BASE-CATALYZED H-D EXCHANGE IN BICYCLO[2.2.1.] HEPTANONES

BASE-CATALYZED PROTIUM-DEUTERIUM EXCHANGE IN BICYCLO[2.2.1.]HEPTANONES

By

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TITLE: Base-Catalyzed Protium-Deuterium Exchange in Bicyclo{2.2.1.}Heptanones

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ABSTRACT

Several ketones in the bicyclo{2.2.1.}heptane system, many of them previously unknown, have been prepared and characterized; these included monoketones, enones and diones. They are listed in Fig. II-1.

The conformations of norbornane-2,5-dione (27) and 3,3-dimethylnorbornane-2,5-dione (26) have been carefully examined by nuclear magnetic resonance spectroscopy. These compounds have been found to exist in two different *synchro* twist conformations.[76]

The stereochemistry of base-catalyzed protium-deuterium exchange of the diones 25, 26 and 27 has been examined and has been found to be similar to the stereochemistry of exchange in monoketones previously observed in these systems, *viz exo* exchange is considerably more rapid than *endo* exchange.

The rates of NaOD-catalyzed protium-deuterium exchange of the ketones, enones and diones have been measured in 60 % dioxane-D_2O at 25°. The rate data is shown in Table II-4. Kinetic analysis showed that these rate constants represent the true reactivity of the hydrogen for which the rate of exchange was measured.

A study of the ^{13}C chemical shift of highly substituted bicyclo{2.2.1.}heptanes has been undertaken, and also a study of the ^{13}C-H coupling constants of many of these compounds has been made. The results

are listed in Tables II-6 and II-8. They suggest that there are no unusual hybridization effects at the enolizable carbon in the diones and enones under study.

The rate data, together with some literature data, shows that hybridization effects, torsional effects, conformational effects and strain effects are of minor importance in the exchange reactions. The rate acceleration observed in the dione systems is almost entirely accountable by an inductive effect of the second carbonyl group, with very little homoconjugative participation.

The kinetic results suggest that an enol is the intermediate in the enolization reaction, and that the transition state occurs relatively early along the reaction coordinate.

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

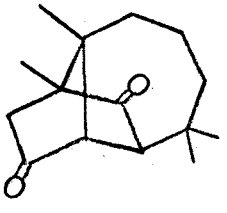
LIST OF SCHEMES

I. INTRODUCTION

Ketones with at least one enolizable hydrogen, react with oxygen in the presence of potassium *tertiary*-butoxide to form α-diketones,[1,2] or α-hydroxyketones.[3] Cleavage of the carbon chain adjacent to the carbonyl has also been observed.[4,5,6] An α-hydroperoxyketone is an intermediate in the reaction and has been isolated in certain favourable cases.[5,7,8,9]

Of particular interest is the autoxidation of 1,4-diones that gives enediones as product.[10] A few examples are listed in Scheme I-1. The mechanism postulated here is depicted in Scheme I-2, where extended conjugation in the dienolate ion, or the ease of electron transfer, would be responsible for the behaviour of such diones. The autoxidation of the isobutylidene-2-oxazolin-5-one (Scheme I-3)[11] would be in agreement with this reason. The autoxidation of culmorindione (1) is another unusual case (*vide infra*).

A key step in the structural elucidation of culmorin (2)[13,14] has been the base-catalyzed autoxidation of the dione 1. The mechanism of the reaction has been postulated[14] to be as shown in Scheme I-4.



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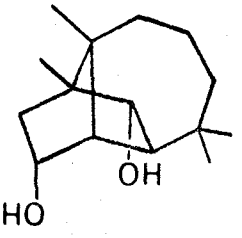

