample collected by v.p.c. was shown to be identical to that of 2,5-dimethylcyclohexanone. The compound was isolated as the 2,4-dinitrophenylhydrazone to give 0.17 g. (48%) of product, m.p. 155-161°, (lit. value (60), 162-163°).

The water layer was acidified with concentrated hydrochloric acid and extracted with two 3 ml. portions of ether. The ether layer was dried over anhydrous sodium sulfate and the ether evaporated. V.p.c. analysis of the residue showed the presence of acetic acid and an unknown keto acid, whose infrared spectrum is shown in Figure 13. Both the 2,4-dinitrophenylhydrazone and the semicarbazone derivatives were oils. The compound was converted to its methyl ester by reaction with diazomethane. The keto ester, which is thought to be methyl 3,6-dimethyl-7-ketooctylate, was shown to be pure by v.p.c., but its 2,4-dinitrophenylhydrazone was an oil which could not be crystallized even after chromatography on alumina. The infrared spectrum of the keto ester is presented in Figure 14.

3. Preparation of 2,5-Dimethylcyclohexanone

This compound, b.p. 88-89°/40 mm., n_D^{20} -1.4445, 2,4-dinitrophenylhydrazone, m.p. 162-4°, (lit. value (60), m.p. 162-3°) was

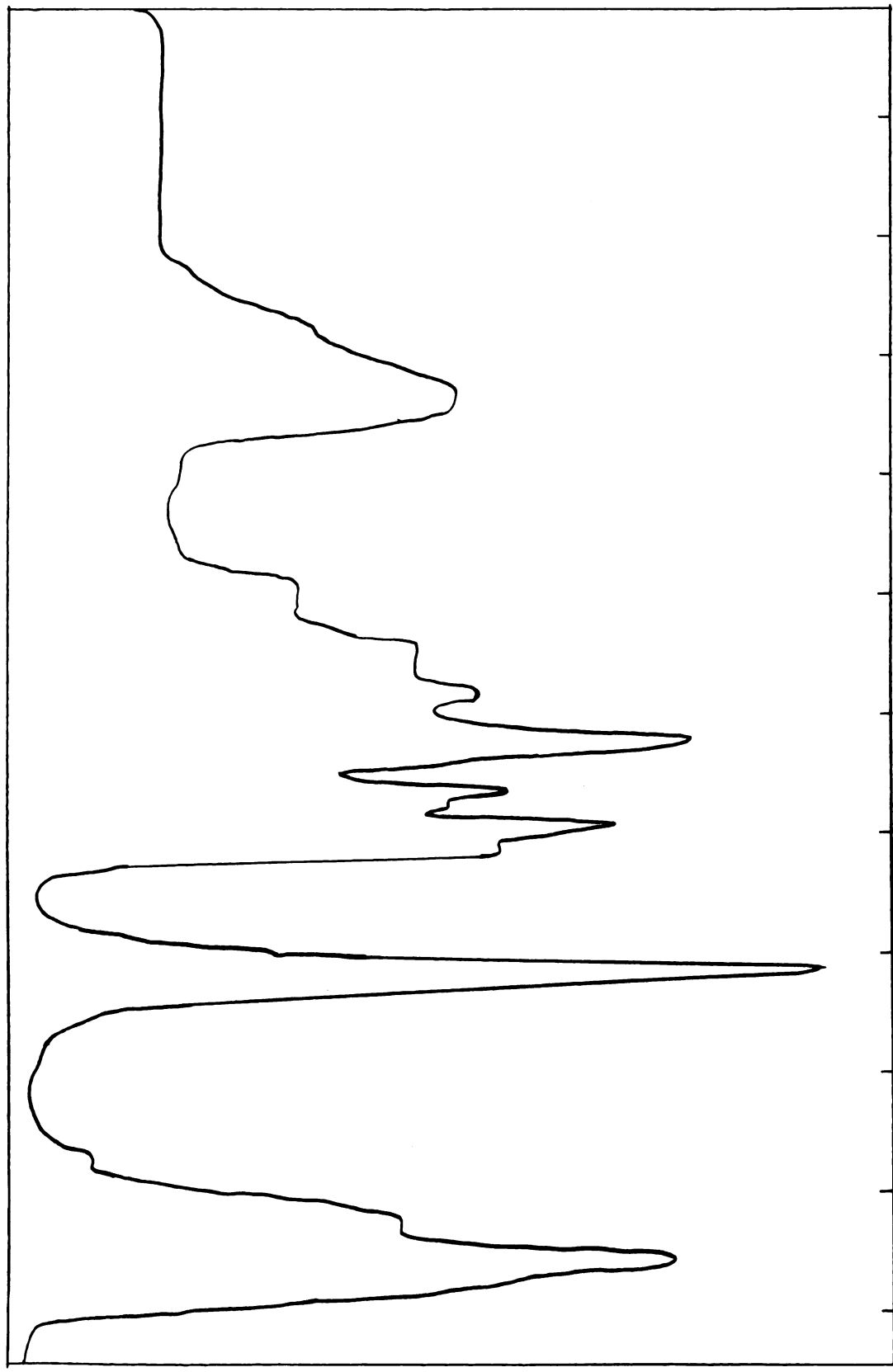


Figure 13. Infrared spectrum of 3,6-dimethyl-7-keto-octanoic acid in carbon tetrachloride.

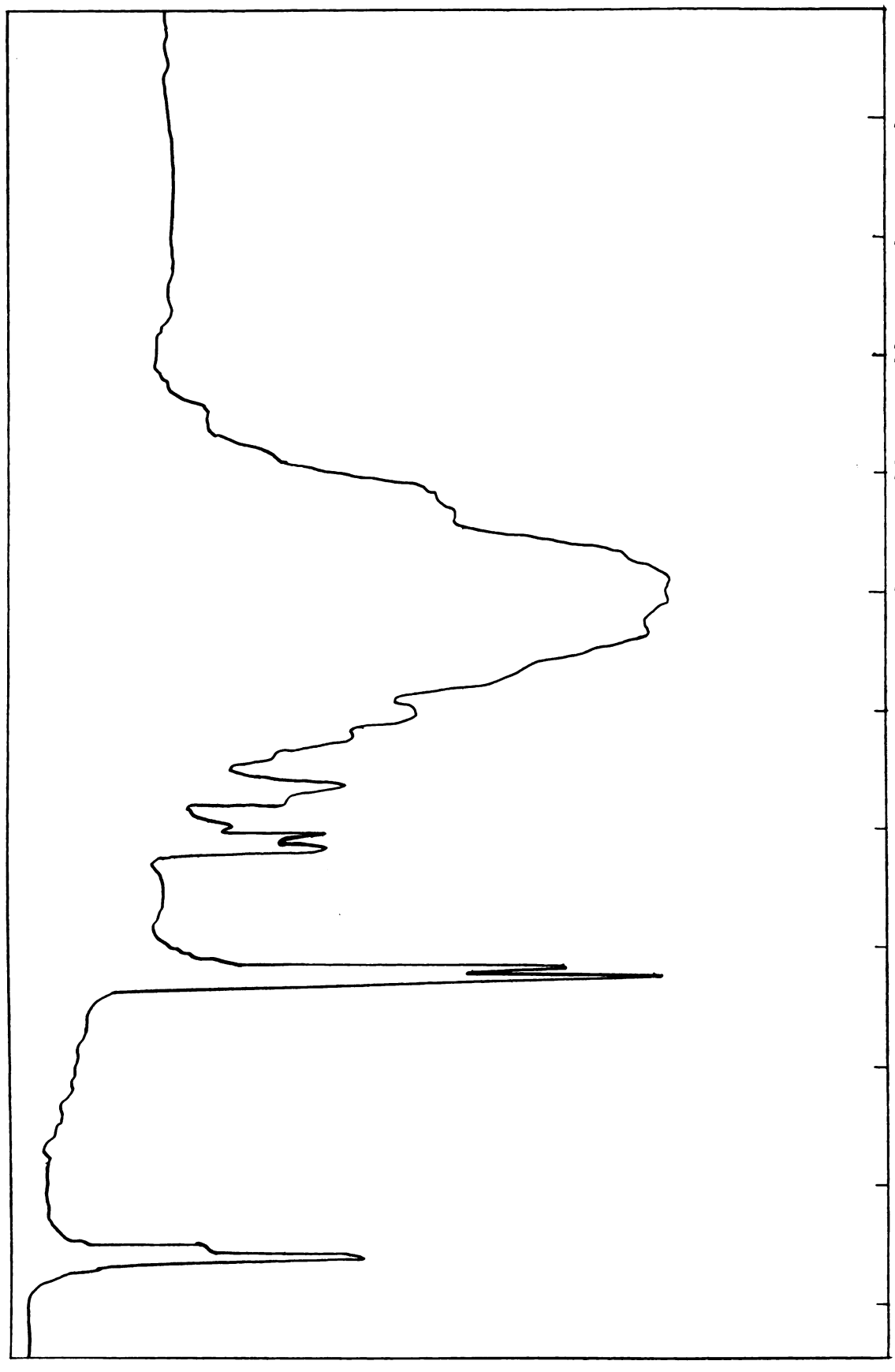


Figure 14. Infrared spectrum of methyl 3,6-dimethyl-7-ketooctylate in carbon tetrachloride.

prepared in 80% yield by the chromic acid oxidation of 2,5-dimethylcyclohexanol according to the procedure of Sandborn (61) for the oxidation of l-menthone.

VII. Synthesis of the Isomers of 2,5-Dimethyl-2-acetylcyclohexanone

A. Preparation of 4-Methyl Isopulegone

This compound was prepared by methylating 53.2 g. of (+)-pulegone with 30.8 cc. of methyl iodide and sodium t-amyl oxide according to the procedure of Djerassi (53). Distillation of the crude product through a 16 inch, vacuum jacketed, tantalum spiral column gave 38 g. (67%) of a mixture of the isomers boiling at 110-114°/25 mm. V.p.c. analysis of the mixture gave 24% isomer VI and 76% isomer V. The reported ratio of VI/V is 17/83. Pure samples of each of the isomers were obtained by preparative vapor phase chromatography using a 15% N.P.G.S. column. Isomer VI formed a semicarbazone, m.p. 196-198°, (lit. value (53), m.p. 197-198.5°) and showed bands at 5.84μ, 6.12μ and 11.21μ in the infrared. Isomer V also formed a semicarbazone, m.p. 201-203°, (lit. value (53), m.p. 201-202.5°) and exhibited bands at 5.88μ, 6.11μ and 11.23μ in the infrared.

B. Ozonolysis of the 4-Methylisopulegone Mixture

A solution of 0.5 g. (0.003 mole) of 4-methylisopulegone (a 24/76 mixture of isomers VI and V) and 10 ml. of methylene chloride was ozonized at dry ice temperature. After completion of the reaction, the mixture was allowed to warm to room temperature, and 10 ml. of water and 2 g. of zinc dust were added. The methylene chloride and all gases were distilled into a methone solution and finally a few ml. of water were distilled. The aqueous mixture was refluxed for 2 hours

and cooled. The mixture was filtered and extracted with ether. The ether solution was dried over anhydrous sodium sulfate and the ether distilled to give 0.3 g. (60%) of product. V.p.c. analysis of the residue showed only 2 compounds in the ratio of 25 to 75. The minor product had the same v.p.c. retention time and infrared spectrum as the minor product (IV) formed in the thermal rearrangement of pulegone oxide. Similarly, the major ozonolysis product was shown to be identical to the major product (III) from the thermal rearrangement of pulegone oxide.

The methone solution was evaporated to a small volume on a steam bath and cooled. The precipitate which formed was filtered, washed with ethanol and dried to give 0.06 g.,66% yield, of solid. Recrystallization from 50% ethanol gave the methone derivative of formaldehyde, m.p. 190-191° (lit. value (62), m.p. 191°).

VIII. Thermal Decomposition of the 2,5-Dimethyl-2-acetylcyclohexanone Isomers

A. Decomposition of Isomer IV

A small sample of isomer IV was placed in a Pyrex tube, degassed, and sealed under nitrogen. The sample was heated at 200° for 15 hours. V.p.c. analysis indicated that no reaction had occurred. It was also shown that neither isomer III nor isomer IV rearranged on the v.p.c. columns.

B. Decomposition of Isomer III

A sample of isomer III was placed in a Pyrex tube, degassed and sealed under nitrogen. It was heated at 200 for 18 hours. Only 5% decomposition had occurred according to v.p.c. analysis. One of the products, formed in 2½% yield, was identified as 2,5-dimethylcyclohexanone.

The structure of the other product, which is also formed in the thermal decomposition of pulegone oxide, is unknown. It should be noted that the thermal decomposition of IV is too slow to account for all of the 2,5-dimethylcyclohexanone formed from pulegone oxide.

IX. Rearrangement of 2,5-Dimethyl-2-acetyl-cyclohexanone on Alumina

A. Chromatography of III and IV on Alumina

A mixture of III and IV was chromatographed on neutral alumina. As soon as a pentane solution of the isomers was added to the column, the column turned yellow. Isomer IV was found to pass through the column unchanged, while isomer III was converted to at least three other compounds. The only product identified was 2,5-dimethylcyclohexanone, which formed a 2,4-dinitrophenylhydrazone, melting 159-161°, (lit. value (60), m.p. 162-3°). This is evidently a base catalyzed reaction since a similar transformation took place on basic alumina but no reaction occurred with acid washed alumina.

X. Acid Catalyzed Rearrangements of Pulegone Oxide

A. Rearrangement with p-Toluenesulfonic Acid

To a small Pyrex tube was added 0.095 g. of pulegone oxide isomer II and 0.005 g. of p-toluenesulfonic acid. The mixture was degassed and sealed under nitrogen. After 15 minutes at 200°, the sample was taken up in 4 ml. of ether, and washed with saturated sodium bicarbonate and water. The ether solution was dried over sodium sulfate and the ether evaporated. V.p.c. analysis of the residue showed that complete reaction had occurred to give approximately equal amounts of three new compounds. None of these compounds were formed in the thermal rearrangement of pulegone oxide.

