

Radical and Thermal Rearrangement of α,β -Epoxy Ketones

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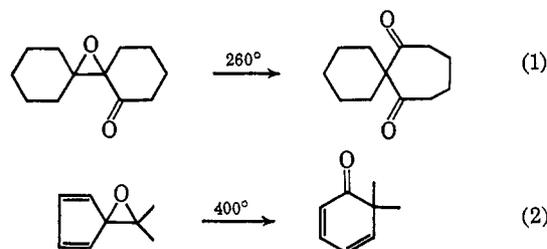
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Abstract: Isophorone oxide (II) reacts with certain radical initiators at temperatures above 200° to give 1,5,5-trimethyl-2-hydroxycyclohexen-3-one (V) and 2,4,4-trimethylcyclopentanone (VI). The former predominates, but as the temperature of the reaction is raised, the proportion of V:VI approaches unity. An acid-catalyzed mechanism is not consistent with the data accumulated for this reaction (Tables II and III), but a radical chain mechanism (eq 5) provides a satisfying rationale. A similar reaction is observed with 4-methyl-3,4-epoxypentan-2-one (I), the products being methyl isopropyl ketone (III) and 4-methyl-2,3-pentanedione (V). If the radical chain decomposition of II is inhibited, a very slow thermal rearrangement of II to IV may be observed. This reaction is surface catalyzed, and 2-formyl-2,4,4-trimethylcyclopentanone (VII) is probably the initial product. An authentic sample of VII is smoothly decarbonylated at 230°. Since VII is found to be an excellent initiator for the radical chain decomposition of both I and II, the decarbonylation must involve homolysis to radical species.

In the course of preparing some α,β -epoxy ketones we noticed that several of these compounds were sensitive to elevated temperatures³ such as those encountered in distillation and vapor phase chromatography. In view of the well-documented reactivity of epoxides and epoxy ketones under a variety of conditions,⁴ we were interested in learning whether a general mode of thermal reaction is exhibited by this class of compounds. Previously published work concerning this question was limited and often inconclusive. House and Wasson⁵ have confirmed the report of Reese⁶ that 2-cyclohexylidene-cyclohexanone oxide rearranges when distilled (bp 260°) and identified the product of the rearrangement as spiro[5.6]dodecane-7,12-dione (eq 1). A similar rearrangement was found with 2-benzylidene-cyclohexanone oxide. Since these transformations parallel known acid-catalyzed rearrangements,⁴ the question of whether they are authentic thermal rearrangements is unsettled. Traces of acidic materials in the reactants or on the walls of the container may have catalyzed the reactions. A report of thermal isomerization and rearrangement of pulegone oxide⁷ is in many respects incorrect; however recent studies in this laboratory⁸ have shown that an interesting thermal rearrangement does in fact occur.

If simple epoxides are included in this preliminary discussion of thermal reactions, early studies by Tiffeneau⁹ must be considered. For example, α -methyl-*trans*-stilbene oxide was reported to rearrange to 2,2-diphenylpropanal when distilled. Inasmuch as we have been unable to repeat this and other "thermal" reactions,¹⁰ we suspect that many of these rearrange-

ments were originally induced by traces of acids. Indeed, early investigators⁹ often added acids to facilitate the transformations being studied. A striking example of what appears to be an authentic thermal rearrangement of an epoxide is found in the conversion of dimethylfulvene oxide to 6,6-dimethylcyclohexa-2,4-dienone (eq 2).¹¹



In this paper we set forth the results of our work with 4-methyl-3,4-epoxypentan-2-one (I) and 3,5,5-trimethyl-2,3-epoxycyclohexanone (II). The latter compound will henceforth be referred to as isophorone oxide.

Free-Radical-Initiated Reactions

When a freshly prepared sample of I was distilled (bp 156° (740 mm)), the distillate was bright yellow and vpc analysis showed the presence of three readily eluted impurities in trace amounts (*ca.* 5%). These decomposition products were identified as acetone, methyl isopropyl ketone (III), and 4-methyl-2,3-pentanedione (IV) by comparison of vpc retention times and infrared spectra with those of authentic samples. Crystalline derivatives were also prepared and characterized. Prolonged heating of I in the presence of air gave increasing amounts of these decomposition products, but also produced large quantities of tars. Since a peroxide and oxygen-free sample of I remained unchanged after being heated for 18 hr at 160°, the reaction observed during distillation was clearly not a simple thermal process. Payne has shown¹² that I, prepared in the usual way (see the Experimental Section), contains the cyclic peroxide 3-hydroxy-3,5,5-trimethyl-1,2-dioxacyclopentane, which may be removed by washing with ferrous ion solutions. Peroxide-free samples of I were slow to react, even in the presence of oxygen,

(11) K. Alder, F. Flock, and H. Lessenich, *Ber.*, **90**, 1709 (1957).

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

(1) Author to whom inquiries should be addressed.

(2) Abstracted from the Ph.D. thesis of C. K. J., 1963, and the M. S. thesis of J. A. M., 1963.

(3) A preliminary report of this work was made several years ago: W. Reusch and C. K. Johnson, *J. Am. Chem. Soc.*, **84**, 1759 (1962).

(4) R. Parker and N. Issacs, *Chem. Rev.*, **59**, 737 (1959).

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

(6) J. Reese, *Ber.*, **75**, 384 (1942).

(7) (a) G. V. Pigulevski and I. K. Mironova, *Zh. Obshch. Khim.*, **27**, 1101 (1957); (b) S. Kozhin, S. Yakimovich, and G. Pigulevski, *ibid.*, **32**, 3455 (1962).

(8) C. K. Johnson, B. Dominy, and W. Reusch, *J. Am. Chem. Soc.*, **85**, 3894 (1963).

