PART I

THE PHOTOCHEMISTRY OF 1, 3, 4, 5, 6,
6- HEXAMETHYLBICYCLO [3. 1. 0] HEX-3-EN-2-ONE

PART II

THE ACID-CATALYZED REARRANGEMENTS OF 1, 3, 4, 6, 6
-HEXAMETHYLBICYCLO [3. 1. 0] HEX-3-EN-2-ONE AND 2, 3, 4, 5
6, 6-HEXAMETHYL- 2, 4-CYCLOHEXADIENONE

Thesis for the Degree of Ph. D.
MICHIGAN STATE UNIVERSITY
DAVID WILLIAM SWATTON
1967

This is to certify that the

thesis entitled

Part I - THE PHOTOCHEMISTRY OF 1,3,4,5,6,6-HEXAMETHYLBICYCLO-[3.1.0]HEX-3-EN-2-ONE

Part II - THE ACID-CATALYZED REARRANGEMENTS OF 1,3,4,5,6,6-HEXAMETHYLBICYCLO[3.1.0]HEX-3-EN-2-ONE AND 2,3,4,5,6,6-HEXAMETHYL-2,4-CYCLOHEXADIENONE

presented by

David William Swatton

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Harold Hart
Major professor

Date August 4, 1967

ABSTRACT

PART I

THE PHOTOCHEMISTRY OF 1,3,4,5,6,6-HEXAMETHYL-BICYCLO[3.1.0]HEX-3-EN-2-ONE

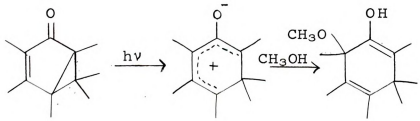
PART II

THE ACID-CATALYZED REARRANGEMENTS OF 1,3,4,5,6,6-HEXAMETHYLBICYCLO[3.1.0]HEX-3-EN-2-ONE AND 2,3,4,5,6,6-HEXAMETHYL-2,4-CYCLOHEXADIENONE

by David William Swatton

The purpose of the first part of this thesis was to investigate the photochemical behavior of 1,3,4,5,6,6-hexamethylbicyclo[3.1.0]hex-3-en-2-one [34].

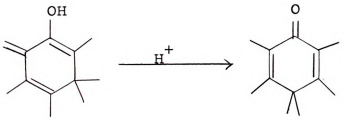
Photolysis of 34 in methanol at 0° through Pyrex gave the crystalline methoxyenol 36, which is thought to result from reaction of a dipolar intermediate 61 with a molecule of methanol. The photolysis could be sensitized by benzophenone. Compound 36, on warming or treatment with dilute



34 61 36

acid, loses methanol to form the enolic triene 40, which, on further treatment with acid, gives dienone 35.

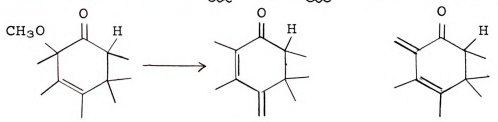
The mechanistic course of the photochemical and acid-



40 35

catalyzed rearrangements was established by using 34 labeled with CD_3 groups at various positions.

The photoproduct 36 was converted by basic methanol to its keto form 45, which underwent thermal elimination of methanol to give dienone 46. Enol 40 could be thermally



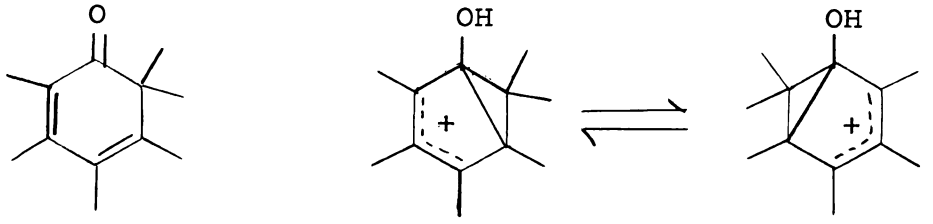
45 46 47

isomerized to its keto form 47, isomeric with dienone 46.

Irradiation of bicyclic ketone 34 in ether afforded the enolic triene 40. This is also proposed to result from dipolar intermediate 61 . Photolysis of 34 in acetic acid gave dienone 35, considered to result from the protonated form of intermediate 61. The general significance of these results with respect to the observed photochemical reactions of bicyclo[3.1.0]hexenones is discussed.

The second part of this thesis is concerned with the acid-catalyzed and thermal reactions of bicyclic ketone 34, and the behavior of fully substituted cyclohexadienones in acid media.

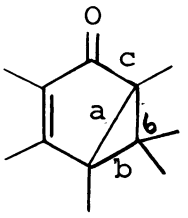
Treatment of 34 with 97% sulfuric acid gave dienone 33 in excellent yield. The course of the acid-catalyzed rearrangement was established using 34 variously labeled with CD_3 groups. The labeling results are in agreement with a mechanism in which 34 undergoes a cyclopropylcarbinyl rearrangement to ion 68, which equilibrates rapidly with its enantiomer 68a prior to ring opening to dienone 33. The



33 68 68a

results also show that ion 68 can revert to bicyclic ketone 34. This is a novel type of rearrangement, not previously obtained from bicyclo[3.1.0]hexenones. The implications of these results for the acid-catalyzed reactions of bicyclo-[3.1.0]hexenones are discussed.

Pyrolysis of bicyclic ketone 34 also led to dienone 33. Labeling studies showed that a methyl migration was not involved, but rather a mechanism which consisted of breakage



34

of bond b, formation of a bond between the carbonyl carbon and the quaternary carbon at C-6, and subsequent fission of bond c.

Treatment of dienone 33 with fuming sulfuric acid gave dienone 35 in good yield. Dienone 35 is stable in concentrated sulfuric acid, but treatment of hexadeutero-35, labeled with CD_3 in the C-3 and C-5 positions, with fuming sulfuric acid led to complete scrambling of the label due to a series of methyl migrations.

PART I

THE PHOTOCHEMISTRY OF 1,3,4,5,6,6-HEXAMETHYL-BICYCLO[3.1.0]HEX-3-EN-2-ONE

PART II

THE ACID-CATALYZED REARRANGEMENTS OF 1,3,4,5,6,6-HEXAMETHYLBICYCLO[3.1.0]HEX-3-EN-2-ONE AND 2,3,4,5,6,6-HEXAMETHYL-2,4-CYCLOHEXADIENONE

By

David William Swatton

A THESIS

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

DOCTOR OF PHILOSOPHY

Department of Chemistry

1967

Dedication

This thesis is dedicated to my wife, Tina, for her patience and invaluable assistance in perfecting this manuscript.

ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to Professor Harold Hart for his invaluable guidance and encouragement during the course of this study.

Appreciation is due to Doctors Peter M. Collins and Richard M. Lange for many fruitful discussions and suggestions.

Appreciation is extended to the National Science Foundation for financial support from June, 1965 to June, 1966 and from January, 1967 to August, 1967.

Appreciation is also extended to the National Institutes of Health for financial support from September, 1966 to December, 1966.

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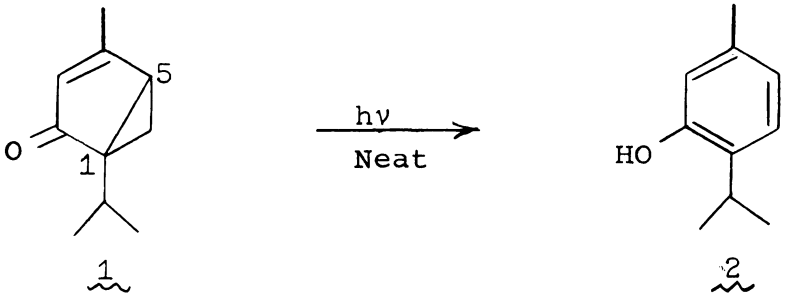
PART I

THE PHOTOCHEMISTRY OF 1,3,4,5,6,6-HEXAMETHYL-BICYCLO[3.1.0]HEX-3-EN-2-ONE

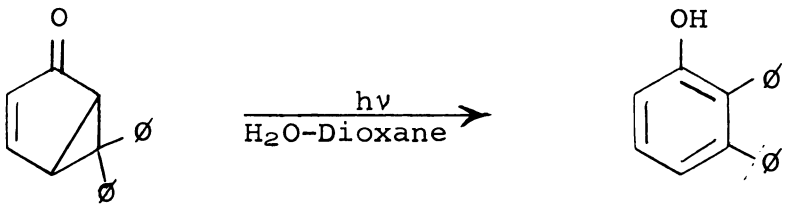
INTRODUCTION

The photochemical transformations of bicyclo[3.1.0]-hex-3-ene-2-ones have received considerable attention within the past decade, and have been extensively reviewed (1,2). The most commonly involved rearrangement is C-1, C-5 bond fission followed by skeletal transformations which furnish isomeric phenols or dienones. A number of representative examples follow:



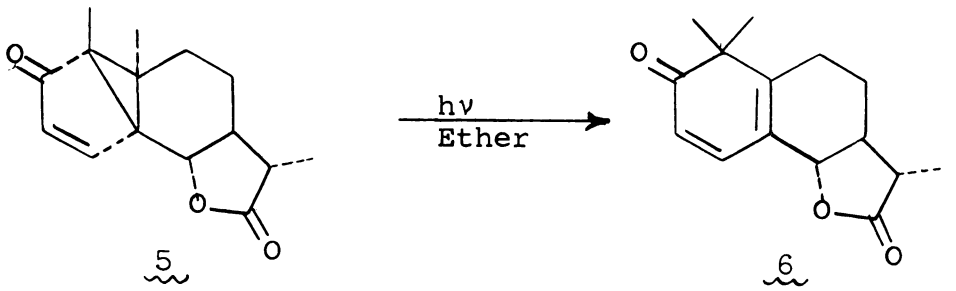
1 2

Wheeler and Eastman (3) (1959)



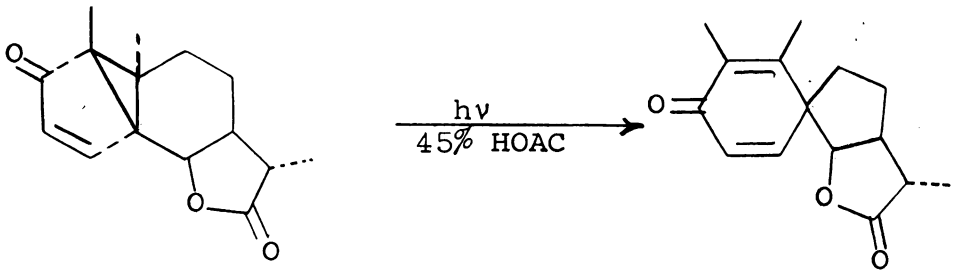
3 4

Zimmerman and Schuster (4) (1961)



5 6

Chapman (5) and Fisch (6) (1963)



7 8

Schuster and Fabian (7) (1966)

The mechanistic scheme presented in Figure 1 has been proposed to account for the principle modes of bicyclohexenone isomerization: (1) $n \rightarrow \pi^*$ excitation (9 ⟶ 10); (2) 1,5 bond fission (10 ⟶ 11); (3) electron demotion to a mesoionic ground state (11 ⟶ 12); and (4) skeletal rearrangement (12 ⟶ 13).

Representation of rearranging intermediates as mesoionic ground state species (12) has gained general acceptance in interpretation of bicyclohexenone photochemistry. The similarity of photochemical to ground state carbonium ion processes suggest that such intermediates are involved.

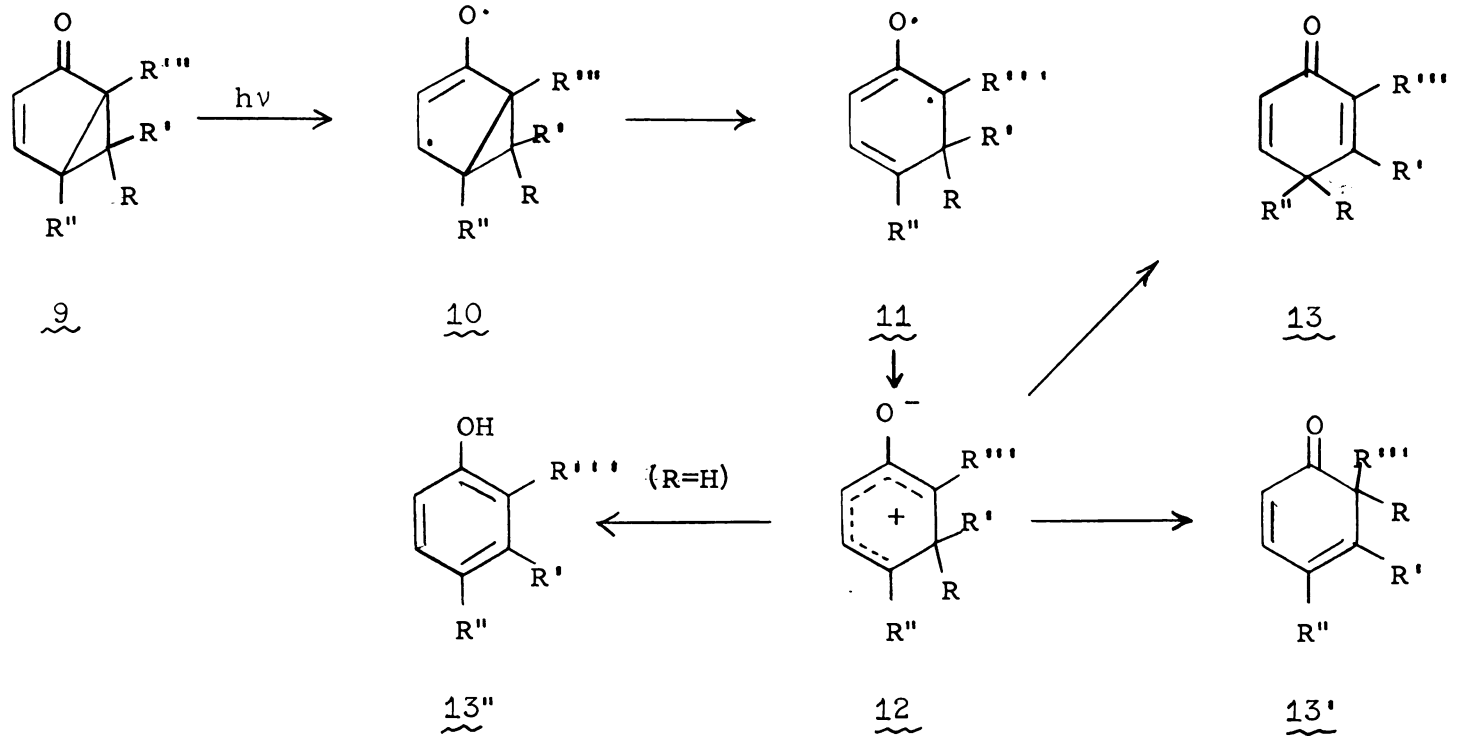
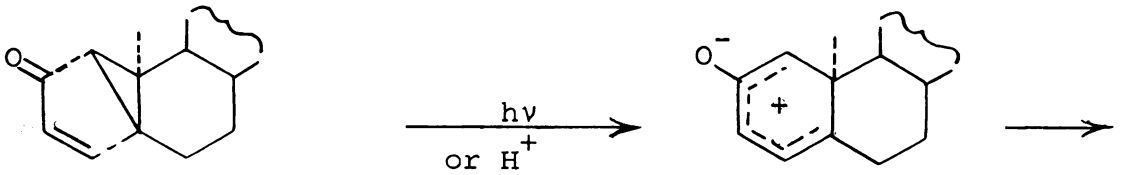
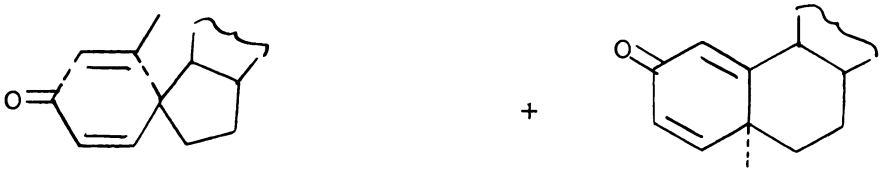


Figure 1. Principle modes of bicyclohexenone isomerization. (Reproduced from K. Schaffner, "Advances in Photochemistry," Vol. 4, W. A. Noyes, Jr., G. S. Hammond, and J. N. Pitts, Jr., Ed., John Wiley and Sons, Inc., 1966, New York, N. Y., p. 96.

Jeger and co-workers have shown (8) that 1-dehydrotestosterone acetate photoisomer 14, on treatment with either acid or ultraviolet light gives a mixture of dienones 16 and 17. These authors suggest that a similar intermediate, 15, is involved in both reactions.

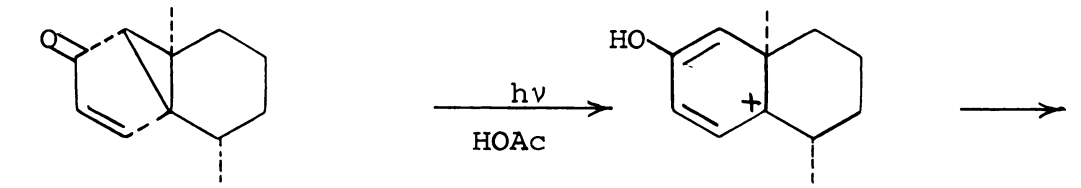


14 15



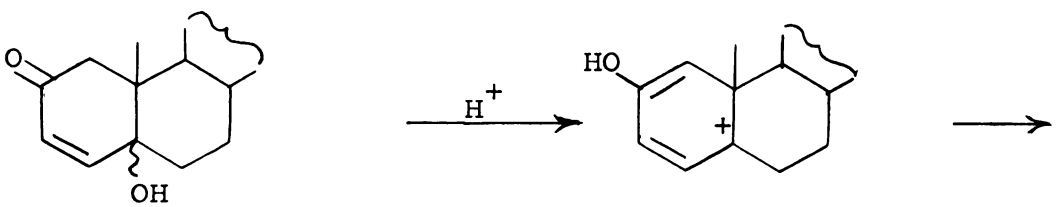
16 17

The intermediacy of ionic species has also been suggested by Kropp, who showed that irradiation of ketone 18 in acetic acid gave phenol 21 as the only product (9). The proposed sequence 19 → 20 → 21 has ample analogy in the series of rearrangements 23 → 24 → 25 proposed by Davis and Halsall to intervene in the acid-catalyzed transformation of hydroxyketone 22 to phenol 25 (10). It was therefore suggested that similar intermediates are involved in both of the above transformations.

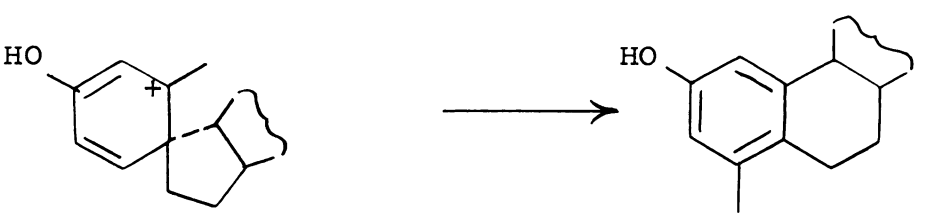


18 19

20 21

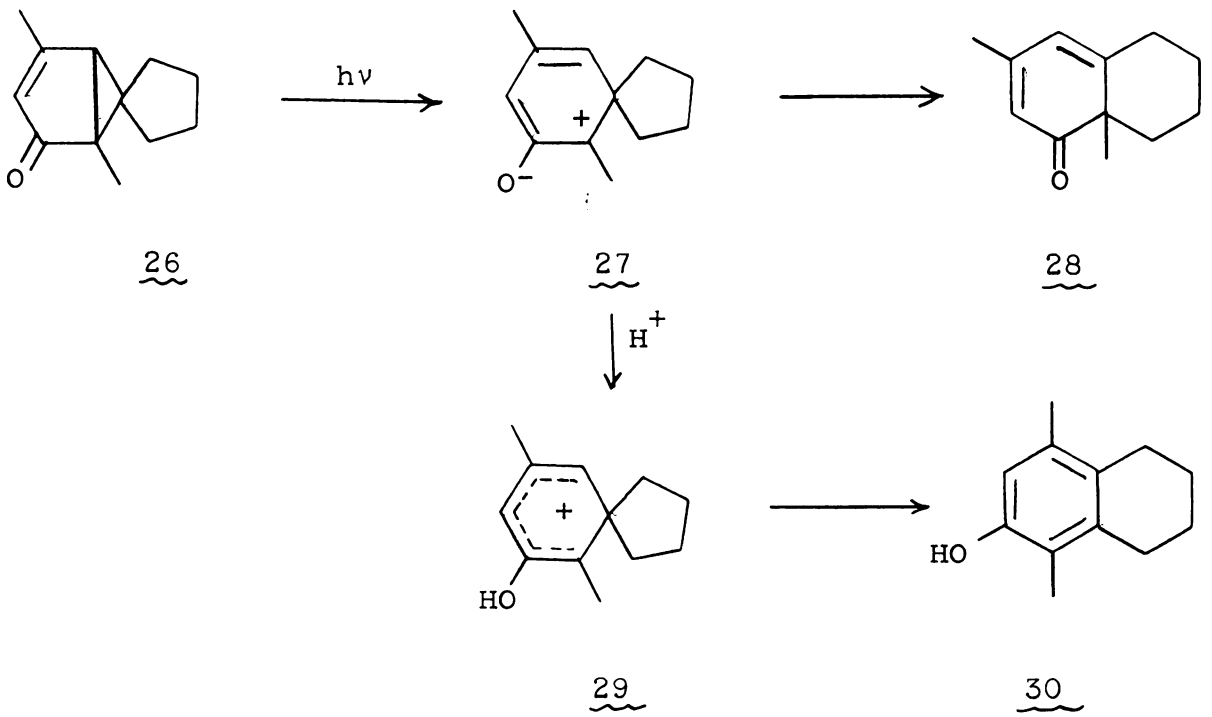


22 23



24 25

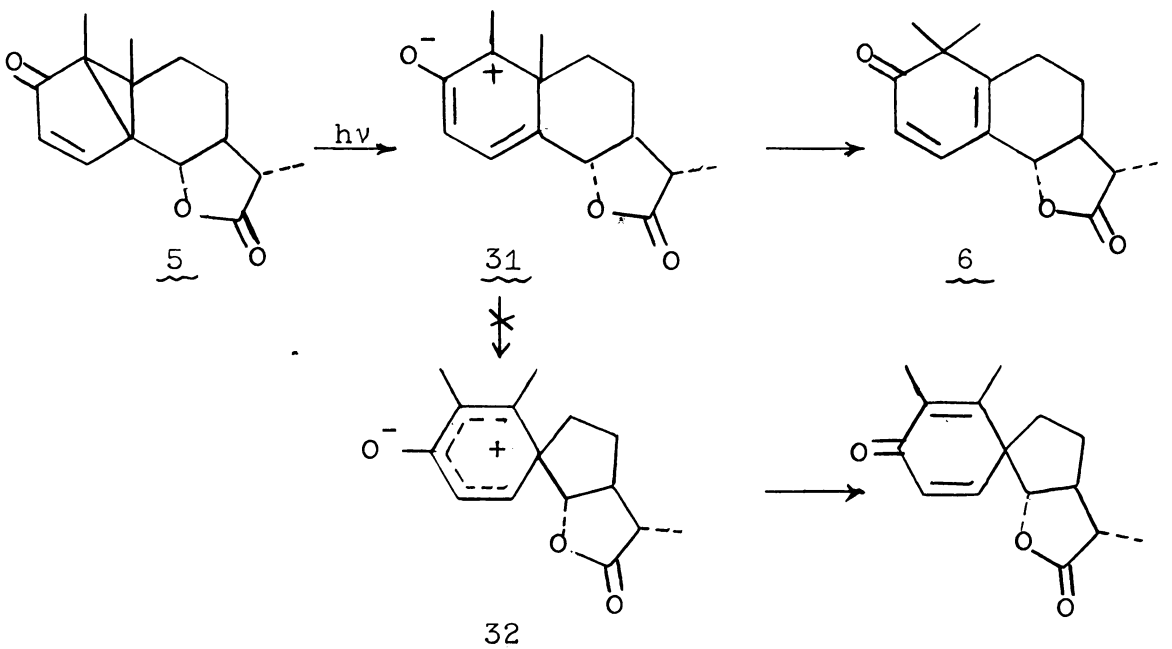
Bicyclohexenone rearrangements depend markedly on the solvent employed. Kropp proposed the mechanistic scheme presented below to account for the photochemical behavior of ketone 26 in neutral and acidic media (11).



Irradiation of 26 in methanol gave the isomeric dienone 28 in 57% yield, whereas photolysis in aqueous acetic acid furnished 47% of 28 and 33% of phenol 30. The author states that in neutral media there is minimum charge separation in ion 27; hence localization of positive charge adjacent to the electron rich oxygen causes preferential rearrangement to 28. In acidic media, however, the ionic species may be protonated on oxygen thereby reducing this electronic stabilization factor. Ion 29 may therefore form products 28 and 30 with approximately equal facility.

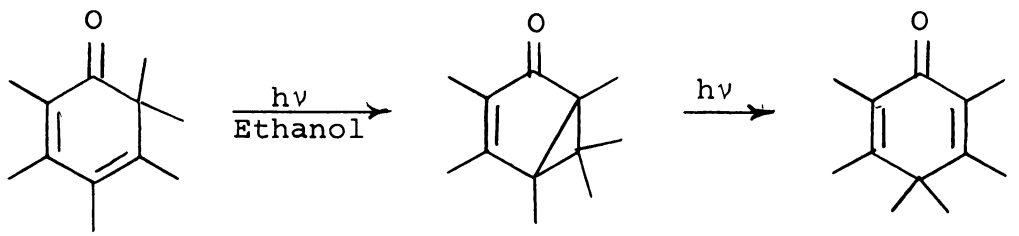
Zimmerman and co-workers have invoked a similar argument to account for the solvent dependence observed in photochemical transformations of ketone 3 (12).

In addition to being dependent on solvent, further rearrangements of species 12 (Figure 1) are influenced by the relative migratory aptitudes of R and R' in the order of CH > CH_2 > CH_3 > C = C (1). Examples of this are the reported conversions 7 ⟶ 8 and 18 ⟶ 21. The hypothetical dipolar species 31 derived from lumisantonin (5), however, undergoes methyl migration to give dienone 6, rather than rearrangement through the spiro intermediate as is normally preferred. Kropp has suggested that this is due to the presence of the trans-γ-lactone ring, since formation of the spiro intermediate 32 would require the highly strained trans fusion of two five-membered rings (13).



It was discovered earlier in our laboratories that irradiation of dienone 33 in ethanol gave bicyclohexenone 34 in excellent yield (14,15). Further irradiation of 34 in

this solvent, however, gave dienone 35 in good yield.



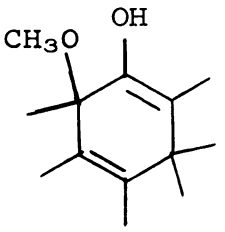
33 34 35

Although a few examples of photochemical conversions of bicyclohexenones to 2,5-cyclohexadienones are known (7,8), this result was somewhat surprising, since the reverse reaction is much more common. Indeed, it was observed that irradiation of 35 in ether gave 34 (14).

The possibility of an isolable intermediate in the photoisomerization of 34 to 35 led us to carry out a careful study of the photolysis of this ketone in methanol (chosen in preference to ethanol in order to simplify the detection of intermediate species by nmr).

The results of this study, presented in Part I of this thesis, show that the transformation of 34 to 35 is not direct, but involves the enolic ether 36, which is converted to 35 via a series of acid-catalyzed rearrangements. It is proposed that 36 is formed by reaction of a dipolar intermediate analogous to 12 (Figure 1) with a molecule of methanol. The photochemical behavior of 34 in ethyl ether and aqueous acetic acid is also described. The mechanistic implications

of the above reactions are discussed.



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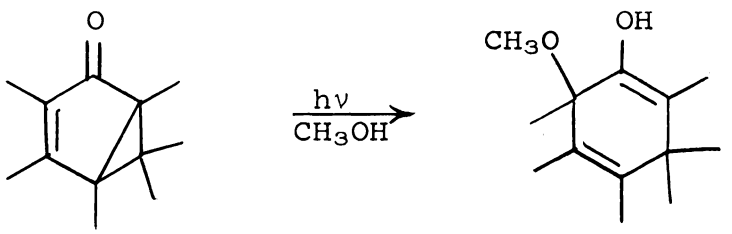
RESULTS AND DISCUSSION

A. Photolysis of Hexamethylbicyclo[3.1.0]-hex-3-en-2-one (34) in Methanol

A solution of 1,3,4,5,6,6-hexamethylbicyclo[3.1.0]-hex-3-en-2-one (34) (15) in methanol which was freshly distilled from sodium methoxide to remove any trace of acid was irradiated at 0° with light of $\lambda > 280$ mμ. The reaction was monitored by the change in the ultraviolet spectrum of the solution. As the photolysis proceeded, bands due to 34 at 234 and 274 mμ decreased in intensity and the ultraviolet region became nearly transparent. Filtration of the solution afforded a 76% yield of a white crystalline photoproduct which was assigned structure 36 (14). The product could be

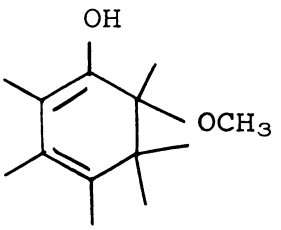


34 36

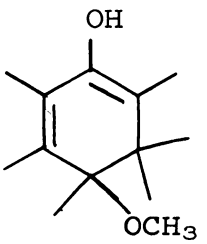
stored for extended periods of time at -80°, but formed a viscous yellow oil on standing overnight at room temperature. Freshly prepared samples had a melting point range of 58-65° and gave a satisfactory microanalysis.