B. Rearrangement on Alumina

One-half gram of pulegone oxide, isomer II, was passed over a bed of acid washed alumina at 250° using nitrogen as a carrier gas. The product was collected in a trap cooled by dry ice. The product was found to consist of a large number of products having both short and long v.p.c. retention times, but none of the thermal products were present. None of the products formed were identified.

XI. Gas Phase Rearrangement of Pulegone Oxide

A. Gas Phase Rearrangement

To a clean Pyrex tube, which had a volume of about 150 ml., was added 0.1 g. of pulegone oxide, isomer II. The sample was degassed and sealed to 0.5 mm. pressure. After 12 hours at 200°, one end of the tube was cooled in ice water to condense the sample and the tube opened. Three new compounds were formed: 2.4% (A), 47.5% (B) and 11.3% (C). The remainder was starting material and a trace of oxide, isomer I, according to v.p.c. analysis. Although the major product had the same retention time as IV, it was shown to be a new compound by its infrared spectrum. The infrared spectra of products B and C are shown in Figures 15 and 16, respectively.

XII. Thermal Rearrangement of Pulegone Oxide in Decalin

A. Rearrangement of a 10% Solution of Pulegone Oxide, Isomer II, in Decalin

A 10% solution of pulegone oxide isomer II in decalin was placed in a Pyrex tube, degassed and sealed under nitrogen. The mixture was

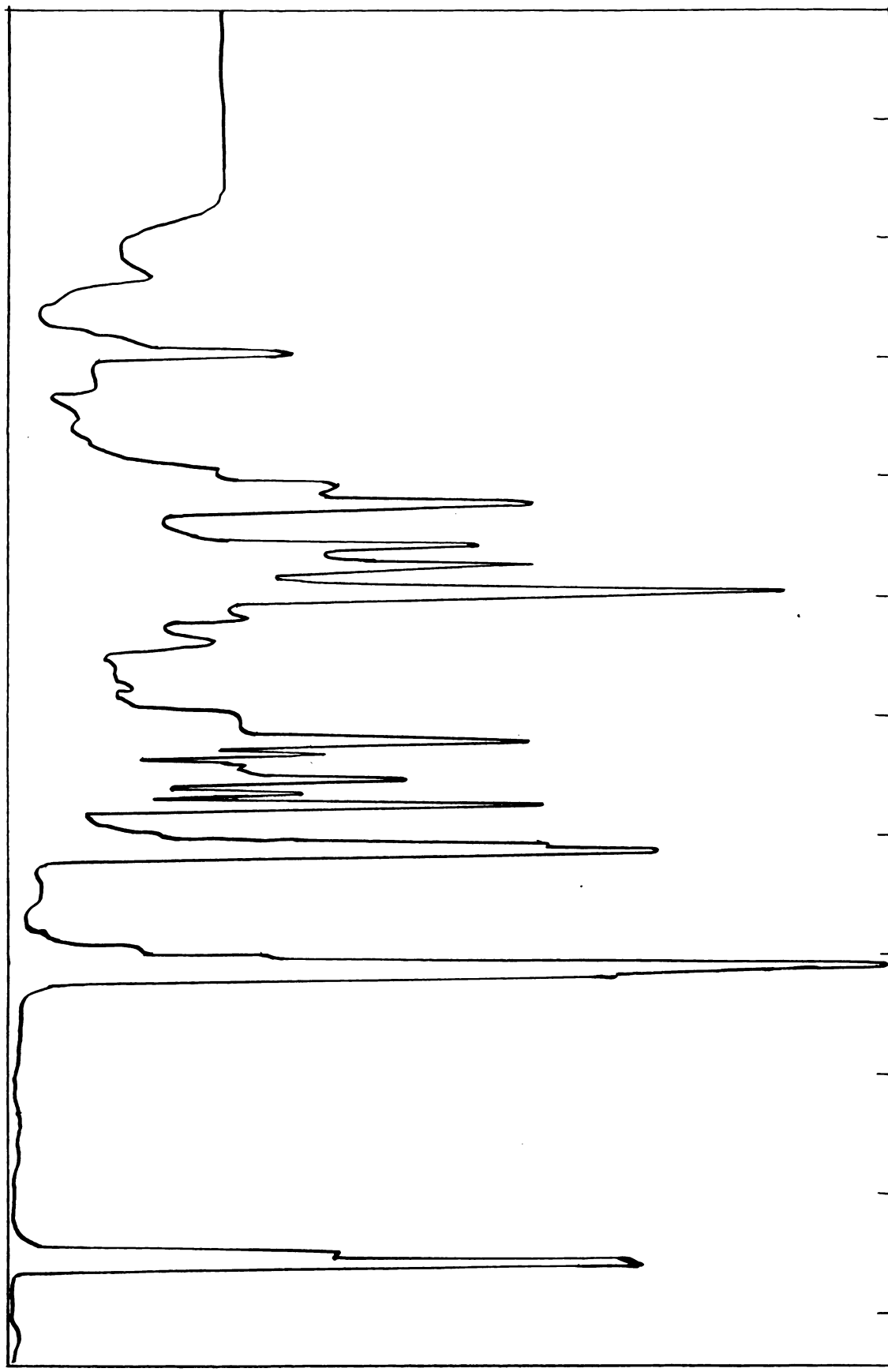


Figure 15. Infrared spectrum of B, formed in the gas phase rearrangement of pulegone oxide, in carbon tetrachloride.

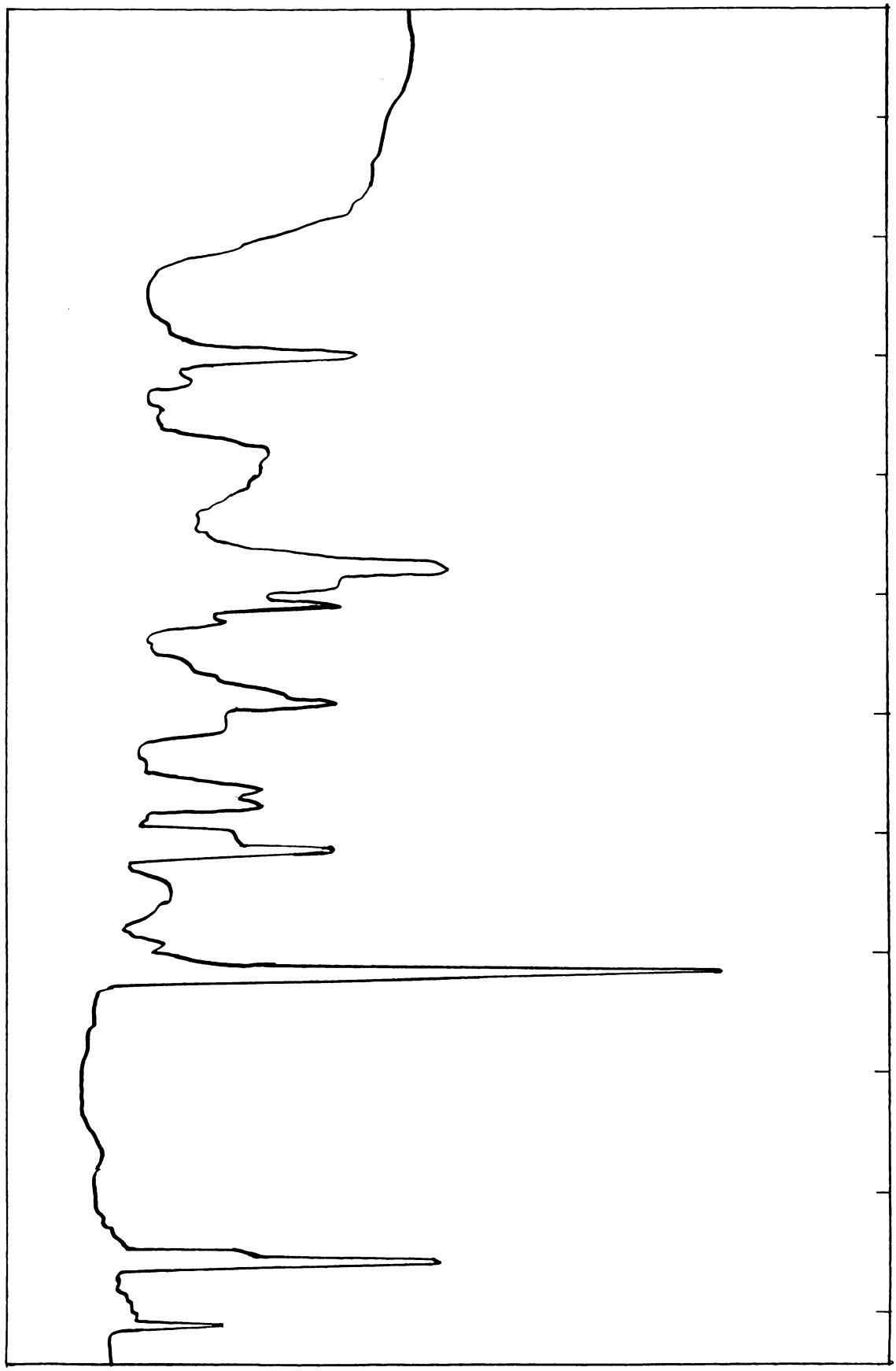


Figure 16. Infrared spectrum of C, formed in the gas phase rearrangement of pulegone oxide, in carbon tetrachloride.

heated at 200° for 18 hours. V.p.c. analysis showed the presence of low boilers (6.4%), A (1%), B (18%), IV (2%), C (3.6%), III (4.0%), oxide isomer II (62.5) and oxide isomer I (3.5%). The yields from a sample heated for 41 hours were as follows: low boilers (9.5%), A (2.0%), B (35.2%), IV (6%), C (5.0%), III (12.8%), oxide isomer II (26.4%) and oxide isomer II (3.7%). The product B was shown to be identical to the major product, B, formed in the gas phase reaction by comparison of the I.R. spectra of both compounds. The amount of IV formed was calculated using the usual ratio of III/IV of 2.

B. Rearrangement of a 0.057 M Solution of Pulegone Oxide, Isomer II, in Decalin

A 0.057 M solution of pulegone oxide isomer II in decalin was prepared and placed in a Pyrex tube. The tube was degassed, sealed under nitrogen, and heated at 200° for 20½ hours. The product was found to consist of A (3.5%), B (54.5%), C (14%) and oxide isomer II (28%).

XIII. Free Radical Rearrangement of Pulegone Oxide

A. Free Radical Reaction Initiated by 2,2'-Azoisobutane

A sample composed of 10% 2,2'-azoisobutane and 90% pulegone oxide, isomer II, was placed in a Pyrex tube. The tube was degassed, sealed under nitrogen, and heated at 200° for 5 hours. The product was composed of four minor components and two major components of 25% and 53%. Comparison by v.p.c. showed that neither major product corresponded to any of the products formed in the thermal rearrangement of neat pulegone oxide.

XIV. Miscellaneous Experiments

A. Preparation of Eucarvone

This compound was prepared by the method of Corey (63). A 70% yield was obtained, b.p. 81°/8 mm., n_D^{21} -1.5080, $\nu_{max}^{CCl_4}$ 6.09μ (lit. values (63), b.p. 82.5-84°/8 mm., n_D^{21} -1.5080).

B. Preparation of Tetrahydroeucarvone

This compound was prepared by the Raney Nickel reduction of eucarvone according to the procedure of Naves (64). A 73.5% yield of product was obtained, n_D^{20} -1.4553, $\nu_{max}^{CCl_4}$ 5.90μ and semicarbazone, m.p. 163-165°, (lit. values (64), n_D^{20} -1.4554, semicarbazone, m.p. 162-5°).

C. Preparation of Tetrahydroeucarvone Ethylene Thioketal

Boron trifluoride etherate (1.2 ml.) was added to a solution of 0.46 g. (3 mmoles) of tetrahydroeucarbone in 1.2 ml. of ethane dithiol and the mixture allowed to stand at room temperature for 1 hour. The mixture was transferred to a separatory funnel with the aid of a few ml. of ether, diluted with 50 ml. of water and extracted with three 20 ml. portions of pentane. The combined extracts were washed with water, dried over anhydrous sodium sulfate and the pentane was distilled. The remaining oil was analyzed by v.p.c. and found to consist of ethane dithiol and a high boiling product. The I.R. spectrum of a sample of the product collected from the v.p.c. had no carbonyl absorption.

D. Preparation of 1,1,4-Trimethylcycloheptane

The oil described above was taken up in 30 ml. of absolute ethanol and added slowly to 9 g. of Raney Nickel. The mixture was refluxed for

12 hours, and the nickel removed by filtration and washed with 30 ml. of ethanol. The alcohol solution was diluted with 300 ml. of water and extracted with three 50 ml. portions of pentane. The combined pentane extracts were washed with water, dried over anhydrous sodium sulfate and the pentane carefully distilled. The residue was distilled to give 0.25 g. (66%) of product, n_D^{20} 1.4418 (lit. values (65), n_D^{20} 1.4420, b.p. 162-3°). The sample was shown to be pure by v.p.c. The infrared spectrum of the compound is shown in Figure 17.