(9) M. Tiffeneau and J. Levy, *Compt. Rend.*, **182**, 391 (1926); *ibid.*, **201**, 277 (1935); *Bull. Soc. Chim. France*, **39**, 763 (1926); *ibid.*, **49**, 1806 (1931).

(10) R. Weiss, Ph.D. Thesis, Michigan State University, 1964.

Table III. Product Composition from Isophorone Oxide Rearrangements^a

Additives (%)	Temp, °C	Time, hr	V, %	VI, %	V/VI
VII (1)	215	6	8	2	4.0
VII (1)	235	6	54	16	3.3
VII (1)	255	6	64	34	1.9
CH ₃ CO ₂ H (2)	235	6	16	3	5.3
C ₆ H ₅ CO ₂ H (2)	235	6	14	2.5	5.6

^a Neat samples were heated under nitrogen in sealed vials.

Thus, if the amount of acid (e.g., 0.5% CH₃CO₂H) conceivably formed from the oxygen present in the *t*-butyl hydroperoxide initiator employed in many of these reactions was added as a catalyst, the amount of reaction after 6 hr at 235° was only a quarter of that observed when the hydroperoxide itself was used.

The possibility that VI was a secondary product formed by subsequent reaction of V was eliminated, inasmuch as the diosphenol did not react after prolonged heating—both in the presence and absence of radical initiators.

In general, it is desirable to use initiators having half-lives of the same magnitude as the reaction time. Only a limited number of initiators useful in the temperature range employed here are known. Thus, benzoyl peroxide and *t*-butyl peroxide have half-lives of 30 (100°) and 24 min (160°), respectively,¹⁶ and are consequently not effective in this case. The decomposition of *t*-butyl hydroperoxide is complex, but in dilute octane solution at 180° a half-life of 16 hr is reported.¹⁷ It is reasonable then that this compound proved to be a useful initiator in our investigation. Benzyl phenyl ether decomposes to benzyl and phenoxy radicals near 250°;¹⁸ however the activation energy for the homolysis is apparently high enough to prevent a useful concentration of radicals from forming at 235°. The C–O bond dissociation energy in 4-biphenyl benzyl ether should be lower than that in phenyl benzyl ether; consequently, the former should be a more efficient initiator—a point verified in Table II. Hexachloroethane has been used to initiate copolymerization of isobutyric acid with ethylene at 238–250°.¹⁹ Although as little as 1% of this compound caused complete decomposition of isophorone oxide after 6 hr at 235°, a considerable amount of tarry material was formed and it is not recommended as an initiator for this reaction. Surprisingly, the most effective initiator yet encountered²⁰ is 2-formyl-2,4,4-trimethylcyclopentanone (VII). The facts leading to this conclusion are discussed later in this paper.

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

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

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

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

(20) An interesting feature of the initiator study was the ineffectiveness of 2,2'-azobispropane and 2,2'-azobisisobutane as initiators despite reasonable half-lives at temperatures above 200°. This suggests that electrophilic radicals such as *t*-C₄H₉O·, C₆H₅O·, and Cl₃C· are much more effective initiators than are the nucleophilic alkyl radicals²³ produced by the azo compounds.

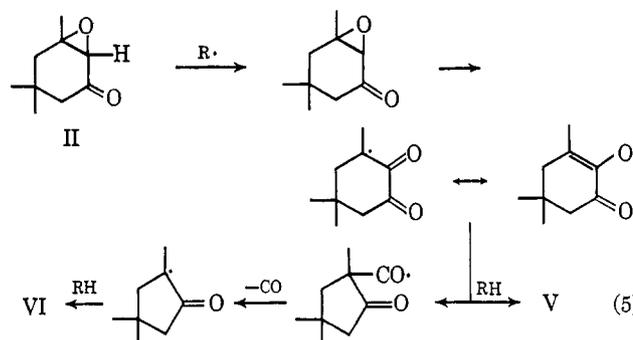
(21) H. C. Ramsperger, *J. Am. Chem. Soc.*, **50**, 714 (1928).

(22) J. B. Levy and B. K. W. Copeland, *ibid.*, **82**, 5314 (1960).

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

A final observation, which supports the radical nature of the isophorone oxide decomposition, is that the reaction induced by refluxing II in air may be inhibited by 2% hydroquinone or 2% *N*-methylaniline.

Having established that isophorone oxide (and probably I as well) undergoes a high-temperature radical chain decomposition, we next considered the mechanism of this reaction. The sequence of steps in eq 5 provides a satisfying rationale and will serve as a model for further discussion. The first step finds support in the report by Walling and Fredricks²⁴ of



liquid-phase chlorination of propylene oxide by *t*-butyl hypochlorite. Since this radical chlorination proceeds well at 0°, the abstraction of an oxirane hydrogen atom by the chain-transferring *t*-butoxy radicals appears to be facile.²⁵ Further analogy is provided by the work of Wallace and Gritter,²⁶ wherein propylene oxide was found to add to 1-octene in a radical chain reaction. The authors proposed a mechanism involving rearrangement of the initially formed oxirane radical to an acetyl radical which then added to the olefin. If this view is accepted, then the facts imply that the activation energy for the hydrogen abstraction step is less than that for the rearrangement step. Since rearrangement of the oxirane radical leads to the resonance-stabilized acetyl radical with loss of considerable ring strain, it is surprising that ring opening occurs only at high temperatures. This is not without precedent, for similar behavior has been found in some reactions of cyclopropane.²⁷ For example, vapor phase chlorination of cyclopropane gave cyclopropyl chloride as the major product,²⁸ with small but increasing amounts of allyl chloride being formed as the temperature of reaction rose above 200°. Likewise, vapor phase nitration of cyclopropane yielded nitrocyclopropane.²⁹ Radical-initiated decarbonylation of 1-substituted cyclopropyl-carboxaldehydes has been observed³⁰ to proceed without ring opening at 130°. Hart and Wyman have re-

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

(25) Note however, that propylene oxide is reported^{26b} to be about as reactive as benzene with respect to hydrogen abstraction by *t*-butoxy radicals.