The structure of 36 follows from its analysis, spectral properties, and chemical transformations. Low wavelength

ultraviolet absorption at 202 mμ (ε 4,300) agrees with the value of λ_{max}^{EtOH} 195 mμ (ε 7,600) reported for 1,2-dimethyl-1,4-cyclohexadiene (16). A structurally similar compound which has also been reported to have intense end absorption is 3,3,6,6-tetramethyl-1,4-cyclohexadiene (17). The two mechanistically feasible isomers, 37 and 38 can therefore be excluded since these compounds should exhibit intense end absorption at about 278 mμ (18). The infrared spectrum



37



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of 36 exhibited no carbonyl band but did contain a hydroxyl stretching frequency at 3555 cm^{-1} consistent with its enolic structure. The nmr spectrum of the photoproduct also supports the assigned structure (see Table I). That the spectrum contains three allylic methyls eliminates the hemiketal structure 39 which could also be postulated for the photoproduct. The assignment for the three allylic methyls presented in Table I is based on labeling studies described

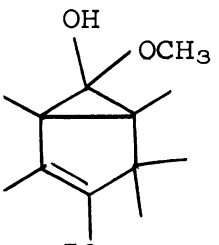

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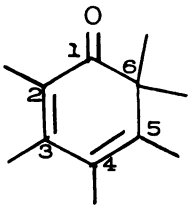
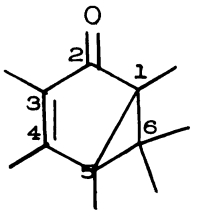
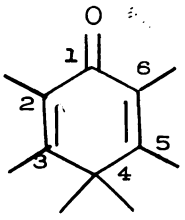
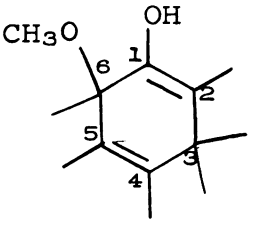
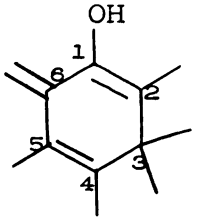
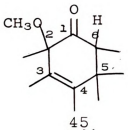
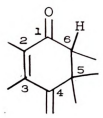
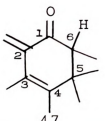
Table I. NMR Spectra[a]

Compound	Chemical Shift (J)[b]		Assignments[c]
 33	7.97 (q, 0.8) 8.14 (m) 8.89 (s)		C-3 methyl C-2,C-4,C-5 methyls C-6 methyls
 34	8.12 (q, 0.9) 8.45 (q, 0.9) 8.78 (s) 8.90 (s) 8.90 (s) 9.08 (s)		C-4 methyl C-3 methyl C-5 methyl C-1 methyl C-6 exomethyl C-6 endo methyl
 35	8.05 (q, 0.8) 8.17 (q, 0.8) 8.79 (s)		C-3,C-5 methyls C-2,C-6 methyls C-4 methyls
 36	5.75 (s) 7.13 (s) 8.33 (s) 8.33 (q, 0.9) 8.38 (q, 0.9) 8.75 (s) 8.92 (s) 8.96 (s)	7.11 (s)[d] 8.30 (s)[d] 8.30 (q, 0.9)[d] 8.37 (q, 0.9)[d] 8.70 (s)[d] 8.90 (s)[d] 8.95 (s)[d]	Hydroxyl proton Methoxyl C-2 methyl C-4 methyl C-5 methyl C-6 methyl (?) C-3 methyls (?)
 40	5.05 (s) 5.20 (s) 8.18 (s) 8.23 (s) 8.89 (s)	8.18 (s)[d] 8.22 (s)[d] 8.88 (s)[d]	Vinyl proton (cis to hydroxyl?) Vinyl proton C-4,C-5 methyls C-2 methyl C-3 methyls

continued

Table I -- continued

Compound	Chemical Shift (J)[b]	Assignments[c]
 45	7.10 (s)	Methoxyl
	7.28 (q, 7.0)	C-6 proton
	8.27 (q, 0.9)	C-3,C-4 methyls
	8.37 (q, 0.9)	
	8.73 (s)	C-2 methyl (?)
	8.85 (s)	C-5 methyl (?)
	9.01 (d, 7.0)	C-6 methyl
	9.22 (s)	C-5 methyl (?)
 46	4.74 (s)	Vinyl protons
	4.90 (s)	
	7.85 (q, 7.0)	C-6 proton
	7.98 (s)	C-3 methyl
	8.20 (s)	C-2 methyl
	8.90 (s)	C-5 methyls
	8.97 (s)	
	9.07 (d, 7.0)	C-6 methyl
 47	4.28 (s)	Vinyl proton (cis to hydroxyl?)
	4.97 (s)	Vinyl proton
	8.13 (s)	C-3,C-4 methyls
	8.89 (s)	C-5 methyls
	9.07 (s)	
	8.96 (d, 7.0)	C-6 methyl[e]

[a] All spectra are in CCl_4 except as noted.

[b] Shifts are reported as τ values, with TMS as an internal reference. J's are in cps. All spectra were run at 60 Mc. All areas are consistent with the assignments. Multiplicity of peaks shown in brackets: s, singlet; d, doublet; q, quartet; m, multiplet.

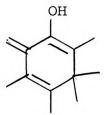
[c] A question mark indicates that the assignment is tentative.

[d] Chemical shifts observed in methanol.

[e] The C-6 proton responsible for the splitting of this methyl was lost in noise and could not be located with certainty.

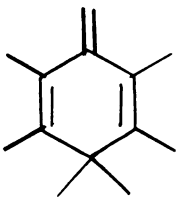
below. Evidence that the methyl groups at τ 8.30 and 8.37 are adjacent is the observed homoallylic coupling of 0.9 cycles between them. Further proof for the enolic structure is the band for the hydroxyl proton of 36 observed in CCl_4 solution and the absence of a methyl group split by an α-hydrogen (compare with spectrum of ketone 45). A definite assignment for the three aliphatic methyls cannot be made, although it is likely that the one at lowest field is bonded to the carbon bearing the methoxyl group.

When a solution of 36 in CCl_4 was warmed to 35° for a few minutes, a band appeared in the nmr spectrum at τ 6.62 due to formation of methanol. This was accompanied by other changes in the spectrum; resonance bands due to 36 decreased in intensity and a new series of bands was observed. These changes are attributed to 1,2-elimination of methanol from 36, leading to enol 40.

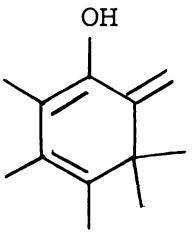


40

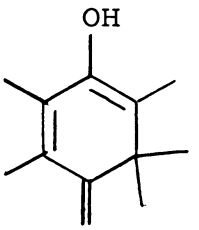
This compound could be isolated as a yellow oil with a λ_{max}^{MeOH} 252 mμ (ε 13,400). This is in good agreement with the uv spectrum of the related triene 41 (15,19) which has a $\lambda_{max}^{isooctane}$ at 256 mμ (ε 21,400). Isomers 42 and 43, which



41



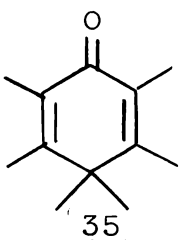
42



43

might result by the 1,4-elimination of methanol from 36, can therefore be excluded since they should exhibit intense ultraviolet absorption at 313 mμ (18). The nmr spectrum of 40 (Table I) is also quite similar to that of triene 41, which consists of three singlets at τ 5.23, 8.22, and 8.91 with relative areas 1:6:3 (15). The observation that one of the vinyl protons in 40 exhibits a chemical shift close to that observed for those of 41 suggests that this proton is trans to the hydroxyl group. The assignment for the allylic methyls presented in Table I is based on labeling experiments described below. An infrared spectrum of 40 exhibited a strong hydroxyl stretching band at 3450 cm^{-1} and no carbonyl absorption, thus confirming the enolic structure.

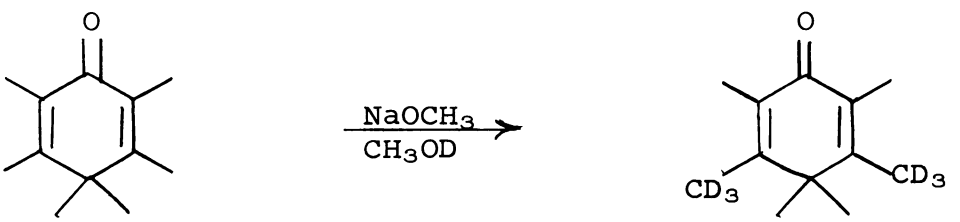
Treatment of either 36 or 40 with dilute hydrochloric acid gave dienone 35 (20) in excellent yield. The structure of this compound is based on its spectral data and micro-



35

analysis. It exhibited infrared bands at 1653 and 1624 cm^{-1}

(C = O and C = C) and λ_{max}^{EtOH} at 246 mμ (ε 14,800), consistent with the 2,5-cyclohexadienone structure. The nmr spectrum of 35 (Table I) is also in agreement with the symmetrical structure. The low-field band is assigned to the β-allylic methyls, which are observed to undergo coupling of about 0.8 cycles with the α-allylic methyl protons, and can be easily exchanged for deuterium (35 ⟶ 44) by refluxing the dienone in basic deuteromethanol. In agreement with the



35 44

above assignment, 44 has no nmr band due to the β-methyls and the band attributed to the α-methyls is a sharp singlet.

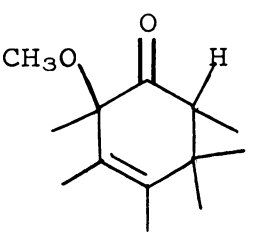
Experimental evidence that 36 is not converted directly to 35 by acid, but first forms 40, was obtained by following the change in ultraviolet spectrum when a trace of acid was added to a solution of 36 in methanol. The absorption maximum shifted rapidly from 202 mμ (36) to 252 mμ (40) then changed to 246 mμ (35) on adding more acid.

1. The Keto Forms of 2,3,3,4,5,6-Hexamethyl-6-methoxycyclohexa-1,4-dien-1-ol (36) and 2,3,3,4,5-pentamethyl-6-methylenecyclohexa-1,4-dien-1-ol (40)

In order to provide further chemical support for the structures of the photoproduct 36, and its elimination

product 40, an attempt was made to convert each enol to its keto form.

A solution of 36 in methanol was treated at 0° for 0.5 hr with 0.2 N sodium methoxide in methanol. Extraction with methylene chloride gave a colorless oil, assigned structure 45, in excellent yield. This structure is based on the spectral and chemical properties of 45.

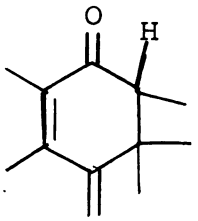


45

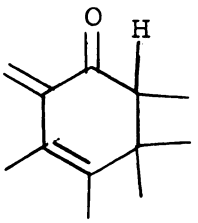
It exhibited a carbonyl frequency of 1716 cm^{-1} corresponding to an unconjugated six-membered ring ketone. Further evidence for the absence of conjugation is the ultraviolet spectrum in ethanol which showed only end absorption (λmax 202 mμ, ϵ 5,350). The nmr spectrum (Table I) is consistent with structure 45; significant features are the presence of two allylic methyls which show homoallylic coupling of about 0.9 cycles, and the splitting pattern for the proton and methyl group on C-6. The low-field aliphatic methyl at τ 8.73 is probably attached to the carbon which bears the methoxyl (compare with spectrum of 36). Also notable is the fact that only one of the two possible stereoisomers of 45 is obtained.

Further support of structure 45 was obtained by its thermal 1,4-elimination of methanol when passed through a gas

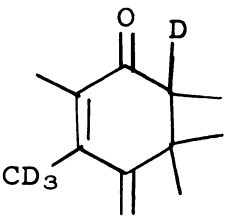
chromatograph at 200°. The product was a colorless oil which was assigned the structure 46 on the basis of its analysis and spectral properties. Its infrared spectrum showed a conjugated carbonyl and carbon-carbon double bond (1667, 1600 cm^{-1}) and a terminal methylene group (905 cm^{-1}).



46



47



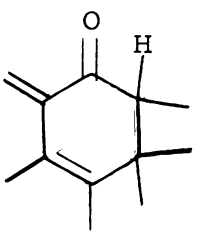
48

The uv spectrum exhibited a λ_{max}^{EtOH} at 280 mμ (ε 13,800), reasonable for the assigned structure. The nmr spectrum (Table I) is also consistent with the structure. Particularly important is the low-field position (τ 7.98) of one of the allylic methyls. This is expected for the β-methyl of an α,β-unsaturated cyclohexenone (compare with the spectrum of 35) and thus rules out isomer 47 which would result from 1,2-elimination of methanol from 45.

Confirmation of structure 46 was obtained by the change in its nmr spectrum on treatment with deuteromethanol containing a catalytic amount of sodium hydroxide (46 ⟶ 48). The bands due to the C-3 methyl and C-6 proton disappeared, and the doublet assigned to the C-6 methyl became a singlet.

The keto form of 40 was also prepared. Injection of an ether solution of 40 on the gas chromatograph at 180° afforded

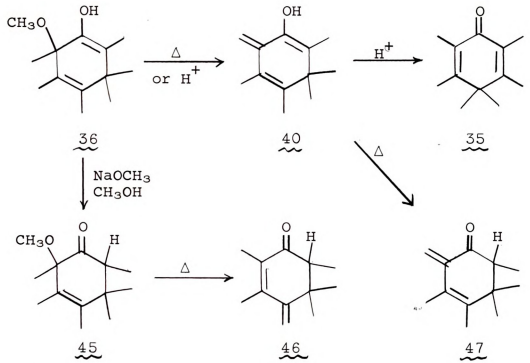
a product assigned structure 47 on the basis of its spectral data and method of synthesis. The infrared spectrum showed a carbonyl band at 1700 cm^{-1} and a terminal methylene at 920 cm^{-1}. Although the carbonyl frequency appears to be rather high for an α,β-unsaturated ketone (usually found at 1675 cm^{-1}), Erskine and Waight (21) have presented a number of examples of cisoid α,β-unsaturated ketones with similarly high carbonyl



47

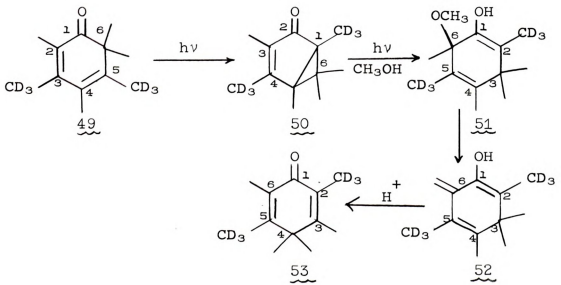
frequencies. The nmr spectrum of 47 (Table I) is consistent with the proposed structure. In particular, the absence of a low-field allylic methyl is significant (compare with 46). Also important is the similarity of the chemical shift of the C-6 methyl of 47 to those of 45 and 46 (Table I). The relatively large chemical shift difference between the methylene protons in 47 (compare with 46) suggests the marked difference in environment expected if the methylene group is adjacent to the carbonyl.

The above experiments establish the following sequence of reactions:



2. Photolysis of Labeled Bicyclo-[3.1.0]hexenones

In order to confirm the structures which have been described, and to assign as many of the nmr positions of the various methyl groups as possible, the photolysis of two labeled bicyclo[3.1.0]hex-3-en-2-ones was carried out in methanol.



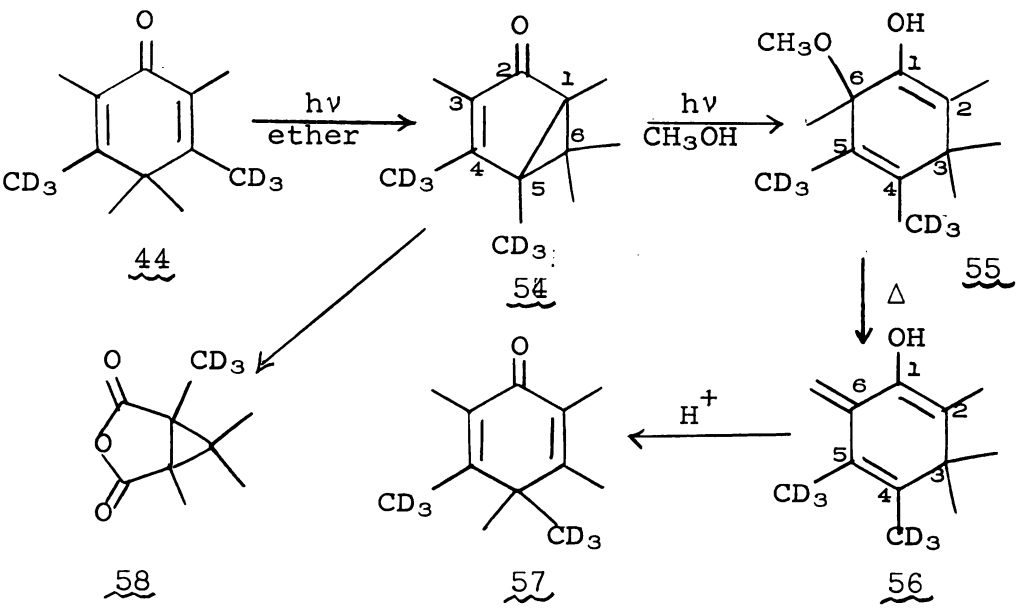
Dienone 49, prepared as previously described (15), gave ketone 50 on photolysis in ethanol. Ketone 50 used in the remainder of the above sequence had only 50% of the label at C-1, but was completely labeled at C-4. The nmr spectrum of 50 was similar to that of 34 (Table I) except that the band at τ 8.12 (due to the C-4 methyl) was missing and the band at τ 8.45 for the other allylic methyl was a sharp singlet, rather than a quartet. The area of the band at τ 8.90 (due to the C-1 and one of C-6 methyls) was consistent with 50% label at C-1. Irradiation of 50 in methanol gave 51, whose nmr spectrum in methanol was similar to 36 (Table I) except that the quartet at τ 8.37 was missing and the peak at τ 8.30 had decreased in intensity to 4.5 protons. This permits the assignment of the C-2 and C-4 allylic methyls of 51 to the band at τ 8.30.

When a solution of 51 in methanol was warmed, it gave 52, whose nmr spectrum in methanol differed from 40 (Table I) in that the peak at τ 8.22 was reduced to a shoulder on the peak at τ 8.18, which had an area of 4.6 protons. This permits the assignment of the high-field allylic methyl in 52 to C-2.

Treatment of 52 or 51 with dilute hydrochloric acid afforded dienone 53, whose nmr spectrum showed only one low-field allylic methyl at τ 8.05; the area of the high-field allylic methyl at τ 8.17 demonstrated that it contained slightly more than one methyl. The observation that both of

these bands were singlets, rather than quartets, establishes that the two CD_3 groups are on opposite sides of the ring.

The other series of experiments with labeled ketones is shown in the following scheme.



Dienone 44 was prepared by refluxing the unlabeled compound (35) in deuteromethanol containing sodium methoxide. Irradiation of 44 in ether afforded ketone 54, whose nmr spectrum differed from 34 in that it lacked a band at τ 8.12 (due to C-4 methyl) and the quartet at τ 8.45 became a sharp singlet. The band at τ 8.78 was also missing; this is therefore assigned to the C-5 bridgehead methyl of 34. In order to verify that the CD_3 group in 54 was on the bridgehead position, this compound was subjected to ozonolysis with

oxidative work-up, affording 58 as the final product. The nmr spectrum of the anhydride (see Experimental) showed the absence of one of the bridgehead methyls.

The photoisomerization 44 ⟶ 54 has ample precedent in other 2,5-cyclohexadienone systems (22). Irradiation of 54 in methanol gave the crystalline photoproduct 55. The nmr spectrum of 55 in methanol was similar to that of 36, except that the quartet at τ 8.37 was missing and the band at τ 8.30 was a sharp three-proton singlet. This confirms the assignment of the latter band to the C-2 allylic methyl.

When a solution of 55 in methanol was allowed to remain in a refrigerator overnight it was converted to 56, whose nmr spectrum in methanol exhibited a 3-proton singlet at τ 8.22 and a small peak (perhaps one proton) for the low-field allylic methyls at τ 8.15. This confirms the assignment of the high-field allylic methyl of 40 to C-2.

In one particular experiment, 54 was irradiated in methanol which contained a trace of acid, and workup gave 57 as the major product. Its nmr spectrum showed three singlets at the same positions as for 35 (Table I) but with relative areas of 3:6:3.

3. The Photosensitized Conversion of Hexamethylbicyclo[3.1.0]hex-3-en-2-one (34) to 2,3,3,4,5,6-Hexamethyl-6-methoxycyclohexa-1,4-dien-1-ol (36)

Previous reports of triplet intermediates in ultraviolet light induced bicyclohexenone rearrangements (6,12) led us to irradiate 34 in the presence of benzophenone, a known triplet energy donor (E^t = 69.2 Kcal. mole^{-1} (23)).

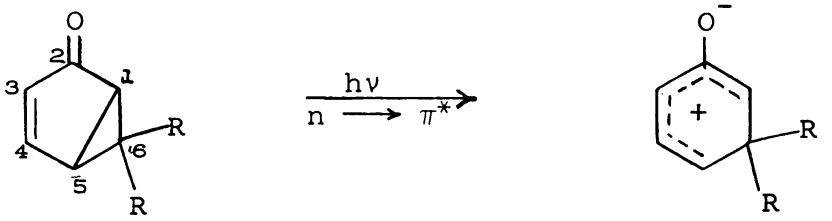
A solution of 0.55 mmoles 34 in 10 ml of methanol was placed in a Pyrex test tube. In a similar tube was placed 0.55 mmoles of 34 and 27.6 mmoles of benzophenone. Both tubes were irradiated with a 200-watt Hanovia mercury vapor lamp cooled by a stream of air (this had the effect of decreasing the photolysis rate of 34). The disappearance of 34 and the appearance of the thermal decomposition product of 36 were followed by vpc. After 225 minutes, photolysis had proceeded to the extent of 13% and 54%, respectively, in the two samples.

The ability of benzophenone to enhance the rate of photolysis of 34, even though it is present in sufficient quantity to act as a filter, together with the observation that the same product was observed in both runs, strongly suggests that a triplet species is involved in the conversion of 34 to 36.

4. The Mechanistic Significance of the Photochemical Rearrangement of Hexamethylbicyclo[3.1.0]hex-3-en-2-one (34)

Several aspects of the photochemical properties of 34 which are mechanistically significant deserve comment. The first of these is the predominant formation of 36 in methanol.

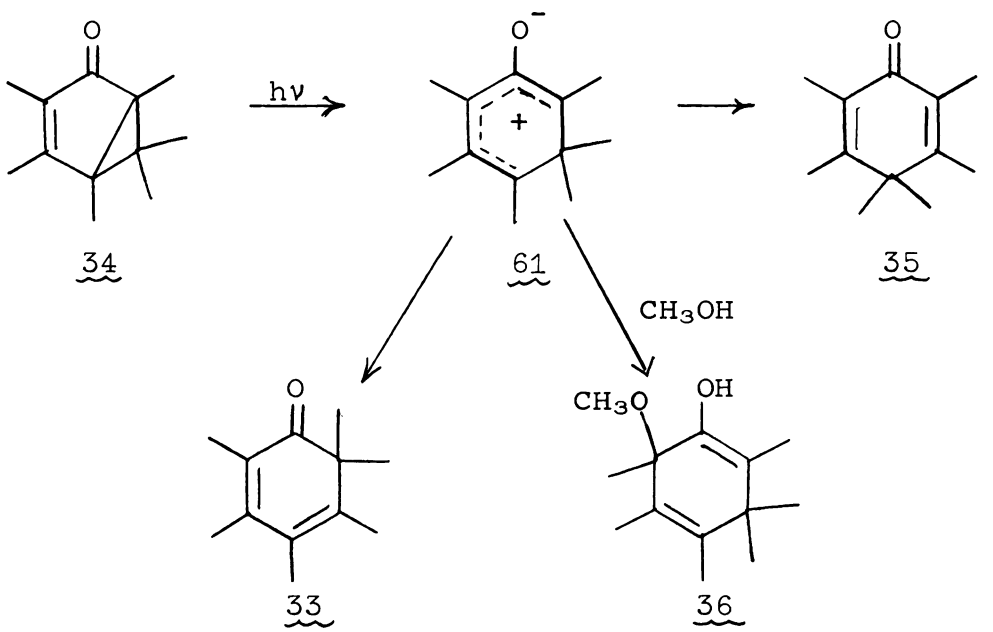
The majority of light induced bicyclo[3.1.0]hexenone rearrangements can be explained by $n \longrightarrow \pi^*$ excitation of the ketone (59) to a dipolar species 60 followed by migration of one of the groups at C-6 to C-1 or C-5 to give isomeric



59 60

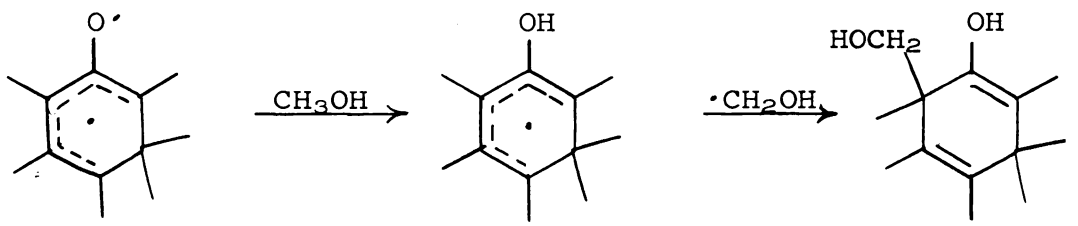
dienones, or, if R = H, loss of a proton from C-6 with subsequent phenol formation (see Introduction).

The dipolar species 61 derived from bicyclohexenone 34, could undergo a 1,2-methyl migration to give dienones 33 or 35, or, if generated in a nucleophilic solvent such as methanol, could react with the solvent to form 36.



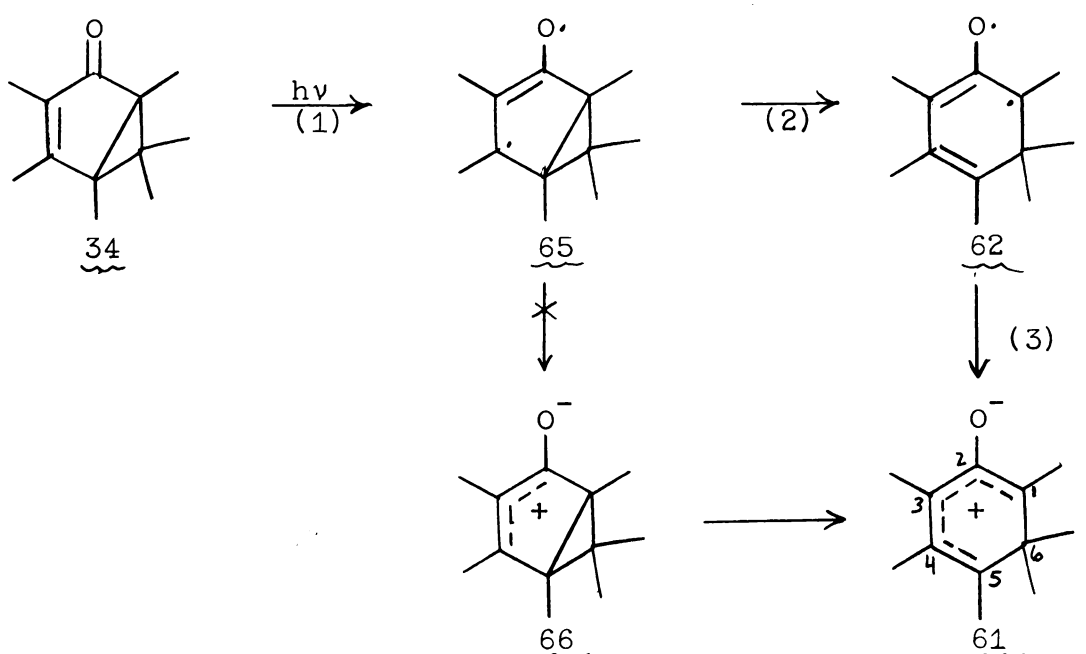
This is the interpretation placed on the isolation of 36 as the major photolysis product of bicyclohexenone 34 in methanol.

The structure of photoproduct 36 strongly suggests that it is produced by addition of methanol to an ionic species such as 61. A radical species 62 isoelectronic with 61 would probably lead to 64 as the major product since the C-H hydrogen atom of methanol is much more easily removed than the O-H (24).



62 63 64

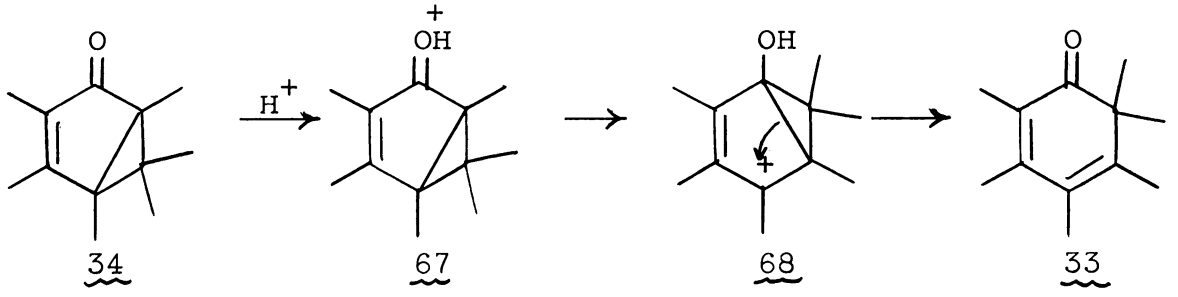
The ultraviolet light-induced conversion of 34 to the dipolar intermediate 61 may proceed via the series of steps presented below: (1) n $\longrightarrow \pi^*$ excitation followed by intersystem crossing to the triplet (34 $\longrightarrow$ 65); (2) bond alteration (65 $\longrightarrow$ 62); and (3) intersystem crossing to a ground state singlet (62 $\longrightarrow$ 61).



34 65 62 66 61

The above rearrangement is proposed to result from excitation of the n $\longrightarrow \pi^*$ band of 34 (λ 320 mμ, shoulder, ϵ 605), since the intense $\pi \rightarrow \pi^*$ bands at 235 mμ (ϵ 6270) and 274 mμ (ϵ 3240) appear at much shorter wavelength and the conversion of 34 to 36 occurs in Pyrex where little light below 300 mμ is available. Evidence for a triplet intermediate in the above scheme is the observation that the reaction could be photosensitized by benzophenone.

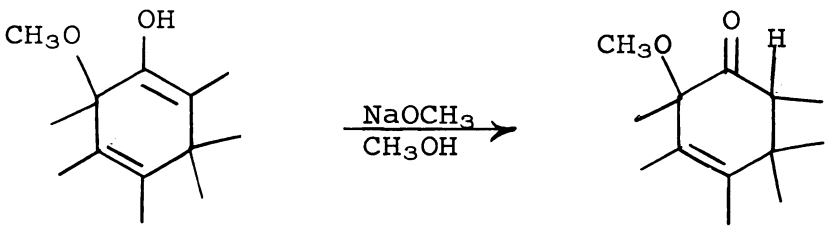
There is also the possibility that 65 undergoes intersystem crossing to the ground state singlet 66, which then undergoes ring opening to 61. The acid-catalyzed reaction of 34 (described in Part II of this thesis) suggests that the latter process does not occur. Treatment of 34 with acid gave dienone 33 in excellent yield. Labeling studies demonstrated that 33 is not formed by a methyl migration (involving the protonated form of 61) but via a cyclopropylcarbinyl rearrangement (67 → 68 → 33).