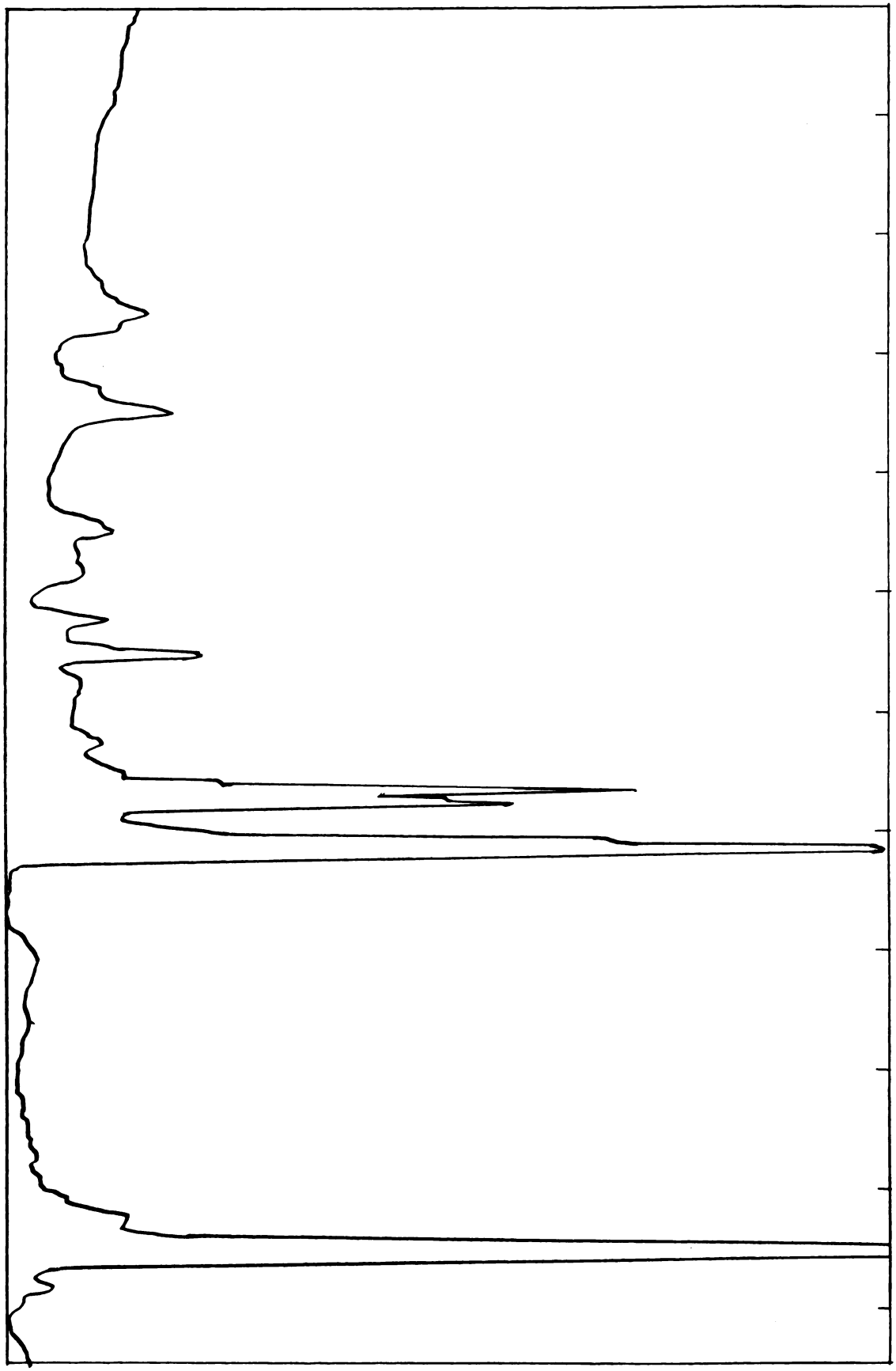


Figure 17. Infrared spectrum of 1,1,4-trimethylcycloheptane.

SUMMARY

1. Pulegone oxide mixtures were prepared in good yield from (+)-pulegone ether by perbenzoic acid oxidation or by reaction with alkaline hydrogen peroxide. The two diastereoisomers were isolated as crystalline solids, and configurations were assigned to them on the basis of their n.m.r. spectra, optical rotatory dispersion curves, thermal isomerization at 200° and a consideration of the possible conformations. Also, a crystalline modification having properties identical to those previously reported for one of the pure isomers was isolated and shown to consist of equimolar amounts of the two diastereomers.

2. Neat samples of the pulegone oxide isomers isomerized at 200° as previously reported (12), but considerable rearrangement and fragmentation simultaneously occurred. The two major rearrangement products were shown to be the diastereomers of 2-acetyl-2,5-dimethylcyclohexanone by degradation to known compounds. This was further confirmed and the configurations of the isomers determined by an unequivocal synthesis of each. Of the six fragmentation products, only acetone and 2,5-dimethylcyclohexanone were identified.

3. A constant ratio of the 2-acetyl-2,5-dimethylcyclohexanone isomers was obtained starting with either diastereomer of pulegone oxide. Since a rapid equilibrium is not established between the pulegone oxides, a concerted mechanism can not account for these results. The observation that oxygen slowed both the rate of rearrangement and isomerization suggested that both reactions proceed by way of a triplet

diradical intermediate. Support for this postulate was obtained by trapping the intermediate with radical scavengers. A radical cleavage recombination mechanism involving a novel 1,2-shift of a methyl radical was proposed as rationale for both the isomerization and rearrangement.

4. Both the thermal isomerization and rearrangements of pulegone oxide are very sensitive to changes in the dielectric constant of the solvent. In dilute decalin solutions and in the gas phase an entirely different reaction occurred to give three products of unknown structure, while in a 10% solution of pulegone oxide in decalin both reactions occurred simultaneously.

PART III

PHOTOCHEMICAL REARRANGEMENTS OF SOME α, β-EPOXY KETONES

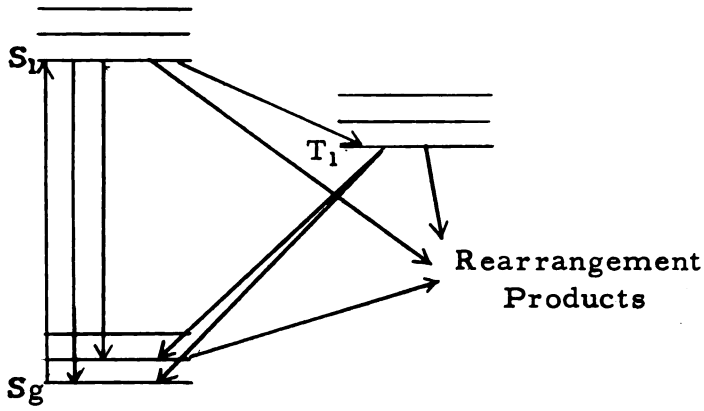
INTRODUCTION AND HISTORICAL

In recent years there has been a great deal of interest in the mechanisms of photochemical reactions of organic molecules, and a number of authors have suggested theories to account for these transformations (66-71).

Most organic molecules contain an even number of electrons, which usually occupy molecular orbitals in pairs with antiparallel spins. By absorption of light, electrons may be excited to unoccupied orbitals of higher energy. Excited singlet states result since the electron spin can not change during this process. The excited singlet may react in any of the following ways: (1) be deactivated to the ground state by fluorescence, internal conversion, or energy transfer through collision, (2) undergo rearrangement reactions, or (3) be converted to a triplet. The triplet may in turn rearrange or be deactivated to the ground state by phosphorescence or energy transfer by collision.

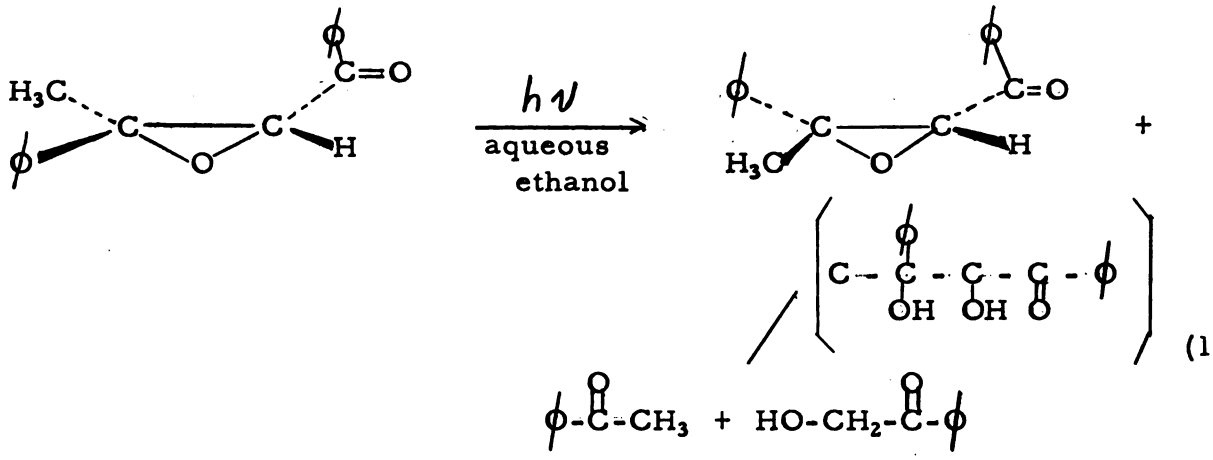
The vibrationally excited molecules resulting from the deactivation of electronically excited molecules may also undergo rearrangements. Since molecules in their vibrationally excited or triplet states are involved in thermal rearrangements, it is possible that thermal and photochemical reactions may be identical in some cases. Recently, it has been shown that 1, 3, 5-cycloheptatriene yields toluene both thermally and by the rearrangement of vibrationally excited molecules produced photochemically (69).

Zimmerman (70) has stated that $n \rightarrow \pi^*$ photochemical reactions are generally different than thermal reactions, but there appears to be little if any experimental justification for this conclusion. A study



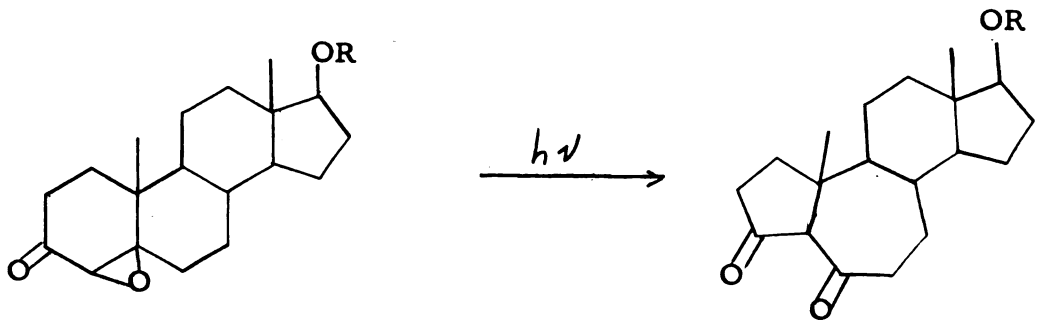
of the photochemical reactions of α,β-epoxy ketones was undertaken in order to compare the thermal and photochmeical reactions of carbonyl compounds and to obtain information about the mechanisms of photochemical reactions.

Several reports of the photochemical rearrangements of α,β-epoxy ketones have appeared in the literature since our work first began. Zimmerman (72) has reported the photochemical isomerization and hydrolysis of trans-dypnone oxide as well as the conversion of an α,β-epoxy ketone to a β-diketone. He has rationalized these reactions in terms of an ionic mechanism.



Jeger and co-workers (73) have observed the photochemical conversion of a number of steroidal α,β-epoxy ketones to β-diketones.

No information with regard to the mechanism of these rearrangements was presented.



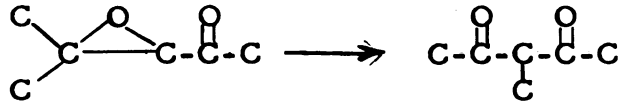
RESULTS AND DISCUSSION

I. Photolysis Products from α, β-Epoxy Ketones

A. Photolysis of 4-Methyl-3, 4-epoxy-2-pentanone

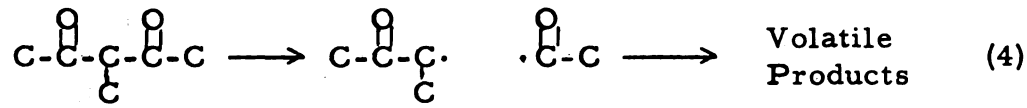
4-Methyl-3, 4-epoxy-2-pentanone (I) rearranged to a single compound when photolyzed under nitrogen in a quartz cell or test tube with a high pressure mercury lamp. On prolonged irradiation, a number of low boiling products and considerable tar were also formed. A similar transformation occurred when the epoxide (I) was photolyzed in a variety of solvents using a mercury arc and a Corex filter; thus indicating that the reaction is initiated by the $n \rightarrow \pi^*$ absorption of the carbonyl group.

The initial photolysis product was isolated from the photolysis of I in ether and shown to be methyl acetylacetone (II) by comparison with an authentic sample.



I II (3)

The reaction mixtures were very complex. Considerable tar and at least 16 volatile products were formed when either benzene or ether were used as solvents. Of the many low boiling products obtained, only acetaldehyde, acetone, methyl ethyl ketone, methyl isopropyl ketone, and the enol acetate of butanone were positively identified. It was shown that these compounds were formed as the result of the photolytic cleavage of the β-diketone (II). The yield of methyl acetylacetone was always low because a steady state was rapidly established between the rate of formation and decomposition of this compound.

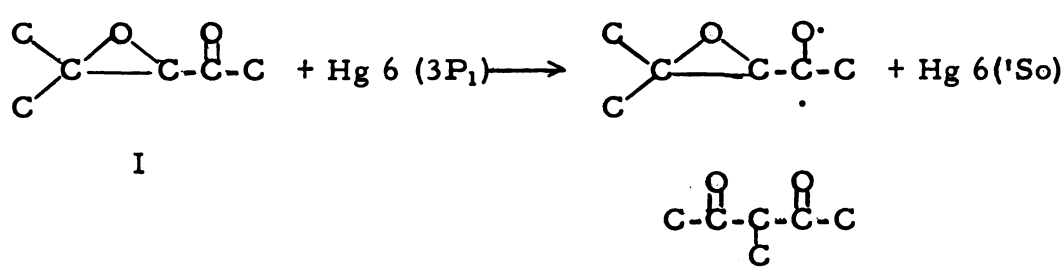


(4)

II

A comparison of the rates of disappearance of the β-diketone (II) and of the epoxide (I) shows that the former decomposes too slowly to account for all of the products formed. This suggested the possibility that an intermediate was involved in the rearrangement which could either form II or react in other ways. A careful study of the products of I showed that some of the products formed in ether were absent in benzene and vice versa; indicating that the solvent was being attacked by some intermediate species. This postulate was substantiated by showing that not all of the products resulting from the photolysis of 4-methyl-3,4-epoxy-2-pentanone in benzene were formed in the photolysis of methyl acetylacetone under the same conditions. Only free radical species would be expected to attack both ether and benzene.