(26) (a) T. J. Wallace and R. F. Gritter, *J. Org. Chem.*, **26**, 282 (1961); (b) T. J. Wallace and R. F. Gritter, *Tetrahedron*, **19**, 657 (1963).

(27) A study of cyclopropyl hydrogen abstraction by trideuteriomethyl radicals has been made by J. R. McNesby and A. S. Gordon, *J. Am. Chem. Soc.*, **79**, 825 (1957). The activation energy is reported to be 13.1 kcal/mole, indicating that the reactivity of cyclopropane is roughly the same order as benzene. Rearrangement of cyclopropyl radicals to allyl radicals occurred above 375°: cf. A. F. Trotman-Dickenson and E. W. R. Steacie, *J. Chem. Phys.*, **19**, 329 (1951).

(28) J. D. Roberts and P. H. Dirstine, *J. Am. Chem. Soc.*, **67**, 1281 (1945).

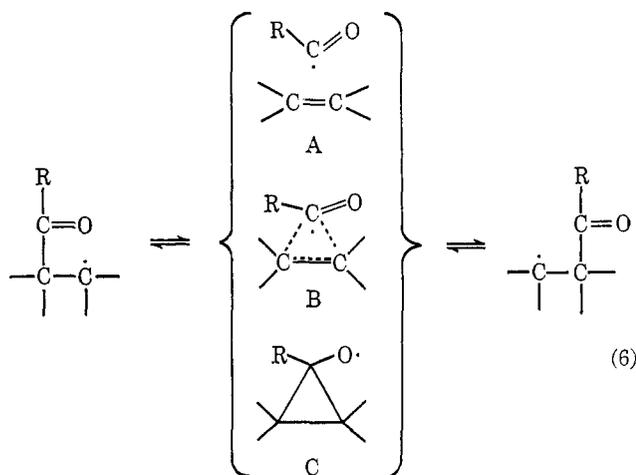
(29) H. Hass and H. Shechter, *ibid.*, **75**, 1382 (1953).

(30) J. D. Roberts and D. Schuster, *J. Org. Chem.*, **27**, 51 (1962).

ported³¹ the decomposition of bicyclopropaneformyl peroxide to cyclopropyl chloride in carbon tetrachloride solution at 70°. Thus, despite the fact that the allyl radical is favored over the cyclopropyl radical by approximately 30 kcal/mole,³⁰ the latter is remarkably stable and survives in a variety of reactions.³²

Returning then to a consideration of epoxides, we conclude that oxirane hydrogen abstraction is probably facile,³³ but that rearrangement of the resulting oxirane radical is slow and occurs only at elevated temperatures.

The most interesting and controversial step in the mechanism proposed in eq 5 is the ring contraction, which formally represents a 1,2 shift of an acyl group to a radical center. This remarkable rearrangement³⁴ merits amplification. At least three different modes of rearrangement can be formulated in the general case (eq 6). Mode A is a two-step process consisting of



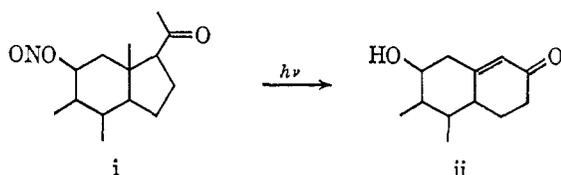
fragmentation to an acyl radical and an olefin followed by recombination to give the rearranged radical. Mode B is a single-step, intramolecular reaction, characterized by delocalization of the unpaired electron over three centers in the transition state. Finally, mechanism C proceeds in two steps *via* a cyclopropoxy radical intermediate. The subject of free-radical rearrangements has been recently reviewed by Walling.³⁵ In general, the only groups unambiguously known to undergo intramolecular 1,2 shifts to radical centers are those able to form three-membered cyclic intermediates analogous to C (*e.g.*, phenyl and chlorine). There are

(31) H. Hart and D. P. Wyman, *J. Am. Chem. Soc.*, **81**, 4891 (1959).

(32) One important factor here is that the bond being cleaved has very poor overlap with the orbital occupied by the odd electron. Hence, there can be very little resonance stabilization of the transition state.

(33) In α,β -epoxy ketones the inductive effect of the carbonyl group will act to decrease the reactivity of the oxirane hydrogen with electrophilic radicals. Thus, propylene oxide reacts more readily²⁹ with *t*-butoxy radicals than does I.

(34) Another example of 1,2-acyl shift in a radical intermediate is found in the photochemical conversion of i to ii reported by D. H. R. Barton, H. Reimann, A. S. Capomaggi, T. Strauss, and E. P. Oliveto, *J. Am. Chem. Soc.*, **83**, 4482 (1961).

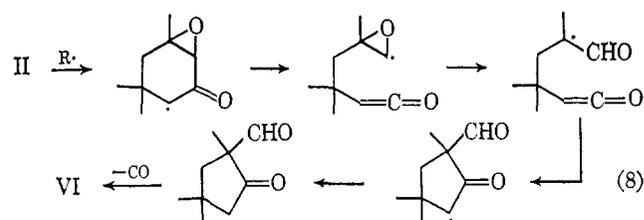
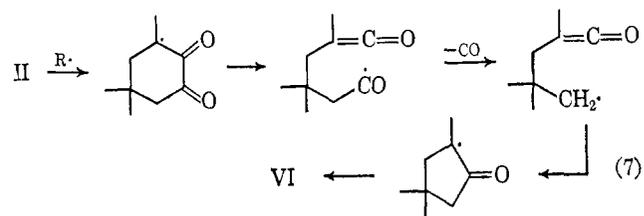


(35) C. Walling, "Molecular Rearrangements," P. de Mayo, Ed., John Wiley and Sons Inc., New York, N. Y., 1963, p 407.

no well-documented cases of 1,2 shifts of hydrogen atoms or alkyl groups proceeding by mechanism B; in fact, Zimmerman and Zweig³⁶ have reported molecular orbital calculations which indicate the transition state for such an alkyl shift would be endothermic by 0.4 β . The recently described rearrangement of the 2-camphanyl radical is believed to proceed by a fragmentation-recombination process.³⁷

On the strength of these facts we favor a type-C mechanism for the proposed 1,2 shift of an acyl group. The exclusion of mechanism B appears to be reasonable, but the rejection of process A is tenuous. Two arguments are employed here. First, it seems unlikely that recombination of the acyl radical olefin fragments should overwhelmingly predominate over hydrogen abstraction by the former—particularly in acyclic substrates. Second, loss of carbon monoxide from the acyl radical should be evident, especially when working at high temperatures. In our work we find no products unique to these side reactions.