34 67 68 33

It is therefore concluded that to the extent that the acid-catalyzed reaction of 34 defines the behavior of the dipolar species 66, such an intermediate is not involved in the photochemical conversion of 34 to 36.

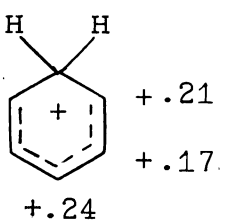
Special comment should be made concerning the formation of enol 36, rather than its keto form. Since treatment of 36 with basic methanol furnishes ketone 45, this tautomer



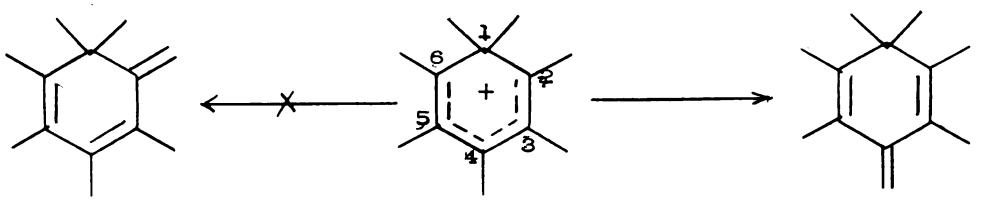
36 45

is assumed to be the more stable of the two. Thus, 36 is probably formed via a kinetically controlled process, perhaps involving a rapid protonation of 61 on oxygen.

Exclusive formation of 36, rather than isomers 37 or 38, in spite of the fact that the two latter structures have conjugated double bonds, may be due to the charge distribution in 61. Preferential attack of methanol at the C-3 position of 61 suggests that the charge density at this position is greater than at C-1 or C-5. This is consistent with recent observations in similar systems. In a study of nmr chemical shifts of protonated alkylbenzenes, MacLean and Mackor (25) have assigned the charge density distribution presented below



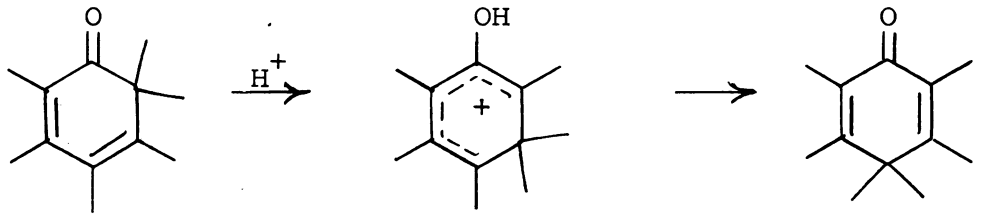
to ions of type 69. The nmr spectrum of heptamethylbenzenonium ion 70 is also in agreement with greater charge density



71 70 41

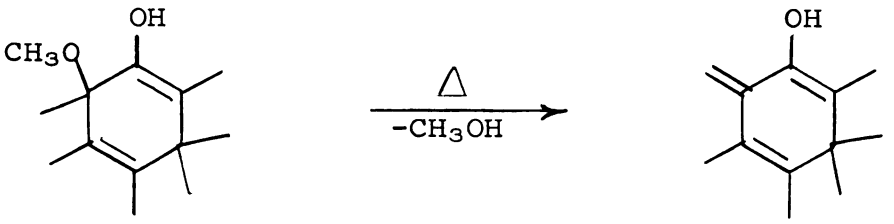
in the C-4 position than in the C-2 and C-6 position (19).

The formation of 1,4- rather than 1,3-conjugated products (36 rather than 37 or 38) also has ample precedent. Doering has shown, for example, that ion 70 loses a proton to give 41 as the only product (19): similarly, treatment of 33 with sulfuric acid converted it exclusively to dienone 35 (14).



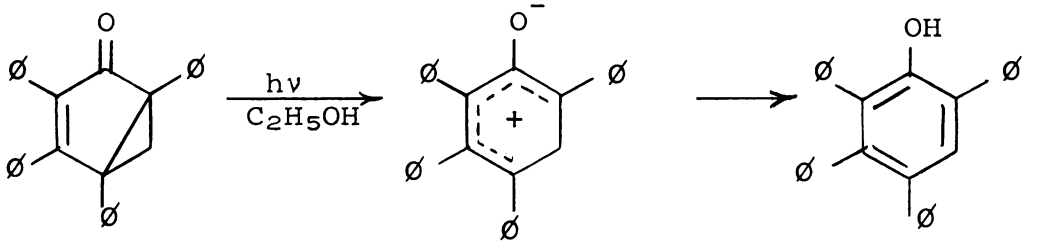
33 72 35

This reaction is considered to proceed via ion 72, which may then undergo a methyl migration in either of two directions. As expected, the product has the 1,4- rather than 1,3-diene structure. Also notable is the 1,2-elimination of methanol from 36 to give 40 (compare with 1,4-elimination of methanol from 45).



36 40

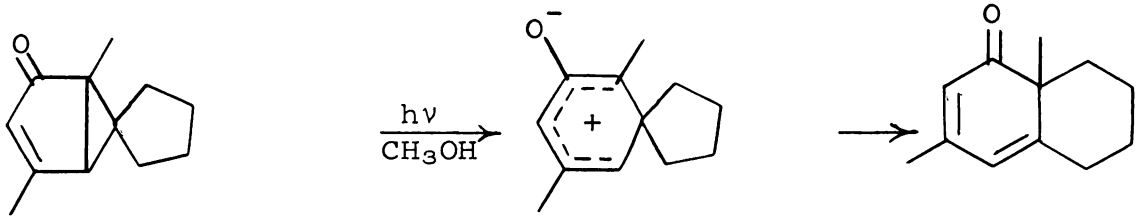
In view of the proposed mechanistic path which rationalizes the photochemical conversion of 34 to 36, it is now of interest to consider why this type of reaction has not been observed previously. One reason is the dearth of examples of bicyclohexenone photolyses in alcoholic solvents, presumably because of the possibility of photoreduction. A few examples of bicyclohexenone isomerizations in alcoholic solvents have been reported, however. Dürr has shown (26) that irradiation of 73 in ethanol or dioxane with light of $\lambda > 280$ mμ gives phenol 74 in excellent yield. The absence



73 73a 74

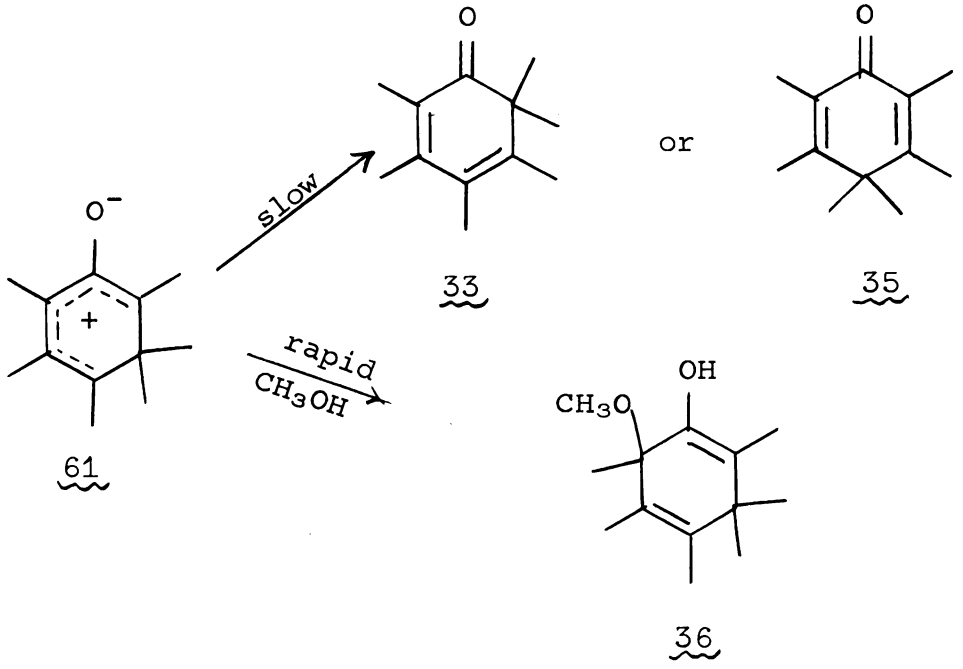
of products resulting from reaction of dipolar species 73a with ethanol is not surprising, as proton loss from this species would be expected to be rapid in comparison to a bimolecular reaction with the solvent.

Kropp has reported that irradiation of bicyclohexenone 26 in methanol or dioxane leads to dienone 28 in good yield (11).



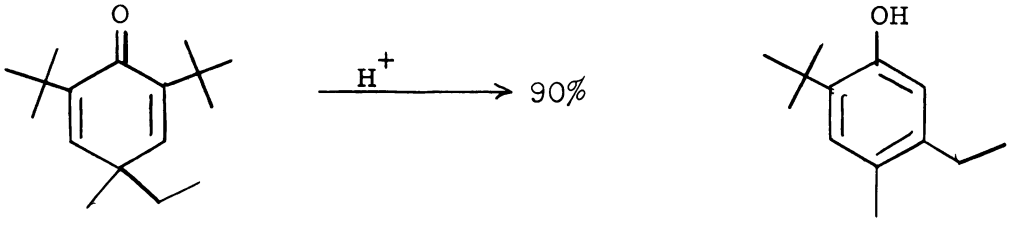
26 27 28

No products resulting from reaction of species 27 with methanol were observed. This suggests that conversion of 27 to 28 is rapid compared to reaction with solvent. Comparison of the above reaction with the photolysis of 34 in methanol leads to the conclusion that the rearrangement of dipolar species 61 (derived from 34) to dienones 33 or 35



61 33 35 36

is quite slow with respect to the reaction of 61 with methanol. The difference in rearrangement rates of 27 and 61 may be due to the observed preference for methylene rather than methyl migration to a positive carbon atom (see Introduction). Stiles and Mayer, for example, have shown that the partial rate factor ratio of ethyl vs. methyl migration in pinacol rearrangements is 17:1 (27). The acid-catalyzed rearrangement of dienone 75 to phenol 75a was reported by Miller and Margulies (28). This reaction also demonstrates the favorable migration of a methylene group with respect to a methyl.



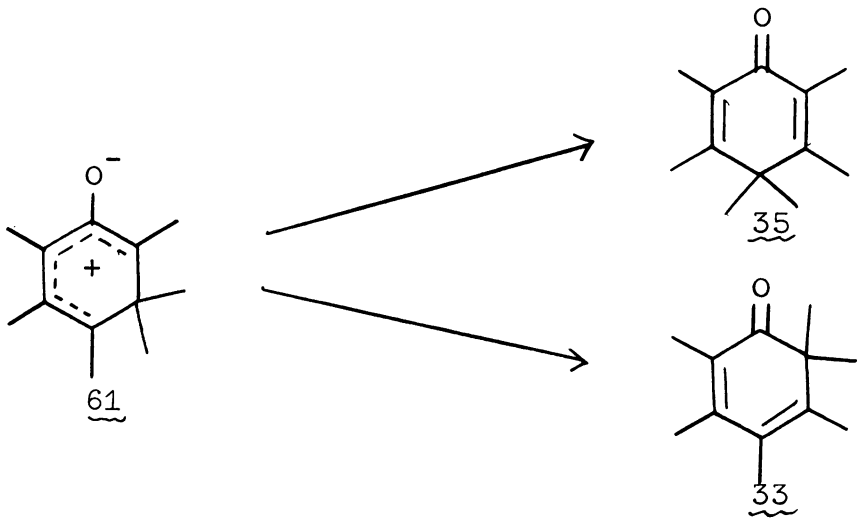
75 75a

There is also the possibility that these dipolar species 73a and 27 do react with the alcoholic solvent to give products similar to 36, but that these are then rapidly converted by a trace of acid in the solvent to phenol 74 and dienone 28, respectively. Evidence for this is the smooth conversion of 36 to 35 on treatment with a trace of acid. Indeed, it was found that irradiation of 34 in ethanol or methanol which had not been previously purified to free it from acid (distillation from sodium methoxide) gave the dienone 35 in good yield. Clearly, the photolysis of bicyclohexenones

73 and 26 in acid-free methanol would be worthwhile to investigate.

B. The Photochemistry of Hexamethylbicyclo-[3.1.0]hex-3-en-2-one (34) in Diethyl Ether

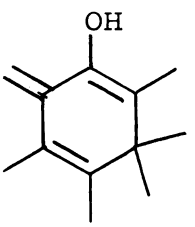
The observation that photolysis of 34 in methanol leads to a single product 36 which is apparently formed by reaction of a dipolar intermediate 61 with a molecule of methanol led us to study the photochemical behavior of 34 in diethyl ether, a non-nucleophilic neutral solvent. It was thought that photolysis of 34 would furnish the dipolar species 61, which, in the absence of a nucleophile (such as methanol) might undergo alkyl migration to give dienones 33 or 35, as has been observed in other systems (see Introduction).



A solution of bicyclohexenone 34 in anhydrous ether was irradiated at 0° with light of $\lambda > 280$ mμ. The reaction was followed by ultraviolet spectroscopy. As the photolysis proceeded, uv bands due to the starting ketone decreased in

intensity and a strong band appeared at 252 mμ. When the reaction was complete (as determined by the absence of any change in the intensity of the 252 mμ band on further irradiation) the ether was evaporated *in vacuo* at room temperature.

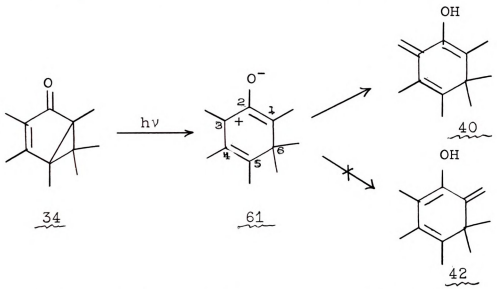
The nmr spectrum of the resulting yellow oil in CCl_4 showed it to contain a small amount of ether; the remaining singlets at τ 5.00, 5.20, 8.17, 8.23, and 8.90 were virtually identical in intensity and chemical shift to the nmr spectrum (Table I) of the enolic triene 40 (prepared by warming 36) in CCl_4 solution. Also consistent with structure 40 was the strong ultraviolet absorption at 252 mμ observed for the photolysis solution.



40

The structure of the photoproduct was further reinforced by converting it to 2,3,4,4,5,6-hexamethyl-2,5-cyclohexadienone (35) with a trace of acid. Addition of 18 μl of 1% hydrochloric acid to 5 μl of the photolysis solution dissolved in about 3 ml of 95% ethanol resulted in the disappearance of the ultraviolet band at 252 mμ (A = 1.42) due to 40 and formation of a new band at λ 244-245 mμ (A = 0.96) corresponding to dienone 35.

A possible pathway for the conversion of 34 to 40 in ether is outlined below. It is proposed that the enol 40 is

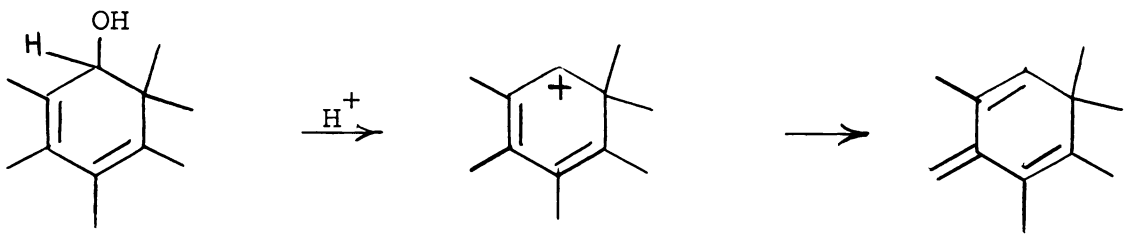


formed via a rapid proton transfer from the C-3 methyl of 61 to the adjacent negatively charged oxygen. Loss of a proton from the C-1 methyl would lead to fully conjugated product 42. The fact that this product is not observed further demonstrates the preferential formation of 1,4- rather than 1,3-conjugated products in these systems. Formation of the enol form of 40 rather than its keto tautomer 47, even though the latter appears to be more stable under equilibrium conditions (heat), suggests that 40 is formed via a kinetically controlled process such as the rapid protonation on oxygen depicted above.

There remains the question of why the intermediate 61 undergoes proton loss from the C-3 methyl, rather than alkyl migration, as is normally observed (see Introduction). The answer may lie in the unexpected stability of enol 40, perhaps due to the double bonds being substituted with alkyl groups.

Formation of 40 as the only product requires that proton loss from 61 be much more rapid than methyl migration to give 33 or 35.

An example of this phenomenon in a similar system is the acid-catalyzed dehydration of alcohol 76 reported by Hart, Collins and Waring (15). These workers found that



76 76a 77

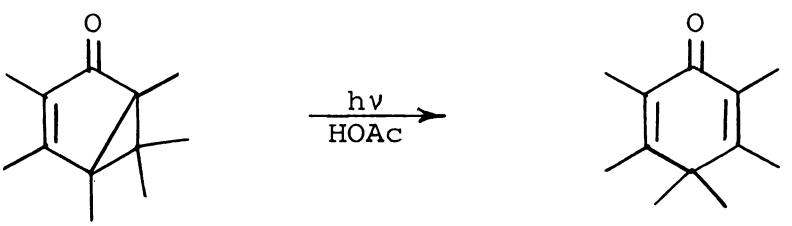
treatment of 76 with HCl in pyridine gave the triene 77 in greater than 95% yield. This was attributed to rapid proton abstraction from 76a by the solvent before aromatization could occur. In the case of 61, the negatively charged oxygen may perform the same function as the basic solvent described above.

C. The Photochemistry of Hexamethylbicyclo-[3.1.0]hex-3-en-2-one (34) in Acetic Acid

In view of the interesting solvent effects observed in bicyclohexenone photochemistry (see Introduction), a study was made of the photochemical behavior of 34 in aqueous acetic acid. A solution of 34 in 45% acetic acid at 0° was irradiated with light of $\lambda > 280$ mμ. The reaction was monitored by vpc. As the photolysis proceeded, the vpc peak

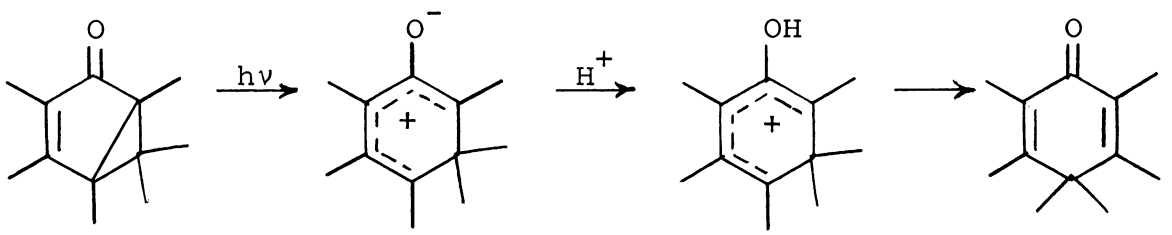
due to 34 decreased in intensity and a new peak with a longer retention time appeared. This peak increased in intensity at the expense of 34 until all the bicyclohexenone had reacted. There was no evidence for the formation of any intermediate between 34 and the observed product. Bicyclic ketone 34 was stable in the dark under the photolysis conditions.

An nmr spectrum of the crude material obtained by work-up of the photolysis solution showed it to contain 7% unreacted 34 and 93% dienone 35. Recrystallization from petroleum ether afforded a white crystalline solid which had an nmr spectrum and vpc retention time identical to that of an authentic sample of 35 (14). The following sequence is therefore established:



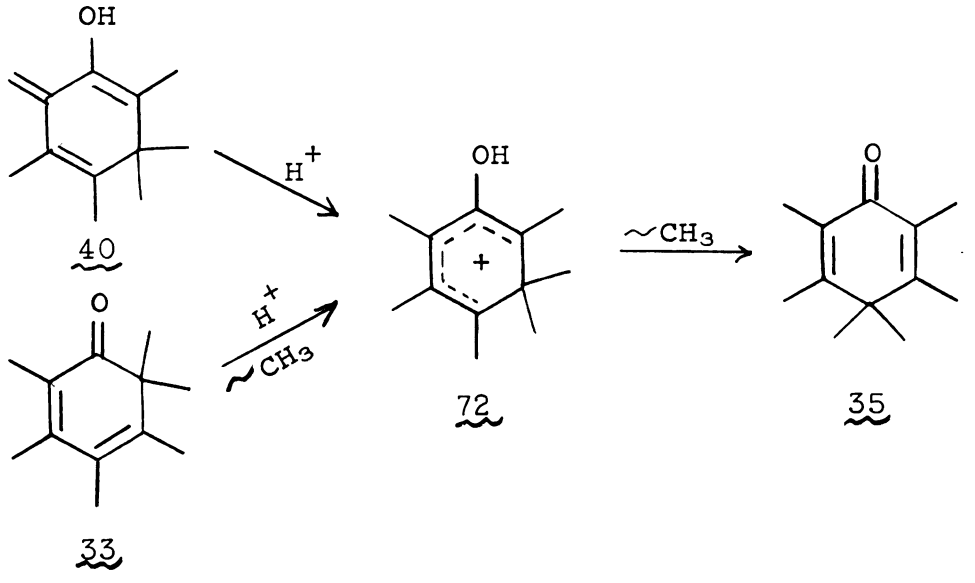
34 35

A possible pathway for the conversion of 34 to 35 in acidic media is outlined below. One significant feature is



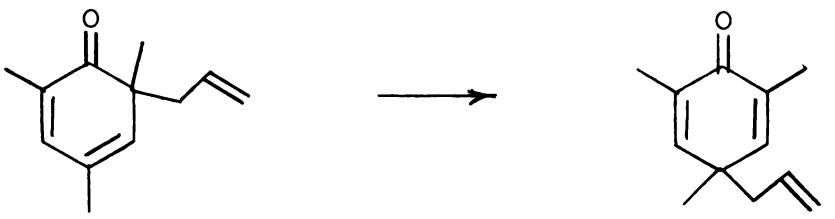
34 61 72 35

the marked sensitivity of the photochemical behavior of 34 to the presence of acid. This constitutes yet another example of a solvent effect in bicyclohexenone photochemistry. The difference in behavior of 34 in acidic media is probably due to protonation of species 61 on oxygen. Strong evidence for ion 72 being a precursor of dienone 35 is the very probable intermediacy of this species in the acid-catalyzed rearrangement of 40 and 33 to 35.



The preferential formation of dienone 35, rather than 33 can be attributed to the low stability of linearly conjugated cyclohexadienones compared to cross-conjugated cyclohexadienones.

Miller has shown, for example, that dienone 78 rearranges smoothly to 79 on heating for 2-3 hours at 100-110° (29).



78 79

Similarly, Denivelle and Fort have reported that 6-bromocyclohexa-2,4-dienones rearrange completely to 4-bromocyclohexa-2,5-dienones on standing (30).

EXPERIMENTAL

A. General Procedures

The nmr spectra were obtained with a Varian A-60 spectrometer, using CCl_4 solutions (unless otherwise stated) with tetramethylsilane as an internal reference. Infrared spectra were taken on a Unicam SP-200 Spectrometer, in CCl_4 solution unless otherwise stated. Varian-Aerograph gas chromatographs were used. Ultraviolet spectra were taken on a Beckman DB spectrophotometer. Mass spectra were carried out by Harold Harris with a Consolidated Electrodynamics Corporation 21-103C instrument. Melting points are uncorrected. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

B. General Photolysis Procedures

All irradiations were conducted using either a Type S 200 or 450w Hanovia lamp. This was placed in a water-cooled quartz jacket which was inserted in a glass vessel of a slightly larger diameter. The resulting annular space held about 450 ml of solution, which could be stirred by a stream of nitrogen gas. Irradiation of small amounts (< 25 ml) of solution was carried out in a Pyrex test tube taped to the side of the quartz immersion well.

C. Photolysis of 1,3,4,5,6,6-Hexamethylbicyclo-[3.1.0]hex-3-en-2-one (34) in Methanol

The methanol should be freshly distilled from sodium methoxide, and all glassware should be washed with alkali before use. A solution of 1.81 g of 34 (15) in 400 ml of methanol, stirred with a stream of dry nitrogen, was irradiated at 15° with a 200-w Hanovia lamp through a Pyrex filter. The reaction, which was complete in about 250 minutes, was followed by vpc (disappearance of enone) or by uv (disappearance of the peaks at 235 and 274 mμ due to 34). Evaporation of the solvent in vacuo at 20° led to the isolation of 2,3,3,4,5,6-hexamethyl-6-methoxycyclohexa-1,4-dien-1-ol (36) as white crystals.

Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54.

Found: C, 74.03; H, 10.43.

Compound 36 showed a λ_{max}^{MeOH} at 202 mμ (ε 4,300). Its nmr spectrum was most easily measured in methanol (see Table I). If one works quickly a similar spectrum is observed in CCl_4 (Figure 2) (bands at τ 7.13, 8.33, 8.38, 8.75, 8.92 and 8.96) except for an additional one-proton singlet at τ 5.75 (-OH); at the usual probe temperature (about 35°), this spectrum changes rapidly (see below).

An infrared spectrum of 36 in CCl_4 was obtained by cooling the cells in a freezing chest; the cells were then filled with a solution of 36, and the spectrum run quickly. Prominent bands appeared at 3555 (O-H), 2980 and 2930 (C-H), 1618 (C=C), 1375, 1345, 1290, 1215, 1105 and 1072 cm^{-1}; there was no carbonyl absorption.

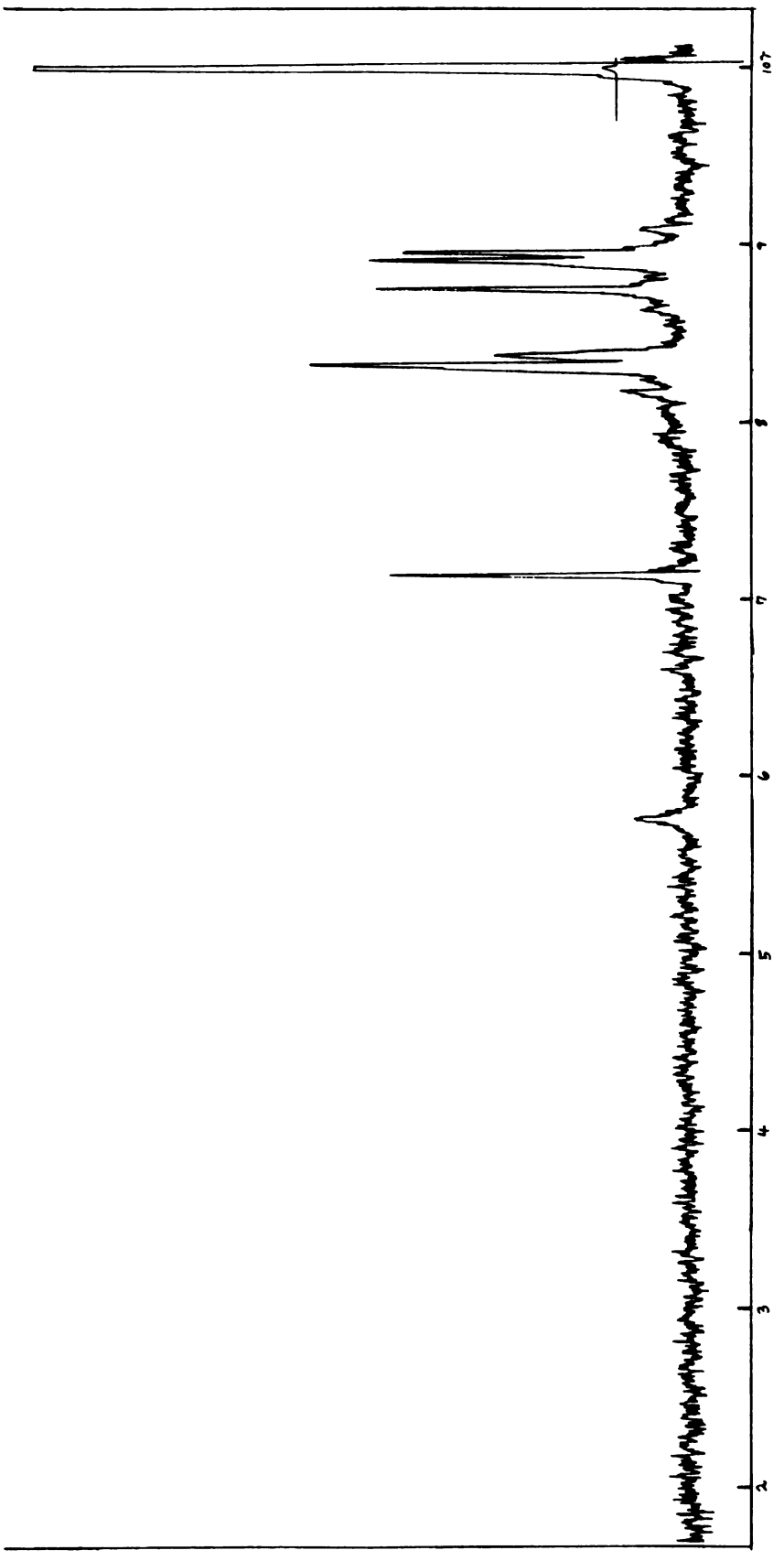


Figure 2. Nmr spectrum of 2,3,3,4,5,6-hexamethyl-6-methoxycyclohexa-1,4-dien-1-ol (36).

In a separate experiment to determine the isolable yield and stability of 36, a solution of 0.327 g of 34 (15) in 2 ml of methanol (freshly distilled from sodium methoxide; all glassware alkali-washed) in a Pyrex test tube sealed with a serum cap was irradiated by attaching it to the side of a water-cooled quartz well containing a 450 watt Hanovia lamp. Photolysis was complete in 130 min (vpc). The solution was cooled to -70°, and the photoproduct was filtered and rinsed with cold (-70°) methanol. The yield of white, crystalline 36 was 0.294 g (76%). The crystals could be stored indefinitely at -70°, but on standing overnight at room temperature they were transformed to a viscous yellow oil. Starting at room temperature, with a heating rate of 2°/min, 36 has a mp of 58-65°.