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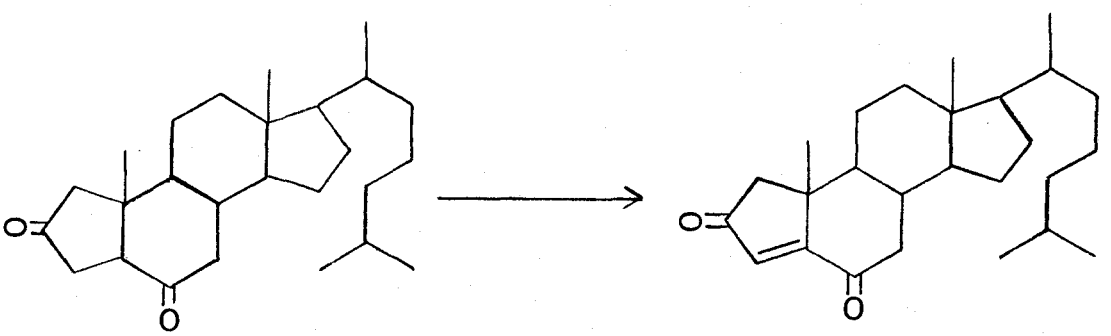
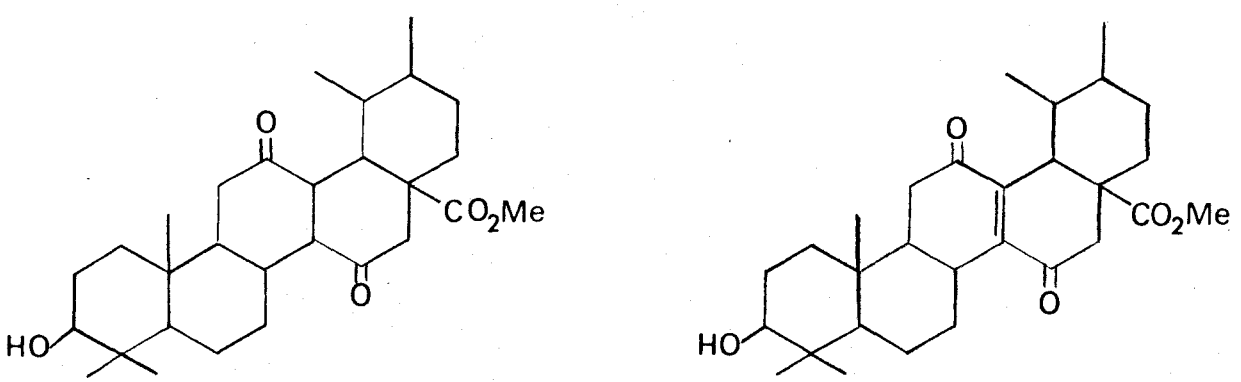
Scheme I-1

Autoxidation of 1,4-Diones, Examples

A) A-norcoprostane-2,6-dione:[10]



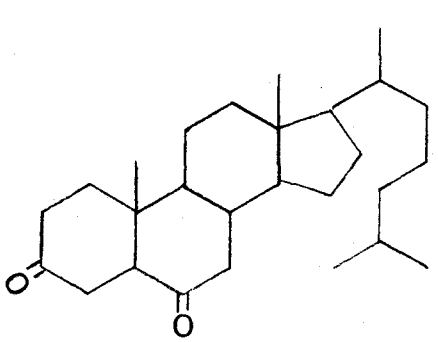
B) Methyldiketopyroquinovate:[12]

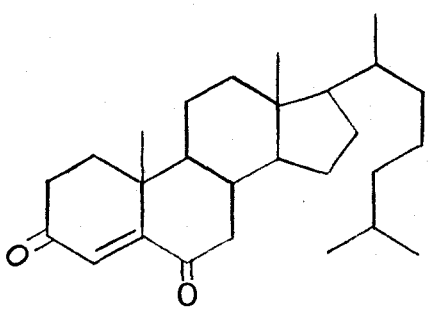


Scheme I-1 (continued)

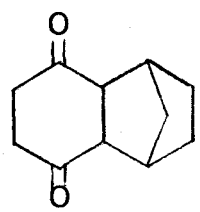
Autoxidation of 1,4-Diones, Examples

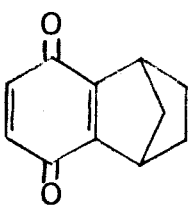
C) Cholestane-3,6-dione:[10]





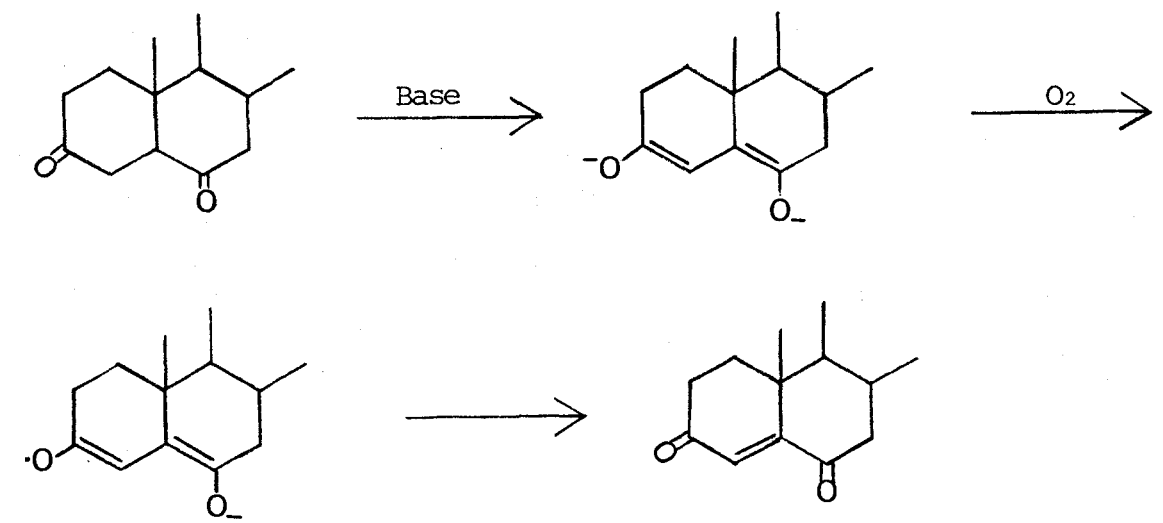
D) Non-steroidal example:[10]