It is not difficult to conceive alternate mechanisms for the rearrangements reported in this paper. Two other mechanisms³⁸ are presented in eq 7 and 8. Both involve a fragmentation-recombination sequence and are therefore subject to the criticisms set forth in the previous paragraph. An attempt to trap ketene intermediates by adding water to the reaction mixture was unsuccessful. Not only was no carboxylic acid detected, but the ratio V/VI remained constant (3.3) after correcting for the reaction induced by the water.



The mechanisms set forth in eq 5 and 7 are distinguished by the fact that different carbon atoms are lost as the carbon monoxide fragment. Examination of an appropriately labeled sample of isophorone oxide should thus permit a choice between these possibilities. Isophorone (3,5,5-trimethyl-2-cyclohexenone) having C¹⁴ labeling at C-1, C-3, and C-5 was prepared by base-catalyzed condensation of acetone-2-C¹⁴. The radioactivity of this ketone was determined by completely oxidizing samples of the corresponding semicarbazone according to the wet combustion procedure of Van Slyke and Folch³⁹ and counting the carbonate produced after precipitating it as barium carbonate. In order to

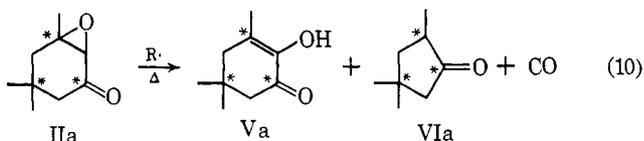
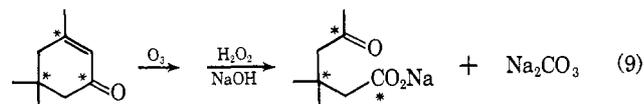
(36) H. E. Zimmerman and A. Zweig, *J. Am. Chem. Soc.*, **83**, 1196 (1961).

(37) J. A. Berson, C. J. Olson, and J. S. Walia, *ibid.*, **84**, 3337 (1962).

(38) We are indebted to one of the referees for our original communication³ for suggesting mechanism (7).

(39) (a) D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, 509 (1940); (b) D. Van Slyke and J. Folch, *ibid.*, **191**, 299 (1951).

show there had been no incorporation of C^{14} at C-2, the labeled isophorone was degraded by ozonolysis followed by peroxide oxidation (eq 9). The carbonate thus formed proved to have negligible radioactivity. This labeled isophorone was converted to the epoxide (IIa), samples of which (containing 1% *t*-butyl hydroperoxide) were rearranged by heating at 235° (eq 10). The carbon monoxide produced was oxidized to carbon dioxide and collected as barium carbonate. The



2,2,4-trimethylcyclopentanone (VIa) also formed in this reaction was isolated by vpc and converted to the semicarbazone derivative prior to total oxidation.³⁹ Specific activities were determined for all the labeled compounds by counting the barium carbonate obtained by the wet combustion method.³⁹ Because of the self-absorption and scattering of β emission from finite C^{14} samples, it is necessary to correct the observed specific activities for variations in sample size and uniformity. This has been accomplished by Hendler's method,⁴⁰ which calculates the specific activity of a standard sample⁴¹ (S_{ref}) from a series of measurements on samples of varying size. The calculated specific activities for the semicarbazones isolated in this study are given in Table IV.

Table IV. Specific Activities of Barium Carbonate Samples

Origin of sample	S, counts per mg
Semicarbazone of isophorone	17.4 ^a
Semicarbazone of IIa	17.2 ^a
Semicarbazone of VIa	24.4 ^a
Carbon monoxide from IIa	0.8 ^b

^a Calculated by Hendler's method. ^b An average of three independent measurements, sample size 20–24 mg.

The three labeled carbon atoms present in isophorone and epoxide IIa constitute 30.0% of the total carbon content of the semicarbazones. If the carbon monoxide lost during rearrangement is inactive, the trimethylcyclopentanone (VIa) derivative will still contain three labeled carbons which represent 33.3% of the total carbon. On the other hand, if a labeled carbon is lost, the semicarbazone of VI will be left with 22.2% labeled atoms. The expected ratio of specific activities (S_{VIa}/S_{IIa}) is 1.11 in the first case, but drops to 0.74 for the second possibility. Since the ratio calculated⁴² from the data in Table IV is 1.4, the labeled carbon atoms are retained during rearrangement and the mechanism of eq 7 may be eliminated from further

(40) R. Hendler, *Science*, **130**, 772 (1960).

(41) In this work the standard sample is 10 mg.

(42) By extrapolating the specific activity data to infinitely small samples *via* log:log graphs, a calculated ratio of *ca.* 1.2 is found.

consideration. Independent support for this conclusion is provided by the lack of significant activity found by direct measurements of the carbon monoxide evolved during reaction of IIa (see Table IV).

Although we have not definitely ruled out the mechanism of eq 8, the mechanism first proposed (eq 5) provides the simplest and most satisfying explanation of the facts. As a final step in supporting this view, we are currently investigating 1,2-acyl shifts in radical species generated by more conventional reactions.⁴³

Thermal Rearrangement of Isophorone Oxide.