D. The Photosensitized Reaction of Hexamethylbicyclo-[3.1.0]hex-3-en-2-one (34)

The following experiment was performed to determine whether the photolysis could be sensitized. Starting enone 34 and benzophenone were washed with 5% sodium hydroxide, then water, before use; methanol was freshly distilled from sodium methoxide, and all glassware was washed with alkali. A solution of 0.098 g of 34 in 10 ml of methanol was placed in a 25 ml Pyrex test tube, sealed with a serum cap. In a similar tube was placed a solution of 0.098 g of 34 and 5.02 g of benzophenone in 10 ml of methanol. Both tubes were taped to the side of a water-cooled quartz well containing a 200

watt Hanovia mercury vapor lamp. A stream of air was passed over the lamp; this had been observed to decrease the photolysis rate of 34. The photolysis was followed by injecting 10 μl samples on a gas chromatograph, 5' x 1/4" 20% SE-30 column, 180°. Disappearance of starting enone and appearance of photoproduct (or vpc decomposition product thereof) were both followed. After 225 min, photolysis had proceeded to the extent of 13.2% and 53.9% respectively, in the two tubes.

E. The Dark Reaction of Hexamethylbicyclo-[3.1.0]hex-3-en-2-one (34) in Methanol

Enone 34 (0.066 g) was dissolved in 3 ml of methanol and the resulting solution was stored in the dark at 0° for 70 hours, at which time the methanol was evaporated in vacuo, yielding a clear oil (0.063 g). The nmr spectrum of the product (Table I) showed it to consist entirely of 34.

F. 2,3,3,4,5-Pentamethyl-6-methylenecyclo-hexa-1,4-dien-1-ol (40)

When an nmr tube containing a solution of 36 in CCl_4 was allowed to remain in the probe (about 35°) for 5 min, it was noted that a new band appeared at τ 6.62, due to methanol. After 10 min, this band reached maximum area, and other spectral changes were complete. The product, which is 2,3,3,4,5-pentamethyl-6-methylenecyclohexa-1,4-dien-1-ol (40), had an nmr spectrum as shown in Table I and Figure 3. Evaporation afforded a yellow oil with a λ_{max}^{MeOH} at 252 mμ (ε 13,400). An ir spectrum of 40 showed a strong hydroxyl

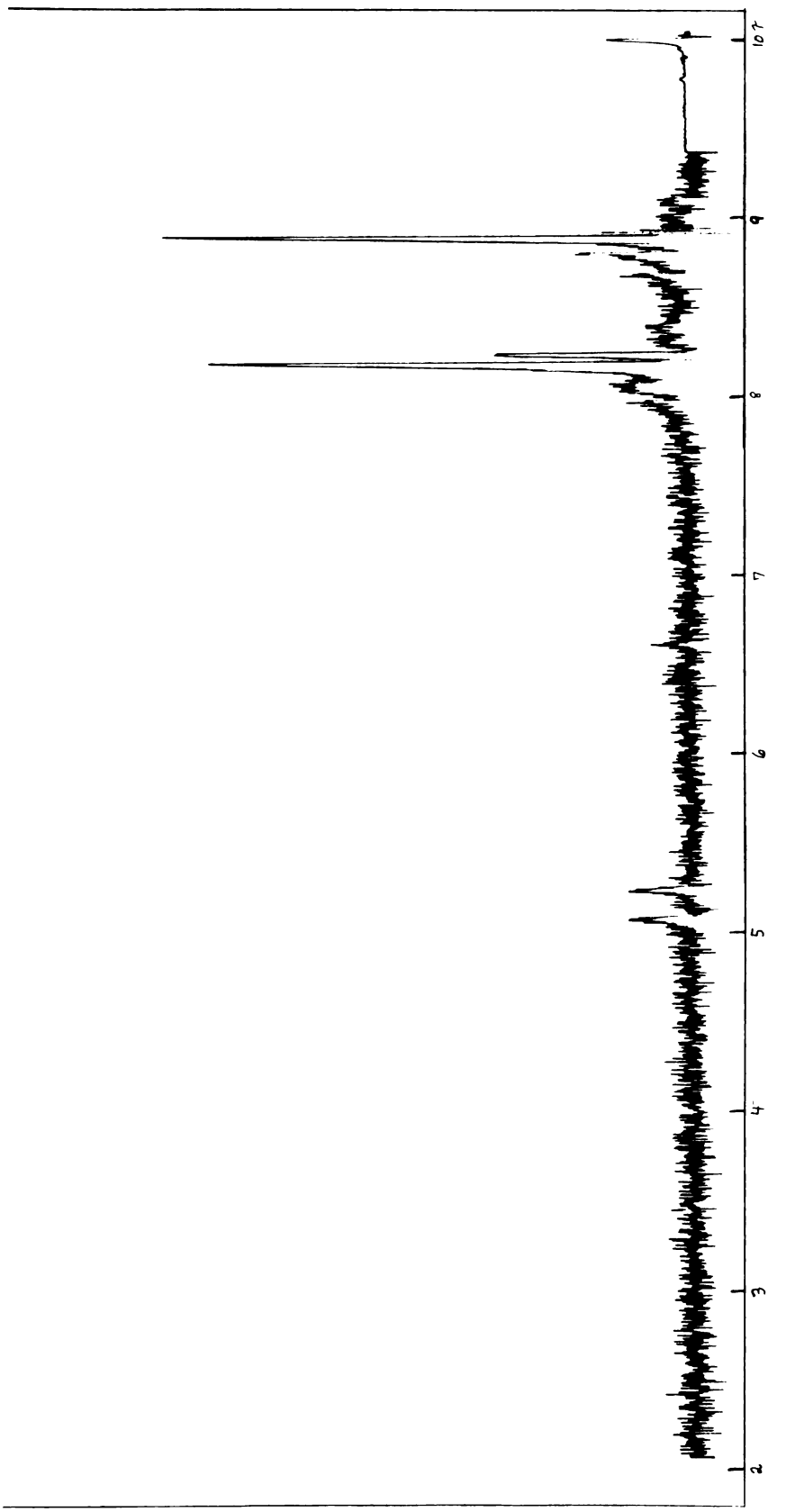


Figure 3. Nmr spectrum of 2,3,3,4,5-pentamethyl-6-methylenecyclohexa-1,4-dien-1-ol (40).

band at 3450 cm^{-1} and other bands at 2945, 2900, 2840 (C-H), 1620, 1575, 1450, 1375, 1270, 1208, 1108, 1075, 1025 and 864 cm^{-1}.

G. Acid-Catalyzed Conversion of 2,3,3,4,5,6-Hexamethyl-6-methoxycyclohexa-1,4-dien-1-ol (36) and 2,3,3,4,5-pentamethyl-6-methylenecyclohexa-1,4-dien-1-ol (40) to 2,3,4,4,5,6-Hexamethyl-2,5-cyclohexadienone (35)

A few crystals of 36 were dissolved in 30 ml of methanol and 2 drops of dilute HCl were added. The solution was evaporated in vacuo at room temperature, and the nmr spectrum of the residue was identical with that of dienone 35 (14,20), except for a small amount of an unknown impurity.

The nmr spectrum of dienone 35 is presented in Table I and Figure 4. Its ir spectrum showed bands at 1653 cm^{-1} (C = O) and 1624 cm^{-1} (C = C). Its uv spectrum had λ_{max}^{EtOH} at 246 mμ (ε 14,800).

A 10% solution containing a 50:50 mixture of 40 and 35 in methanol was acidified with 2 drops of dilute HCl. An nmr spectrum run on the resulting solution showed peaks due only to 35.

To 3 ml of a solution of 36 in methanol in a uv cell (λ_{max} 202 mμ, A = 0.97) was added 4 μl of 1% HCl in methanol. The solution now had a strong absorbance at 252 mμ (A = 0.88) due to the formation of 40. After 10 μl additional HCl, the solution had a λ_{max} at 251 mμ (A = 0.79), and after another 10 μl of HCl, λ_{max} at 247 mμ (A = 0.68), due to conversion to 35.

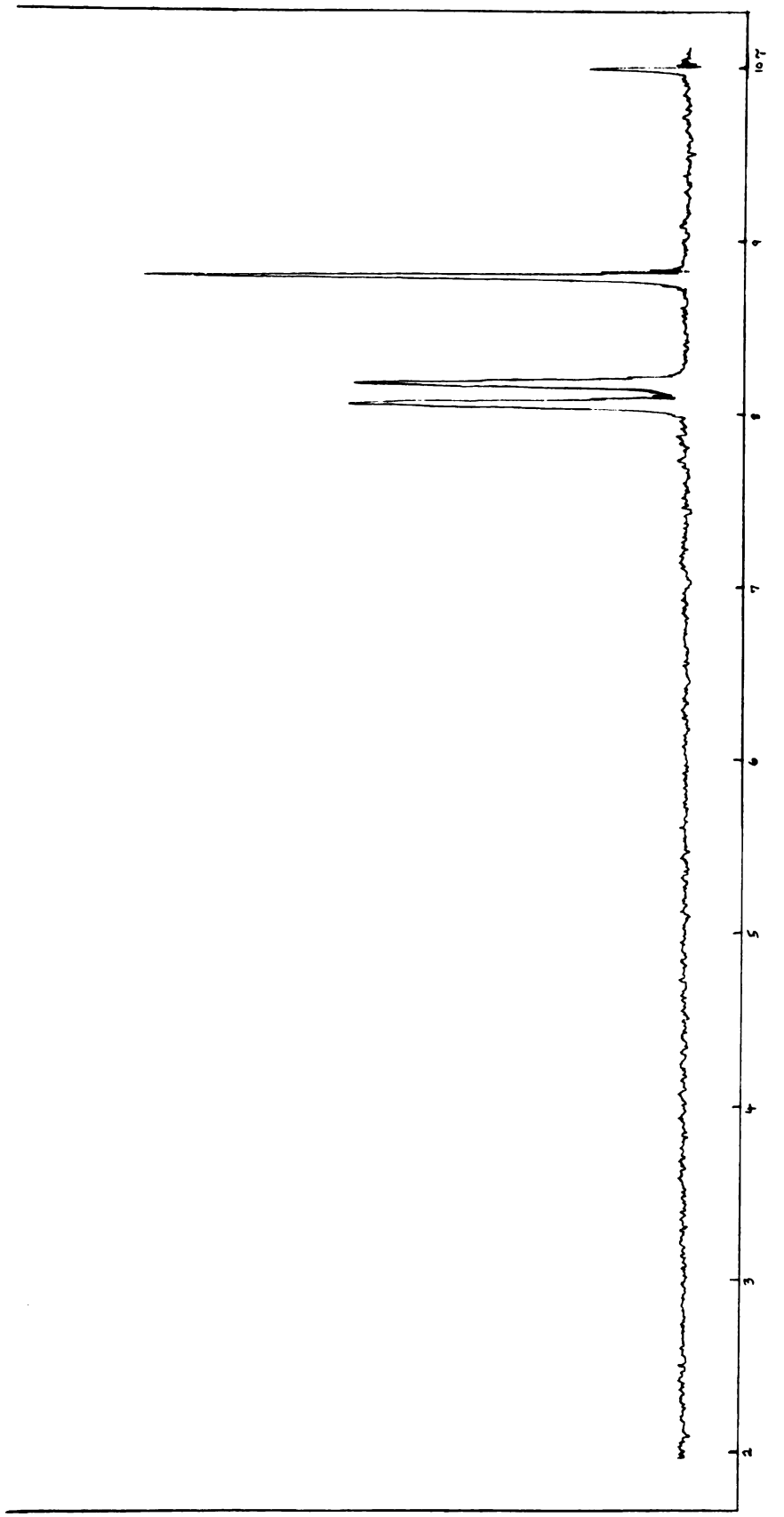


Figure 4. Nmr spectrum of 2,3,4,4,5,6-hexamethyl-2,5-cyclohexadienone (35).

H. Preparation of 2,4,4,6-Tetramethyl-3,5-bis(trideuteromethyl)-2,5-cyclohexadienone (44)

To a solution of 35 (7.8 g) in 63 ml of CH_3OD (31) was added a 0.5 cm^3 piece of sodium. The resulting solution was refluxed for 70 hrs, after which time an nmr spectrum showed that exchange was complete. Most of the methanol was evaporated *in vacuo*, and the remaining solution was poured into 200 ml of methylene chloride. This was extracted with cold (0°) water to remove the remaining methanol, and the solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 7.6 g (97%) of crystalline 44 which had an nmr spectrum with two equal singlets at τ 8.18 and 8.78.

I. 2-Methoxy-2,3,4,5,5,6-hexamethylcyclohex-3-en-1-one (45)

A solution of 34 (0.81 g) in 25 ml of methanol was irradiated at 0° in a Pyrex test tube for 74 min with a 450 watt Hanovia lamp. After this time white crystals of 36 could be seen suspended in the methanol, and photolysis was complete (vpc). The photolysis solution was poured into 25 ml of 0.2N sodium methoxide in methanol and stirred for 30 min at 0°. Water (35 ml) was added, the solution was extracted with methylene chloride, and the latter solution was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave 2-methoxy-2,3,4,5,5,6-hexamethylcyclohex-3-en-1-one (45) as a colorless oil in nearly quantitative yield. Its ir spectrum showed bands at

1716 cm^{-1} (C = O) and 1115 cm^{-1} (C-O-CH_3). Its nmr spectrum is shown in Table I and Figure 5. Its uv spectrum had a λ_{max}^{EtOH} at 202 mμ (ε 5,350).

J. 2,3,5,5,6-Pentamethyl-4-methylenecyclohex-2-en-1-one (46)

When 45 was injected on a gas chromatograph (5' SE-30 column, 200°) one major peak was observed; collection of the product showed that 45 had lost a mole of methanol. The new product, which was a colorless oil, is assigned the structure 2,3,5,5,6-pentamethyl-4-methylenecyclohex-2-en-1-one (46).

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18.

Found: C, 80.79; H, 10.09.

46 had ir bands at 1667 cm^{-1} (C = O), 1600 cm^{-1} (C = C) and 905 cm^{-1} (terminal CH_2). Its uv spectrum had a λ_{max}^{EtOH} at 280 mμ (ε 13,800). Its nmr spectrum in CCl_4 is shown in Table I and Figure 6.

The nmr spectrum of 46 in CD_3OD consisted of bands at τ 4.66 (1H,s), 4.88 (1H,s), 8.06 (1H, q, J = 7.0 cps), 8.20 (3H,s), 8.45 (3H,s), 9.22 (6H,s) and 9.37 (3H, d, J = 7.0 cps). Sodium hydroxide (0.0033 g) was added to a solution of 46 (0.075 g) in 0.2 ml of CD_3OD. After the solution had remained at room temperature for 16 hrs, its nmr spectrum showed that the quartet at τ 8.06 and the singlet at τ 8.20 were missing, and the peak at τ 9.37 had become a singlet.

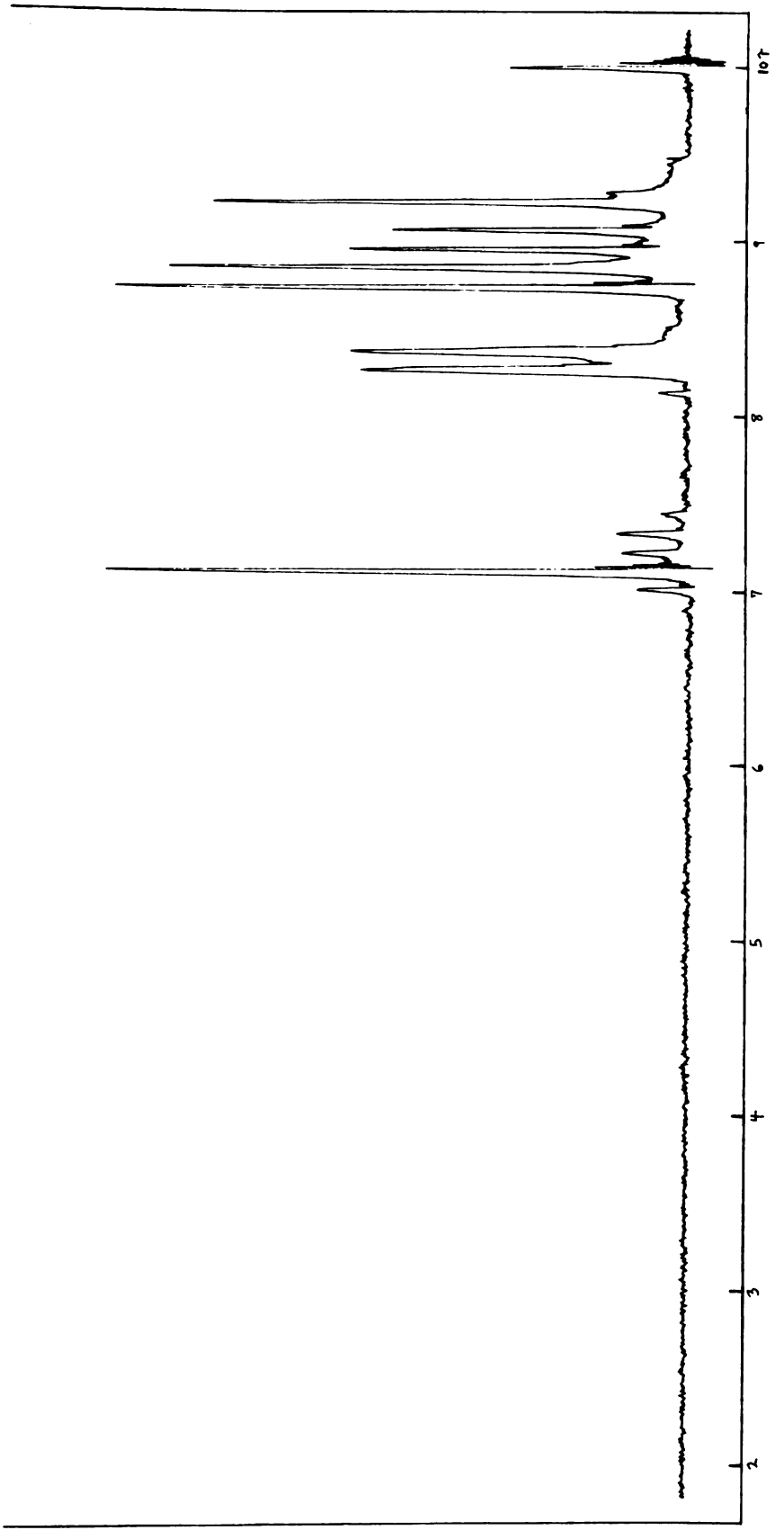


Figure 5. Nmr spectrum of 2-methoxy-2,3,4,5,5,6-hexamethylcyclohex-3-en-1-one (45).

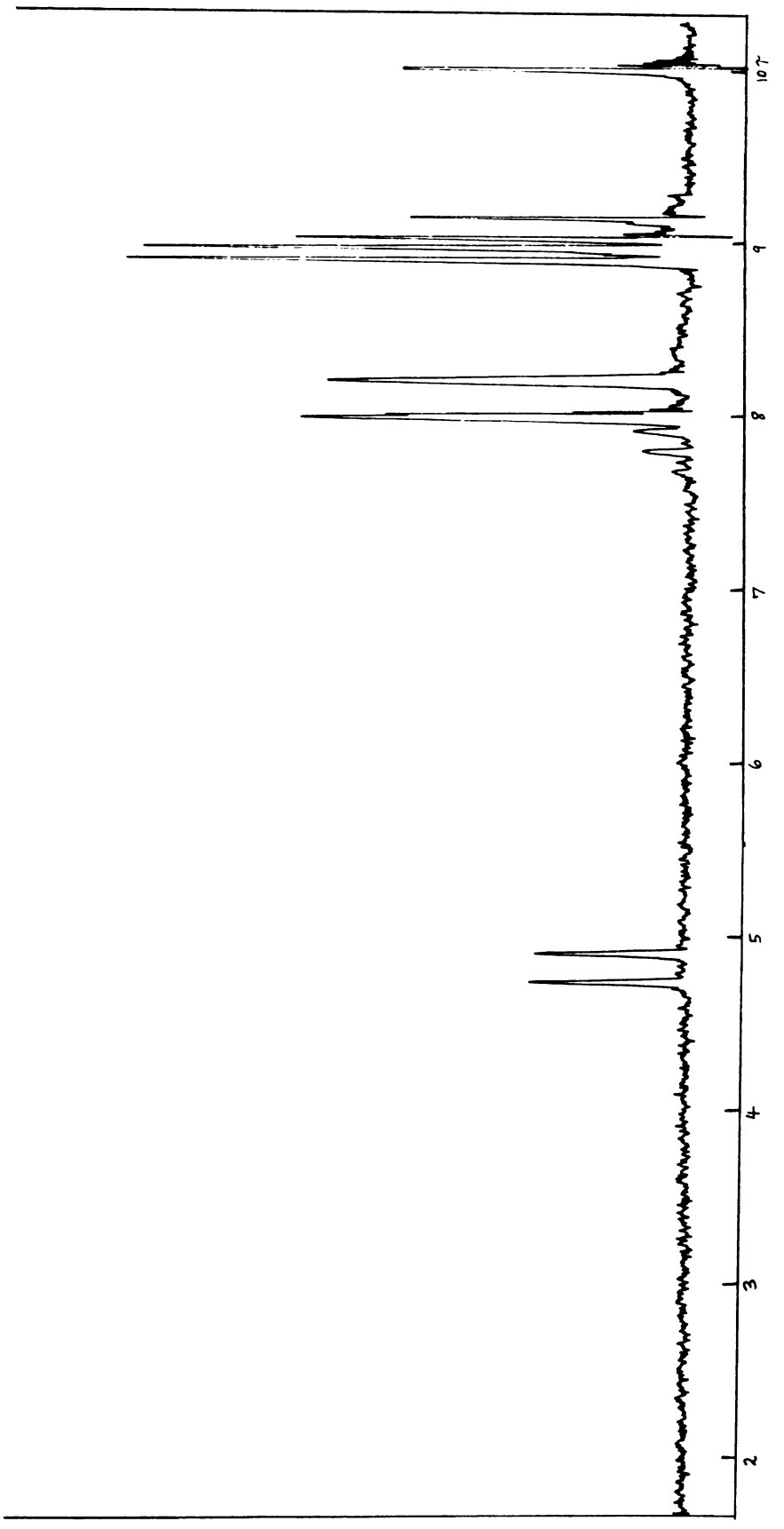


Figure 6. Nmr spectrum of 2,3,5,5,6-pentamethyl-4-methylenecyclohex-2-en-1-one (46).

K. 3,4,5,5,6-Pentamethyl-2-methylenecyclohex-3-en-1-one (47)

When an ether solution of 40 was injected on a gas chromatograph (10' Apiezon-L column, 180°) one major peak (other than solvent) was observed; collection gave a clear oil which is assigned the structure 3,4,5,5,6-pentamethyl-2-methylenecyclohex-2-en-1-one (47). Its ir spectrum had prominent bands at 1700 cm^{-1} (C = O) and 920 cm^{-1} (terminal CH_2). Its nmr spectrum is reported in Table I and Figure 7.

L. Preparation of 2,4,6,6-Tetramethyl-3,5-bis(trideuteromethyl)-2,4-cyclohexadienone (49)

Dienone 49 was prepared by a modification of the method of Hart, Collins, and Waring (15). To a solution of unlabeled dienone 33 (9.66 g) in 50 ml of CH_3OD was added a 0.8 cm^3 piece of sodium. The resulting solution was refluxed for 96 hours, at which time most of the methanol was evaporated *in vacuo*, and 25 ml of CH_3OD was added. The resulting solution was refluxed for 49 hours, after which time an nmr spectrum showed that exchange was complete. Most of the methanol was evaporated *in vacuo*, and the remaining solution was poured into 200 ml of methylene chloride. This was extracted with cold (0°) water, and the solution was dried over anhydrous magnesium sulfate. Evaporation yielded an oil, which on distillation gave 6.94 g (70%) of dienone 49 (bp 84-87° at 1.4 mm). Its nmr spectrum in CCl_4 consisted of three singlets at τ 8.13 (3.3H), 8.18 (3.0H) and 8.90 (6.0H).

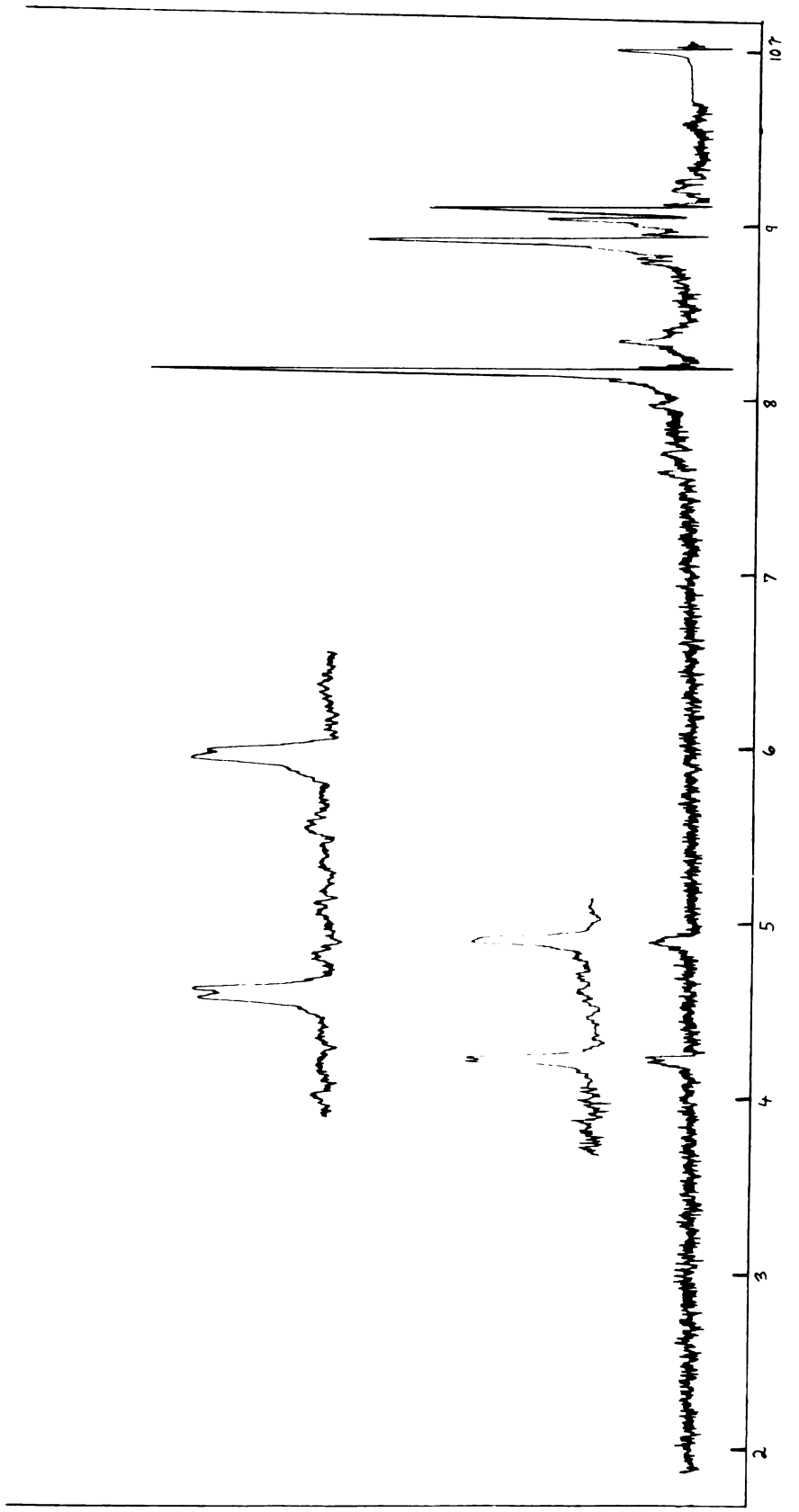


Figure 7. Nmr spectrum of 3,4,5,5,6-pentamethyl-2-methylenecyclohex-3-en-1-one (47).

M. Photolysis of 3,5,6,6-Tetramethyl-1,4-bis-(trideuteromethyl)bicyclo[3.1.0]hex-3-en-2-one (50)

Labeled enone 50 was prepared as previously described (15). Its nmr spectrum showed that label was essentially complete at the C-4 methyl, and 50% complete at the C-1 methyl. The enone was irradiated in methanol as described above for the unlabeled compound. The nmr spectrum of the resulting crystalline photoproduct (51) in methanol was identical with that of unlabeled 36 (Table I) except that the peak at τ 8.37 was almost absent, and the peak at τ 8.30 was a very sharp singlet, area 4.5H.

Thermal conversion of this labeled photoproduct (as described above for unlabeled 34) gave a mixture of 52 and 53. Disregarding bands due to the latter (see below) gave an nmr spectrum for 52 in methanol which was identical with that of unlabeled material, except that the allylic methyls appeared as a sharp singlet at τ 8.18 with a shoulder at τ 8.22, total area 4.6H.

Treatment of labeled 51 or 52 with a little dilute HCl led (as described above for unlabeled compounds) to labeled 53 whose nmr spectrum had bands at τ 8.05, 8.18 and 8.80 with relative areas 2.6:3.4:6.0. The two low-field peaks were singlets.

N. Photolysis of 2,3,4,4,5,6-Hexamethyl-2,5-cyclohexadienone (35) in Ether

A solution of 2.0 g of 35 in 400 ml of anhydrous ether kept at 15° under a nitrogen atmosphere was irradiated with

a 200 watt Hanovia lamp through a Vycor filter with magnetic stirring. After 81 min the photoproduct had reached a maximum concentration as shown by vpc and the reaction was terminated. Preparative vpc afforded 0.39 g of hexamethylbicyclo-[3.1.0]hex-3-en-2-one (34). The photolysis was not allowed to proceed to complete disappearance of the dienone, because the enone photoproduct undergoes further photorearrangement under these conditions.

O. Photolysis of 2,4,4,6-Tetramethyl-3,5-bis-(trideuteromethyl)-2,5-cyclohexadienone (44) in Ether

The deuterated dienone was photolyzed as described above for the unlabeled dienone. The photoproduct 1,3,6,6-tetramethyl-4,5-bis(trideuteromethyl)bicyclo[3.1.0]hex-3-en-2-one (54) had the following nmr spectrum: singlets at τ 8.45, 8.90 and 9.07 with relative areas 3:6:3.

P. Degradation of 1,3,6,6-Tetramethyl-4,5-bis-(trideuteromethyl)bicyclo[3.1.0]hex-3-en-2-one (54)

The hexadeuterated enone 54 was subject to ozonolytic degradation, followed by an oxidative work-up. The procedure used was similar to that employed by Hart, Collins and Waring (15) to degrade the unlabeled enone 34, except that the esterification step was omitted. Ozonolytic degradation of 54 led to a tri-deuterated anhydride 58, whose nmr spectrum in acetone-d_6 differed from that of the unlabeled compound in that the band at τ 8.63 (due to the equivalent methyls on the

ring junctions) was reduced in area from 6H to 3H; in other respects, the nmr spectrum was identical with that of the unlabeled anhydride (15).