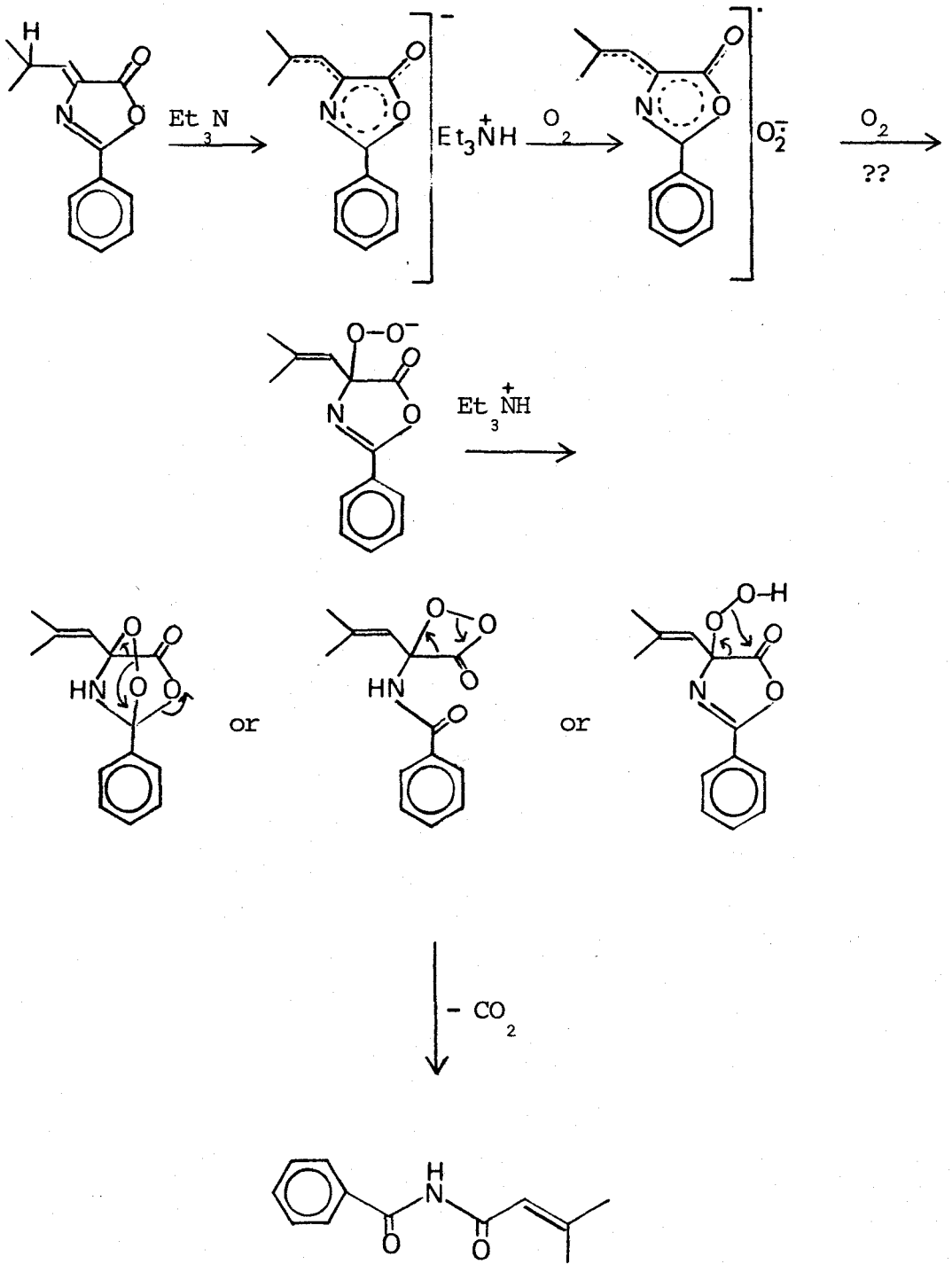
Scheme I-2

Mechanism of Autoxidation of 1,4-Diones [10]