Pure isophorone oxide remained unchanged after 6 hr at 235° in the absence of oxygen. Consequently, we were surprised to find that heating an identical sample for 12 hr completely transformed it to a 3:1 mixture of V and VI (Table V). The yields in this capricious reaction varied from 0 to 100% over a period of time.⁴⁴ Furthermore, the reaction was completely inhibited by *N*-methylaniline and tetrahydrothiophene and partly inhibited by nitrobenzene and *m*-dinitrobenzene. Quinone and hydroquinone exhibited no effect at the low concentrations used in this study.

Table V. Thermal Reactions of Isophorone Oxide at 235°^a

Additives ^b	Reaction, time, hr	Reaction, %	No. of runs
...	6	0	3
...	7.5	5	1
...	12	100	4
$C_6H_5NHCH_3$	12	0	2
$(CH_2)_4S$	12	0	2
$C_6H_5NO_2$	12	19	2
<i>m</i> - $C_6H_4(NO_2)_2$	12	14	2
<i>p</i> - $C_6H_4(OH)_2$	12	100	2
<i>p</i> - $C_6H_4O_2$	12	100	2
100 × surface area ^c	6	80	1

^a Neat samples of II were heated under nitrogen in sealed vials.

^b Additives were present as 1% of the total sample. ^c Powdered Pyrex glass was added.

At this point we adopted the hypothesis that a very slow thermal reaction was generating an intermediate which initiated the faster radical chain reaction described in the previous section. In order to study this thermal reaction without interference from the radical chain process, we chose to examine the reactions of II in dilute decalin solution and in the presence of *N*-methylaniline as an inhibitor. The sealed-vial technique was employed, and since the reaction at 235° was known to be slow, higher temperatures were used. The reaction of II was followed by measuring the disappearance of the 5.85- μ band in the infrared and noting the appearance of absorptions characteristic of V and VI. In some experiments these spectroscopic measurements were checked by vpc analysis. Although there was some scattering of the data, fairly good first-order decomposition was observed within a concurrent series of reactions, and the apparent first-order rate constants (*k*) are summarized in Table VI. The reac-

(43) Note in this respect the recent demonstration of 1,2-vinyl shifts: L. H. Slaugh, *J. Am. Chem. Soc.*, **87**, 1522 (1965).

(44) In order to obtain consistent results the epoxy ketone must be carefully purified, the reaction vials must be scrupulously cleaned, and contamination by inhibitors must be avoided during the degassing and sealing of the vials.

tions inhibited with N-methylaniline yielded VI as the only product, while in the uninhibited cases a small amount of V was also formed. For example, after 4.5 hr at 280° a 0.028 M solution of II in decalin contained 50% II, 45% VI, and 5% V. Since the rate constants for the uninhibited reactions were greater than those for reactions with inhibitor present, there is evidently some induced radical chain decomposition in the former case. We consequently assume that the thermal reaction of II, referred to at the beginning of this paragraph, is a unimolecular process leading only to VI.

Table VI. Rate of Rearrangement of Isophorone Oxide in Decalin Solution

Concn, mole l.		Temp, °C	$k \times 10^3$ ^a min ⁻¹	Vial ^b batch
II	N-Methyl-aniline			
0.028	...	270	1.4	1
0.031	0.031	270	0.96	1
0.032	0.191	270	0.38	1
0.032	0.191	270	0.89 ^c	1
0.031	...	270	0.89	2
0.031	0.200	270	0.17	2
0.016	0.200	280	0.13	3
0.031	0.200	280	0.14	3

^a The estimated error in the rate constants is 10%. ^b Refers to vials prepared at the same time from a uniform batch of tubing. ^c 72% increase in surface area.

The thermal reaction of II is surface catalyzed. When the surface area was increased *ca.* 70% by adding small lengths of Pyrex tubing, the rate of decomposition increased by over 100%. Also, the addition of powdered Pyrex glass to a neat sample of II led to extensive radical chain reaction after 6 hr at 235°—presumably because the thermal decomposition was accelerated. The formation of VI from II in the thermal reaction suggests an acid-catalyzed process. House¹⁵ has shown that boron trifluoride catalyzed rearrangement of II yields 2-formyl-2,4,4-trimethylcyclopentanone (VII) and small amounts of VI. Since Pyrex glass is composed of silica, boric oxide, and alumina, it is not at all unlikely that Lewis acid sites should occur on the glass surface.⁴⁵ Subsequent formation of VI by thermal decarbonylation of the primary rearrangement product (VII) was easily confirmed using a synthetic sample of VII¹⁵ (a neat sample exhibited 15% decarbonylation after 3 hr at 235°).

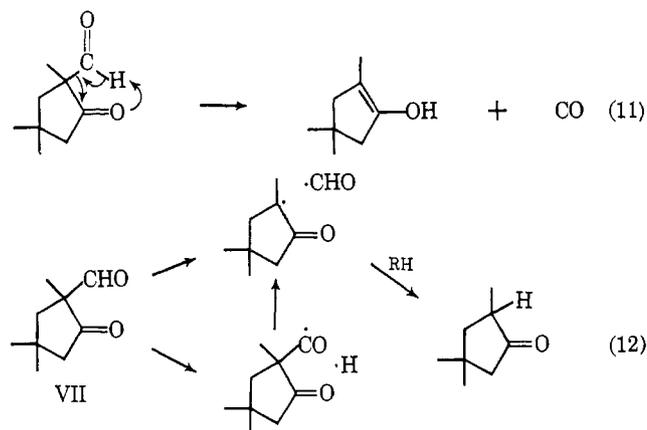
One troublesome point still remained. We previously suggested that the thermal reaction generated an intermediate capable of initiating the radical chain process. This intermediate has not been identified. Since the surface reaction seemed to be ionic in nature, we first considered the decarbonylation of VII, which can be viewed as either a unimolecular fragmentation or a radical chain process. The latter would be significant only when the concentration of VII was relatively high; consequently, our interest in the former mechanism increased. Dilute decalin solutions of VII were found to undergo first-order decarbonylation to VI at temperatures above 200°. Some rate constants for this thermolysis are given in Table VII. Since a

(45) C. S. Rondstedt, Jr., *J. Am. Chem. Soc.*, **84**, 3307, 3319 (1962), has recently observed a silica gel catalyzed decomposition of 1,3-dioxanes, which he attributes to acidic sites on that catalyst.