Q. Photolysis of 1,3,6,6-Tetramethyl-4,5-bis-(trideuteromethyl)bicyclo[3.1.0]hex-3-en-2-one (54) in Methanol

Labeled enone 54 was irradiated in methanol as described above for the unlabeled compound. An nmr spectrum of the product in MeOH showed it to be a mixture of 55 and 56. If peaks due to the hydroxytriene 56 were disregarded, a spectrum due to labeled 55 resulted which lacked the band at τ 8.37 and showed only a 3 proton singlet at τ 8.30; in other respects, the nmr spectrum was identical with that of unlabeled 36.

The methanol solution of photoproduct was allowed to remain in the refrigerator overnight. It was then evaporated *in vacuo* to 0.5 ml, giving a solution of labeled 56 whose nmr spectrum showed a small singlet (about 1H) at τ 8.15, and singlets at τ 8.22 (3H) and 8.88 (6.7H).

In one photolysis of 54, a trace of acid must have been present, since the major reaction product was labeled hexamethyl-2,5-cyclohexadienone, 57. Its nmr spectrum showed singlets at τ 8.05 (3H), 8.18 (5.2H) and 8.80 (3.2H).

R. Photolysis of 1,3,4,5,6,6-Hexamethylbicyclo-[3.1.0]hex-3-en-2-one (34) in Diethyl Ether

A solution of 0.096 g of 34 in 6 ml of anhydrous ether (freshly distilled from lithium aluminum hydride), was

irradiated at 0° with a 450 watt Hanovia lamp through a Pyrex filter. The reaction, which was complete in 131 min, was followed by ultraviolet spectroscopy (disappearance of the bands at 235 and 274 mμ due to 34). Evaporation of the solvent in vacuo at 20° led to the isolation of 2,3,3,4,5-pentamethyl-6-methylenecyclohexa-1,4-dien-1-ol (40) as a yellow oil (0.117 g). Compound 40 showed a λ_{max}^{MeOH} at 252 mμ. Its nmr spectrum in CCl_4 was virtually identical with a spectrum of an authentic sample of 40 (Table I), and consisted of bands at τ 5.00, 5.20, 8.17, 8.23, and 8.90. To 3 ml of a solution of photoproduct 40 in ethanol in a uv cell (λ_{max} 252 mμ, A = 1.42) was added 18 μl of 1% aqueous HCl. The solution now had a strong absorbance at 244 mμ (A = 0.96) owing to the formation of 35.

S. Photolysis of 1,3,4,5,6,6-Hexamethylbicyclo-[3.1.0]hex-3-en-2-one (34) in 45% Acetic Acid

A solution of 0.112 g of 34 in 8 ml of 45% aqueous acetic acid kept at 0° was irradiated with a 200 watt Hanovia lamp through a Pyrex filter. After 150 min, the photoproduct had reached a maximum concentration as shown by vpc, and the reaction was terminated. Water (40 ml) was added, the solution was extracted with methylene chloride. The latter solution was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo gave 0.119 g of yellow crystals whose nmr spectrum in CCl_4 showed the presence of 93% of 35 and 7% unreacted 34. Recrystallization from

petroleum ether gave 0.046 g of white crystals of 35 (14, 20), identified by its nmr spectrum and retention time.

After a solution of 0.099 g of 34 in 8 ml 45% acetic acid had remained in the dark at 0° for 150 min, its vpc trace showed that no 35 had been formed.

SUMMARY

1. Photolysis of 1,3,4,5,6,6-hexamethylbicyclo[3.1.0]hex-3-en-2-one (34) in methanol at 0° gave a crystalline photoproduct, 2,3,3,4,5,6-hexamethyl-6-methoxycyclohexa-1,4-dien-1-ol (36), in 76% yield.

2. The photoproduct (36) was quite unstable and lost methanol on treatment with acid or on warming to give 2,3,3,4,5-pentamethyl-6-methylenecyclohexa-1,4-dien-1-ol (40), which was converted to 2,3,4,4,5,6-hexamethyl-2,5-cyclohexadienone (35) on further acidification.

3. The course of the photochemical and acid-catalyzed rearrangement was established by using enone 34 variously labeled with CD_3 groups.

4. The photoproduct 36 was converted by basic methanol to its keto form, 2-methoxy-2,3,4,5,5,6-hexamethylcyclohex-3-en-1-one (45), which thermally lost methanol to give 2,3,5,5,6-pentamethyl-4-methylenecyclohex-2-en-1-one (46).

5. Photolysis of enone 34 in ether at 0° gave the enolic triene 40 in excellent yield.

6. Photolysis of 34 in 45% acetic acid afforded dienone 35 as the only product.

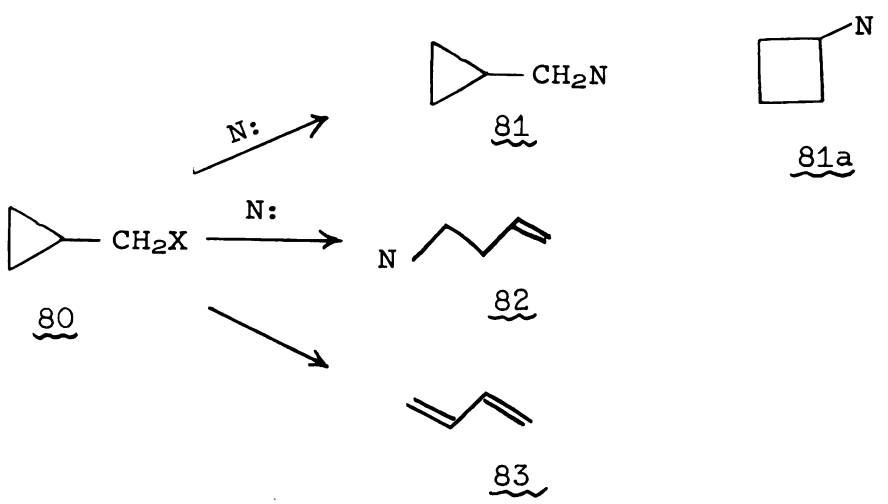
7. A mechanism is presented which accounts for the observed photochemical reactions of 34.

PART II

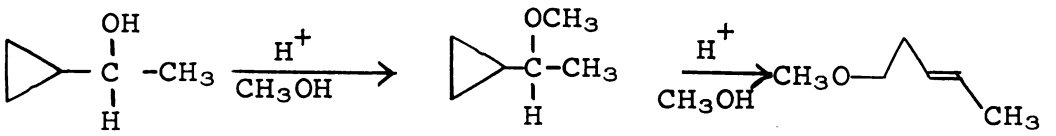
THE ACID-CATALYZED REARRANGEMENTS OF 1,3,4,5,6,6-HEXAMETHYLBICYCLO[3.1.0]HEX-3-EN-2-ONE AND 2,3,4,5,6,6-HEXAMETHYL-2,4-CYCLOHEXADIENONE

INTRODUCTION

Rearrangements of cyclopropylcarbinyl derivatives (80) have been the subject of numerous investigations in a variety of systems. These reactions have been extensively reviewed by Breslow (32) and Richey (33). The most common modes of reaction observed are the formation of either cyclopropylcarbinyl derivatives (81), cyclobutyl derivatives (81a) (34), or products resulting from cleavage of the cyclopropane ring (82 and 83).

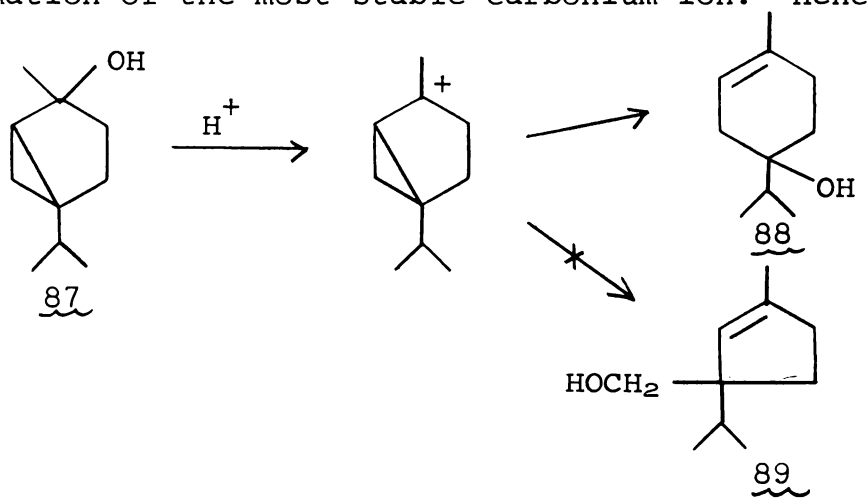


The unrearranged cyclopropyl products have the fastest rate of formation, but the more stable ring-opened products predominate under thermodynamically controlled conditions. One of the many examples of this is the initial formation of the methyl ether 85 on treatment of 84 with acid (35), followed by the slower conversion to the ring-opened product 86 on prolonged refluxing.



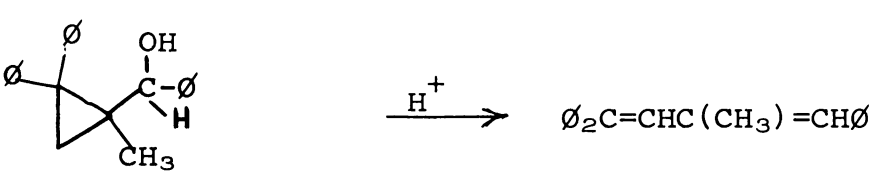
84 85 86

The ring-opened products obtained from cyclopropylcarbinyl cations are usually those which correspond to the formation of the most stable carbonium ion. Hence, 87, on



87 88 89

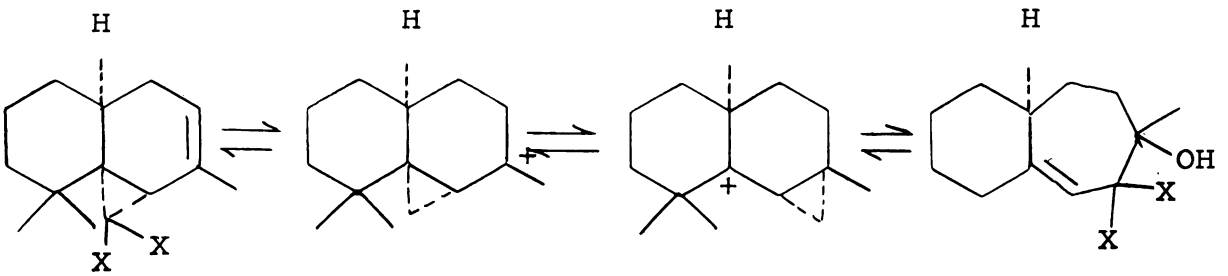
treatment with sulfuric acid, gives the cyclohexenol 88 rather than the isomeric cyclopentenol 89 (36). Similarly, treatment of 90 with p-toluenesulfonic acid gives the more



90 91

stable ring-opened product 91 in 95% yield (37).

A different mode of reaction has been observed for cyclopropylcarbinyl derivatives incorporated in 6-membered rings. In a study of cyclopropylcarbinyl rearrangements in the thujopsene series, Dauben and Friedrich have shown (38) that treatment of dideuterothujopsene (92) with refluxing dioxane acidified to .02N with perchloric acid



92, X = D
92a, X = H

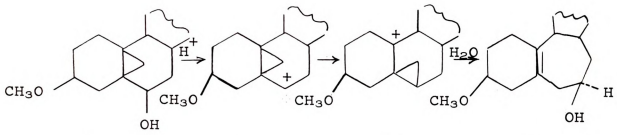
93

93a

94, X = D
94a, X = H

gives 94 as the most rapidly formed product. Similar treatment of 94a gives thujopsene (92a) as the initial product with the fastest rate of formation. To explain these results, the authors proposed the intervention of two discrete cyclopropylcarbinyl cations 93 and 93a, which are readily interconvertible. Proton loss from 93 gives 92, while ring opening of 93a, followed by reaction of the resulting cation with water affords 94.

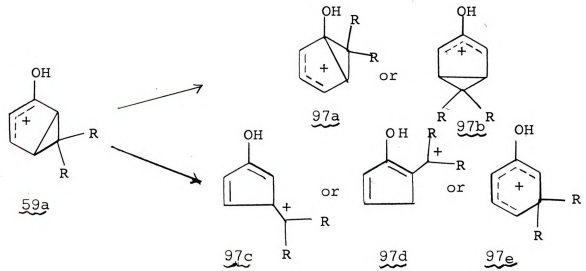
A similar cyclopropylcarbinyl rearrangement was proposed by Tadanier (39) to account for the acid-catalyzed conversion of the cyclosteroid 95 to the ring-opened product 96.



95 95a 95b 96

A cyclopropylcarbinyl rearrangement of the above type has also been proposed to account for the conversion of the benzenesulfonate of 10-hydroxymethyl-$\Delta^{1(9)}$-octalin, under acetolysis conditions, to 1-acetoxymethyl-$\Delta^{9(10)}$-octalin reported by Hikino and de Mayo (40).

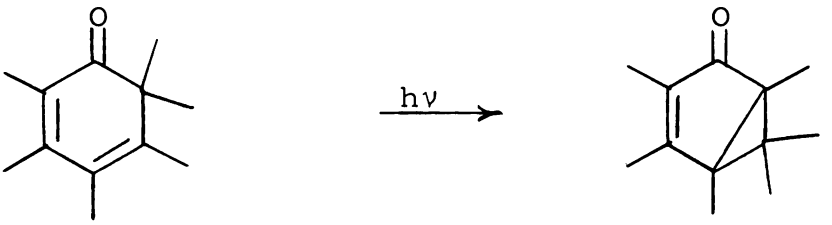
The possibility for cyclopropylcarbinyl rearrangements also exists in acid-catalyzed reactions of bicyclo[3.1.0]-hex-3-en-2-one systems. The cation 59a generated on



59a 97a 97b 97c 97d 97e

protonation of bicyclic ketone 59 can undergo isomerization to 97a or 97b (comparable with 93 ⟶ 93a, 95a ⟶ 95b) or direct ring opening to 97c, 97d, or 97e.

In view of the interesting possibilities for rearrangement of this system, a study of the behavior of 1,3,4,5,6,6-hexamethylbicyclo[3.1.0]hex-3-en-2-one (34) in acidic media was undertaken. This ketone can be obtained in good yield by ultraviolet irradiation of dienone 33 in ether (15).

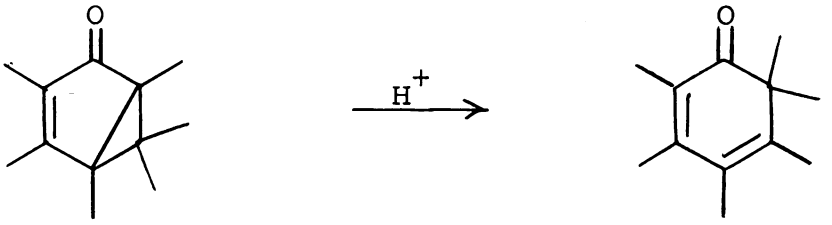


33 34

The results of this study, and the mechanistic implications derived from it, are presented in Part II of this thesis.

RESULTS AND DISCUSSION

Treatment of bicyclic ketone 34 (15) with 97% sulfuric acid at 22.6° for 30 minutes gave the fully conjugated dienone 33 in excellent yield. Its structure follows from the nmr and infrared spectra, which are identical to those



34 33

of an authentic sample (15). The nmr spectrum consists of three bands at τ 7.97, 8.14, and 8.89 (see Table I for assignments) with relative areas of 1:3:2. The infrared spectrum of 33 shows the expected carbonyl absorption at 1642 cm^{-1} (CCl_4).

On the basis of previously reported reactions of cyclopropylcarbinyl derivatives (see Introduction) two principal modes of rearrangement might be expected for the conversion of 67, the conjugate acid of bicyclic ketone 34, to dienone 33: (A) cleavage of the C-1, C-5 bond followed by methyl migration to C-1, or (B) a cyclopropylcarbinyl rearrangement to 68 attended by consequent ring opening to give 33 directly (Chart I).

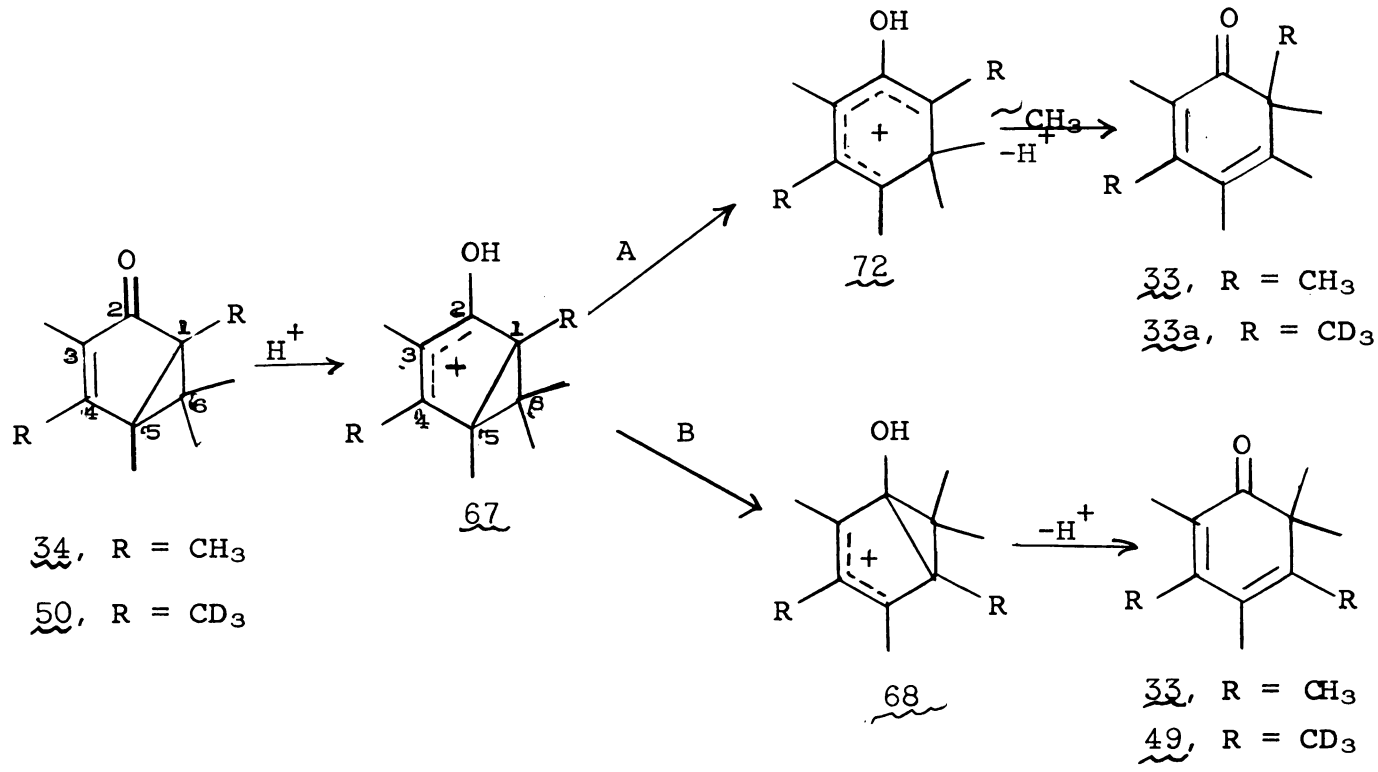
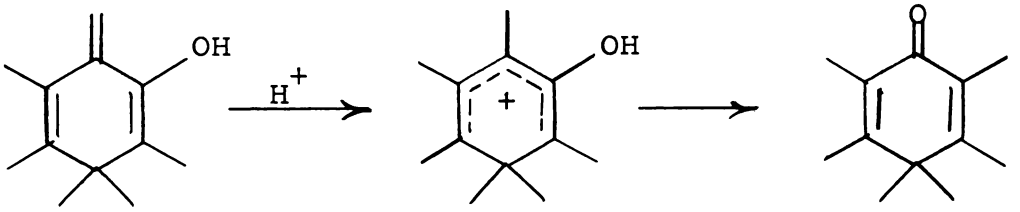

O
R
H+
OH
A
B
72
33, R = CH3
33a, R = CD3
67
34, R = CH3
50, R = CD3
68
-H+
33, R = CH3
49, R = CD3

Chart I

The rearrangement of ion 72 to dienone 33 presented in Path A represents a deviation from the previously observed tendency of similar systems to form cross-conjugated, rather than fully conjugated products (see Part I of thesis). It was found, for example, that treatment of 40 with a trace

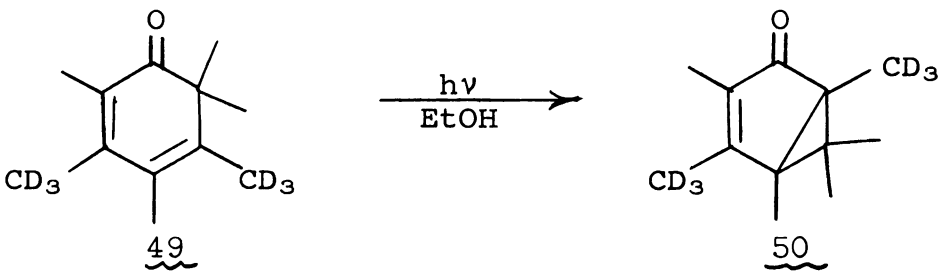


40 72 35

of HCl gave dienone 35 as the major product. The selective rearrangement of ion 72, produced by protonation of 40, to the cross-conjugated dienone 35, strongly suggests that Path A, which requires conversion of this ion to dienone 33, is not operative in the rearrangement of 34 to 33.

A. Acid-Catalyzed Rearrangement of Labeled Bicyclo[3.1.0]hexenones

To determine which, if either, of the two mechanistic paths A or B was responsible for the rearrangement, it was decided to carry out the acid-catalyzed reaction using 50 labeled in the C-1 and C-4 positions with CD_3 groups. This compound was prepared by photolysis of labeled dienone 49

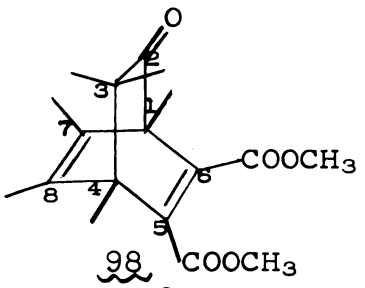
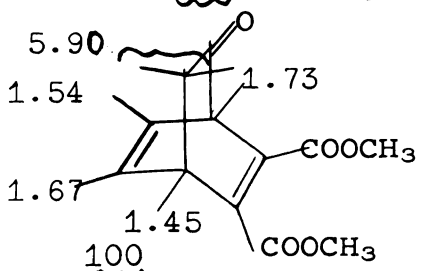
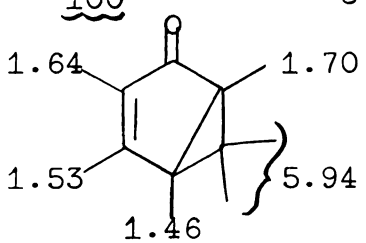
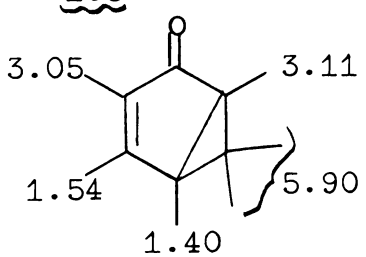


49 50

(synthesized by a variation of the method of Hart, Collins, and Waring (15)) in 95% ethanol. The sample of 50 which was used in this study was completely labeled at the C-4 methyl, but only 91% labeled at the C-1 methyl, as determined from its nmr spectrum. Thus, the nmr spectrum of 50 was similar to that of 34 (see Table I) except that it lacked the quartet at τ 8.12 (due to the C-4 allylic methyl) and the band at τ 8.45 for the C-3 allylic methyl was a singlet, rather than a quartet. The singlet at τ 8.90 was reduced in area from 6.00H to 3.27H, consistent with 91% label at C-1.

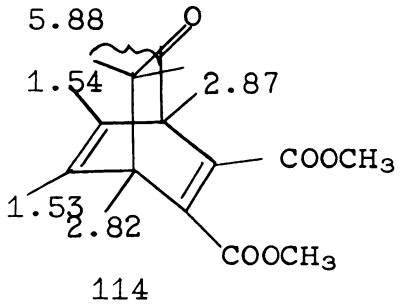
Rearrangement of bicyclic ketone 50 via Path A (see Chart I) would give dienone 33a, labeled with CD_3 groups in the C-3 and C-6 positions, whereas Path B would furnish dienone 49 with CD_3 in the C-3 and C-5 positions. Although dienones 33a and 49 could be differentiated on the basis of their respective nmr spectra, the similarity in chemical shift of the C-2, C-4, and C-5 allylic methyls of 33 (all appear as a broad band at τ 8.14) would make it difficult to distinguish between 49 and an isomer containing CD_3 groups at the C-3 and C-2, or C-3 and C-4 positions. Consequently, it was decided to convert the dienone obtained on treatment of 50 with acid to its dimethyl acetylenedicarboxylate adduct (98) (41). The nmr bands of this compound which correspond to the C-2, C-4, and C-5 allylic methyls of 33 (see Table II) are well resolved; the band at τ 6.34 due to

Table II. NMR Spectra[a]

Compound	Chemical Shifts (area)	Assignments
 98	6.34 (d, 6.0H) 8.22 (m, 3.0H) 8.30 (m, 3.0H) 8.57 (s, 3.0H) 8.60 (s, 3.0H) 9.02 (s, 3.0H) 9.08 (s, 3.0H)	C-5,C-6 methyls C-8 methyl C-7 methyl C-4 methyl C-1 methyl C-3 methyls
 100	6.34 (d, 6.00H) 8.22 (s, 1.67H) 8.30 (s, 1.54H) 8.57 (s, 1.45H) 8.60 (s, 1.73H) 9.02 (s, 2.88H) 9.08 (s, 3.02H)	Same as for 98
 108[b]	8.12 (s, 1.53H) 8.45 (s, 1.64H) 8.78 (s, 1.46H) 8.90 (d, 4.70H) 9.08 (s, 2.94H)	C-4 methyl C-3 methyl C-5 methyl C-1,C-6 methyls C-6 methyl
 112[c]	8.10 (q,J=1,1.54H) 8.45 (m, 3.05H) 8.77 (s, 1.40H) 8.92 (s, 6.11H) 9.08 (s, 2.90H)	C-4 methyl C-3 methyl C-5 methyl C-1,C-6 methyls C-6 methyl

continued

Table II -- continued

Compound	Chemical Shifts (area)	Assignments
 114	6.34 (d, 6.00H) 8.22 (s, 1.53H) 8.30 (s, 1.54H) 8.57 (s, 2.82H) 8.60 (s, 2.87H) 9.02 (s, 2.92H) 9.08 (s, 2.96H)	Same as for 98

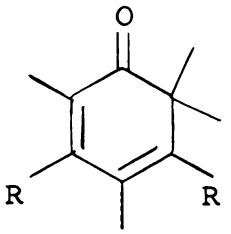
[a]All spectra are in CCl_4. Shifts are reported as τ values, with TMS as an internal reference. All spectra were run at 60 Mc. All areas are the average of three electronic integration measurements. Multiplicity of peaks shown in brackets: s, singlet; d, doublet; q, quartet; m, multiplet.

[b]The spectrum is normalized to a total of 12.27 protons.

[c]Normalized to a total of 15.00 protons.

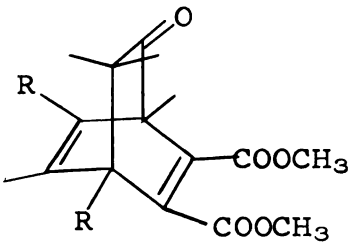
the carbomethoxy protons of 98 can also serve as an internal standard for measurement of the total amount of deuterium in the molecule.

When a solution of dienone 33 was refluxed in xylene with an equimolar amount of dimethyl acetylenedicarboxylate,



33, R = CH_3

49, R = CD_3

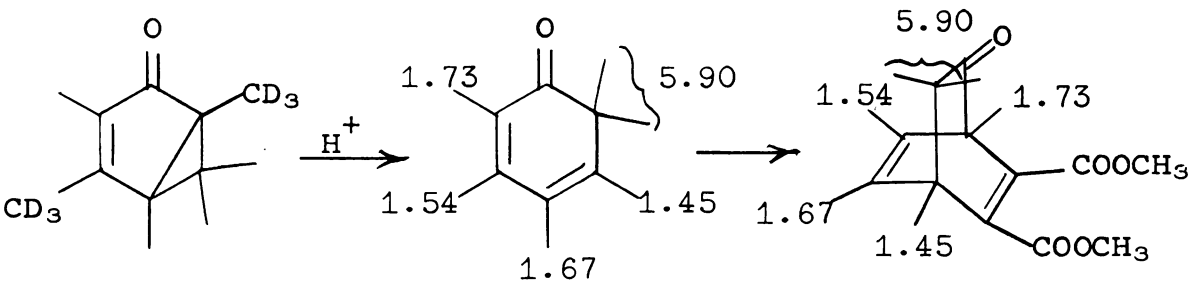


98, R = CH_3

98a, R = CD_3

the adduct 98 was obtained in good yield. Its nmr spectrum is presented in Table II. Hexadeuterated dienone 49 was also converted to its dimethyl acetylenedicarboxylate adduct 98a. The nmr spectrum of the adduct differed from that of 98 in that the bands at τ 8.30 and 8.57 were missing and the band at 8.22 was a sharp singlet. The high-field allylic and bridgehead methyls of 98 are therefore adjacent to the carbonyl group, a result which has also been found for the maleic anhydride adduct of 33 (15).

Treatment of bicyclic ketone 50 with 97% sulfuric acid at 22.6° for 30 minutes gave dienone 99, whose deuterium content and distribution were determined by converting it to

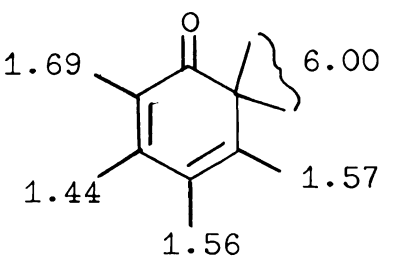


50 99 100

the adduct 100. The nmr spectrum of 100 is presented in Table II.

The number of protons in each band was calculated by assigning the band at τ 6.34 (due to the carbomethoxy methyls) a value of 6.00 protons. Dienone 99 therefore has the hydrogen distribution shown above; since 99 contains 12.29 protons (compare with 12.27 protons in 50) it is apparent that no appreciable loss of deuterium occurred in the conversion of 50 to 99.