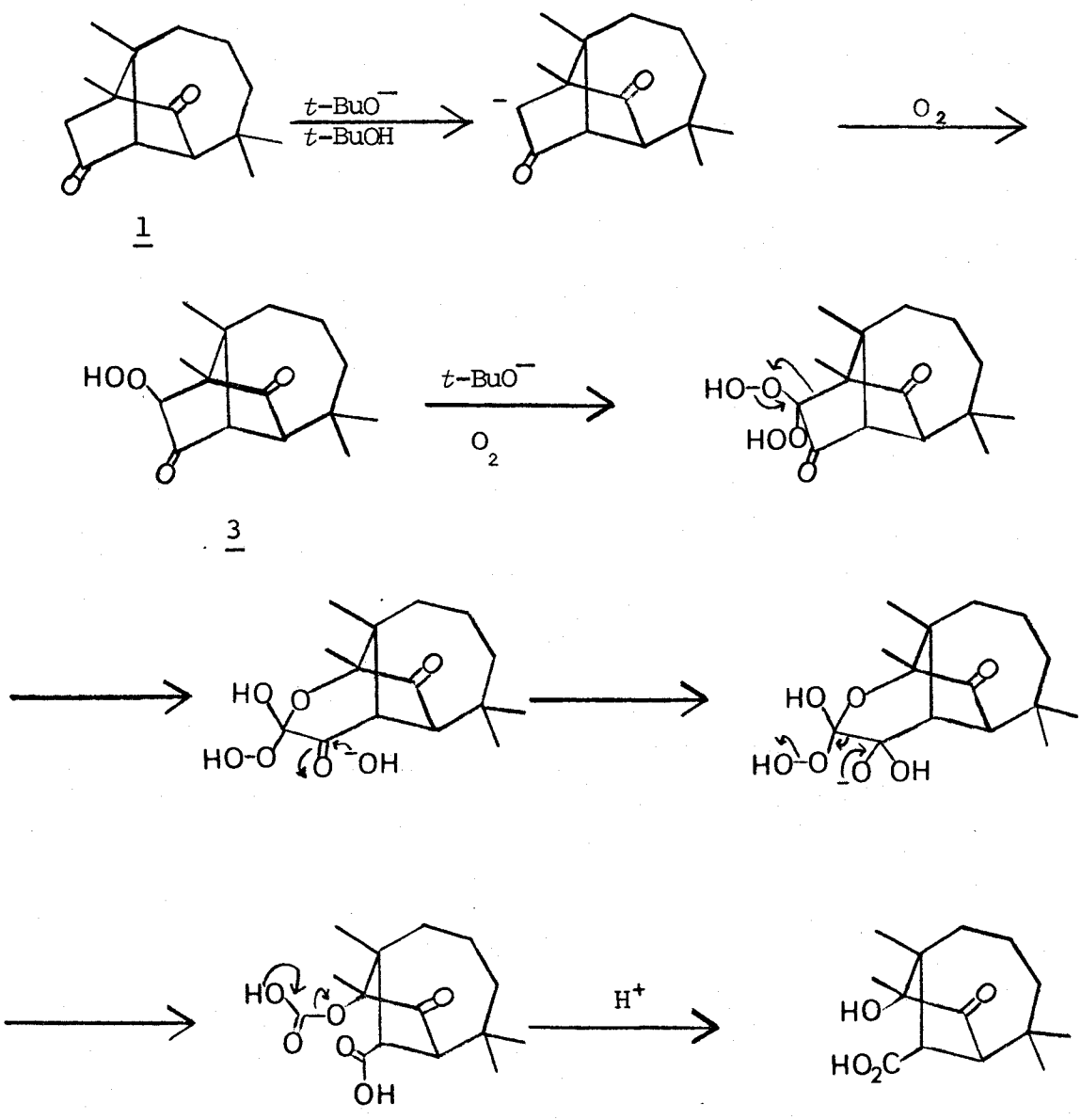
Scheme I-3

Autoxidation of 4-Isobutylidene-2-Phenyl-2-Oxazoline-5-One [11]