The gas phase photolysis of the epoxide in a Vycor flask produced methyl acetylacetone (6.9%) plus the usual fragmentation products and tar (19%) after 50% of the starting material had decomposed. The mercury sensitized gas phase rearrangement was accomplished by irradiating a mixture of I and mercury with the 2537 Å resonance line of mercury. A 9.3% yield of methyl acetylacetone was obtained, thus proving that the rearrangement may occur via a triplet state.



I

(5)

II

Table 10. Photolysis of Neat Samples of 4-Methyl-3,4-epoxy-2-pentanone under Nitrogen at 40°.

Cell	Time, hr.	I,[a] %	II, %	Low boilers, %
0.2 mm. quartz	22	84	12	4
Quartz T.T.[b]	24	99	1	-
Quartz T.T.	168	88	10	2
Quartz T.T.[c]	504	65	30	5

[a] Percentages of volatile products are reported.

[b] A 1.4 g. sample was photolyzed in a quartz test tube.

[c] Distillation proved the sample to be 50% tar.

Table 11. Photolysis of 4-Methyl-3, 4-epoxy-2-pentanone and Methyl Acetylacetone in Different Solvents at 25°.

Compound	Solvent	Conc., moles/liter	Time, hr.	Extent of reaction, %	II, %
I[a]	ether	0.88	24	10	5
I	ether	0.88	36	15	4
I	ether	0.351	24	29	2
I	benzene	0.351	24	30	2.5
I	pentane	0.351	24	16	1
I	ethanol	0.351	24	15	1
II[b]	ether	0.193	40	20	80
II	benzene	0.351	24	13	87
II	benzene	0.351	48	25	75

[a] 4-Methyl-3, 4-epoxy-2-pentanone.

[b] Methylacetylacetone.

Table 12. Photolysis of Neat Samples of Isophorone Oxide under Nitrogen at 40°.

Sample cell	Time, hr.	III, %	IV, %	V, %
0.2 mm. quartz	2	100	---	---
0.2 mm. quartz	20	95	---	5
0.2 mm. quartz	72	83.5	1.5	15

[a]Percentages refer to the volatile portion only.

Table 13. Photolysis of Isophorone Oxide in Solution at 25°

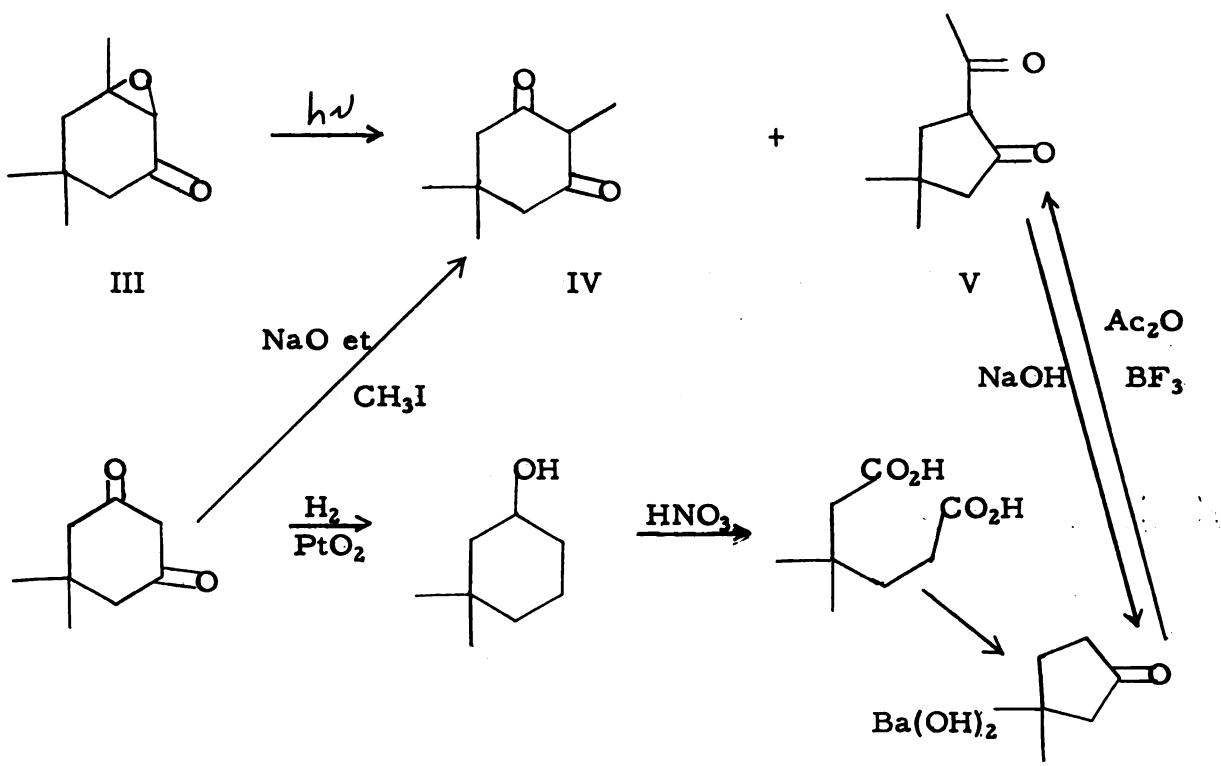
Solvent	Moles/ liter	Time, hr.	Filter	Extent of reaction, %	IV, %	V, %
ether	0.43	14	none	12	1	9
ether	0.43	20	none	18	1	9
ether[a]	0.43	39	none	34	1	8
ether	0.65	27	Corex	9.7	0.8	8.8
benzene	0.65	27	Corex	10	1	9
acetic acid	0.65	7	Corex	2.3	0.3	2.5

[a]The solution was dark yellow.

B. Photolysis of Isophorone Oxide

When isophorone oxide was photolyzed either in solution or neat, it was converted to a 9:1 mixture of two products. Both compounds were readily separated from the photolysis solutions by extraction with dilute alkali. The minor product (IV) crystallized from a petroleum ether solution of the photolysis products and was identified as 2, 5, 5-trimethyl-1, 3-cyclohexanedione by mixed melting point and comparison of its I.R. spectrum and v.p.c. retention time with those of an authentic sample. The major product (V) was purified by distillation of the filtrate. Basic cleavage of V with sodium hydroxide gave acetic acid and 3, 3-dimethylcyclopentanone; therefore, this compound must be 2-acetyl-3, 3-dimethylcyclopentanone. This was confirmed by synthesizing the latter substance and showing it to be identical to the main photolysis product. No other neutral or basic products could be detected. The photochemical reaction as well as the reactions employed in the proofs of structure are outlined in Chart I.

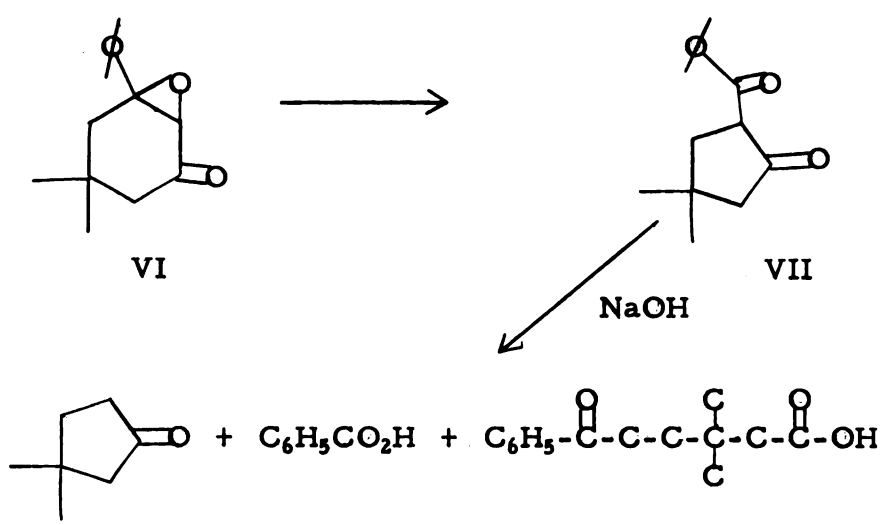
Chart I



As was the case with 4-methyl-3,4-epoxy-2-pentanone, the yields of the primary photolysis products were low, 9% of V and 1% of IV, and prolonged irradiation only increased the quantity of high molecular weight material. It should be noted that the rate of reaction was about the same in all solvents studied.

C. Photolysis of 2,3-Epoxy-3-phenyl-5,5-dimethylcyclohexanone

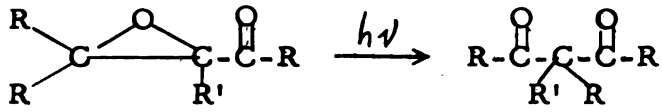
Photolysis of a 0.093 M solution of 2,3-epoxy-3-phenyl-5,5-dimethylcyclohexanone in ether, with a mercury lamp fitted with a Corex filter, produced a single isomeric base soluble produce, m.p. 84-85°, in 15% yield. This compound was not 2-phenyl-5,5-dimethyl-1,3-cyclohexanedione, which would result from a 1,2-shift of the phenyl group, since it is a known compound melting at 197-198° (74). The band at 5.76μ in the infrared spectrum of the product suggested that it was a cyclopentanone analogous to compound V formed in the photolysis of isophorone oxide. The product was shown to be 2-benzoyl-3,3-dimethylcyclopentanone by cleaving it with base to a mixture of 3,3-dimethylcyclopentanone, benzoic acid and 6-phenyl-3,3-dimethyl-6-ketohexanoic acid.



(6)

II. Mechanism of the Photochemical Rearrangements

The $n \longrightarrow \pi^*$ transitions of carbonyl groups initiate the conversion of α, β-epoxy ketones to β-diketones. These transformations formally require the cleavage of the α-carbon oxygen bond and a 1, 2-shift of a group originally attached to the β-carbon.



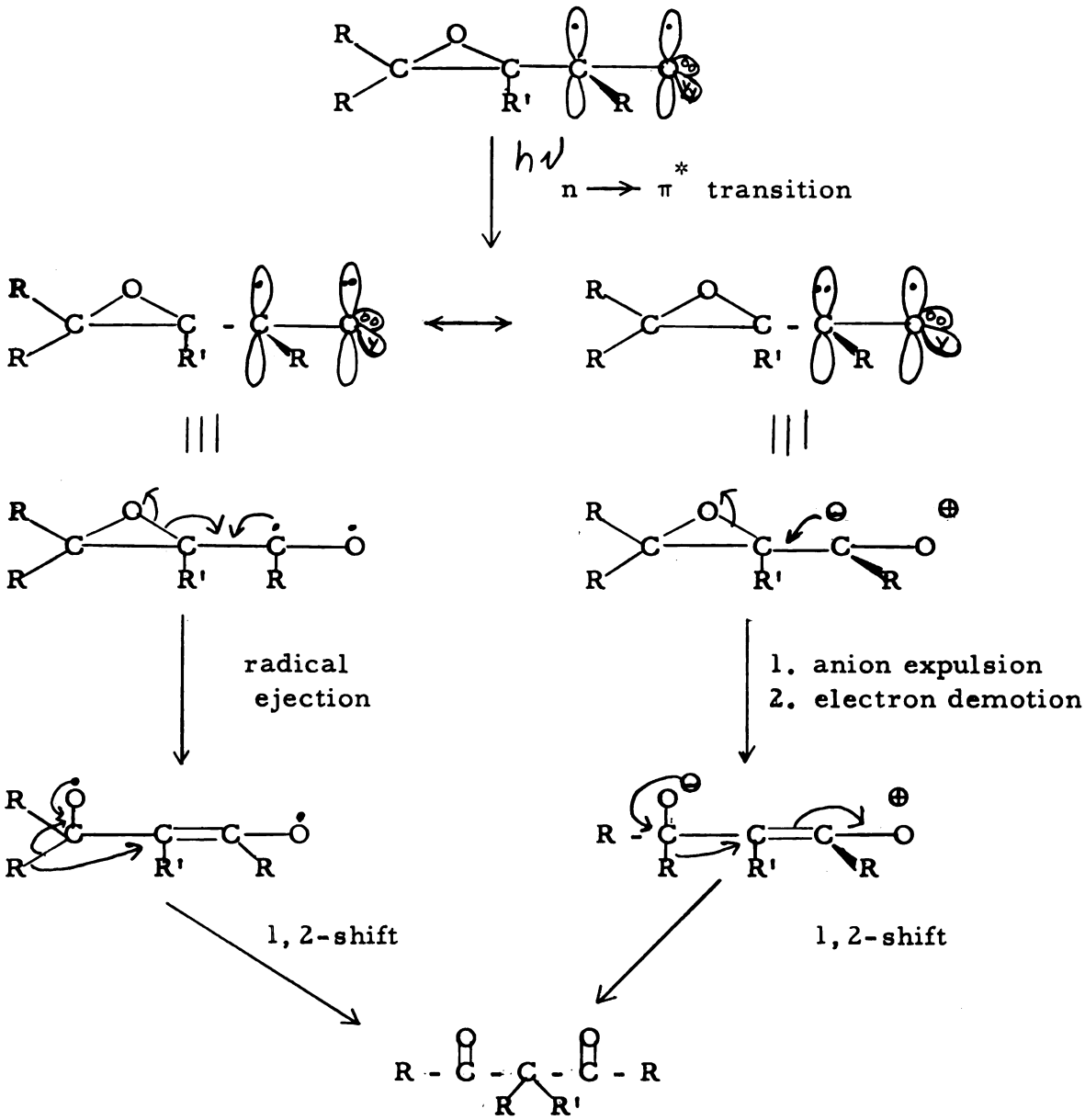
(7)

These rearrangements may be rationalized by either diradical or ionic mechanisms involving 1, 2-shifts to a positive site. Mechanisms of the latter type have been used to explain several photochemical rearrangements (70). Both a diradical and an ionic mechanism have been suggested by Zimmerman as rationals for the rearrangements of α, β-epoxy ketones; however, he favors the latter possibility (72). Zimmerman's proposals are shown in Chart II.