The label distribution of dienone 99 is not consistent with its being formed by path A or B (see Chart I), but best corresponds (within the experimental error of the nmr integration measurements of about ± 8%) to a mixture of 52% 49 and 48% 104 (see Chart II), which should have the hydrogen distribution presented in structure 101, taking into account



101

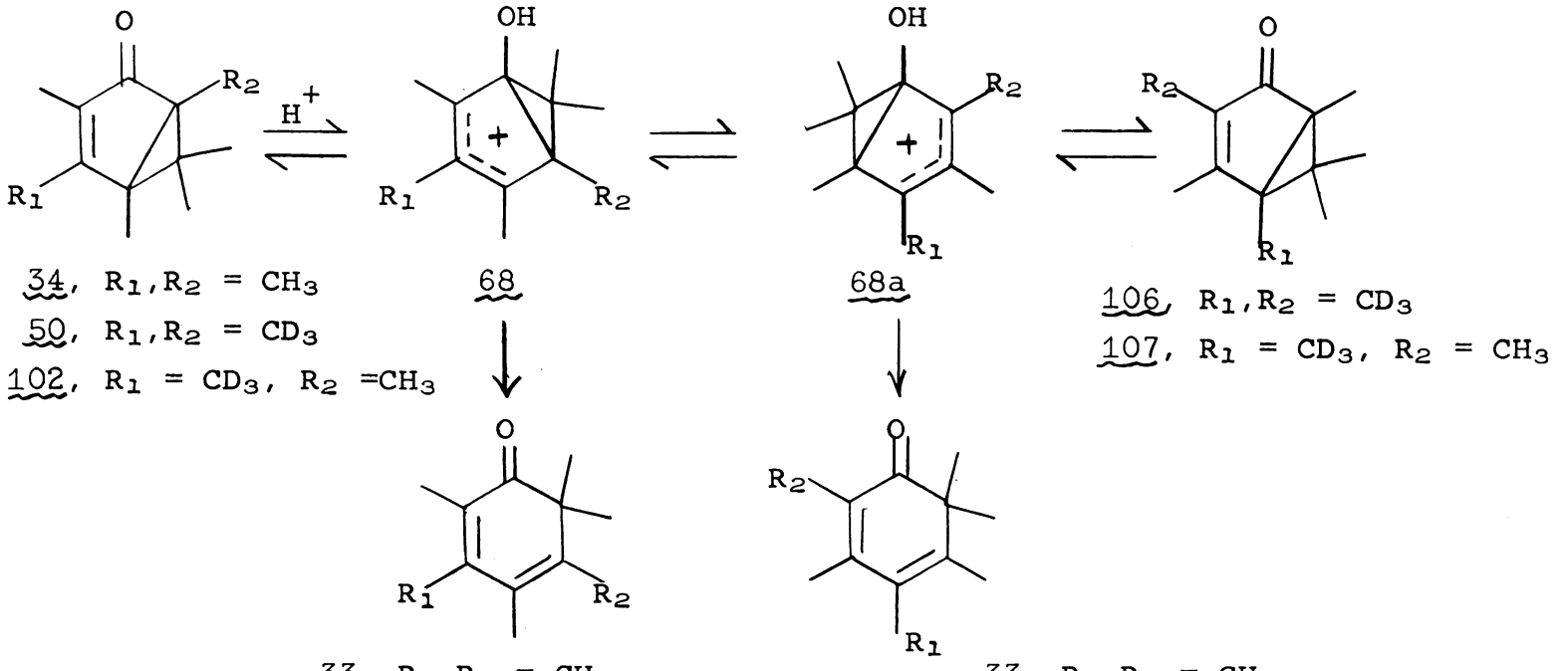

O
R2
H+
R1
OH
+
R1
R2
OH
R2
+
R1
O
R2
R1
34, R1,R2 = CH3
50, R1,R2 = CD3
102, R1 = CD3, R2 =CH3
68
68a
106, R1,R2 = CD3
107, R1 = CD3, R2 = CH3
O
R1
R2
O
R2
R1
33, R1,R2 = CH3
49, R1,R2 = CD3
103, R1 = CD3, R2 = CH3
33, R1,R2 = CH3
104, R1,R2 = CD3
105, R1 = CD3, R2 = CH3

Chart II

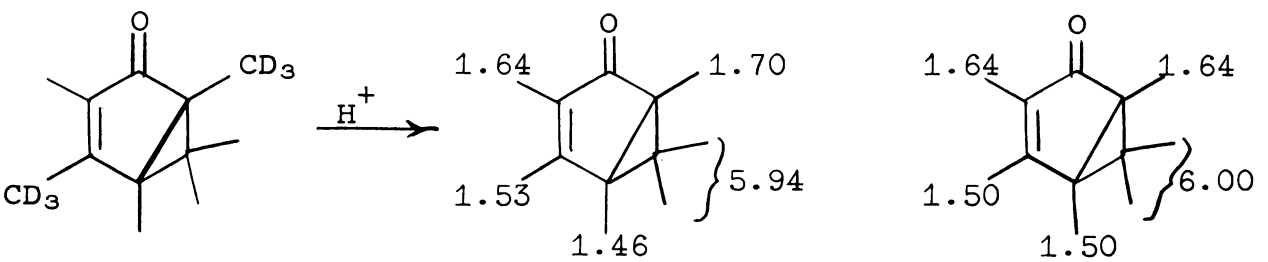
the fact that the starting ketone 50 is only 91% labeled.

Dienones 49 and 104 may be formed via the series of reactions presented in Chart II: protonation of bicyclic ketone 50 followed by a cyclopropylcarbinyl rearrangement gives ion 68, which can either ring open to give 49, or undergo further rearrangement to 68a, which can furnish dienone 104. The almost equal mixture of 49 and 104 (obtained on treatment of 50 with acid) requires a rapid, nearly complete interconversion of ions 68 and 68a prior to ring opening to the respective dienones.

Dienone 49 could be recovered unchanged after treatment with 97% sulfuric acid for 30 minutes at 25.5°; the nmr spectrum of the recovered dienone (which consisted of three singlets at τ 8.12, 8.17, and 8.90; the relative area of the first two bands to the third was 1.00:0.97) was identical to that of the starting material and therefore no scrambling of the CD_3 groups had occurred. This result demonstrates that dienone 49 does not revert to ion 68 under these acidic conditions; if 68 was formed it would isomerize to 68a and thus some dienone 104 would be produced.

In order to ascertain whether the conversion of 50 to 68 (Chart II) is rapidly reversible under the isomerization conditions, the acid-catalyzed reaction of 50 was carried out in such a way that the bicyclic ketone was only partially converted to the dienone. Inspection of the nmr spectrum of the recovered ketone would show whether or not any scrambling

of the CD_3 groups had occurred. Treatment of 50 with 97% sulfuric acid at 18.7° for 1 minute resulted in a 37% conversion to the dienone. The nmr spectrum of the recovered bicyclic ketone 108 (Table II) shows it to have the label distribution presented below, in good agreement with a 50:50 mixture of ketones 50 and 106 which would exhibit the

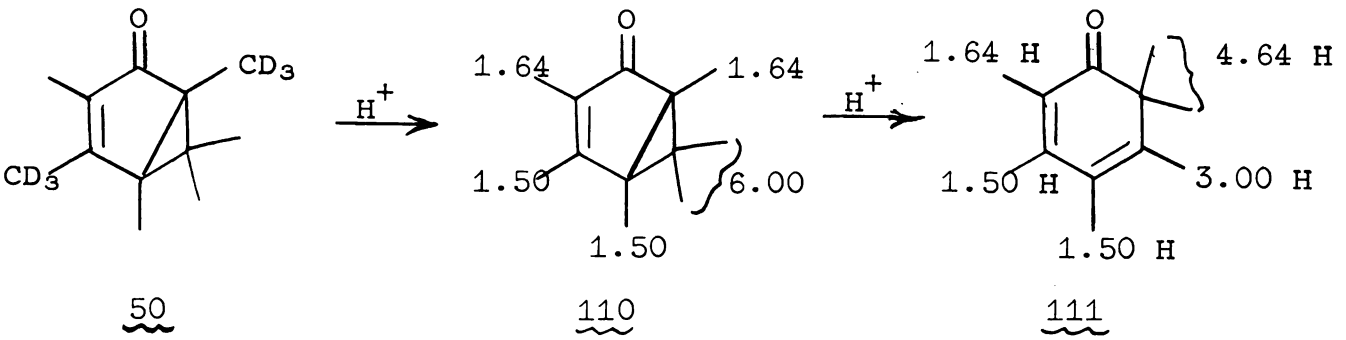


50 108 109

distribution of label presented in structure 109 (taking into account that 50 is 91% labeled at C-1). Further support for the formation of a mixture of the two labeled ketones 50 and 106 is the observation that the nmr bands due to the allylic methyls are singlets, rather than quartets.

The formation of an equimolar mixture of 50 and 106 on treatment of 50 with acid demonstrates that there is a rapid interconversion between 50, 68, 68a, and 106 (see Chart II).

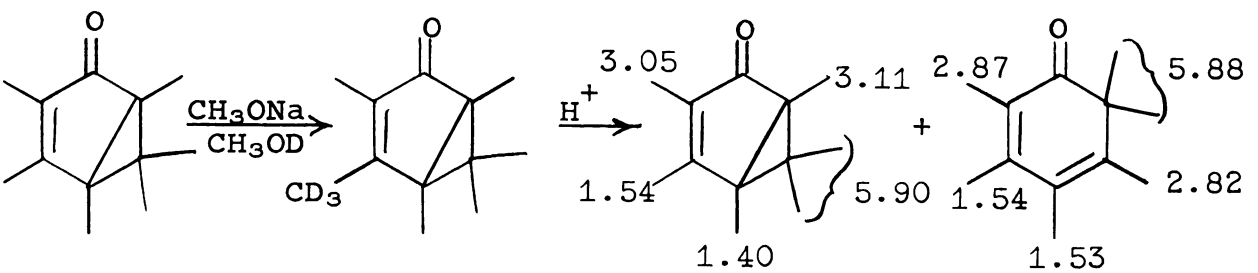
Since it has been established that in the presence of strong acid 50 equilibrates rapidly with the isomeric ketone 106, an alternative mechanism for the conversion of bicyclic ketone 50 to the dienone must be considered. Complete equilibration of 50 and 106 (see Chart II) would produce a



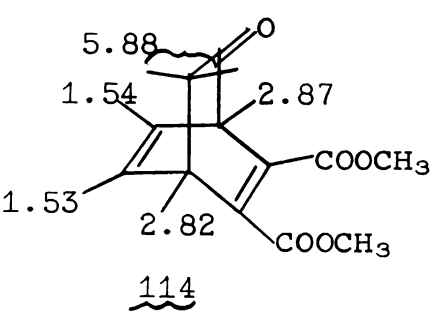
50 110 111

bicyclic ketone labeled as in 110. Ring opening of this ketone followed by methyl migration to C-1 (see Chart I, Path A) would give dienone 111. As the label distribution of 111 is quite different from that of 99, the actual product obtained on treatment of 50 with acid, it is concluded that the above mechanism is not operative.

The mechanistic sequence proposed in Chart II for the conversion of 34 to 33 was further reinforced by treating labeled bicyclic ketone 102 with acid. This ketone was prepared by warming a solution of 34 in deuteromethanol containing sodium methoxide. The nmr spectrum of 102 was similar to that of 34 (Table I) except that the quartet at τ 8.12

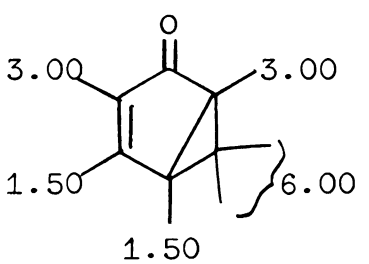


34 102 112 113



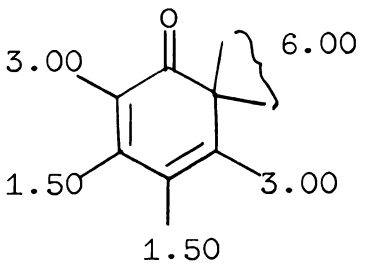
114

due to the C-4 methyl was missing (consistent with 100% label at C-4) and the band at τ 8.45 due to the C-3 allylic methyl was a sharp singlet. Treatment of 102 with 97% sulfuric acid at 18.8° for 12 minutes resulted in an 83% conversion to dienone 113. The nmr spectrum of the recovered bicyclic ketone 112 (see Table II) was in agreement with the hydrogen distribution presented in 112, which corresponds, within experimental error, to the expected equimolar mixture of 102 and 107 (see Chart II); this mixture would exhibit the label distribution presented in structure 115. The deuterium content and distribution of the dienone (113) was



115

determined from the nmr spectrum (Table II) of its dimethyl acetylenedicarboxylate adduct 114. The labeling pattern observed corresponds to an equimolar mixture of labeled dienones 103 and 105 (Chart II) which would exhibit the label distribution presented for structure 116.

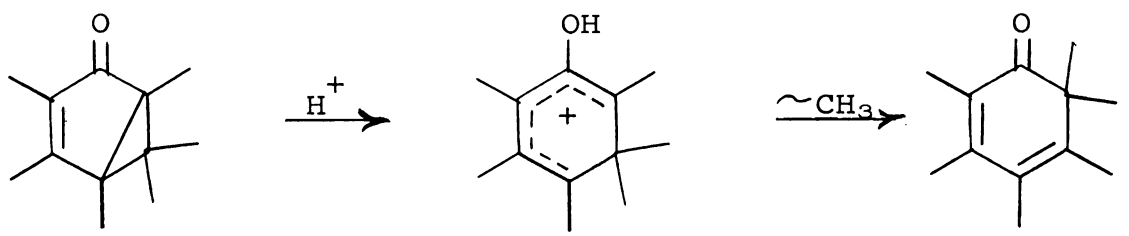


116

This result further reinforces the mechanistic sequence presented in Chart II; i.e., dienones 103 and 105 are formed *via* ring opening of ions 68 and 68a respectively.

B. Discussion of The Rearrangement Mechanism

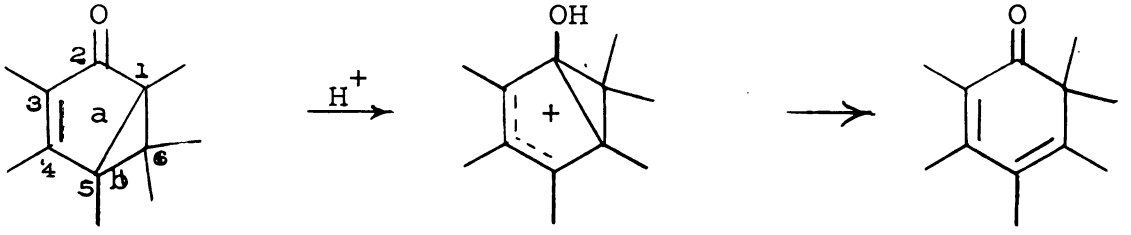
The labeling experiments described above agree with the proposal that the acid-catalyzed conversion of 34 to 33 proceeds *via* the mechanistic scheme presented in Chart II; 34 rearranges to 68, which equilibrates with its enantiomeric form 68a prior to ring opening to furnish dienone 33. The conversion of 34 to 68 has also been shown to be reversible; ring opening of 68 to 33 is not reversible, however. The results obtained also demonstrate that the conversion of 34 to 33 does not involve the series of rearrangements presented below.



34 72 33

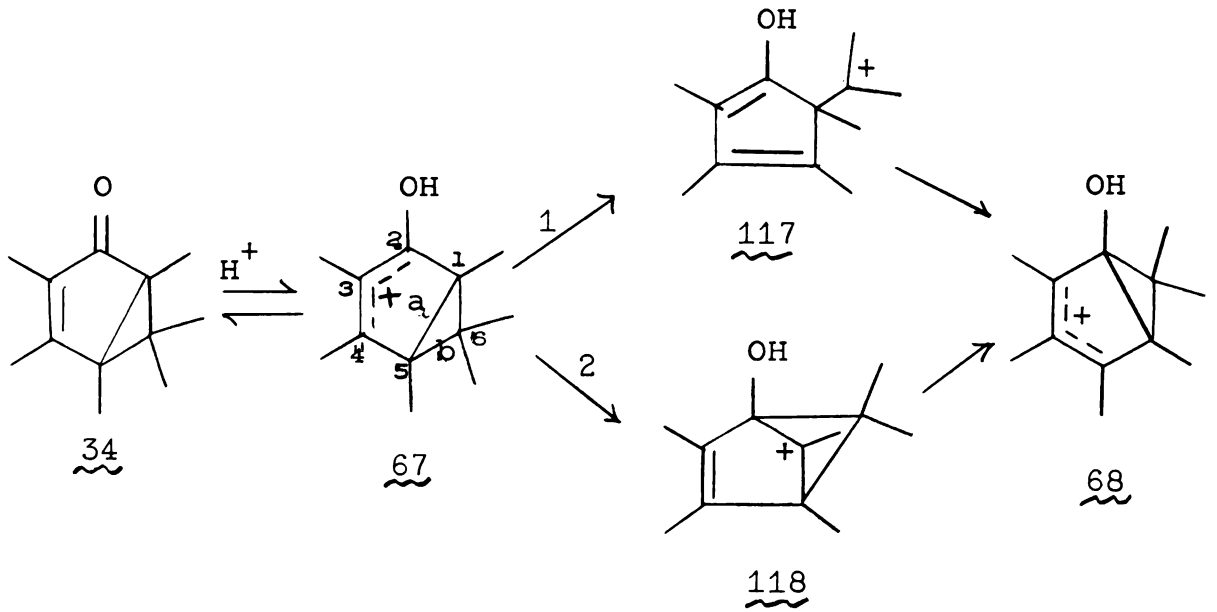
The sequence 34 → 68 → 33 is analogous to the mechanistic scheme proposed by Dauben and Friedrich (38) to account for the acid-catalyzed rearrangement of dideuterothujopsene (92) to widdrol (94) (see Introduction).

The conversion of bicyclo[3.1.0]hexenone 34 to dienone 33 via ion 68 requires that bond b (structure 34) be broken and

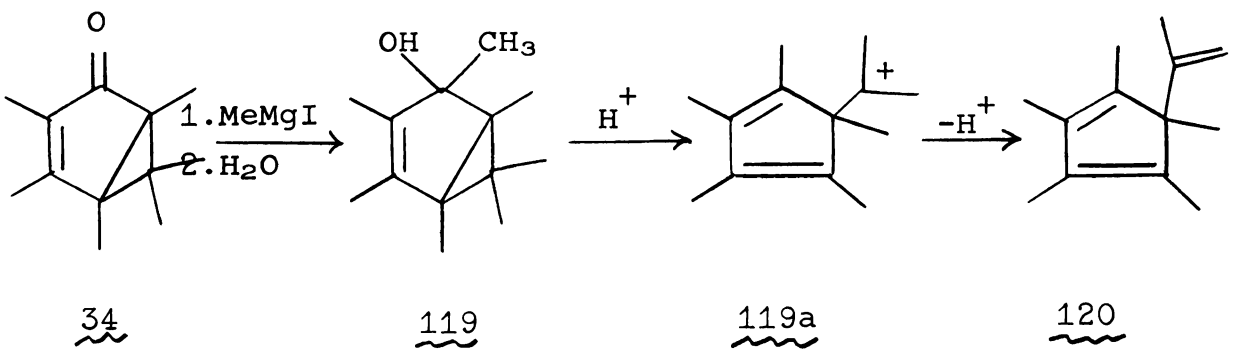


34 68 33

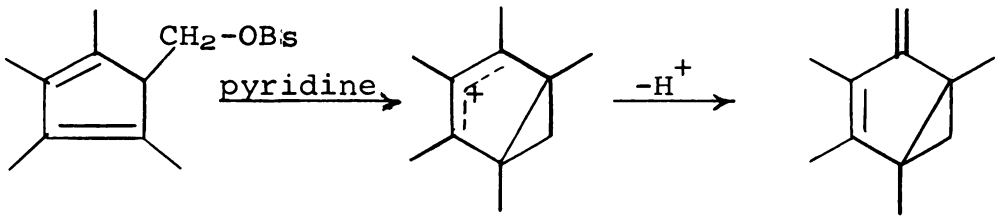
that a new bond be formed between the carbonyl carbon and the quaternary carbon at C-6. Two possible routes can be written to describe this process: (1) After (or simultaneously with) fission of bond b there is bond formation between the C-2 and C-6 carbon atoms of 67. (2) Migration of C-6 to the carbonyl group, followed by a second migration to C-1, to give the ionic species 68. Cleavage of the cyclopropane ring gives dienone 33. It should be noted that exo and endo substituents on C-6 may invert, or retain their stereochemistry, depending on whether or not there is rotation about the C_1-C_6 bond in the rearrangement of 67 to 68.



A decision between paths 1 and 2 may be based on the following results. It was recently discovered in our laboratories (42) that treatment of 34 with methylmagnesium iodide, followed by hydrolysis with saturated ammonium chloride solution gave 120 as the only product. This reaction may proceed via the mechanistic scheme presented below. Ring opening of 119 to give 119a is analogous to the conversion of 34 to 117 proposed in mechanism 1.



There is also precedent for ring closure of 117 to give 68. DeVries has shown (43) that the cyclopentadienyl derivative 121 undergoes ring closure to the bicyclo[3.1.0]hexene 122 in pyridine at room temperature. The double bonds may participate in aiding the departure of the brosylate anion.

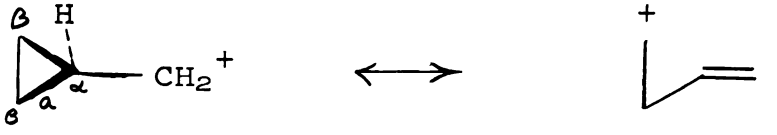


121 122

The failure of 119a to undergo a similar ring closure is probably due to the large amount of water present which can act as a base and remove a proton, thereby affording 120. It is clear that mechanism 1 agrees with these results inasmuch as there is a precedent for each step involved. On the other hand, mechanism 2 requires the formation of the highly strained intermediate 118. Since path 1 does offer a satisfactory rationalization for the rearrangement of 67 to 68, there appears to be no need to invoke the unusual reactions required for path 2. A mechanistic sequence similar to that presented in path 1 can also account for the interconversion of 68 and its enantiomeric form 68a (see Chart II).

The conversion of ion 67 to 117 requires that there be considerable overlap of bond b with the positive charge on C-4. This is in agreement with recent reports (33) that

there is a substantial amount of positive charge on the β-carbon atoms of cyclopropylcarbinyl cations. This can be accounted for by resonance forms such as 123a. Evidence has also been presented which demonstrates that cyclopropyl-



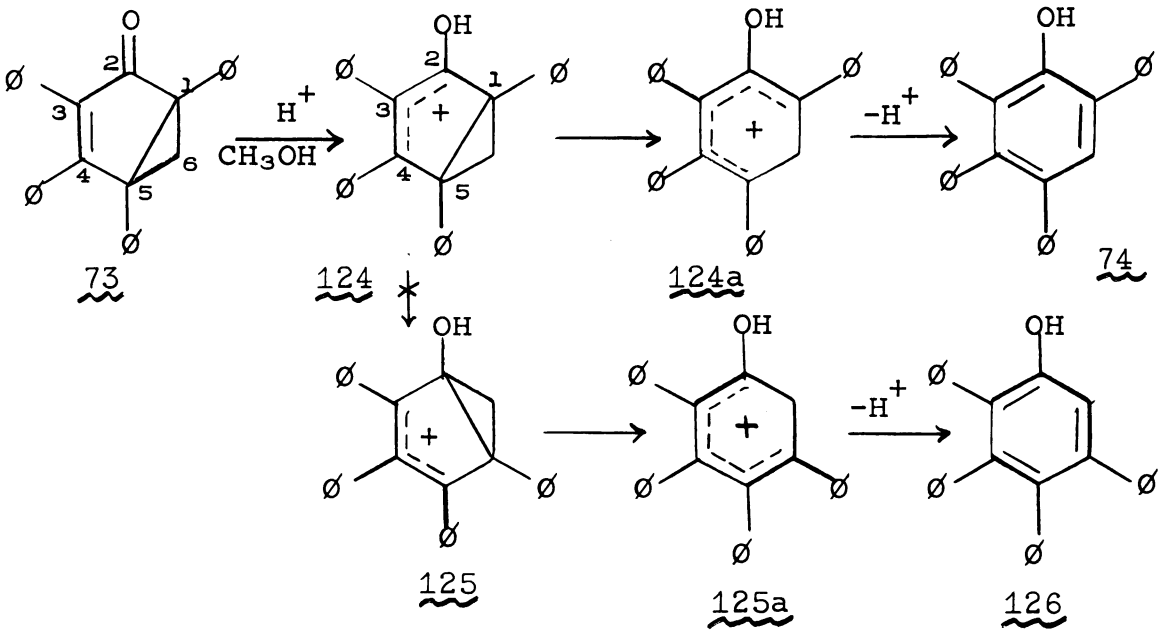
123 123a

carbinyl cations have the bisected geometry shown for structure 123 (44). This geometry is most favorable for overlap of bond a with the positively charged carbon atom.

It is therefore clear why rearrangement of ion 67 to 117 is favored over ring opening to ion 72. Bond b is ideally situated for overlap with the positively charged C-4 carbon of 67, whereas bond a is not.

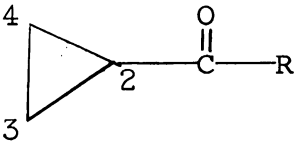
It is of interest that a few reported examples of acid-catalyzed bicyclo[3.1.0]hexenone reactions do not involve a cyclopropylcarbinyl rearrangement of the type 34 → 68, but can be better explained by cleavage of the cyclopropane ring to give products corresponding to formation of the most stable cation.

Eistert and Langbein have shown (45), for example, that treatment of bicyclic ketone 73 with sulfuric acid gave the isomeric phenol 74, rather than 126.

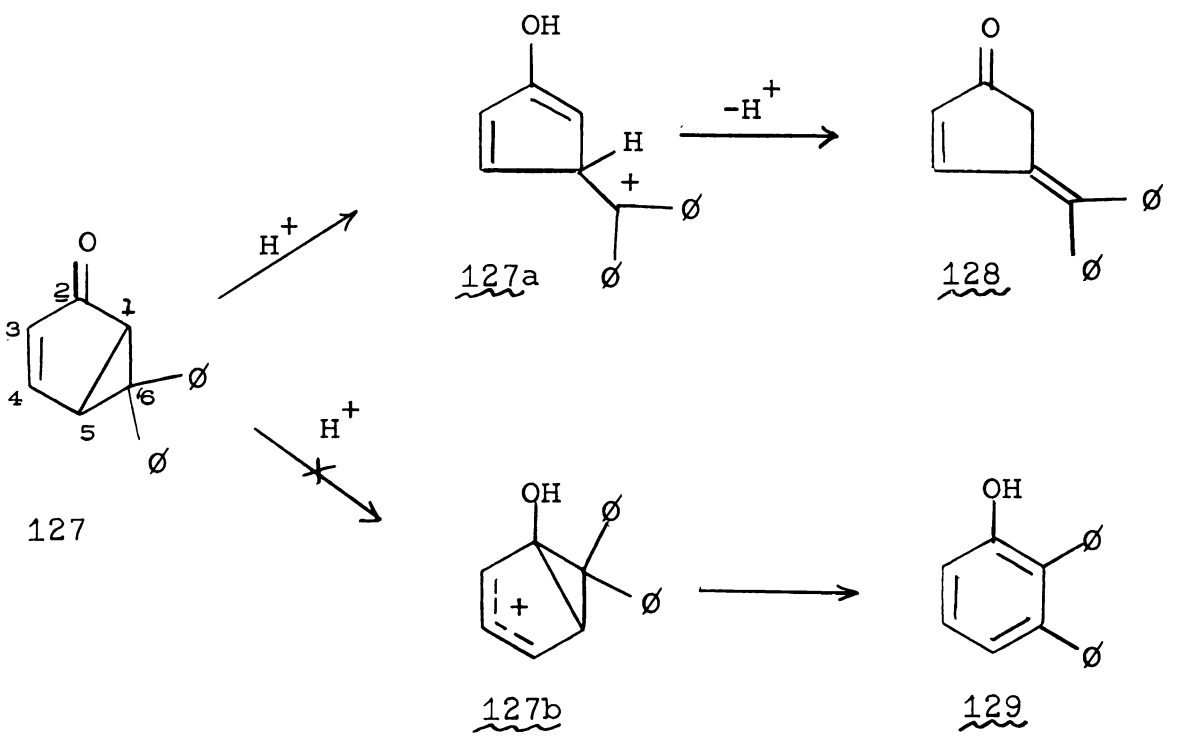


Ring opening of 124 to give 124a is therefore much more rapid than the possible rearrangement to 125. The fast rate of ring opening is probably a consequence of the presence of phenyl groups on the C-1 and C-5 positions of 73. The conversion of 124 to 124a must involve development of positive charge on either the C-1 or C-5 position of ion 124 (depending on which way the C-1, C-5 bond cleaves); the presence of phenyl groups at these positions stabilizes the developing positive charge and thereby enhances the rate of the reaction.

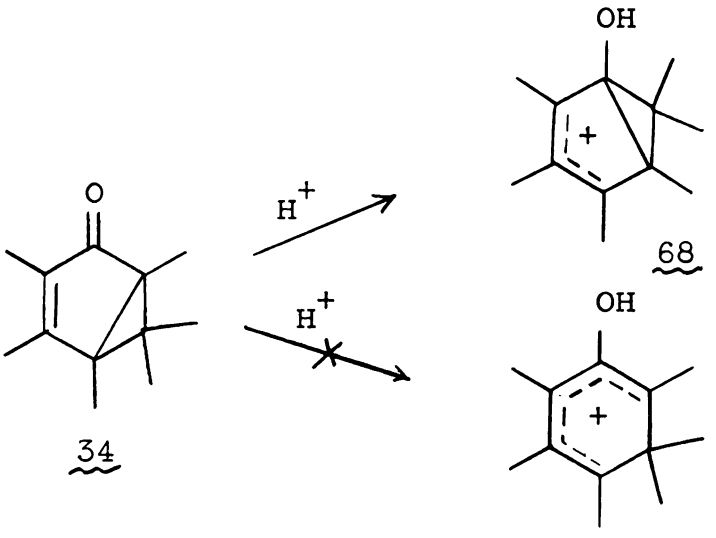
Support for this argument is the report by Walborsky and Plonsker (37) that the rate of ring opening of cyclopropyl ketones is greatly enhanced by the presence of phenyl groups on the 3- or 4-position of the cyclopropane ring (see below).