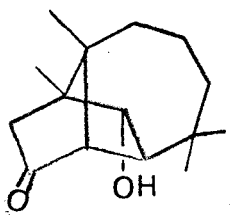


Scheme I-4

Mechanism of Autoxidation of Culmorindione [14]



The formation of the α-hydroperoxyketone 3 is thought to go through the mechanism depicted in Scheme I-5.[8] Step from 4 to 5 (Scheme I-5) may consist of the radical chain process depicted in Scheme I-6.[15] The autoxidation of culmorindione (1) is of interest because the closely related hydroxyketone 6[13,14] and camphor (7),[16] under similar experimental conditions, do not react. It is clear therefore, that the second keto group in dione 1 plays an important role in facilitating the reaction. In 1,4-diones of the steroid-type, extensive conjugation was thought to be important. In dione 1, this is also possible,[14] *via* homoenolic participation* of the second carbonyl, as in structure 8. That such homoenolic participation is possible is illustrated



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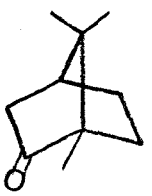

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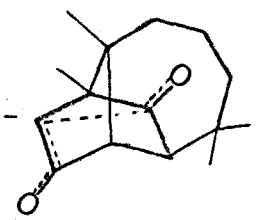

8

by the fact that it may have been detected before in the reactions of phosphines with 4-trihalomethylcyclohexa-2,5-dien-1-ones (9):

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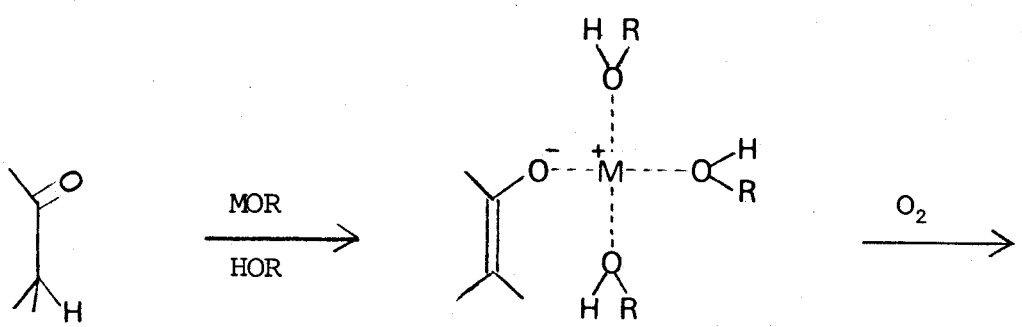
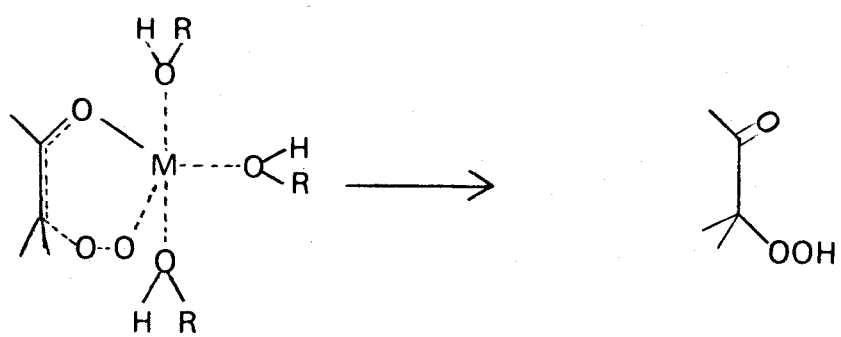
*This will be discussed in detail in the discussion part of this dissertation.

Scheme I-5

Mechanism of Formation of the α-Hydroperoxyketone [8]