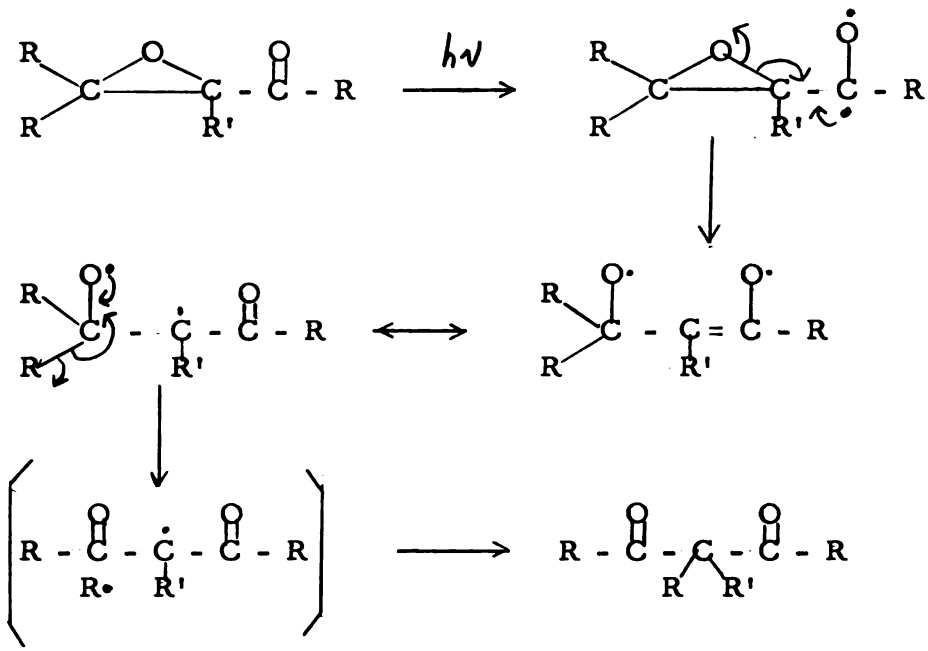
The rates of rearrangement of both 4-methyl-3, 4-epoxy-2-pentanone and isophorone oxide in polar and nonpolar solvents are approximately the same. If an ionic intermediate was involved in the reaction, the rate might be expected to increase as the dielectric constant of the solvent increases, but the absence of such an effect does not eliminate an ionic mechanism.

The order of the migratory apptitude of the groups studied was surprising: neopentyl > methyl > phenyl. Usually, a phenyl group migrates to either positive or radical centers in preference to alkyl groups (75). It is possible that steric interactions prevent the phenyl group from attaining the conformation necessary for migration, but a study of models indicates this is unlikely. However, if the rearrangement

Chart II



occurs by way of a radical cleavage recombination mechanism (8), alkyl groups would preferentially migrate since it is known that the tendency of a group to participate in the homolytic cleavage of a carbon-carbon bond of an alkoxy radical, R—C—O•, increases in the order; phenyl, methyl, ethyl, hydrogen (76).



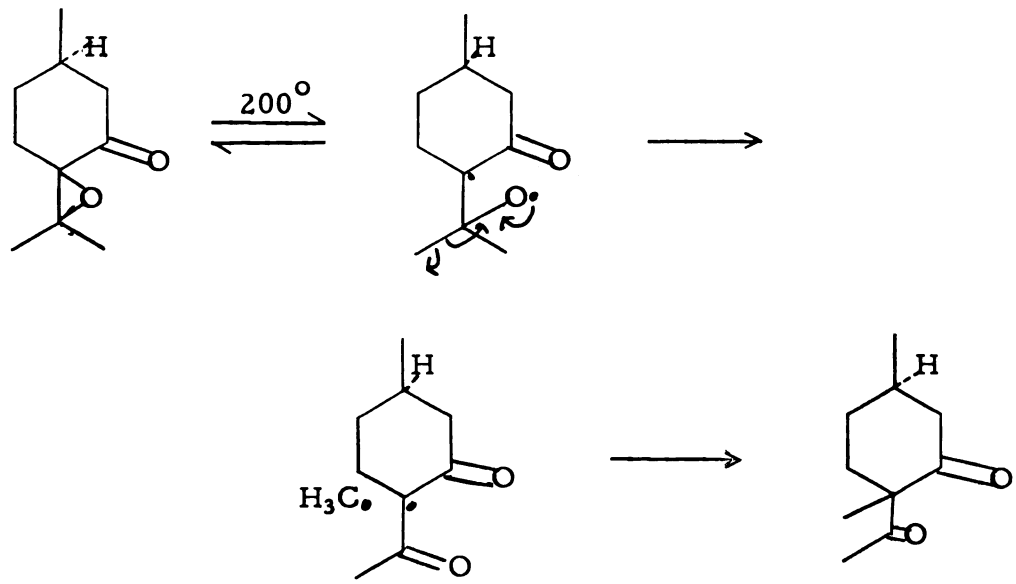
(8)

The two free radicals may couple within the solvent cage to produce a β-diketone or attack the solvent. It was previously pointed out that a species capable of attacking both ether and benzene were formed in the photolysis of 4-methyl-3,4-epoxy-2-pentanone. The radical intermediates postulated in equation 8 account for this phenomenon, whereas ionic intermediates can not. The second step in this mechanism involves the heterolytic cleavage of the α-carbon oxygen bond. This step is analogous to the photolytic fission of the α-carbon chlorine bond of chloroacetone (77).

Whether the photolysis reactions proceed via a singlet or triplet diradical is uncertain, but the fact that mercury sensitized the rearrangement of 4-methyl-3,4-epoxy-2-pentanone, proves that the rearrangement can take place in the triplet state.

It is impossible to compare the thermal and photochemical rearrangements of these α,β-epoxy ketones because of the interference of radical chain reactions and surface effects in the former case. However, the photochemical rearrangements of these compounds are completely analogous to the thermal rearrangement of pulegone oxide

discussed in Part II of this thesis. Convincing evidence for a radical cleavage recombination mechanism was presented for the latter reaction.



(9)

Recently, Reusch and Dominy (78) have demonstrated that the thermal and photochemical rearrangements of pulegone oxide produce the same products, thus showing that the photochemical and thermal rearrangements of some carbonyl compounds are identical.

EXPERIMENTAL

I. General Techniques

A. Apparatus

The same general laboratory methods and equipment described in detail in Part I of this thesis were used in this work. Vapor phase chromatography analyses were made with a Beckman G. C-2 Gas Chromatograph using a 30% silicon column.

B. Solvents

1. Pentane

C. p. grade pentane was purified by passing it through a column of silica gel and stored over sodium.

2. Benzene

C. p. grade benzene was distilled through a 24 inch Vigreux column prior to use.

3. Other Solvents

Reagent grade acetic acid and absolute ethanol were used without purification. C. p. grade ethyl ether was dried over sodium before use.

II. Synthesis of α, β-Epoxy Ketones

A. Preparation of 4-Methyl-3, 4-epoxy-2-pentanone and Isophorone Oxide

The preparations of these compounds were described in Part I of this thesis.

B. Preparation of 2, 3-Epoxy-5, 5-dimethyl-3-phenylcyclohexanone

1. Preparation of 5, 5-Dimethyl-3-ethoxy-2-cyclohexene-1-one

5, 5-Dimethyl-3-ethoxy-2-cyclohexene-1-one was prepared by a modification of the method of Desai (79). An alcoholic solution of sodium ethoxide was prepared by dissolving 11.5 g. (0.5 mole) of sodium in 150 ml. of absolute ethanol and 70 g. (0.5 mole) of dimadone was added. The resulting solution was stirred for 15 minutes, cooled to 0°, and 80.5 g. (0.52 mole) of ethyl iodide was slowly added with stirring. The mixture was heated on a steam bath for 3 hours, cooled to room temperature, and then poured into 300 ml. of water. The aqueous layer was extracted with two 300 ml. portions of ether and the combined organic layers extracted with 10% sodium hydroxide until it no longer gave a ferric chloride test. The ether layer was washed with water and dried over anhydrous magnesium sulfate. The ether was evaporated and the residue crystallized from 30-60° petroleum ether to give 48 g. (57%) of product, m.p. 60-60.5°, $\nu_{max}^{CCl_4}$ 6.0μ, 6.19μ and 8.23μ (lit. value (80), m.p. 60°). The aqueous layer was acidified with concentrated hydrochloric acid. The precipitate was removed by filtration and washed with 75 ml. of ice water. The crude 1, 1-dimethyl-4-ethylcyclohexane-3, 5-dione weighed 15.5 g. (18.5%), m.p. 151-153° (lit. value (79), 153°).

2. Preparation of 3-Phenyl-5, 5-dimethyl-cyclohex-2-enone

3-Phenyl-5, 5-dimethylcyclohex-2-enone was prepared by the method of Wood (80). 3-Ethoxy-5, 5-dimethylcyclohex-2-enone (20 g.) was reacted with phenyl magnesium bromide and the complex which formed was decomposed with acid to give 14 g. (59%) of the desired

product, m.p. 53-54°, $\nu_{max}^{CCl_4}$ 6.02μ and 6.22μ (lit. value (80), m.p. 54-5°).

3. Preparation of 2,3-Epoxy-3-phenyl-5,5-dimethylcyclohenanone

To a 300 ml. three necked flask equipped with a stirrer and a thermometer were added 12 g. (0.06 mole) of 3-phenyl-5,5-dimethyl-2-cyclohexenone, 17.5 ml. (0.18 mole) of 30% hydrogen peroxide, 60 ml. of methanol and 5 ml. of 6 N sodium hydroxide. The mixture was kept at 30-35° for 6 hours with stirring and then cooled in an ice bath. The solid which formed was removed by filtration, washed with ice water and dried to give 8 g. (62%) of the epoxide. It was recrystallized from 30-60° petroleum ether to give a solid, m.p. 71-72°, $\nu_{max}^{CCl_4}$ 5.82μ and 11.32μ, $\lambda_{max}^{95\% \text{ ethanol}}$ 260 mμ (326), 267 mμ (239), and 301 mμ (145). The infrared spectrum of this compound is shown in Figure 18.

Anal. Calc'd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46.
Found: C, 77.32; H, 7.54.

III. Photolysis of 4-Methyl-3,4-epoxy-2-pentanone

A. Neat Samples

Samples of pure 4-methyl-3,4-epoxy-2-pentanone were placed in a 0.2 mm. thick quartz cell, which had been flushed with oxygen free nitrogen, and the cell was sealed. The samples were irradiated with a Hanovia type SH mercury lamp while keeping the temperature at 40° by air cooling. Larger samples (1.4 g.) were similarly irradiated in a quartz test tube. The results of these experiments are summarized in Table 10, page 102.

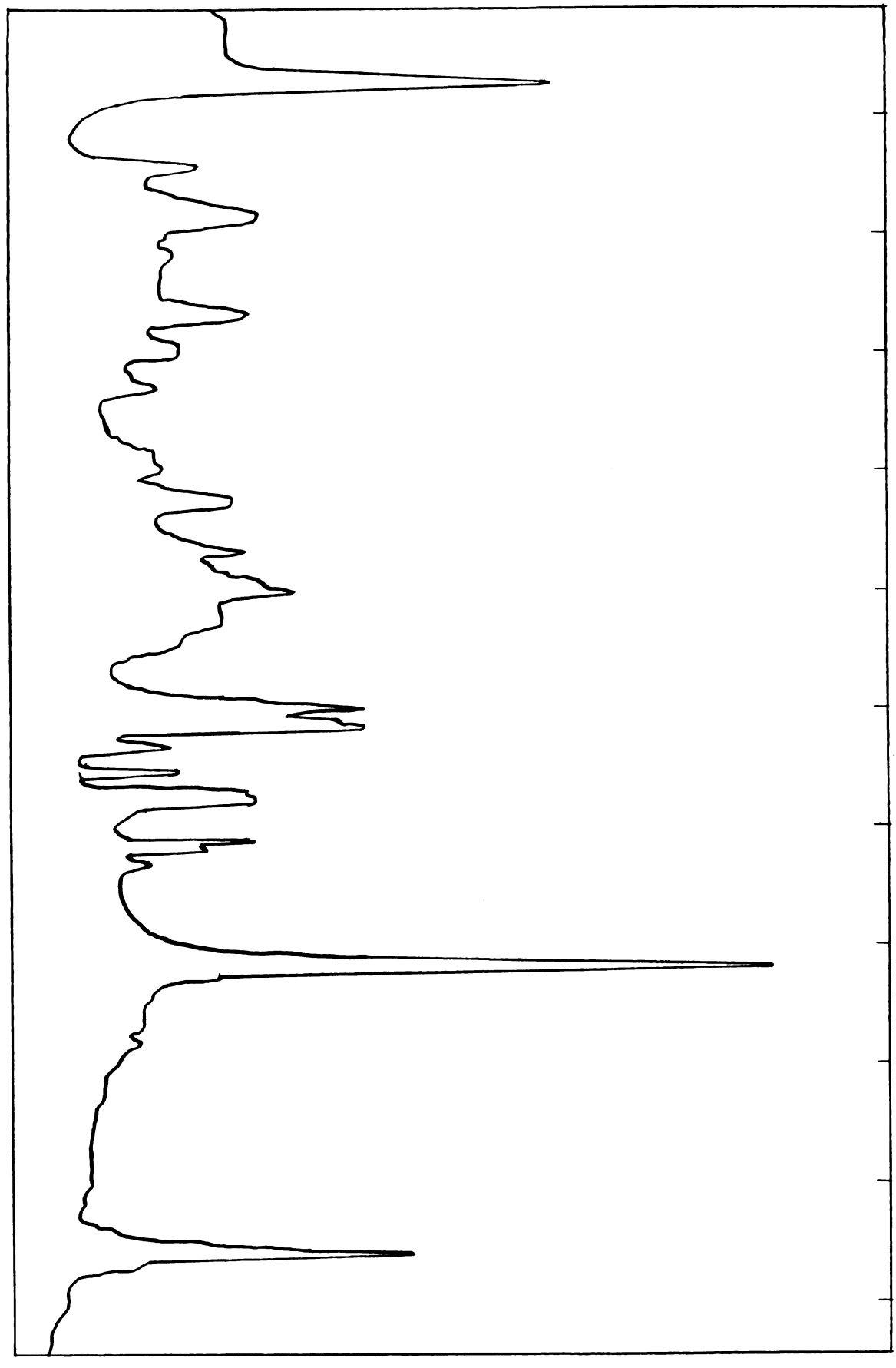


Figure 18. Infrared spectrum of 2,3-epoxy-3-phenyl-5,5-dimethylcyclohexanone.