A similar argument would account for the acid-catalyzed conversion of bicyclic ketone 127 to 128 (and not 129) reported by Zimmerman and his co-workers (12). The phenyl groups on the C-6 position of 127 stabilize the positive charge developed on this position in the transition state going to 127a, thereby favoring this process over rearrangement to 127b.



In the case of bicyclic ketone 34, however, a cyclopropylcarbinyl rearrangement to 68 might be expected to compete with ring opening to 72, as the methyl groups on 34



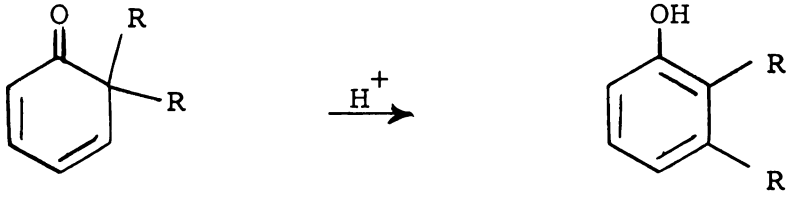
34 68 72

would not favor direct cleavage of the cyclopropane ring to the extent that the phenyl groups on 73 and 119 would; a phenyl group may be more effective at stabilizing an adjacent positive charge than a methyl group.

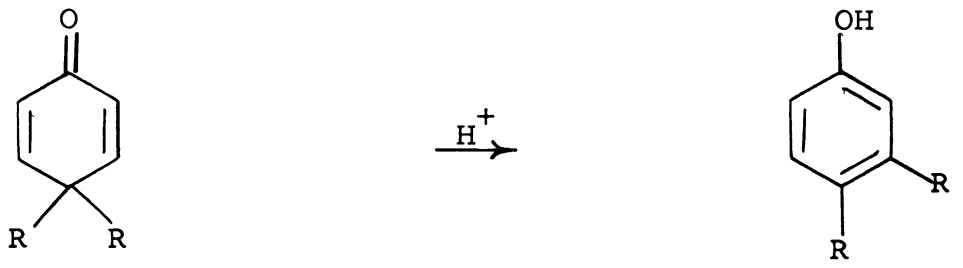
C. Miscellaneous Experiments

1. Acid-Catalyzed Rearrangements of Fully Substituted Cyclohexadienones

The most commonly observed reaction of 2,4- or 2,5-cyclohexadienones on treatment with acid is the dienone-phenol rearrangement. This reaction may be represented by the equations:



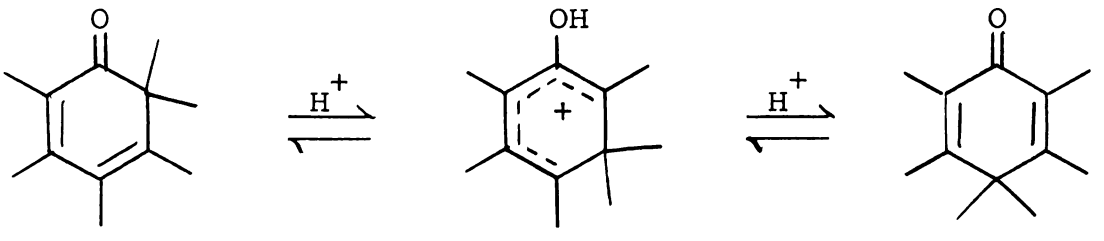
130 131



132 133

The rearrangement involves protonation of the dienone on oxygen followed by alkyl or aryl migration to afford the isomeric phenol. Two representative examples are the conversion of 130 (R = CH_3) to 131 on treatment with sulfuric acid reported by Marvel and Magoon (46), and the formation of phenol 133 on treatment of 132 (R = Ø) with hydrochloric acid reported by Zimmerman and Schuster (47).

This reaction is not available to the isomeric dienones 33 (15) and 35 (14), however, since these compounds are fully substituted with methyl groups and therefore cannot form phenols on treatment with acid. A possible mode of rearrangement for these dienones is presented below.



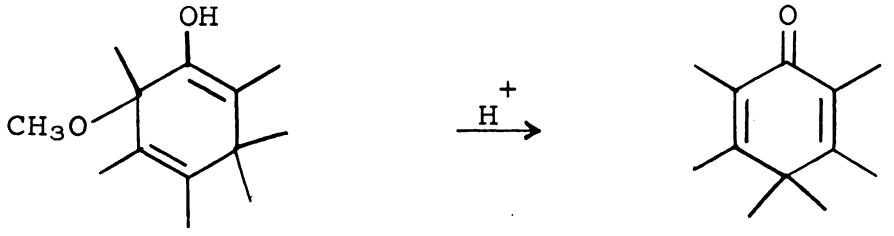
33 72 35

It is seen that these two compounds should be readily interconvertible under acidic conditions via a series of methyl migrations.

In view of the known stability of cross-conjugated versus fully conjugated dienones (see Part I of this thesis), it was thought that 33, on treatment with acid, would furnish dienone 35. This hope was fulfilled. The acid-catalyzed rearrangement of 33 to 35 and the interesting behavior of 35 in concentrated sulfuric acid is reported below.

a. The Acid-Catalyzed Rearrangement of 2,3,4,5,6,6-Hexamethyl-2,4-cyclohexadienone (33)

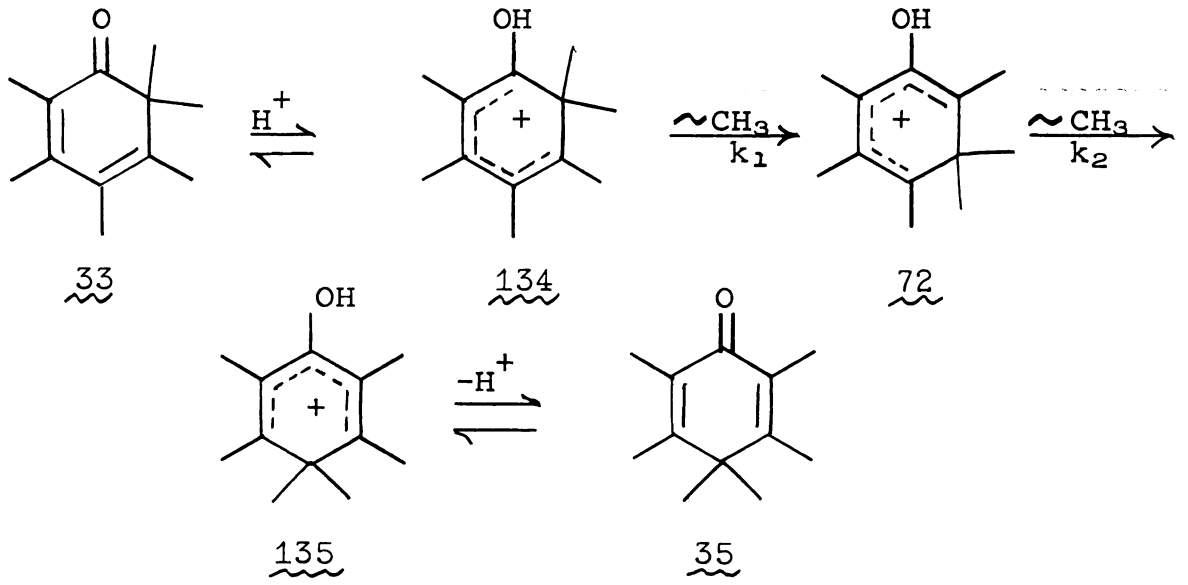
Treatment of 33 with fuming sulfuric acid for 10 minutes at room temperature, followed by quenching on ice and work-up, gave dienone 35 in good yield. This compound was isolated as a white solid (mp 117.5-118.2°). Its nmr (Table I) and infrared spectra were identical to those of 35 prepared by treatment of 36 with dilute acid.



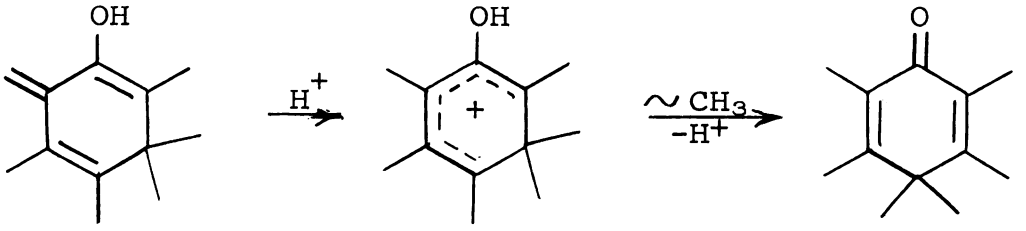
36 35

The conversion of 33 to 35 also occurs slowly in 97% sulfuric acid. The first-order rate constant for the reaction, measured in 97.0% sulfuric acid at 48.2°, was found to be $2.06 \pm .01 \times 10^{-2}$ min^{-1}. The percent conversion of 33 to 35, as determined by the uv spectrum of the acid solution at the end of the kinetic run, was essentially quantitative.

The conversion of 33 to 35 can be accounted for by the mechanistic scheme presented below: rapid, reversible



protonation of 33 to give 134, followed by a series of methyl migrations to furnish dienone 35. The first-order kinetics are in agreement with either k_1 or k_2 being the rate-determining step. Evidence that k_1 is the rate-determining step is the observation (presented in Part I of this thesis) that the acid-catalyzed conversion of 40 to 35, which



presumably involves ion 72 as an intermediate, proceeds rapidly under very mildly acidic conditions (methanol containing a few drops of 1% HCl).

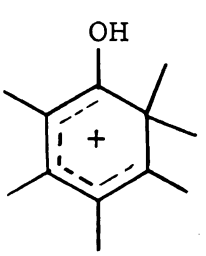
b. The Ultraviolet Spectrum of 2,3,4,5,6,6-Hexamethyl-2,4-cyclohexadienone (33) in Sulfuric Acid

The uv spectrum of dienone 33 was studied as a function of acid concentration. The results are presented in Table III. The marked difference in the spectrum of 33 in 10.0 and 77.9% sulfuric acid strongly suggests that, in the latter solvent, 33 exists as the protonated ion 134. Since there is no

Table III. Ultraviolet Spectrum of 2,3,4,5,6,6-Hexamethyl-2,4-cyclohexadienone (33) in Sulfuric Acid

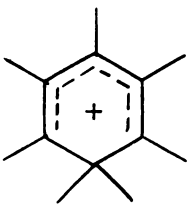
% H_2SO_4	$\lambda_{max,m\mu}$ (ϵ)	$\lambda_{max,m\mu}$ (ϵ)
10.0	235(2,630)	352(5,750)
77.9	266(4,680)	402(9,750)
97.0	266(4,690)	402(9,750)

appreciable difference between the uv spectrum of 33 in 77.9%



134

and 97.0% sulfuric acid, it is further concluded that the dienone is 100% protonated in this region. The uv spectrum of 134 is quite similar to that of the structurally related heptamethylbenzenonium ion (70) which has λ_{max}^{HCl} at 287 mμ

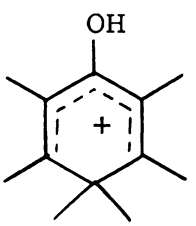


70

(ε 6,760) and 397 mμ (ε 8,500) (19).

c. The Behavior of 2,3,4,4,5,6-Hexamethy-2,5-cyclohexadienone (35) in Sulfuric Acid

Dienone 35 is quite stable in concentrated sulfuric acid; the nmr spectrum of a solution of 35 in 98% sulfuric acid exhibited no new bands after 56 hours at room temperature. The ultraviolet spectrum of 35 in different concentrations of sulfuric acid is presented in Table IV. The marked change in the spectrum with increasing acid concentration is attributed to a reversible protonation of 35 to give ion 135. The pKa of 35 was calculated to be -2.6 (see Experimental).



135

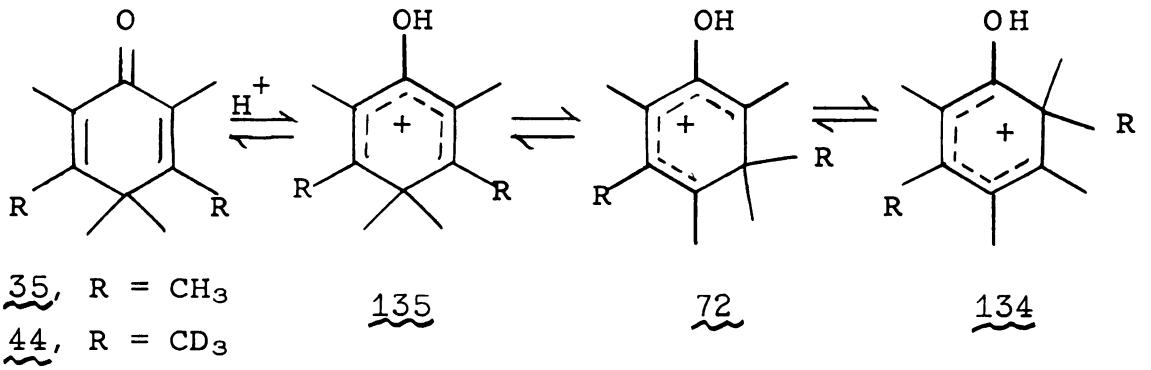
Table IV. Ultraviolet Spectrum of 2,3,4,4,5,6-Hexamethyl-2,5-cyclohexadienone (35) in Sulfuric Acid

% H_2SO_4	$\lambda_{max,m\mu}$ (ϵ)	$\lambda_{max,m\mu}$ (ϵ)
10.0	254(14,500)	---
20.0	254(14,100)	---
30.0	257(12,600)	---
39.0	265(11,700)	333(4,700)
49.0	270(12,600)	335(7,100)
59.0	271(12,600)	336(7,800)
68.0	271(12,500)	338(7,950)
78.0	271(12,500)	338(8,150)
97.0	271(12,500)	340(8,200)
105.0	271(11,300)	340(7,900)

The nmr spectrum of 35 in fuming sulfuric acid exhibited three singlets at τ 7.55, 7.80, and 8.57 (with respect to internal $N(CH_3)_4BF_4$ at τ 6.87) with relative areas of 1:1:1. These are assigned to the C-3, C-5 methyls, the C-2, C-6 methyls, and the C-4 methyls of 135, respectively. The spectrum was quite clean and showed no other bands besides those due to 135.

d. Acid-Catalyzed Rearrangement of 2,4,4,6-Tetramethyl-3,5-bis(trideuteromethyl)-2,5-cyclohexadienone (44)

The intriguing possibility exists that 135 may equilibrate with ions 72 and 134 (see Chart III) via a series of



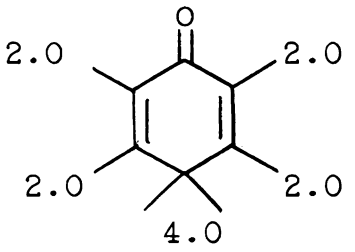
35, R = CH_3
44, R = CD_3

135 72 134

Chart III

methyl migrations. The existence of such an equilibrium could be determined by treatment of dienone 44 with sulfuric acid and inspecting the nmr spectrum of the recovered dienone. If 135 (R = CD_3) equilibrates with 72, some label would end up in the C-4 position of the recovered dienone; similarly, equilibration of 72 (R = CD_3) with ion 134 would introduce label into the C-2 and C-6 positions of the dienone.

Treatment of hexadeuterated dienone 44 with fuming sulfuric acid for 5 minutes at room temperature gave dienone 136, whose nmr spectrum in CCl_4 consisted of three singlets at τ 8.03 (C-3, C-5 methyls), 8.15 (C-2, C-6 methyls), and 8.78 (C-4 methyls) with relative areas 1:1:1. The mass spectra of dienones 44 and 136 (see Experimental) were essentially identical in the high mass/charge region; therefore no deuterium was lost in the conversion of 44 $\longrightarrow$ 136 and the recovered dienone has the hydrogen distribution presented below.



136

The complete scrambling of the CD_3 groups in 136 demonstrates that there is indeed a rapid equilibration between ions 135, 72, and 134 in fuming sulfuric acid.

This equilibrium also occurs in 70% and 98% sulfuric acid, but much more slowly. The results obtained on treatment of 44 with these solvents are summarized in Tables V and VI.

Table V. NMR Spectrum of 2,4,4,6-Tetramethyl-3,5-bis-(trideuteromethyl)-2,5-cyclohexadienone (44) in 70% Sulfuric Acid at 25° [a]

Time	7.65(C-3,C-5)	7.92(C-2,C-6)	8.66(C-4)	protons/molecule [b]
30 min.	2.18H	5.90H	6.08H	14.65
18 hrs.	2.34H	6.17H	5.74H	14.88
47 hrs.	2.24H	6.11H	5.80H	14.01
44 days	4.40H	5.79H	4.29H	14.30

[a] Shifts are reported as τ values, with $N(CH_3)_4BF_4$ (τ = 6.87) as an internal reference. All spectra were run at 60 Mc. In each case, the number of protons per molecule was normalized to a total of 14.16, in agreement with 2.16H at the C-3 and C-5 positions of 44.

[b] Calculated using a known weight of internal standard and dienone.

Table VI. NMR Spectrum of 2,4,4,6-Tetramethyl-3,5-bis-(trideuteromethyl)-2,5-cyclohexadienone (44) in 98% Sulfuric Acid at 25° [a]

Time	7.61(C-3,C-5)	7.84(C-2,C-6)	8.59(C-4)	protons/molecule[b]
30 min.	2.11H	6.00H	6.03H	15.15
56 hrs.	2.22H	6.09H	5.84H	15.01
56 hrs.[c]+ 20 min. at 80°	3.52H	6.12H	4.50H	14.64
86 hrs.[c]+ 810 min. at 80°	4.79H	4.98H	4.37H	15.01

[a] Shifts are reported as τ values, with $N(CH_3)_4BF_4$ (τ = 6.87) as an internal reference. All spectra were run at 60Mc. In each case, the number of protons per molecule was normalized to a total of 14.16, in agreement with 2.16H at the C-3 and C-5 positions of 44.

[b] Calculated using a known weight of internal standard and dienone.

[c] Amount of time sample remained at 25°.

The sample of 44 used was only 64.0% labeled in the C-3 and C-5 positions, as judged from its nmr spectrum. Thus the nmr spectrum of 44 in CCl_4 was similar to that of 35 (Table I) except that the band at τ 8.05 (due to the C-3 and C-5 methyls) was reduced in area from 6H to 2.16H, consistent with 64.0% label at these positions.

The change in the nmr spectrum of 44 in 70% sulfuric acid (Table V) after 44 days can be rationalized by the mechanistic scheme presented above for 44 (Chart III). The essentially

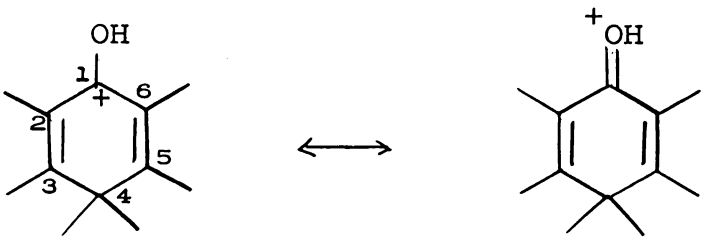
complete scrambling of the label between the C-3, C-5 positions (τ 7.65) and the C-4 position (τ 8.66) observed after 44 days can be explained by equilibration of ions 135 (R = CD_3) and 72. The small change in area of the band at τ 7.92 (due to the C-2,C-6 methyls) demonstrates that only a small amount of the label (CD_3) is incorporated into these positions; thus equilibration of ions 135 (R = CD_3) and 72 is much more rapid than interconversion of 72 and 134 in this solvent.

Similar results were obtained on heating a solution of 44 in 98% sulfuric acid (Table VI). Prolonged heating at 80° resulted in incorporation of a substantial amount of the label into the C-2, C-6 positions (τ 7.84) of the dienone; the label was introduced much more rapidly into the C-4 positions (τ 8.59), however, in agreement with the results obtained for 44 in 70% sulfuric acid.

It is of interest at this point to consider the relative stabilities of ions 72, 134, and 135 (Chart III). The results obtained on treatment of 44 with fuming sulfuric acid demonstrate that these ions equilibrate rapidly in this solvent; the nmr spectrum of 35 in fuming sulfuric acid, however, is in agreement with its being completely converted to ion 135. Similarly, the uncomplicated nmr spectrum of 44 in 70% and 98% sulfuric acid (Tables V, VI) is consistent with that of the symmetrical ion 135, rather than the unsymmetrical species 72 and 134, even though the observed scrambling of the label suggests that the interconversion of ions 72, 134, and 135

is occurring. Hence, it is concluded that the ionic species 135 is more stable than either 72 or 134.

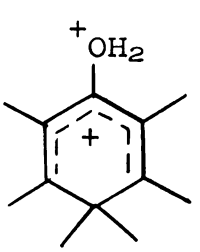
McLean and Mackor have calculated that the positive charge in ions such as 135 is concentrated mainly on the C-1 position (25); the presence of hydroxyl at this position in



135

135, compared with methyl at this position in ions 72 and 134, may account for the stability of 135 with respect to the two latter ions. The positive charge can be delocalized onto the hydroxyl group of 135 as shown above, thereby enhancing the stability of this ion.

A brief comment seems in order regarding the extremely rapid scrambling of the label observed on treatment of dienone 44 with fuming sulfuric acid. One possible explanation is that 44 may be doubly protonated in this strongly acidic medium to give ion 137, which undergoes rapid equilibration

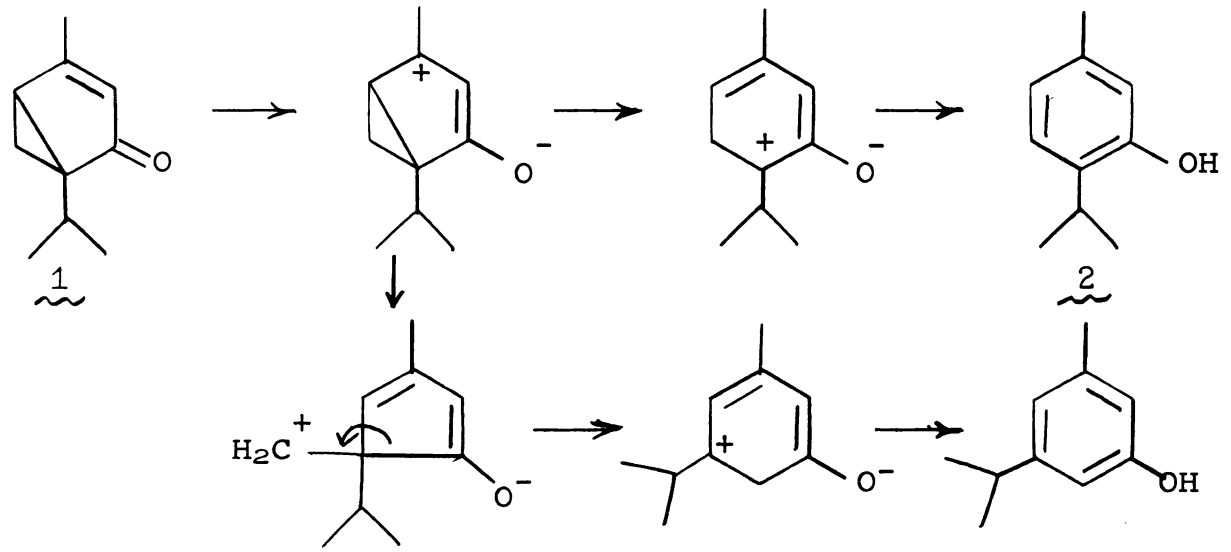


137

with the diprotonated form of ions 72 and 134.

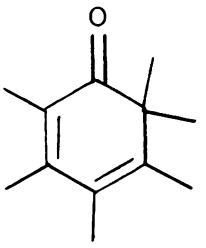
2. Pyrolysis of 1,3,4,5,6,6-Hexamethylbicyclo[3.1.0]hex-3-en-2-one (34)

Wheeler and Eastman reported (3) that pyrolysis of umbellulone (1) gave thymol (2) as the major product, along with 5-10% sym-thymol (138). They proposed that the reaction proceeded via the ionic pathway presented below.



The possibility that similar rearrangements might be observed for bicyclic ketone 34 led us to carry out the pyrolysis of this compound.

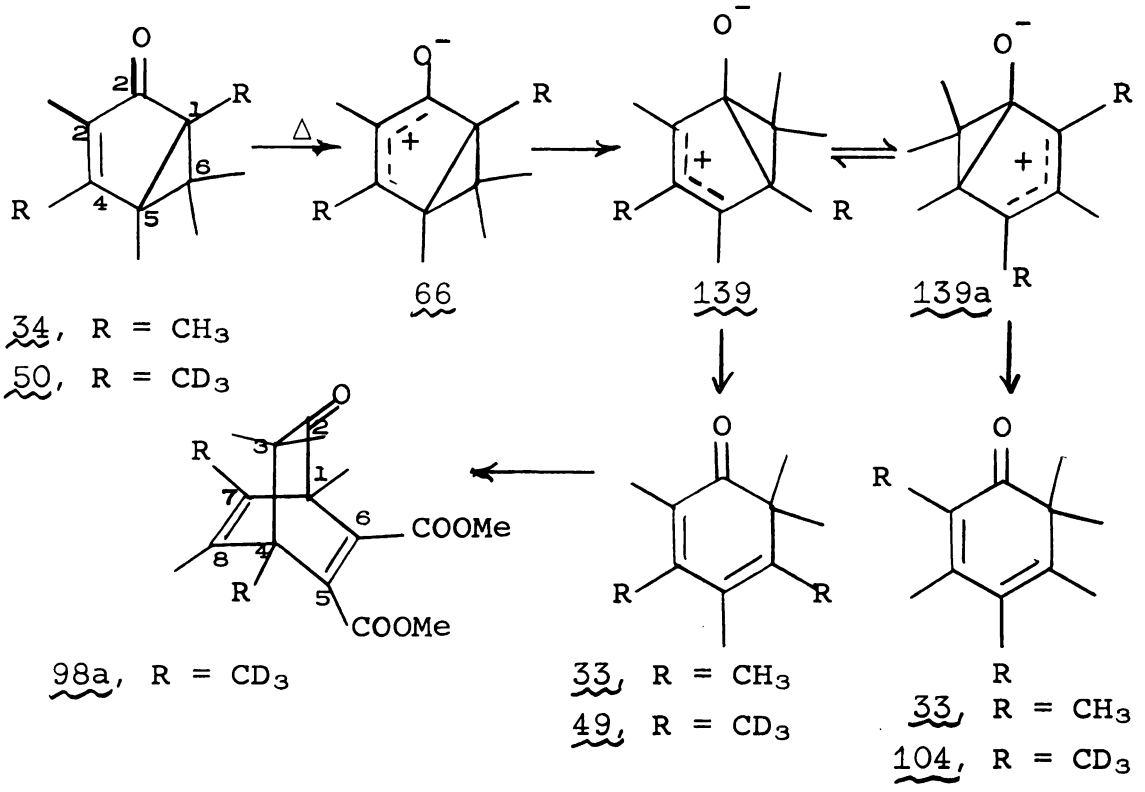
When 34 was injected on a gas chromatograph (injector temp. = 390°, column temp. = 170°) two major peaks were observed; collection of the product showed that the one with the shortest retention time was due to recovered enone 34, and the other was due to dienone 33. The dienone was identified by its infrared spectrum and retention time, which



33

were identical to those of an authentic sample (15). Injection of 34 on a gas chromatograph with the injector temp at 250° (column temp = 170°) gave no peak due to 33; this demonstrates that the rearrangement of 34 to 33 is occurring in the injector block, and not on the VPC column.

The conversion of 34 to 33 can be formulated as a cyclopropylcarbinyl rearrangement analogous to the mechanism of the acid-catalyzed conversion of 34 to 33 (see Chart II), in which the zwitterionic species 66 rearranges to 139, which equilibrates completely with its enantiomer 139a prior to ring opening to give 33. It is seen that, if the C-1 and C-4 positions of 34 are labeled with CD_3, this mechanistic sequence would give hexadeutero-33 with the label equally distributed among the C-2, C-3, C-4, and C-5 positions (i.e., a 50-50 mixture of dienones 49 and 104).



Bicyclic ketone 50 was pyrolyzed as described above for the unlabeled compound. This gave the hexadeuterated dienone 49, whose deuterium content and distribution were determined by converting it to the adduct 98a, the nmr spectrum of which lacked the bands at τ 8.30 (due to the allylic methyl at C-7; the other allylic methyl, τ 8.22, was now a singlet rather than a multiplet) and τ 8.57 (due to the C-4 bridgehead methyl). Comparison of the area of the band at τ 6.34 (due to the C-5, C-6 carbomethoxy protons) with the remaining bands in the spectrum showed that the dienone contained 12 protons per molecule; thus, no deuterium was lost during the pyrolysis. The nmr spectrum of recovered 50 was essentially identical to that of the starting material. Therefore no scrambling of the label occurs under the pyrolysis conditions.

The labeling results prove that the reaction does not involve an equilibrium of the type 139 $\rightleftharpoons$ 139a, analogous to that found for the acid-catalyzed rearrangement of 34 to 33. The results are, however, in agreement with the mechanistic sequence 34 $\rightarrow$ 66 $\rightarrow$ 139 $\rightarrow$ 33, or a similar sequence involving free radical, rather than ionic intermediates.

Finally, it should be pointed out that the rearrangement of 34 to 33 is analogous to the thermal conversion of umbellulone (1) to sym-thymol (which may also proceed via a free radical path). Phenol formation in the latter case is due to the presence of hydrogen atoms on the ring carbons (compare with 34) which are easily removed.

EXPERIMENTAL

A. Acid-Catalyzed Rearrangement of 1,3,4,5,6,6-Hexamethylbicyclo[3.1.0]hex-3-en-2-one (34)

A solution of 0.214 g of 34 (15) in 97% sulfuric acid was kept at 22.6° for 30 min, and then poured on ice. The resulting solution was extracted with methylene chloride, and the latter solution was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* gave 0.203 g of amber colored oil which was shown by vpc to consist of 2% 34 and 98% 2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (33). The nmr spectrum (Table I) and ir spectrum of 33 were identical with those of an authentic sample (15).

B. 1,3,3,4,7,8-Hexamethyl-5,6-dicarbomethoxybicyclo[2.2.2]octa-5,7-dien-2-one (98)

The dienone 33 (0.140 g) in 4 ml of xylene was heated under reflux with 0.113 g of dimethyl acetylenedicarboxylate for 22 hrs. Preparative vpc afforded 0.080 g of 98 (41) as a clear oil.

The nmr spectrum is presented in Table II. Hexadeutero-33, labeled at C-3 and C-5 with CD_3 groups, was also converted to its dimethyl acetylenedicarboxylate adduct (98a). The nmr spectrum differed from that of unlabeled 98 (Table II) in the following ways: the bands at τ 8.30 and 8.57 were

absent, and the band at 8.22 was a singlet. Thus, the high-field allylic and bridgehead methyls are adjacent to the carbonyl group.