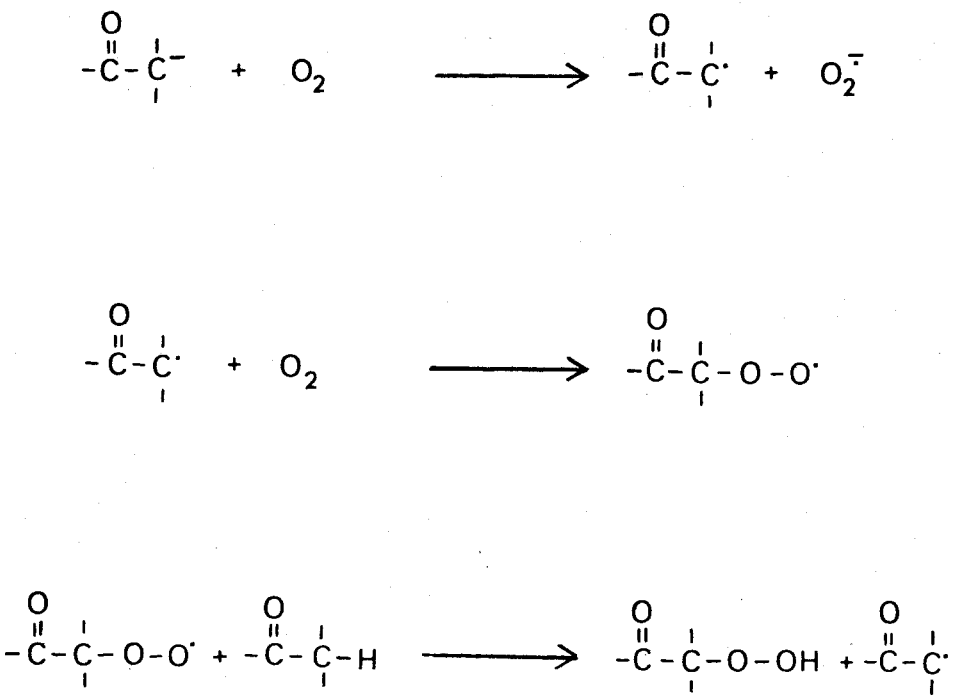


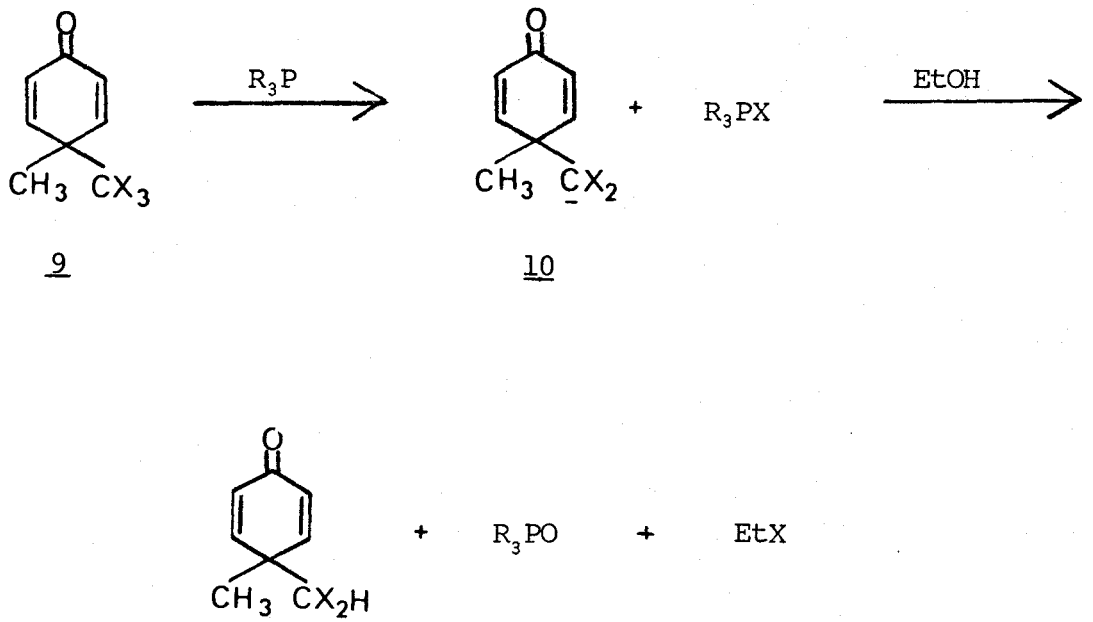


4 5

Scheme I-6

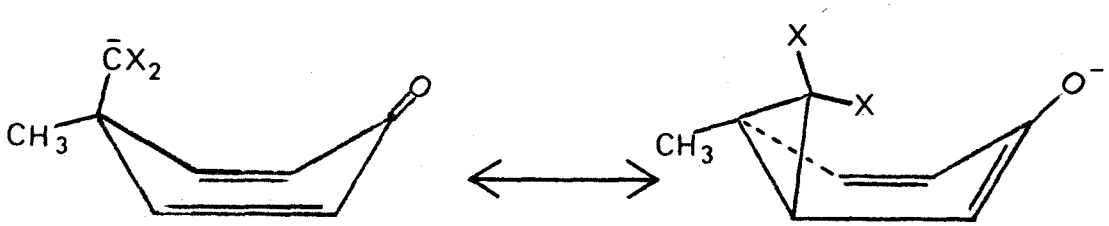
Oxidation Step in Formation of the α-Hydroperoxyketone [15]