Table VII. Rate Constants for the Decarbonylation of 2-Formyl-2,4,4-trimethylcyclopentanone in Decalin

Temp, °C	Concn, mole/l.	$k \times 10^3$ min ⁻¹
225	0.0219	0.79
235	0.0219	1.62
235	0.0435	1.53

doubling of the concentration (last two entries) has virtually no effect on the observed rate constant, induced decomposition must be negligible. A very crude estimate of 35 ± 7 kcal/mole for E_{act} was made from these data. Now the decarbonylation of VII may occur by a cyclic process (eq 11) or by homolysis of a carbon-carbon and/or carbon-hydrogen bond (eq 12). The former possibility is attractive but would



not serve to explain the genesis of the radical chain reaction. A critical experiment is thus suggested: *Will ketoaldehyde VII act as a high-temperature radical initiator?* Our investigations show that VII is in fact an excellent initiator for the radical decomposition of isophorone oxide (Table II)! Other experiments designed to demonstrate the effectiveness of VII as an initiator have met with only limited success. Small amounts of VII served as an effective initiator for rearrangement of I (Table I), but when a 10% solution of VII in toluene was heated for 10 hr at 235°, no biphenyl could be detected among the products. An attempt to initiate the decarbonylation of *n*-heptaldehyde by heating it with VII for 6 hr at 230° resulted in high-boiling materials, water, and 2% hexane. A control experiment, run under similar conditions without VII, gave the same mixture of resinous organic materials and water but no hexane. A thermal aldol condensation may be producing unsaturated aldehydes which might serve as inhibitors for the chain reaction. Finally, VII initiated decomposition of chloral at 230° to a tarry mixture containing no detectable amount of chloroform. A similar decomposition was initiated by 2,2'-azobisisobutane; however, heating chloral alone or in the presence of oxygen for equivalent periods gave no reaction.

Experimental Section

All routine infrared spectra were obtained with a Perkin-Elmer Model 21 recording spectrophotometer. Quantitative measurements were made in part with a Beckman I.R. 7 spectrophotometer. Ultraviolet spectra were obtained with a Beckman DK-2 spectrophotometer. Proton magnetic spectra were determined with a

Varian A-60 high-resolution spectrometer, using tetramethylsilane as an internal standard. Vapor phase chromatography was carried out with a Beckman G.C.-2 and an Aerograph A-90-P instrument.

Measurements of C^{14} β emission were made with a Radiation Instrument Development Laboratory Model 2-7 windowless preflush flow counter, combined with a Packard proportional counting amplifier, Model 220, and a Baird-Atomic glow tube scaler, Model 1035.

Preparation and Heating of Sealed-Vial Reactions. Vials were prepared from 15-cm lengths of 8-mm, heavy wall Pyrex tubing which were immersed in hot, concentrated nitric acid for 24 hr, rinsed with distilled water, immersed in concentrated ammonium hydroxide for 1 hr, rinsed again with distilled water, and dried for 24 hr at 200°. These tubes were sealed at one end, a constriction was made about 5 cm from the closed end, and the ampoules were then stored in a desiccator. From 0.5 to 1.0 ml of the sample to be heated was introduced into an ampoule; the sample was degassed by evacuating the ampoule as it was repeatedly frozen in liquid nitrogen and allowed to warm to room temperature. The ampoule was filled with pure nitrogen⁴⁶ and the degassing-nitrogen flushing sequence was repeated several times before the ampoule was finally sealed at ca. 700 mm of nitrogen pressure. The sample vials were heated in an aluminum block furnace, the temperature of which was controlled to $\pm 2^\circ$ over a 36-hr period.

4-Methyl-3,4-epoxy-2-pentanone (I). This compound was prepared by the procedure developed by Payne.¹² A methanol solution of mesityl oxide was treated with alkaline hydrogen peroxide and gave a 79% yield of I, bp 63–65° (20 mm), n_D^{20} 1.4234, strong infrared absorption at 5.86, 7.67, and 10.91 μ . This colorless liquid was pure according to vpc analysis, but a ferrous ion test showed the presence of a little peroxide. An ether solution of this material was washed with cold $FeSO_4$ solution until no color change occurred, and the dried ether portion was then distilled under reduced pressure to give pure I, bp 63–64° (20 mm), n_D^{20} 1.4236.

Isophorone Oxide (II). A methanolic solution of freshly distilled isophorone was epoxidized with alkaline hydrogen peroxide according to the procedure of House and Wasson⁴⁸ and gave a 73% yield of II.

Preparation of C^{14} -Labeled Isophorone Oxide (IIa). Two 50- μ curie samples of acetone-2- C^{14} were diluted with purified acetone to give 1 mole of this ketone, which was dissolved in 75 ml of anhydrous ether. This solution was cooled in an ice bath and 0.33 mole of sodium hydride (a 52.8% suspension in mineral oil) was added with stirring. The reaction mixture was then refluxed for 1 hr, cooled, and finally quenched by pouring into water. The aqueous portion was extracted with ether and the combined ether extracts were washed and dried. Fractional distillation gave 10 g (22%) of isophorone, bp 47–50° (1 mm).