B. Identification of the Photolysis Products

A 0.88 M solution of 4-methyl-3,4-epoxy-2-pentanone was prepared by diluting 30 g. of the epoxide to 300 ml. with anhydrous ether. The solution was placed in a Hanovia type S, 200 watt, water cooled, Vycor immersion apparatus which was fitted with a Corex filter. After 24 hours of irradiation, v.p.c. analysis showed the presence of methyl acetylacetone (5%), epoxide (90%) and a number of other products. After an additional 12 hours, 15% decomposition had occurred but only 4% of methyl acetylacetone was present. Irradiation was stopped and the solution distilled. The main products were identified as described below.

1. Acetaldehyde

The fraction boiling between 25° and 36° was composed of ether and a compound having the same v.p.c. retention time as acetaldehyde. A 2,4-dinitrophenylhydrazone was prepared and recrystallized from 95% ethanol, m.p. 156-160° (lit. value, m.p. 147° and 168°). There was no depression of a mixed melting point with an authentic sample.

2. Acetone

The product having the same v.p.c. retention time as acetone was collected from the v.p.c. and its I.R. spectrum was identical to that of acetone.

3. Methyl Ethyl Ketone

The v.p.c. peak which corresponded to methyl ethyl ketone was collected and its infrared spectrum was shown to be identical to that of an authentic sample.

4. Methyl Isopropyl Ketone

Methyl isopropyl ketone was identified by comparison of its v.p.c. retention time and infrared spectrum with those of an authentic sample.

5. Methyl Acetylacetone

The primary photolysis product was found to have the same v.p.c. retention time and I.R. spectrum as a sample of methyl acetylacetone. Further, both samples gave identical purple ferric chloride tests.

C. Photolysis of 4-Methyl-3,4-epoxy-2-pentanone in Solution

1. Photolysis in Ether

A 0.351 M solution of 4-methyl-3,4-epoxy-2-pentanone was prepared by diluting 10 g. of the epoxide to 250 ml. with ethyl ether. The solution was placed in a Hanovia type S, 200 watt, water cooled, Vycor immersion apparatus fitted with a Corex filter and a magnetic stirrer and irradiated for 24 hours at 25°. V.p.c. analysis of the solution indicated that 29% of the epoxide had reacted. The ether was removed by distillation and the mixture was separated into high and low boiling fractions and tar (9%) by distillation. V.p.c. analysis showed the presence of acetaldehyde (0.5%), acetone (1%), methyl ethyl ketone (4%), methyl isopropyl ketone (0.3%), butanone enol acetate (1%), 4-methyl-3,4-epoxy-2-pentanone (71%), and methyl acetylacetone (2%). Small amounts of 9 other unidentified products were also formed.

2. Photolysis in Benzene

A 0.351 M solution of 4-methyl-3,4-epoxy-2-pentanone was prepared by diluting 10 g. of the oxide to 250 ml. with benzene. The solution was placed in a Hanovia type S, 200 watt, water cooled, Vycor

immersion apparatus, which was fitted with a Corex filter and a magnetic stirrer, and irradiated for 24 hours at 25°. V.p.c. analysis of the solution indicated that 30% of the epoxide had reacted. The mixture was separated into high and low boiling fractions and tar (13%) by distillation through a 12 inch vacuum jacketed Vigreux column. The lowest boiling products could not be detected by v.p.c. due to the presence of benzene. However, the enolacetate of butanone (0.8%), 4-methyl-3,4-epoxy-2-pentanone (70%), methyl acetylacetone (2.5%), acetophenone (1%) and eight unidentified products were shown to be present by v.p.c. analysis. The acetophenone was identified by comparison of the v.p.c. retention time and I.R. spectrum of the product with those of an authentic sample.

3. Comparison of the Products Formed in Ether and Benzene

A careful comparison of the photolysis products of 4-methyl-3,4-epoxy-2-pentanone by v.p.c. showed that two of the low boiling products formed in ether were not formed in benzene. It also showed that a number of the high boiling products formed in ether solution were not formed in benzene and vice versa.

4. Photolysis in Other Solvents

Solutions of the epoxide in pentane and absolute ethanol were photolyzed as described above and the extent of reaction determined by v.p.c. analysis. However, no detailed product analysis was attempted. The results of these experiments are summarized in Table 11, page 103.

D. Gas Phase Photolysis of 4-Methyl-3,4-epoxy-2-pentanone

A small sample (0.1 g.) of 4-methyl-3,4-epoxy-2-pentanone was placed in a 250 ml. Vycor flask, the sample degassed and sealed off from the vacuum pump at 2 mm. pressure. The flask was irradiated with both the 200 watt and 100 watt mercury lamps. The flask was air cooled to keep the temperature at 45°. After 8 hours, the irradiation was stopped and the bottom of the flask cooled in dry ice to condense the gases. V.p.c. analysis of the product showed the following compounds to be present: acetone (4.3%), methyl ethyl ketone (6.2%), methyl isopropyl ketone (3.3%), butanone enol acetate (2.2%), 4-methyl-3,4-epoxy-2-pentanone (50%), methyl acetylacetone (6.9%), three unidentified compounds (7.3%) and tar (19%). This experiment was repeated and the same results obtained.

E. Mercury Sensitized Rearrangement of 4-Methyl-3,4-epoxy-2-pentanone

To a 250 ml. Vycor flask were added 0.1 g. of epoxide and 0.4 g. of mercury and the sample carefully degassed. The flask was sealed off from the pump at 2 mm. and irradiated for 3½ hours with two 15 watt, G15T8, G.E. germicidal lamps. The heat from the lamps conveniently maintained the temperature at 40°. The gases were condensed by cooling the bottom of the flask in dry ice and the product analyzed by v.p.c. The mixture was composed of acetone (1%), methyl ethyl ketone (2%), methyl isopropyl ketone (0.8%), 4-methyl-3,4-epoxy-2-pentanone (28%), methyl acetylacetone (9.3%), tar (45.4%), and two new compounds (7.5% and 6.0%), which are not formed in the ordinary gas phase photolysis. However, these new compounds were alsc formed in the mercury sensitized decomposition of methyl acetylacetone. No reaction occurred in the absence of mercury.

IV. Photolysis of Methyl Acetylacetone

A. Preparation of Methyl Acetylacetone

To a 500 ml. three necked flask equipped with a stirrer, a dropping funnel and a reflux condenser were added 12 g. (0.52 mole) of sodium and 180 ml. of absolute ethanol. After the sodium had dissolved, the solution was cooled in an ice bath and 50 g. (0.5 mole) of acetylacetone added with stirring. The solution was stirred for 15 minutes and 85 g. (0.6 mole) of methyliodide slowly added. The ice bath was removed, the mixture stirred for 1 hour, and finally warmed on a steam bath for 2 hours. The reaction mixture was poured into 200 ml. of water and the water layer extracted with ether. The combined organic layers were extracted with 5% sodium hydroxide until the ether layer no longer gave a ferric chloride test. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. The ether solution was washed with water and dried over anhydrous magnesium sulfate. The ether was removed on a rotary evaporator and the residue distilled to give 19.65 g. (34.5%) of product, b.p. 77-78°/30 mm., n_D^{20} 1.4437 (lit. values (81), b.p. 77-79°/30 mm., n_D^{20} 1,4437). The product gave a purple ferric chloride test.

B. Photolysis of Neat Samples

A 0.2 g. sample of methyl acetylacetone was placed in a quartz test tube and irradiated with a Hanovia type S, 200 watt, mercury lamp for 36 hours. V.p.c. analysis showed the presence of acetaldehyde (0.6%), acetone (1.7%), methyl ethyl ketone (5.7%), methyl isopropyl ketone (0.8%), methyl acetylacetone (74.2%), three unknown compounds (7.0%) and high boiling material (10%).

C. Photolysis in Ether

A 0.193 M solution of methyl acetylacetone was prepared by diluting 6.6 g. of this compound to 300 ml. with ether. The solution was poured into a Hanovia type S, 200 watt, water cooled, Vycor immersion apparatus, which was fitted with a Corex filter and a magnetic stirrer, and irradiated for 40 hours. V.p.c. analysis indicated that 20% of the compound had reacted. The ether was removed by distillation through a 12 inch vacuum jacketed Vigreux column and the products were separated by v.p.c.

1. Acetaldehyde, Methyl Ethyl Ketone and Methyl Isopropyl Ketone

These compounds were identified as previously described in section III, B.

2. Acetone

A 2,4-dinitrophenylhydrazone of the compound having the same v.p.c. retention time as acetone was prepared, m.p. 122-125° (lit. value, m.p. 126°). There was no depression of a mixed melting point with an authentic sample.

3. Enol Acetate of Butanone

The enol acetate of butanone was identified as one of the products by comparison of its v.p.c. retention time and infrared spectrum with those of an authentic sample.

D. Photolysis in Benzene

A 0.351 M solution of methyl acetylacetone was prepared by diluting 10 g. of 250 ml. with benzene. The solution was placed in a Hanovia type S, 200 watt, water cooled, Vycor immersion apparatus,

which was fitted with a Corex filter and a magnetic stirrer. After 24 hours of irradiation at 25°, v.p.c. analysis showed that 13% reaction had occurred. At the end of 48 hours, 25% decomposition had taken place and irradiation was stopped. The benzene was removed by distillation and the mixture separated into high and low boiling fractions, by distillation through a short vacuum jacketed Vigreux column. It was impossible to determine the quantity of the low boiling products due to the large amount of benzene present, but acetone and acetaldehyde were both detected by v.p.c. V.p.c. analysis of the fractions showed the presence of the enol acetate of butanone (1.1%), methylacetylacetone (75%), acetophenone (0.8%), tar (6%) and eight unidentified products (8.5%).

E. Comparison of the Photolysis Products of 4-Methyl-3,4-epoxy-2-pentanone and Methyl Acetylacetone in Benzene

A careful comparison of the products formed in the photolysis of 4-methyl-3,4-epoxy-2-pentanone in benzene with those formed from methyl acetylacetone in the same solvent was made by v.p.c. A number of the products formed from the epoxide were not formed from the latter compound, but none of these were identified.

F. Mercury Sensitized Rearrangement of Methyl Acetylacetone

To a 250 ml. Vycor flask were added 0.1 g. of methyl acetylacetone and 0.4 g. of mercury and the mixture carefully degassed. The flask was sealed off from the vacuum pump at 2 mm. pressure and irradiated for 3½ hours with two 15 watt, G15T8, G. E. germicidal lamps. The heat from the lamps kept the flask at 40°. The gases were condensed by cooling the bottom of the flask in dry ice and the product

analyzed vy v.p.c. the mixture was composed of low boilers (13%), methyl acetylacetone (62%), high boiling material (21.2%), and two new compounds (2.1% and 1.7%) which were also formed in the mercury sensitized decomposition of 4-methyl-3,4-epoxy-2-pentanone. As far as could be determined by v.p.c. analysis, the products formed from the epoxide and methyl acetylacetone were identical.

V. Photolysis of Isophorone Oxide

A. Photolysis of Neat Samples

A 0.2 g. sample of isophorone oxide was placed in a 0.2 mm. thick quartz cell, which had been flushed with oxygen free nitrogen, and the cell was sealed. The sample was irradiated with a Hanovia type SH mercury lamp, the temperature being kept at 40° by air cooling. Small aliquots were removed periodically and subjected to v.p.c. analysis. The results of this experiment are summarized in Table 12, page 104.

B. Photolysis in Solution

1. Photolysis in Ether without a Filter

A 0.43 M solution of isophorone oxide was prepared by diluting 20 g. of oxide with anhydrous ethyl ether to give 300 ml. of solution. The solution was placed in a Hanovia type S, 200 watt, water cooled, Vycor immersion apparatus fitted with a magnetic stirrer and irradiated at 25°. Aliquots were periodically removed from the solution and analyzed by v.p.c. The results of these experiments are summarized in Table 13, page 105.

2. Photolysis in Benzene

A 0.65 M solution of isophorone oxide was prepared by diluting 30 g. of the oxide with benzene to give 300 ml. of solution. The solution was poured into a Hanovia type S, 200 watt, water cooled, Vycor immersion apparatus, which was fitted with a Corex filter and a magnetic stirrer, and irradiated at 25° for 27 hours. The solution was found to contain epoxide (90%) and two new compounds (1% and 9%). The solution was extracted with 5% sodium hydroxide until the benzene layer no longer gave a ferric chloride test. The basic solution was acidified with concentrated hydrochloric acid and extracted with ether. The ether layer was washed with saturated sodium bicarbonate and water, and then dried over anhydrous magnesium sulfate. The ether was removed on a rotary evaporator to give 2.6 g. (8.7%) of base soluble products. V.p.c. analysis showed the residue to be a 9:1 mixture of two new compounds, which proved to be 2-acetyl-4,4-dimethylcyclopentanone and 2,5,5-trimethyl-1,3-cyclohexanedione, respectively.

The benzene layer was washed with water and dried over anhydrous magnesium sulfate. The benzene was distilled to give 27 g. of isophorone oxide. No neutral products could be detected by v.p.c. analysis or I. R. spectroscopy.

3. Photolysis in Ether

A 0.65 M solution of isophorone oxide in ether was photolyzed as described in the previous experiment. A 9.7% yield (2.9 g.) of the base soluble products were isolated. V.p.c. analysis of the product showed it to be a 9:1 mixture of 2-acetyl-4,4-dimethylcyclopentanone and 2,5,5-trimethylcyclohexane-1,3-dione, respectively.

4. Photolysis in Acetic Acid

To a Hanovia type S, 200 watt, water cooled, Vycor immersion apparatus fitted with a magnetic stirrer and a Corex filter was added

300 ml. of a 0.65 M solution of isophorone oxide in purified acetic acid. At the end of seven hours the solution was pink and irradiation was stopped. It was treated in the cold with 10% sodium hydroxide until almost all of the acid was neutralized. This solution was extracted with three 250 ml. portions of ether and the combined ether layers washed with saturated sodium bicarbonate solution. The ether layer was extracted with 20% potassium hydroxide until it no longer gave a ferric chloride test and then washed with water. The combined aqueous solutions were acidified with concentrated hydrochloric acid and the solution extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and the ether removed on a rotary evaporator to give 0.8 g. (2.7%) of product. V.p.c. analysis of the product showed it to be a 9:1 mixture of 2-acetyl-4, 4-dimethylcyclopentanone and 2, 5, 5-trimethylcyclohexane-1, 3-dione respectively.