9 10

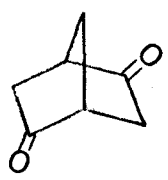
Miller has reported[17] a rate acceleration of 10^6 due to homodienolic participation in the reaction of 9 as compared to chloroform. The intermediate anion (10) in the reaction has been suggested to be:



10

On the other hand, the ease of autoxidation does not only depend on the degree of conversion to the anion (enhanced by extensive conjugation), but also on the relative stability of the carbanion and the corresponding radical.[18] This is illustrated by the fact that many β-dicarbonyl compounds[18] are stable to autoxidation, presumably

because the second carbonyl group stabilizes the anion more than the radical.[18] (*Cf.* Scheme I-6). Thus structure 8, although attractive as an explanation, may not be responsible for the autoxidation of 1. Other factors could operate in the autoxidation of culmorindione (1). Consider a generalized bicyclo{2.2.1.}heptane-2,5-dione, structure 11, to be taken as a model for culmorindione (1).



11

In addition to the homoconjugative effect mentioned above, the following factors could conceivably be responsible for the easy autoxidation:*

1) Hybridization effect

Introduction of a second sp^2 center in the bicyclo{2.2.1.}skeleton may give rise to additional strain which in turn may cause a rehybridization of the C-H bond, α to the carbonyl, in the same way that in cyclopropane the C-H bonds are formed with an orbital on carbon approaching sp^2 in character.[19,20] The net effect would be an increase in the acidity of the hydrogens.

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* Effects are listed here with no reference to their influence on a) enolization, or the stability of the carbanion, and b) the stability of the radical.

2) Strain effects

The additional strain introduced by the second sp^2 center may be an important factor. The sp^2 angle (*ca.* 120°) at C(2) may force the angle at C(6) (the enolizable center) to increase or decrease, depending on the exact conformation of 11.

3) Torsional effects

Torsional interactions between the α-protons and a) the carbonyl[21,22] and b) the bridgehead protons[23] could constitute in the dicarbonyl compounds an important effect, relative to the same interactions in the monocarbonyl compounds.

4) An inductive effect

The inductive effect of the carbonyl 1,3 to the enolizable center may be important.

Enolization in the autoxidation mechanism is important (*vide supra*). To gain some insight into the role of the second carbonyl group, firstly on the enolization step, a study of enolization of some model compounds in the bicyclo{2.2.1.}heptane system was undertaken, and is the subject of this dissertation.

It is well known that basic reagents remove an α-hydrogen from ketones to form enol or enolate intermediates. It is also well known that the rate-determining step in H-D exchange reaction of ketones, is the formation of enols in acid medium and enolates in strongly basic medium.[24] In acid medium the transition state leading to enol intermediate should be enol-like while in basic medium it should be enolate-like. These represent two extremes of a large spectrum of transition

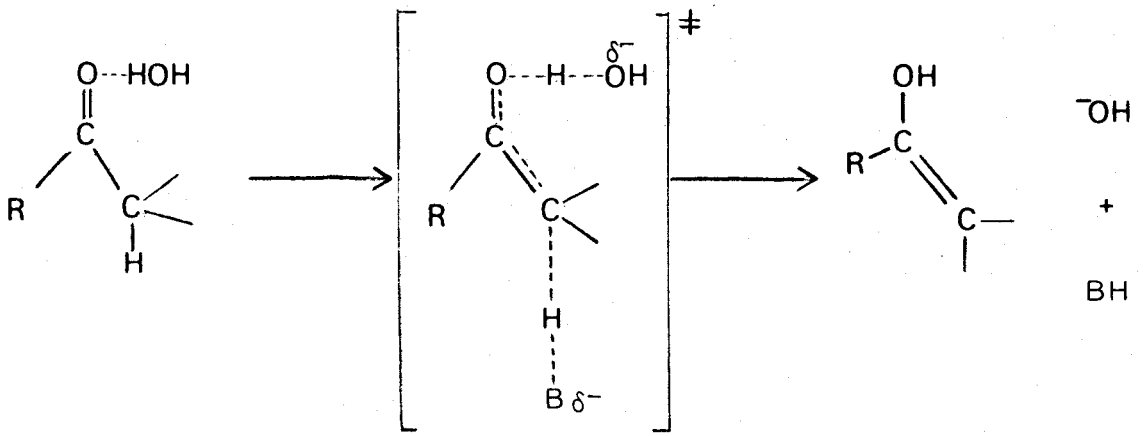
states. In general, in base-catalyzed enolization, the weaker the base, the more the transition state should resemble an enol.[25 26 27] Warkentin and Tee have suggested[26] that even with bases as strong as ^{-}OD in D_2O (or ^{-}OH in H_2O), enolization may be represented as involving an enol as the intermediate. With this in mind, the two mechanisms are summarized in Scheme I-7. The ^{-}OD-catalysed enolization of bicyclic ketones has not been studied in detail such that it is not known at this time whether enol or enolate intermediates are involved. It might be possible however, to gain information on the problem by determining the effect of the second carbonyl group on the rate of enolization. An acceleration due to the carbonyl is expected to be more important in the case where there is a charge development in the O-C-C system than in one where charge development is minimal (Enol-like transition-states and intermediates). Further, for an enolate-like transition-state (as in Miller's case[17]), a substantial acceleration due to homoenolic participation would be expected.