The labeled epoxide IIa was prepared from this isophorone in 63% yield by the method described above. The infrared spectrum of IIa was identical with that of authentic II. The semicarbazone of IIa, mp 213–214 dec, did not depress the melting point of an authentic sample prepared from II (lit.⁴⁹ mp 216 dec).

Purification of Solvents, Initiators, and Inhibitors. A. Decalin (CP grade) was washed with concentrated sulfuric acid until the yellow color was no longer apparent. After washing with distilled water and drying over anhydrous sodium sulfate, the decalin was passed through a column of silica gel, distilled at reduced pressure, and stored over sodium.

B. 2-Formyl-2,4,4-trimethylcyclopentanone (VII) was prepared by the method of House and Wasson.¹⁵

C. 2,2'-Azobispropane was prepared by the procedure of Renaud and Leitch.⁵⁰

D. 2,2'-Azobisisobutane was prepared in 19% yield by silver oxide treatment of N-bromo-*t*-butylamine according to the procedure of Farenhorst and Kooyman.⁵¹

E. Benzyl phenyl ether was prepared by treating a solution of benzyl chloride and phenol in acetone with potassium carbonate.^{52a}

(46) Oil pump nitrogen was purified by passing through Fieser's solution⁴⁷ followed by drying agents.

(47) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p 296.

(48) R. L. Wasson and H. O. House, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 552.

(49) W. Treibs, *Ber.*, **66B**, 1483 (1933).

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

(51) E. Farenhorst and E. C. Kooyman, *Rec. Trav. Chim.*, **72**, 993 (1953).

4-Biphenyl benzyl ether was also prepared according to this procedure and a 67% yield, mp 136° (lit.^{52b} mp 136°), was obtained.

F. Hexachloroethane was purified by sublimation.

G. *t*-Butyl hydroperoxide was obtained from Wallace and Tiernan Inc., Lucidol Division, Buffalo, N. Y.

H. N-Methylaniline (reagent grade) was distilled twice from potassium hydroxide pellets.

Radical-Initiated Reactions of 4-Methyl-3,4-epoxy-2-pentanone (I). A. **In Air.** To a 25-ml flask fitted with a gas inlet tube and a short Vigreux column was added 12 g of I containing a little peroxide formed during synthesis of the epoxy ketone. The flask was heated to 170° while air was slowly passed through the solution. A yellow liquid began to distil from the flask within 1 hr, and after 36 hr 1.2 g of distillate had been collected—the remainder of the material consisted of tars. The volatile products consisted of acetone (20%), methyl isopropyl ketone (30%), and 4-methyl-2,3-pentanedione (50%).

B. **Under Nitrogen with Added Initiator.** To a large Carius tube was added 19 g of I and 0.5 g (ca. 0.04 molar equiv) of *t*-butyl hydroperoxide. The sample was degassed and flushed with nitrogen, and the reaction vial was sealed. After heating at 190° for 25 hr, vpc analysis of the mixture showed 12% acetone, 6% methyl isopropyl ketone (III), and 22% α -diketone IV in addition to unreacted I. Pure samples of each component were isolated by vpc.

Acetone was identified by the 2,4-DNP derivative, mp 124–125° (lit. mp 126°), which gave no depression in mixture melting with authentic material.

Methyl isopropyl ketone (III) was identified by its infrared spectrum and by the 2,4-DNP derivative, mp 115–117° (lit. mp 117°), which gave no depression in mixture melting with authentic material.

The 4-methyl-2,3-pentanedione (IV) isolated from this reaction was a yellow liquid, bp 114–115° (lit.⁵³ bp 115–116°), which yielded a bis-2,4-dinitrophenylhydrazone, mp 239–240°.

An authentic sample of IV was prepared by heating a mixture of 0.8 g of I and 0.05 g of *p*-toluenesulfonic acid for 1 hr at 100°. Distillation of this mixture gave 9% III and 39% IV, bp 115°, which was identical in all respects with that isolated above.

Radical-Initiated Reactions of Isophorone Oxide (II). A. **In Air.** A 1-g sample of isophorone oxide, bp 206°, was refluxed for 3.5 hr. Analysis by vpc showed that ca. 5% of a new substance had been formed. This compound crystallized from the mixture on standing and was identified as the diosphenol V (see below). When a 1-g sample of II was refluxed in air for 12 hr, 1.5% VI and 13.5% V were produced according to vpc analysis.

This reaction was not observed if 2% (by weight) hydroquinone or N-methylaniline was added to the isophorone oxide or if II was heated in the absence of air.

B. **Under Nitrogen with Added Initiator.** A 15-g sample of pure II containing 0.5 ml of *t*-butyl hydroperoxide was added to a Carius tube, the mixture was degassed and flushed with nitrogen, and the tube was sealed. After 24 hr at 235°, the tube was cooled in liquid nitrogen and opened. Analysis of the crude mixture by vpc showed two major components, V (73%) and VI (22%). On standing overnight the diosphenol crystallized from the mixture. Recrystallization from petroleum ether (bp 60–110°) gave 4.5 g (30%) of V: mp 91–92°, $\lambda_{max}^{alcohol}$ 274 $m\mu$ (ϵ 9000), $\lambda_{max}^{CCl_4}$ 2.92, 5.96, and 6.06 μ (lit.¹⁵ mp 92–92.5°, λ_{max} 274 $m\mu$ (ϵ 9400), $\lambda_{max}^{CCl_4}$ 2.90, 5.95, and 6.05 μ).

Distillation of the filtrate gave 1.5 g (12%) of VI, bp 85–90° (80 mm), $\lambda_{max}^{CCl_4}$ 5.75 μ , which formed a 2,4-DNP derivative, mp 159–160° (lit.¹⁵ mp 160.5–161°). An authentic sample of VI was identical with the isolated material in all respects.