C. Acid-Catalyzed Rearrangement of Labeled Bicyclo-[3.1.0]hexenones, General Procedure

The acid was equilibrated to the reaction temperature prior to each run. All reactions were run in a constant temperature bath with occasional stirring. Control runs showed that labeled dienone 49, enone 50, and Diels-Alder adduct 98a suffered no scrambling or loss of the label when subject to the same vpc conditions (5-ft 20% SE-30 column at 165-220°) used to collect the products of the acid-catalyzed rearrangements of the labeled bicyclo[3.1.0]hexenones.

D. Acid-Catalyzed Rearrangement of 3,5,6,6-Tetra-methyl-1,4-bis(trideuteromethyl)bicyclo[3.1.0]-hex-3-en-2-one (50)

Labeled enone 50 was prepared as previously described (15), except that 95% ethanol was used as the photolysis solvent. The nmr spectrum of vpc purified material consisted of four singlets at τ 8.45 (C-3 methyl), 8.78 (C-5 methyl) and 8.90, 9.08 (gem-methyls) with relative areas 1.00:0.91:1.06:1.00, respectively. A comparison of the areas of the bands at τ 8.45, 8.78, and 9.08 with that of the band at 8.90 indicates that the C-1 methyl is 91% deuterated (0.27H at C-1). The absence of the band at τ 8.12 (due to the C-4 methyl) demonstrates that this position is 100% labeled. Enone 50 (0.908 g) was dissolved in 25 ml of 97% sulfuric

acid and the resulting solution kept at 22.6° for 30 min. Quenching on ice, followed by the usual work-up, gave 0.931 g of a yellow oil. Preparative vpc afforded 0.184 g of hexadeuterated dienone 99, which was converted to its dimethyl acetylenedicarboxylate adduct 100. The adduct was purified by vpc, its nmr spectrum is reported in Table II and Figure 8.

A solution of 0.251 g of 50 in 10 ml of 97% sulfuric acid was kept at 18.7° for 1 min. Quenching on ice, followed by the usual work-up yielded 0.216 g of a yellow oil which was shown by vpc to consist of 63% hexadeuterated enone 108 and 37% hexadeutero-33. The nmr spectrum of 108 is reported in Table II and Figure 9.

E. Treatment of 2,4,6,6-Tetramethyl-3,5-dimethyl-d_3-2,4-cyclohexadienone (49) with 97% Sulfuric Acid

The dienone 49 (0.192 g) was dissolved in 5 ml of 97% H_2SO_4 and the resulting solution kept at 22.5° for 34 min. Quenching on ice, followed by the usual work-up gave 0.187 g of a yellow oil. Preparative vpc afforded dienone 49. The nmr spectrum was identical to that of the starting material and consisted of three singlets at τ 8.12, 8.17, and 8.90. The relative area of the two bands at τ 8.12 and 8.17 to the band at 8.90 is 1.00:0.97.

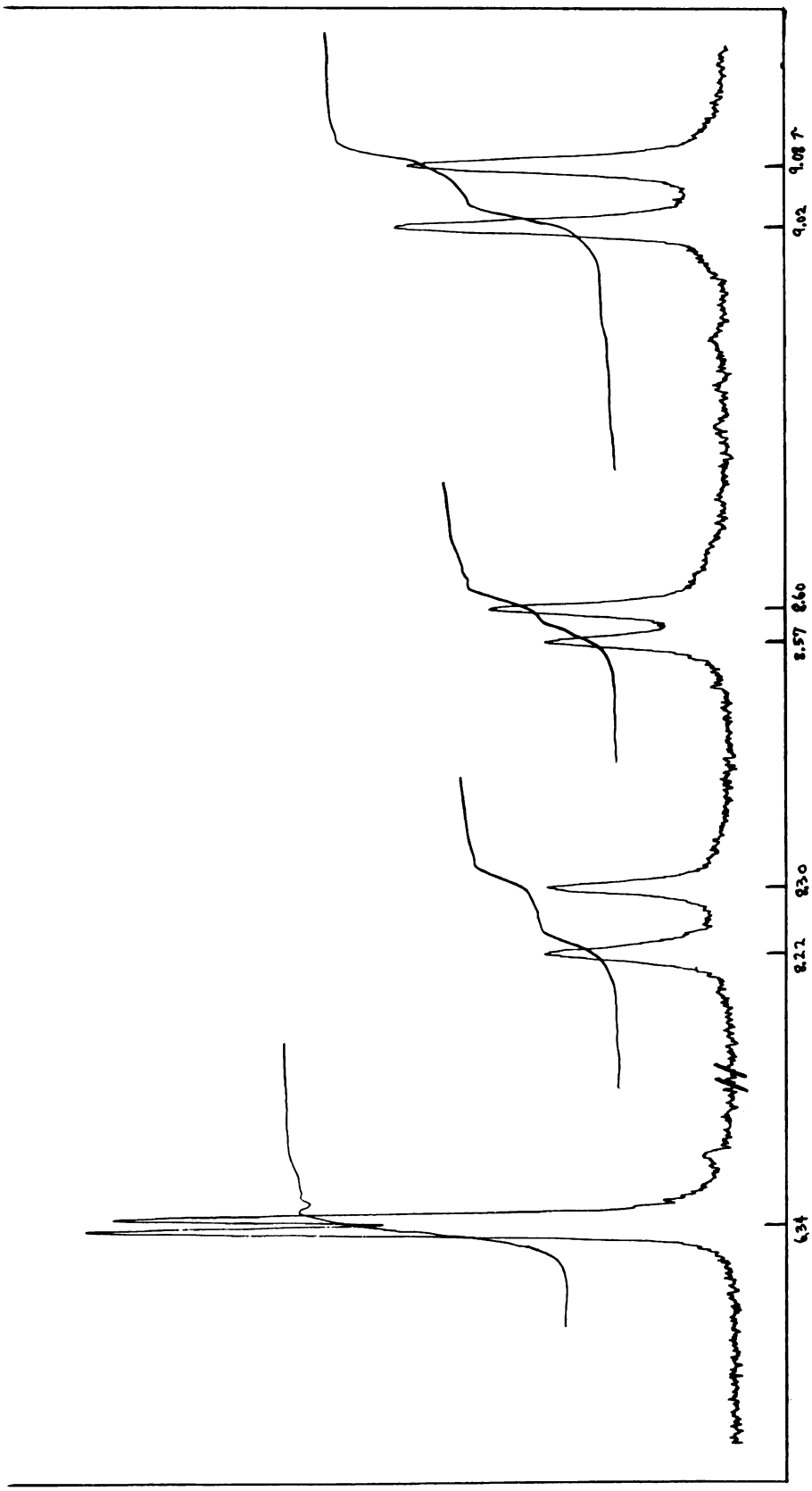


Figure 8. Nmr spectrum of hexadeuterated dimethyl acetylenedicarboxylate adduct 100.

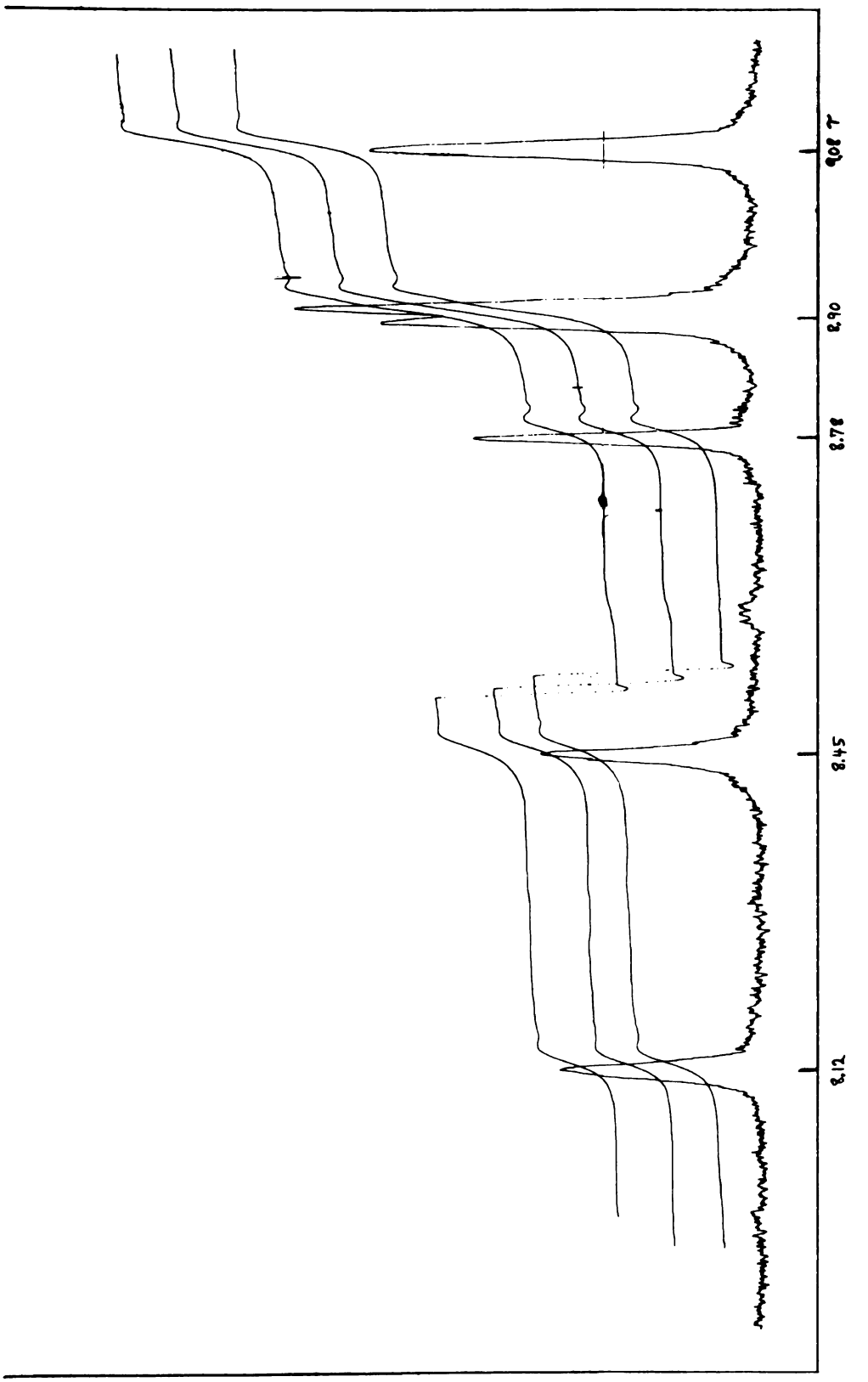


Figure 9. Nmr spectrum of hexadeuterated bicyclic ketone 108.

F. Preparation of 1,3,5,6,6-Pentamethyl-4-methyl-d_3-bicyclo[3.1.0]hex-3-en-2-one (102)

The enone 34 (2.09 g) was dissolved in 15 ml of methanol-d (31) containing a 0.5-cm^3 piece of sodium. The resulting solution was refluxed for 65 min, after which time an nmr spectrum showed that exchange was not quite complete. Most of the methanol was evaporated *in vacuo*, and 10 more ml of methanol-d was added. The resulting solution was refluxed for 70 min. Most of the methanol was evaporated *in vacuo*, and the remaining solution was poured into methylene chloride. This was extracted with cold (0°) water to remove the remaining methanol, and the solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded an oil (2.09 g), which on distillation at 1 mm gave 1.47 g (70%) of 102 with bp 66-68°. The nmr spectrum of 102 differed from that of 34 (Table I) in that the band at τ 8.12 was missing and the band at τ 8.45 was a sharp singlet.

G. Acid-Catalyzed Rearrangement of 1,3,5,6,6-Pentamethyl-4-methyl-d_3-bicyclo[3.1.0]hex-3-en-2-one (102)

A solution of enone 102 (0.937 g) in 25 ml of 97% sulfuric acid was allowed to remain at 18.8° for 15 min, after which time the solution was poured on ice and worked-up. The product, 0.900 g of yellow oil, was shown by vpc to contain 17% trideuterated enone 112 and 83% dienone 113. Preparative vpc afforded 0.059 g 112 and 0.189 g 113. The nmr spectrum of enone 112 is reported in Table II and Figure 10. Dienone 113

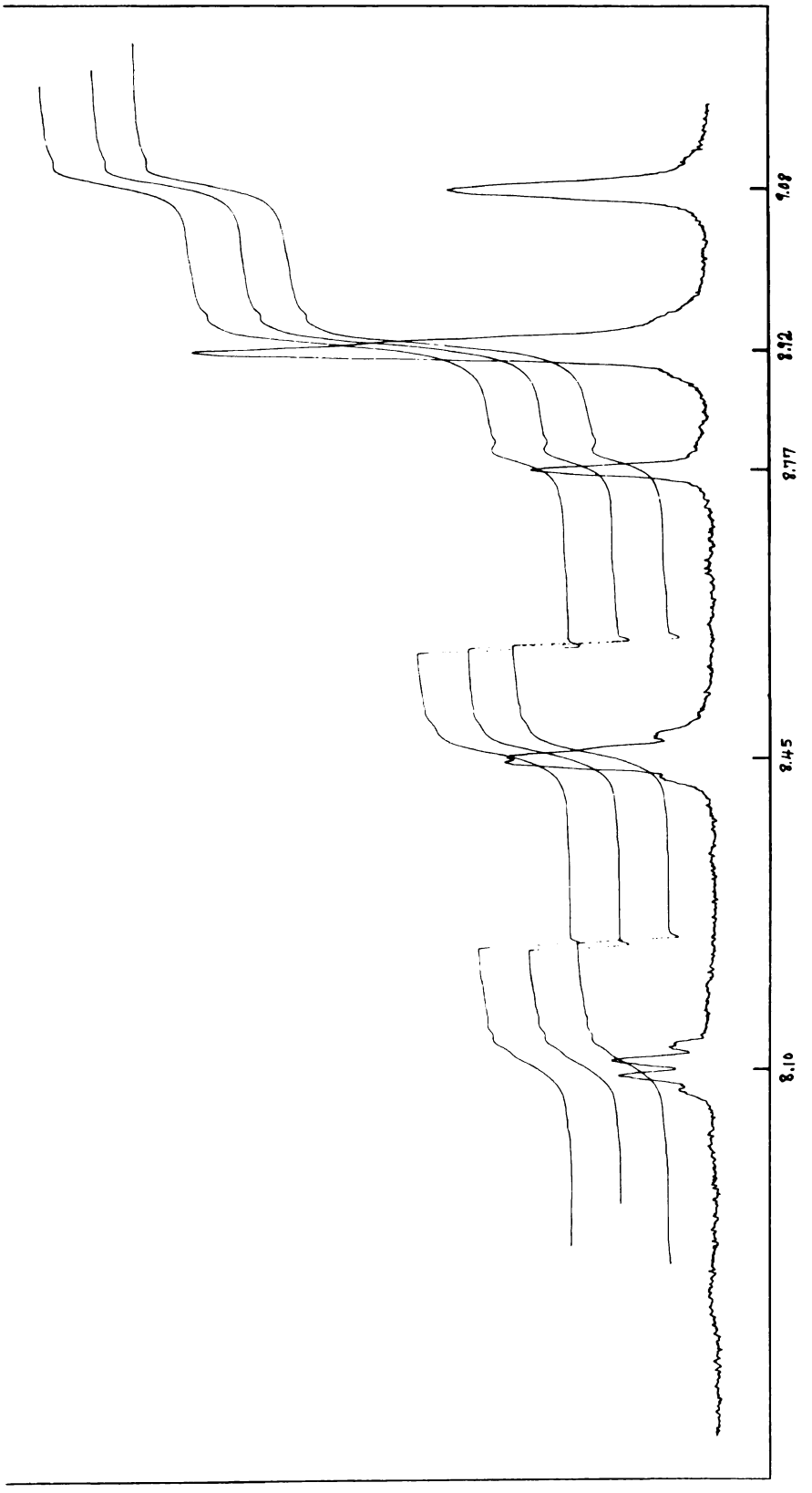


Figure 10. Nmr spectrum of trideuterated bicyclic ketone 112.

was converted to its dimethyl acetylenedicarboxylate adduct 114 which was purified by vpc. Its nmr spectrum is reported in Table II and Figure 11.

H. 2,3,4,4,5,6-Hexamethyl-2,5-cyclohexadienone (35)

2,3,4,5,6,6-Hexamethyl-2,4-cyclohexadienone (33), 15.2 g, was added slowly to 70 ml of 20% fuming sulfuric acid at 0°. The resulting brown solution was stirred at room temperature for 10 min, then poured on ice. After dilution to 2 liters with ice water, and filtration, the resulting tan solid was dissolved in ether. The ether solution was washed with water and dried over magnesium sulfate. Recrystallization from hexane gave 8.76 g of colorless crystals of 2,3,4,4,5,6-hexamethyl-2,5-cyclohexadienone (35), mp 117.5-118.2°.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18.

Found: C, 80.91; H, 10.11.

35 had prominent ir bands at 1653 and 1624 cm^{-1}, and a λ_{max}^{EtOH} at 246 mμ (ϵ = 14,800). Its nmr spectrum is in Table I and Figure 4.

I. Kinetics of the Acid-Catalyzed Rearrangement of 2,3,4,5,6,6-Hexamethyl-2,4-cyclohexadienone (33)

The rearrangement of dienone 33 to 35 was followed spectrophotometrically (ultraviolet), by measuring the decrease in absorbance of 33 at 402 mμ. A solution of 33 in 95% ethanol was added to a solution of 97% sulfuric acid at 48.2°. The concentration of the stock solution was such that the

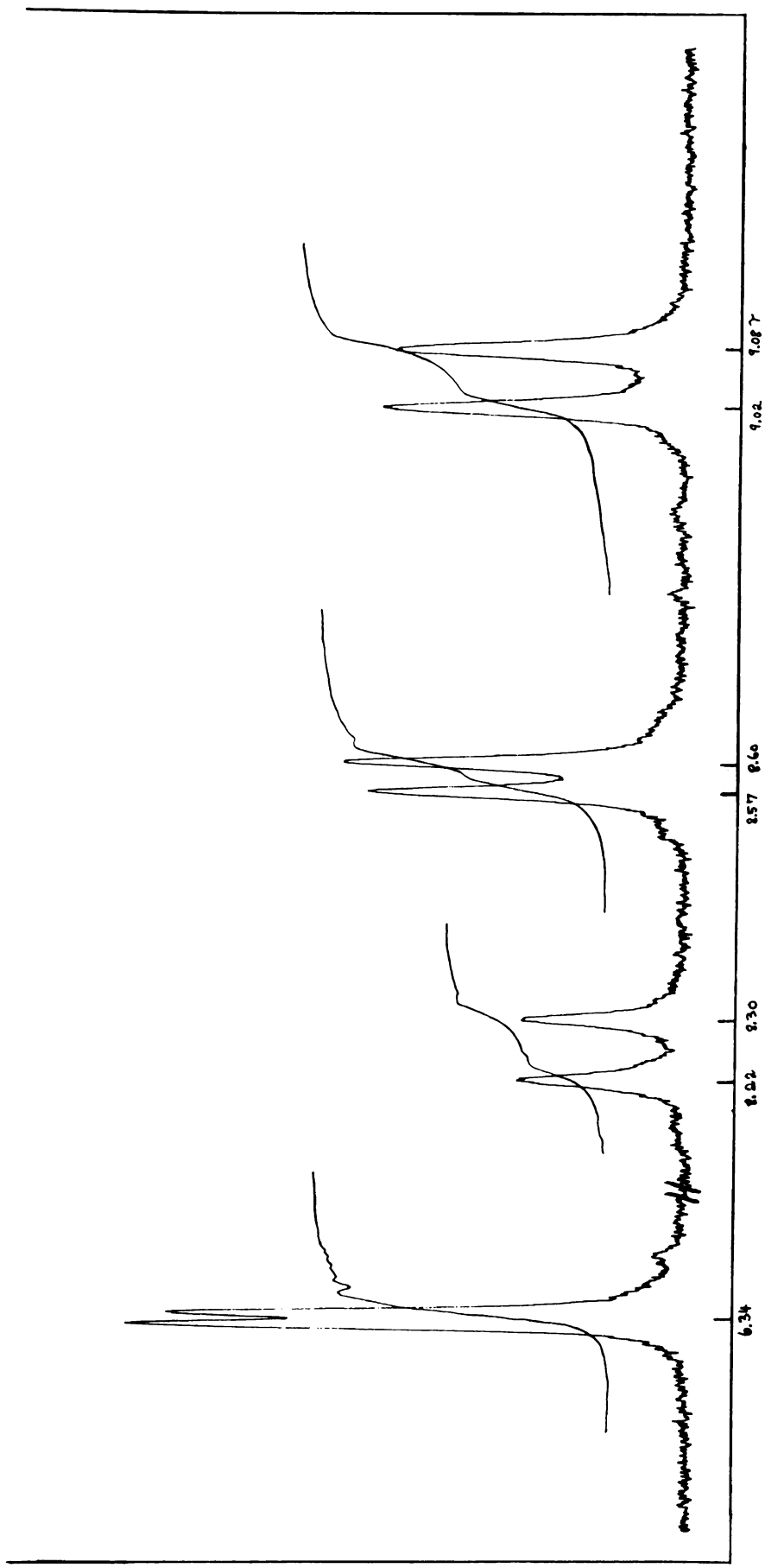


Figure 11. Nmr spectrum of trideuterated dimethyl acetylenedicarboxylate adduct 114.

initial absorbance was 0.90 and the acid concentration was 97.0%. The reaction was followed to at least 75% completion and the first-order rate constant determined from a plot of log A(λ 402 mμ) versus time, which was linear up to about 2 half lives. The pseudo first-order rate constant k was 0.02055 ± 0.00005 min^{-1}. Comparison of the uv spectrum before, and after, one kinetic run, showed that the percent conversion of 33 to 35 was 98%.

J. Measurement of the pKa of 2,3,4,4,5,6-Hexamethyl-2,5-cyclohexadienone (35)

The spectra of various sulfuric acid solutions 1.068 x 10^{-4} molar in dienone were measured at ~25°. The sample of 35 used was twice recrystallized from hexane (mp 117.2-118.0°). The solutions were prepared by adding 8 μl of a stock solution of 35 in 95% ethanol to 5 ml of acid. The spectrum was measured as soon as possible (~ 5 min) after preparation of each solution. The spectral data are summarized in Tables IV and VII.

The first method of Hammett, Flexser, and Dingwall (48) was used to calculate pKa. Values of Ka and ϵBH^+ at various wavelengths in solutions of known h_o values (49) were obtained by simultaneous solutions of the equation:

$$Ka + \epsilon BH^+ \left(\frac{h_o}{\epsilon B - \epsilon}\right) - \frac{h_o \epsilon}{(\epsilon B - \epsilon)} = 0 \qquad (1)$$

The wavelengths were chosen in the region in which the εB curve (the plot of A vs λ in 10% sulfuric acid) was relatively flat, and therefore the effect of a lateral shift in

the spectrum caused by a medium effect was small. The two values of ϵ, the extinction coefficient measured at a particular wavelength, used in each solution of equation (1), were those measured in 30.0 and 39.0% sulfuric acid. The value obtained for pKa of 35 was -2.57 ± 0.11. In Table VII are summarized the spectral measurements used in calculating pKa.

K. Rearrangement of 2,4,4,6-Tetramethyl-3,5-bis-(trideuteromethyl)-2,5-cyclohexadienone (44) in Fuming Sulfuric Acid

Dienone 44 was prepared as described above. Its nmr spectrum consisted of two singlets at τ 8.17 and 8.79 with relative areas 1:1. The band at τ 8.05 due to the C-3, C-5 methyls was reduced in size to a small bump, consistent with essentially complete label at these positions. The uncorrected mass spectrum of 44 showed it to contain 1.6%-d_2, 7.15%-d_3, 22.2%-d_4, 36.5%-d_5, 28.6%-d_6, and 4.0%-d_7.

Dienone 44 (.0457 g) was added to 1 ml of 20% fuming sulfuric acid at 25°. The resulting amber solution was kept at room temperature for 5 min, then poured on ice. Work-up, followed by preparative vpc, afforded .0212 g of hexadeuterodienone 136. The uncorrected mass spectrum of 136 showed it to contain 1.4%-d_2, 7.6%-d_3, 22.0%-d_4, 36.5%-d_5, 28.3%-d_6, and 4.1%-d_7. The nmr spectrum of 136 (CCl_4) consisted of three singlets at τ 8.03, 8.15, and 8.78 with relative areas 1:1:1. Dienone 44 was recovered unchanged (nmr) when subjected to vpc conditions used to collect 136.

Table VII. Extinction Coefficients of 2,3,4,4,5,6-Hexamethyl-2,5-cyclohexadienone (35) in H_2SO_4 + H_2O Mixtures

%H_2SO_4	λ=327 mμ	λ=330 mμ	λ=333 mμ	λ=336 mμ	λ=340 mμ
10.0	188	281	94	94	94
20.0	468	468	375	375	281
30.0	1690	1690	1590	1500	1410
39.0	4500	4590	4680	4590	4210
49.0	6460	6930	7120	7120	6740
59.0	6660	7210	7590	7690	7500
68.0	6560	7210	7590	7860	7960
78.0	6560	7210	7590	7960	8160
97.0	6190	7120	7590	7960	8250

Table VIII. Extinction Coefficients and pKa Values for 2,3,4,4,5,6-Hexamethyl-2,5-cyclohexadienone (35) in H_2SO_4 + H_2O Mixtures

	% H_2SO_4			
λ(mμ)	10.0 ε	30.0 ε	39.0 ε	pKa
327	188	1690	4500	-2.49
330	281	1690	4590	-2.38
333	94	1590	4680	-2.62
336	94	1500	4590	-2.70
340	94	1410	4210	-2.65
			Avg.	-2.57 ± 0.11

L. NMR Study of 2,4,4,6-Tetramethyl-3,5-bis(trideuteromethyl)-2,5-cyclohexadienone (44) in 70% and 98% Sulfuric Acid

Dienone 44 was prepared as described above. The sample of 44 used was 64.0% labeled in the C-3 and C-5 positions; thus, its nmr spectrum was similar to the undeuterated dienone 35 (Table I) except that the band at τ 8.05 (due to the C-3 and C-5 methyls) was reduced in area from 6H to 2.16H, consistent with 64.0% label at these positions.

1. 70% Sulfuric Acid

Dienone 44 (0.0924 g) and $N(CH_3)_4BF_4$ (0.0368 g) were dissolved in $\sim$ 0.5 ml 70% sulfuric acid. The sample was stored at room temperature in an nmr-tube and the nmr spectrum run at various times (see Table V for nmr spectra).

2. 98% Sulfuric Acid

Dienone 44 (0.0761 g) and $N(CH_3)_4BF_4$ (0.0293 g) were dissolved in $\sim$0.3 ml of 98% sulfuric acid. The sample was stored at room temperature in an nmr-tube, except for when it was heated to 80° in an oil bath. The nmr spectra are presented in Table VI.

M. Pyrolysis of 1,3,4,5,6,6-Hexamethylbicyclo[3.1.0]hex-3-en-2-one (34)

When 34 was injected on a gas chromatograph (5-ft SE-30 column, column temp = 170°, injector temp = 390°) two major peaks were observed; collection of the products showed that the peak with the shortest retention time was due to enone

34, while the other peak was due to 2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (33). The infrared spectrum of 33 ($\nu_{max}^{CCl_4}$ = 1642) and retention (5.8 min) were identical to those of an authentic sample of 33 (15). Injection of 34 on a gas chromatograph (column temp = 170, injector temp = 250°) gave only one peak due to 34; no peak for 33 was observed.

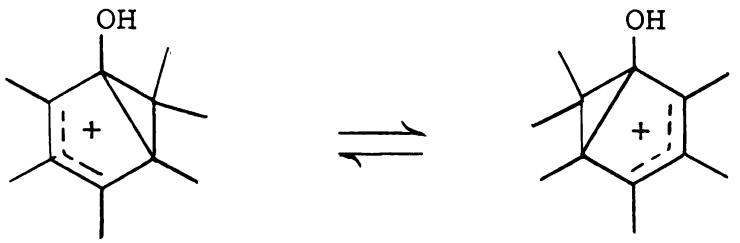
N. Pyrolysis of 3,5,6,6-Tetramethyl-1,4-bis-(trideuteromethyl)bicyclo[3.1.0]hex-3-en-2-one (50)

Labeled enone 50 was prepared as previously described (15). Its nmr spectrum showed that the label was complete at the C-4 methyl, and 91% complete at the C-1 methyl. The enone was pyrolyzed as described above for the unlabeled compound. The vpc trace of the product showed it to consist of 31% enone 50, and 69% dienone 49, labeled at the C-3, C-5 positions with CD_3. The nmr spectrum of unreacted 50 was essentially identical with that of the starting material. The dienone was converted to its dimethyl acetylenedicarboxylate adduct 98a as described above for the unlabeled compound. The nmr spectrum of the adduct 98a differed from that of unlabeled 98 (Table II) in the following ways: the bands at τ 8.30 and 8.57 were missing and the band at τ 8.22 was a singlet. The ratio of the area of the nmr band at τ 6.34 to the rest of the bands in the spectrum was 6:12.

SUMMARY

1. Treatment of 1,3,4,5,6,6-hexamethylbicyclo[3.1.0]hex-3-en-2-one [34] with 97% sulfuric acid gave 2,3,4,5,6,6-hexamethyl—2,4—cyclohexadienone (33) in excellent yield.

2. Labeling experiments (using 34 variously labeled with CD_3) show that a methyl migration is not involved; the results are, however, in agreement with a mechanism in which 34 undergoes a cyclopropylcarbinyl rearrangement to ion 68, which rapidly equilibrates with its enantiomeric form 68a prior to ring opening to afford dienone 33. It is also shown that ion 68 can revert to enone 34.



68 68a

3. Pyrolysis of bicyclic ketone 34 gave dienone 33 as the only product. The reaction course was determined using enone 34 labeled with CD_3 groups.

4. Treatment of dienone 33 with fuming sulfuric acid gave 2,3,4,4,5,6-hexamethyl-2,5-cyclohexadienone (35) in good yield.

5. The ultraviolet spectra of dienones 33 and 35 in sulfuric acid show that these compounds exist as their conjugate acids in concentrated acid. The pKa of dienone 35 is -2.6.

6. Hexadeutero-35, labeled at the C-3 and C-5 positions with CD_3, underwent rapid scrambling of the label on treatment with fuming sulfuric acid. This reaction also occurred in 70% and 98% sulfuric acid, but much more slowly.

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