The ether layer was dried over anhydrous magnesium sulfate and the ether distilled. Isophorone oxide was the only neutral compound that could be detected by v.p.c. or I.R. analysis of the residue.

C. Structure of the Photolysis Products

1. Isolation of the Products

The base soluble portions of a number of photolysis reactions were combined to give 7.5 g. of material which was diluted with 6 ml. of ether and cooled at 0° for eight hours. The crystals which formed were removed by filtration, washed with ether and dried to give 0.6 g. (8%) of the minor photolysis product melting at 162-163°. This compound was shown to be 2, 5, 5-trimethylcyclohexane-1, 3-dione by comparison of its I.R. spectrum and v.p.c. retention times with those of an authentic sample. Further, there was no depression of a mixed melting point with a known sample (lit. value (79), m.p. 163°). The ether

was evaporated and the filtrate distilled to give 4.35 g. (59%) of a compound, b.p. 90°/12 mm., n_D^{25} 1.4738, $\nu_{max}^{CCl_4}$ 5.75μ, 5.85μ, 6.00μ and 6.20μ. The n.m.r. spectrum was complex, but it exhibited a triplet at 6.49τ, J = 9 c.p.s. This compound was shown to be 2-acetyl-4,4-dimethylcyclopentanone by its basic cleavage to 3,3-dimethylcyclopentane and by comparison with an authentic sample.

2. Preparation of 2,5,5-Trimethylcyclohexane-1,3-dione

2,5,5-Trimethylcyclohexane-1,3-dione was prepared by the method of Desai (79). The methylation of dimethyl dihydroresorcinol (28 g.) with sodium ethoxide and methyl iodide gave 10 g. (33%) of the desired product, m.p. 163° (lit. value (79), m.p. 163°).

3. Basic Cleavage of the Major Photolysis Product

The major photolysis product was cleaved with sodium hydroxide by the method of Houser (82). One gram of material gave 0.1 g. (14%) of a single neutral compound. This compound was identified as 3,3-dimethylcyclopentanone by comparison of its v.p.c. retention time and infrared spectrum with those of an authentic sample.

4. Preparation of 3,3-Dimethylcyclopentanone

a. Preparation of 3,3-dimethylcyclohexanol.--3,3-Dimethylcyclohexanol was prepared by the method of Doering (83). Methone (46.7 g.) was dissolved in 33 ml. of acetic acid and reduced over platinum oxide to give 25 g. (60%) of the alcohol, b.p. 78°/10 mm., $\nu_{max}^{CCl_4}$ 2.85μ (lit. value (84), b.p. 78°/10 mm.).

b. Preparation of β,β-dimethyladipic acid.--β,β-Dimethyladipic acid was prepared by the nitric acid oxidation of 3,3-dimethylcyclohexanol according to the procedure of Ellis (87). A 57.5% yield was obtained, m.p. 83-84° (lit. value (85), m.p. 85-86°).

c. Preparation of 3,3-dimethylcyclopentanone.--This compound was prepared by the method of Pines (86). β,β-Dimethyladipic acid (10 g.) and 1.14 g. of barium hydroxide were heated to 300°. The distillate gave 4.27 g. (66%) of the cyclopentanone, b.p. 90°/10 mm., n_D^{20} 1.4340, 2,4-dinitrophenylhydrazone (m.p. 159-160°), (lit. value (86), n_D^{20} 1.4342).

5. Synthesis of 2-Acetyl-4,4-dimethylcyclopentanone

2-Acetyl-4,4-dimethylcyclopentanone was prepared by the method of Hauser (82). Acylation of 2 g. of 3,3-dimethylcyclopentanone with acetic anhydride and BF_3 gave 1.4 g. (51%) of product, b.p. 88-89°/12 mm., n_D^{25} 1.4760. The infrared spectrum of this compound is shown in Figure 19. Treatment with 2,4-dinitrophenylhydrazine led to the formation of a pyrazole, m.p. 144-145°.

Anal. Calc'd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71.
Found: C, 57.09; H, 5.43; N, 17.70.

VI. Photolysis of 2,3-Epoxy-5,5-dimethyl-3-phenylcyclohexanone

A. Photolysis of 2,3-Epoxy-5,5-dimethyl-3-phenylcyclohexanone

To a Hanovia type S, 200 watt, water cooled, Vycor immersion apparatus fitted with a magnetic stirrer and a Corex filter was added 300 ml. of a 0.093 M solution of 2,3-epoxy-5,5-dimethyl-3-phenylcyclohexanone in ether. The solution was irradiated for 24 hours at 30°. The ether solution was extracted with 5% sodium hydroxide until it no longer gave a ferric chloride test. The basic solution was acidified with concentrated hydrochloric acid and the solution cooled at zero degrees for 8 hours. The solution was filtered and the crystals washed

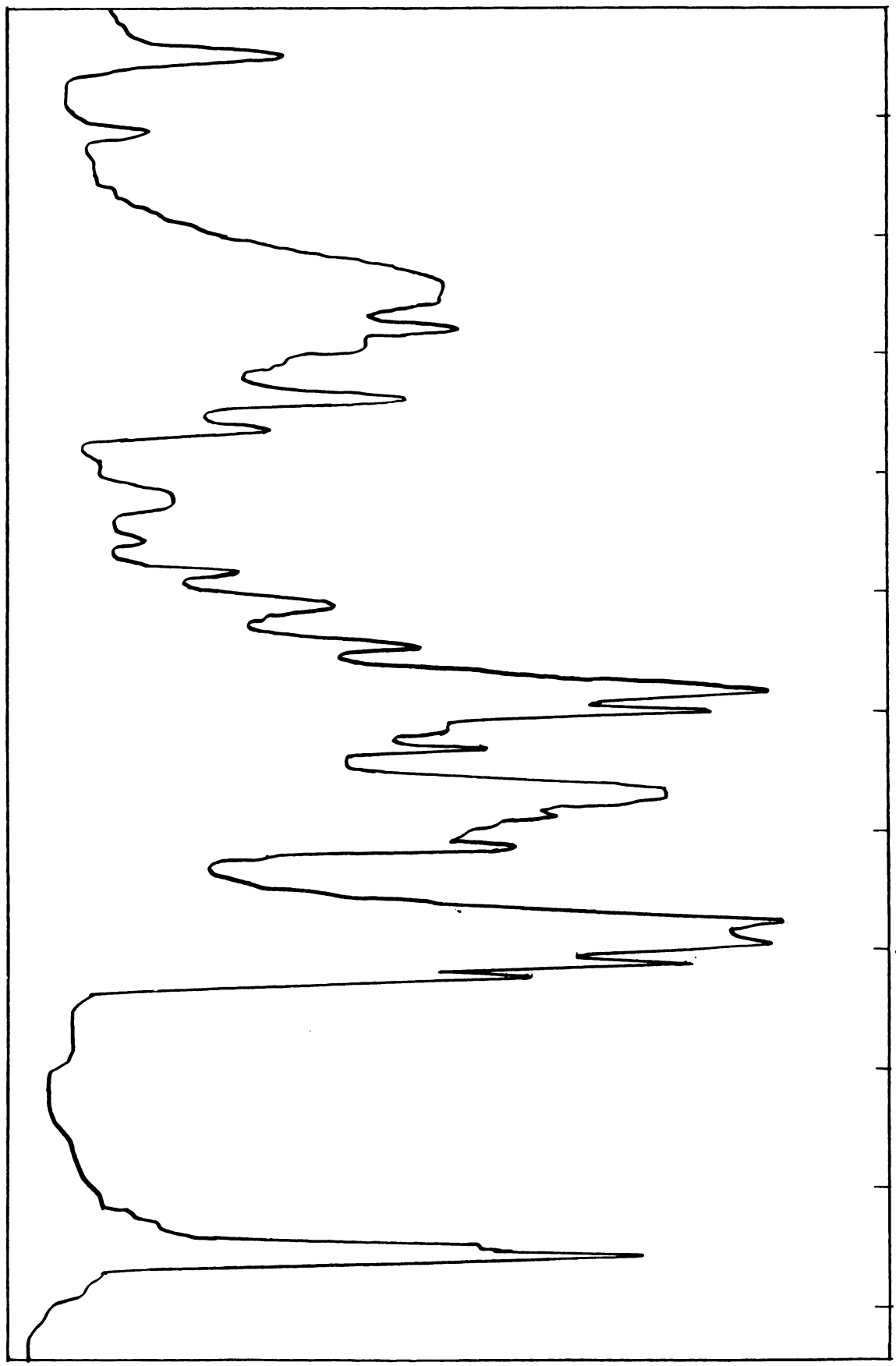


Figure 19. Infrared spectrum of 2-acetyl-4,4-dimethylcyclopentanone.

with cold water and dried to give 0.9 g. (15%) of crude product, m.p. 83.5-85°. V.p.c. analysis of the crude product showed the presence of a single pure compound. A sample recrystallized from 30-60° petroleum ether melted at 84-85°. The compound gave a purple ferric chloride test and exhibited bands at 5.76μ, 6.09μ and 6.22μ in the infrared. The product was not 5,5-dimethyl-2-phenyl-1,3-cyclohexanedione since it melts at 197-8° (74). The neutral material contained only starting material.

B. Basic Cleavage of the Photolysis Product

The photolysis product was cleaved with sodium hydroxide by the method of Hauser (82). The unknown compound (0.25 g.) gave 0.05 g. of neutral material. The neutral compound had the same v.p.c. retention time as 3,3-dimethylcyclopentanone and formed a 2,4-dinitrophenyldrazone, m.p. 154-158°, which did not depress the melting point of an authentic sample of 3,3-dimethylcyclopentanone 2,4-dinitrophenylhydrazone, m.p. 159-160°. The alkaline solution was acidified with concentrated hydrochloric acid and cooled to 0°. The precipitate was removed by filtration and washed with ice water. The crude product (0.15 g.) melted at 91-94°. Recrystallization gave pure 3,3-dimethyl-6-phenyl-6-ketohexanoic acid, m.p. 93-94°.

1. Preparation of the Methyl Esters

The crude acid mixture from the previous experiment was treated with diazomethane in ether and the product analyzed by v.p.c. The mixture was composed of a compound having the same retention time as methyl benzoate (5%) and another compound (95%) which formed a 2,4-dinitrophenylhydrazone, m.p. 148-149°. The I.R. spectrum of this compound, methyl 3,3-dimethyl-6-phenyl-6-ketohexanoate is shown in Figure 21.

Anal. Calc'd for $C_{21}H_{24}N_4O_6$: C, 58.87; H, 5.65; N, 13.08.
Found: C, 58.78; H, 5.58; N, 13.19.

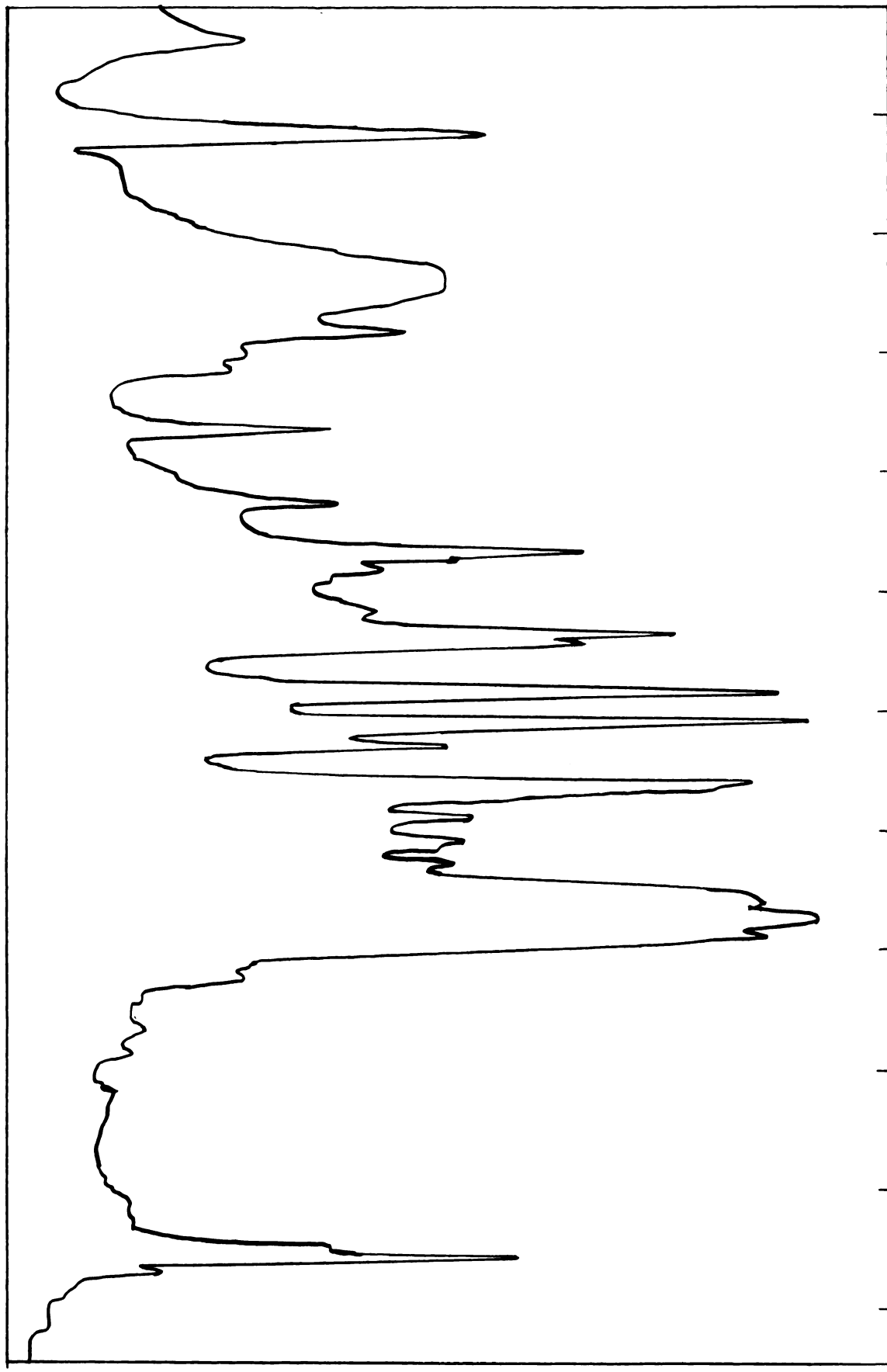


Figure 20. Infrared spectrum of 2-benzoyl-4,4-dimethylcyclopentanone.