The gas evolved during reaction of a 0.5-g sample of II was collected and analyzed by partitioning on a 12-ft molecular sieve column. A peak having the same retention time as an authentic carbon monoxide sample was observed. An infrared spectrum of the gas showed a peak at 4.64 μ (lit. for carbon monoxide, 4.66 μ).

Rearrangement of II in the Presence of Water. A. **Without Initiator.** A mixture of 0.4 g of II (0.0026 mole) and 0.0234 g of water (0.0013 mole) was placed in a Pyrex vial, degassed, flushed with nitrogen, and sealed. The sample was heated for 7 hr at 235°. The product mixture was analyzed by vpc and proved to be 83% II, 2.6% VI, and 14.4% V.

(52) (a) S. G. Powell and R. Adams, *J. Am. Chem. Soc.*, **42**, 656 (1920); (b) C. M. Brewster and I. J. Putnam, Jr., *ibid.*, **61**, 3085 (1939).

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

B. With Initiator. A similar mixture containing 0.004 g of VII was sealed in a reaction vial after the usual degassing and nitrogen flushing procedure. After 7 hr at 235°, vpc analysis showed 26% II, 16% VI, and 60% V. No other compounds were present.

Isolation of C¹⁴-Labeled VI. A series of ampoules, each containing 0.2 g of labeled isophorone oxide (IIa) and *t*-butyl hydroperoxide (ca. 1%), were heated at 235° for 12 hr. The 2,4,4-trimethylcyclopentanone (VI) produced in this reaction was separated from the major product (V) by vpc, using a 5 ft × 0.25 in. column packed with 20% S.E. 30 on Chromosorb W. The semicarbazone of VI was prepared, mp 167–169° (lit.¹⁶ mp 171°).

Total Oxidation of Labeled Semicarbazones. The method of Van Slyke and Folch³⁹ was used to effect complete oxidation. A small flask, equipped with an addition funnel and gas inlet and exit tubes, served as the reaction chamber. The exit tube passed to a sulfuric acid washing bottle followed by a series of three wash bottles containing saturated barium hydroxide solution. A solid oxidizing mixture consisting of two parts of potassium iodate and one part of potassium dichromate and a liquid reagent made by dissolving 1 g of potassium iodate in a mixture of 66 ml of fuming sulfuric acid and 33 ml of concentrated phosphoric acid were employed in the oxidation. The sample to be oxidized was mixed with the "solid reagent" and added to the reaction flask. The entire system was then swept by dry nitrogen and the "liquid reagent" was added to the reaction. The oxidation mixture was heated briefly to initiate the oxidation and the gaseous products were swept from the reaction flask by a stream of nitrogen. The carbon dioxide thus produced was precipitated as barium carbonate, which was filtered, washed with water and methanol, and finally dried in a desiccator.

Conversion of Carbon Monoxide to Carbon Dioxide. An ampoule containing 0.2 g of labeled isophorone oxide (IIa) was degassed and sealed under nitrogen. After heating for 12 hr at 235°, the ampoule was attached to a manifold which carried a stream of nitrogen through a combustion furnace and into a gas-scrubbing bottle containing saturated barium hydroxide solution. The contents of the ampoule were frozen by a Dry Ice–acetone bath and the ampoule was broken open while a slow stream of nitrogen passed through the system. The carbon monoxide evolved was converted to carbon dioxide by copper oxide heated to 700° in the combustion furnace. The barium carbonate thus formed was filtered and dried prior to counting. The activities found for these samples are given in Table IV.

Partial Degradation of Labeled Isophorone. A 200-mg sample of the isophorone was dissolved in 10 ml of methylene chloride contained in a flask equipped with gas inlet and exit tubes. After cooling the solution in a Dry Ice bath, ozone was bubbled through

the solution until a distinct blue color was observed. The reaction mixture was allowed to warm to room temperature and a 10% alkaline solution of hydrogen peroxide was added. The solvent was evaporated on a steam bath and the remaining material was added to a 200-ml, three-necked flask equipped with a stirrer, an addition funnel, and gas inlet and outlet tubes. Nitrogen was slowly passed through this system and into a series of washing bottles containing saturated barium hydroxide solution. Sulfuric acid was slowly added to the reaction mixture with stirring and the carbon dioxide evolved was collected as barium carbonate. Two samples were determined and exhibited an average specific activity of 0.8 count per min/mg.

Thermal Decomposition of II in Decalin Solution. A. Without Inhibitor. A 0.8-ml sample of a 0.028 *M* solution of II in decalin was degassed and sealed under nitrogen in a Pyrex vial. After being heated at 280° for 4.5 hr, the sample was cooled and analyzed by infrared absorption spectroscopy. The carbonyl stretching fundamental at 5.85 μ had decreased in intensity and new absorptions at 5.75 and 6.05 μ were observed. The approximate composition of the product mixtures was 50% II, 45% VI, and 5% V.

B. With *N*-Methylaniline as an Inhibitor. A 1-ml sample of a 0.041 *M* solution of II in decalin containing *N*-methylaniline (0.19 *M*) was degassed and sealed under nitrogen. After heating at 285° for 8 hr, vpc analysis showed that 50% of the epoxide had decomposed to VI. No detectable amount of V was observed.

C. Kinetic Measurements. A series of vials of uniform size (ca. 3 ml), prepared from a single batch of Pyrex tubing, was used for these measurements. Aliquots of a decalin solution of II were introduced into these vials, and the vials were degassed and sealed under nitrogen. The sealed vials were heated in a tube furnace controlled to $\pm 0.5^\circ$ for this study. Samples were removed from the furnace at various intervals, cooled, and analyzed by infrared spectroscopy. Zero time was assumed to be 5 min after the sample was placed in the furnace. The rate constants were calculated from a plot of time *vs.* the log of the concentration. The estimated error in these rate constants is ca. 10%. These data are reported in Table VI.

A similar procedure was used for determining the rate of decomposition of VII in decalin solution (Table VII). The only product observed in this thermolysis was VI.

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