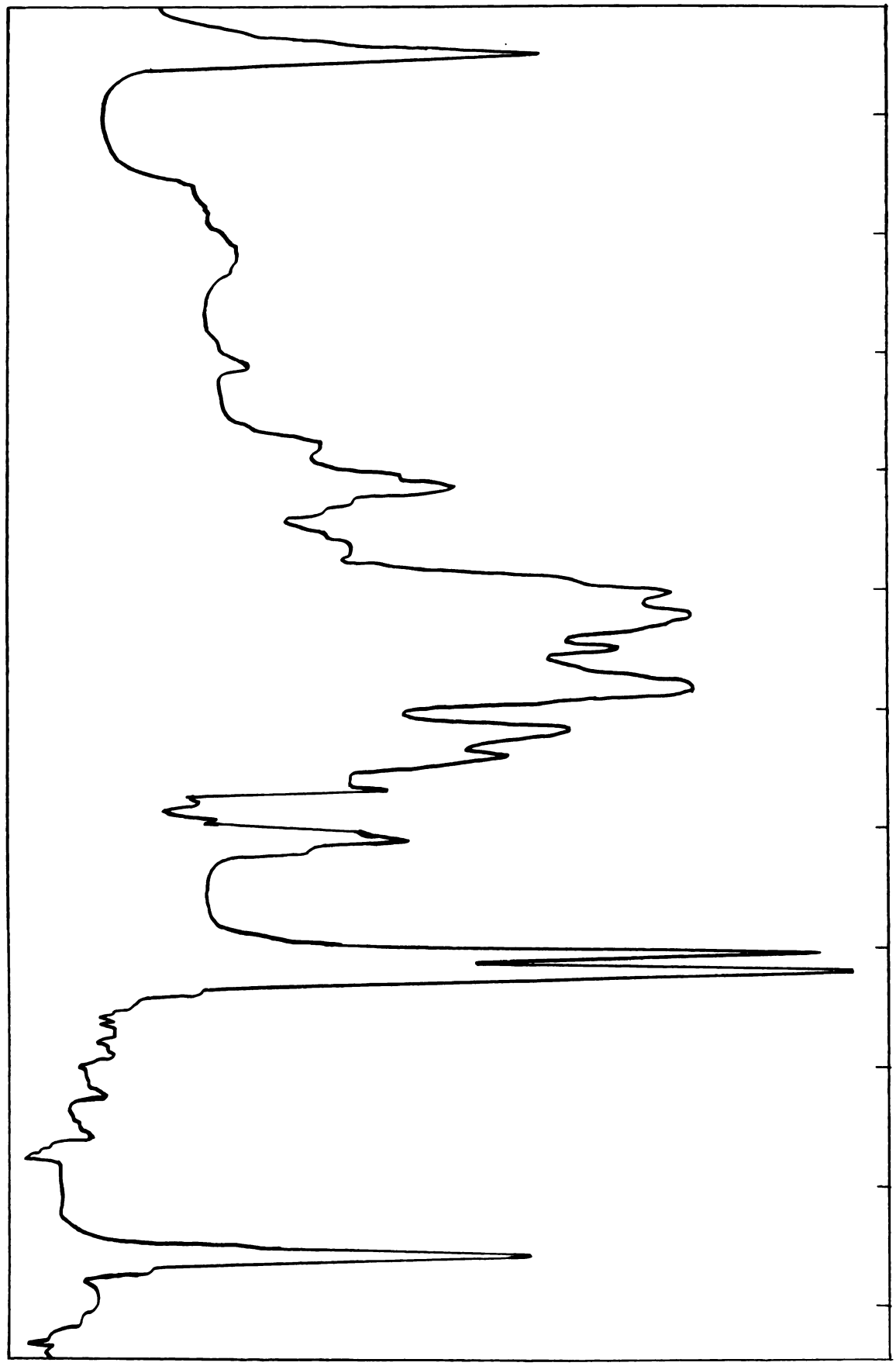


Figure 21. Infrared Spectrum of Methyl 3,3-Dimethyl-6-phenyl-6-ketohexanoate.

SUMMARY

1. The $n \rightarrow \pi^*$ excitation of the carbonyl group of α,β-epoxy ketones resulted in the formation of β-diketones produced by 1,2-shifts of β-alkyl groups. Thus, 4-methyl-3,4-epoxy-2-pentanone gave methyl acetylacetone, and isophorone oxide rearranged to a 9:1 mixture of 2-acetyl-3,3-dimethylcyclopentanone and 2,5,5-trimethyl-1,3-cyclohexanedione, respectively. When 2,3-epoxy-3-phenyl-5,5-dimethylcyclohexanone was photolyzed, a single produce, 2-benzoyl-3,3-dimethylcyclopentanone, was formed. The yields were low in all cases due to the photolytic decomposition of the primary products.

2. The tendency of a group to migrate decreased in the following order: neopentyl, methyl, phenyl. This order plus the observation that intermediates capable of attacking both ether and benzene were formed in the photochemical rearrangement of 4-methyl-3,4-epoxy-2-pentanone are inconsistent with an ionic mechanism, and were rationalized in terms of a radical cleavage recombination mechanism. Whether these reactions proceed via singlet or triplet diradicals is uncertain, but the fact that mercury sensitized the rearrangement of 4-methyl-3,4-epoxy-2-pentanone proves that the transformation may occur in the triplet state.

LITERATURE CITED

1. J. Berson and J. Patton, J. Am. Chem. Soc., 84, 3406 (1962).

2. G. Büchi and E. Burgess, J. Am. Chem. Soc., 84, 3104 (1962).

3. W. von E. Doering, M. Wilcott and M. Jones, J. Am. Chem. Soc., 84, 1224 (1962).

4. R. Eastman and A. Winn, J. Am. Chem. Soc., 82, 5908 (1960).

5. C. Stevens et al., J. Am. Chem. Soc., 84, 2272 (1962).

6. K. Alder, F. Flock and H. Lessenrich, Ber., 90, 1709 (1957).

7. M. Tiffeneau and J. Lévy, Compt. rend., 182, 391 (1926).

8. M. Tiffeneau and J. Lévy, Bull. soc. chim. Fr., 49, 1806 (1931).

9. J. Reese, Ber., 75, 384 (1942).

10. H. O. House and R. L. Wasson, J. Am. Chem. Soc., 78, 4394 (1956).

11. M. N. Prileschaev, Bull. Soc. Chim., (iv), 41, 687 (1927).

12. G. V. Pigulevsky and I. K. Mironova, Zhur. Obs. Khim., 27, 1101 (1957).

13. D. J. Cram, "Steric Effects in Organic Chemistry," Edited by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., Chapter 5, p. 283.

14. J. A. Berson, C. J. Olsen and J. S. Walia, J. Am. Chem. Soc., 84, 3337 (1962).

15. T. J. Wallace and R. J. Gritter, Tetrahedron, 19, 657 (1963).

16. C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 287.

17. C. Walling and P. S. Fredricks, J. Am. Chem. Soc., 84, 3327 (1962).

18. G. Payne, J. Org. Chem., 23, 310 (1958).

19. J. Manner, Masters Thesis, Michigan State University, 1963.

20. Gordon and Smith, J. Phys. Chem., 66, 521 (1962).

21. B. R. Cowley, R. C. Norman and W. A. Waters, J. Chem. Soc., 1799 (1959).

22. W. A. Waters, "The Chemistry of Free Radicals," Oxford University Press, New York, N. Y., 1946, p. 171.

23. J. R. Roland and J. Harmon, U. S. Patent 2,433,015 (1947).

24. D. H. R. Barton, H. Reimann, A. S. Capomaggi, T. Strauss and E. P. Oliveto, J. Am. Chem. Soc., 83, 4482 (1961).

25. B. G. Tucker and E. Whittle, Proc., 93 (1963).

26. H. C. Ramsperger, J. Am. Chem. Soc., 50, 714 (1928).

27. H. O. House and W. F. Gilmore, J. Am. Chem. Soc., 83 3972 (1961).

28. C. S. Rondestvedt, Jr., J. Am. Chem. Soc., 84, 3307, 3319 (1962).

29. H. O. House and R. L. Wasson, J. Am. Chem. Soc., 79, 1488 (1957).

30. C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 277.

31. L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, Boston, 1955, p. 299.

32. R. L. Wasson and H. O. House, Org. Syn., Vol. 37, 58 (1957).

33. H. Pauly and H. Liech, Ber., 33, 503 (1900).

34. L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, Boston, 1955, p. 296.

35. R. Renaud and L. C. Leitch, Can. J. Chem., 32, 545 (1954).

36. N. Kijner, J. Prakt. Chem., 64, 121 (1901).

37. E. Farenhorst and E. C. Kooyman, Rec. trav. chim., 72, 993 (1953).

38. S. G. Powell and R. Adams, J. Am. Chem. Soc., 42, 656 (1920).

39. C. M. Brewster and I. J. Putman Jr., J. Am. Chem. Soc., 61, 3085 (1939).

40. C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 469.

41. E. R. Bell, J. H. Raley, F. F. Rust, F. H. Seubold, Jr., and W. E. Vaughan, Discussions Faraday Soc., 10, 242 (1951).

42. J. B. Leoy and B. K. W. Copeland, J. Am. Chem. Soc., 82, 5314 (1960).

43. W. Treibs, Ber., 66, 1492 (1933).

44. R. C. Cookson and S. H. Dandegaonker, J. Chem. Soc., 352 (1955).

45. L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 122.

46. W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerani, J. Am. Chem. Soc., 83, 4013 (1957).

47. C. Djerassi and W. Klyne, J. Am. Chem. Soc., 79, 1506 (1957).

48. W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger and W. Hubbard, J. Am. Chem. Soc., 83, 606 (1961).

49. N. L. Allinger and L. A. Freiberg, J. Am. Chem. Soc., 82, 2393 (1960).

50. J. B. Hendrickson, J. Am. Chem. Soc., 83, 4537 (1961).

51. Jackman, op. cit., p. 57.

52. E. G. Meek, J. H. Turnbull and W. Wilson, J. Chem. Soc., 2891 (1953).

53. C. Djerassi, J. Osiecki and E. J. Eisenbraum, J. Am. Chem. Soc., 83, 4433 (1961).

54. R. A. Nelson and R. S. Jessup, J. Research Nat'l. Bur. Standards, 48, 206 (1952).

55. P. Gary, Trans. Faraday Soc., 52, 344 (1956).

56. Backstrom, A. Steneryr and P. Perlman, Acta. Chem. Scand., 12, 8 (1958).

57. H. E. Zimmerman and A. Zweig, J. Am. Chem. Soc., 83, 1196 (1961).

58. J. M. Tedder, Quart. Rev., 14, 336 (1960).

59. I. M. Koltoff, T. S. Lee and M. A. Mairs, J. Polymer Sci., 2, 199 (1947).

60. M. Mousseron, R. Jacquier and H. Christol, Compt. rend., 236, 927 (1953).

61. L. T. Sandborn, "Organic Synthesis," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 340.

62. E. C. Horning and M. G. Horning, J. Org. Chem., 11, 95 (1946).

63. E. J. Corey and H. J. Burke, J. Am. Chem. Soc., 78, 177 (1956).

64. Y. R. Naves and P. Andizio, Helv. Chim. Acta., 32, 206 (1949).

65. L. Ruzicka and C. F. Seidel, Helv. Chim. Acta., 19, 424 (1936).

66. J. P. Simons, Quart. Rev., 13, 3 (1959).

67. P. de Mayo, "Advances in Organic Chemistry," Interscience Publ. Inc., New York, N. Y., 1960, Vol. II, p. 367.

68. P. de Mayo and S. T. Reid, Quart. Rev., 15, 393 (1961).

69. R. Srinivasan, J. Am. Chem. Soc., 84, 3432 (1962).

70. H. E. Zimmerman and D. I. Schuster, J. Am. Chem. Soc., 84, 4527 (1962).

71. H. E. Zimmerman and S. Somasekhara, J. Am. Chem. Soc., 85, 922 (1963).

72. H. E. Zimmerman, Abstract of papers Presented at the Organic Symposium, 1961, p. 38.

73. von C. Lehman, K. Schaffner and O. Jeger, Helv. Chim. Acta., 45, 1031 (1962).

74. F. M. Beringer, P. S. Forgione and M. D. Yudis, Tetrahedron, 8, 4963 (1960).

75. E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, Inc., New York, pp. 607, 756.

76. M. S. Kharasch, A. Fono and W. Nudenberg, J. Org. Chem., 15, 774 (1950).

77. A. N. Strachan and F. E. Blacet, J. Am. Chem. Soc., 77, 5254 (1954).

78. W. Reusch and B. Dominy, Private Communication.

79. R. D. Desai, J. Chem. Soc., 1079 (1932).

80. G. F. Woods and I. W. Tucker, J. Am. Chem. Soc., 70, 2174 (1948).

81. C. R. Hauser and J. T. Adams, J. Am. Chem. Soc., 66, 348 (1944).

82. C. R. Hauser, Swamer and Ringler, J. Am. Chem. Soc., 70,

83. W. von E. Doering and F. Marshall, J. Am. Chem. Soc., 71, 2229 (1949).

84. T. Henshall, J. Chem. Soc., 128 (1943).

85. A. W. Crossley and N. Renouf, J. Chem. Soc., 87, 1495 (1905).

86. H. Pines, E. J. Pavlik, V. N. Ipatieff, J. Am. Chem. Soc., 73, 5740 (1941).

87. A. Ellis, "Organic Synthesis," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 18.