At the start of this work, only several scattered and incomplete studies of base-catalyzed hydrogen-deuterium exchange in bicyclo{2.2.1.}heptanones had been reported, and this further prompted our kinetic studies. Thomas and Willhalm[28] exchanged isofenchone (12) in dioxane-D_2O-NaOD solutions for 3 days at room temperature, and obtained a monodeuterated compound (97 % isotopic purity). The deuterium content was not appreciably altered after a second exchange for 20 minutes at 90°. Camphor (7) and norcamphor (13) were found to behave similarly. In other work,[29] norcamphor (13) was exchanged under the more

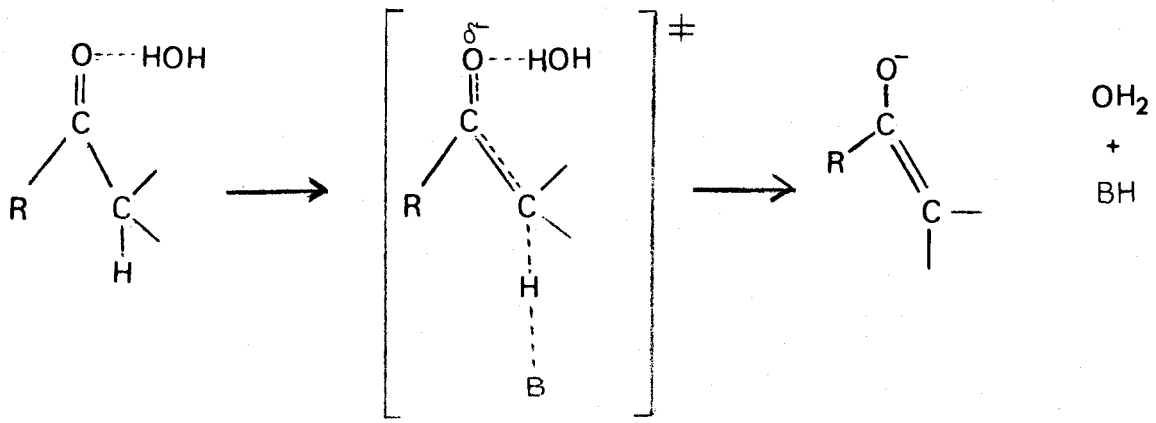
Scheme I-7

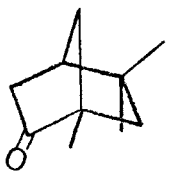
Enolization Mechanism in Water [25–27]

A) Acid and Weakly Alkaline Medium



B) Strongly Alkaline Medium





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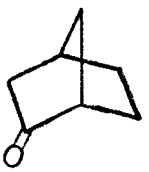

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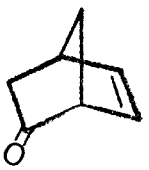

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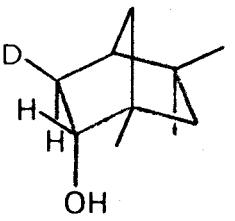


15

vigorous conditions of $NaOCH_3$-$DOCH_3$-D_2O at 100° for 12 hours, and was found to contain 50% of 2 deuteriums per molecule. Dehydronorcamphor (14) under the same conditions, incorporated 95% of 2 deuteriums per molecule. On the other hand, Barraclough and Young[30] treated dehydronorcamphor (14) to the same conditions reported by Thomas and Willhalm[28] and found a product containing 84% of a monodeuterated species, *i.e.* the behavior of dehydronorcamphor (14) was similar to that of the other bicyclic ketones.

The stereochemistry of these reactions was investigated by all the authors cited so far, [28,29,30] and also by Thomas, Schneider and Meinwald.[31] In all cases the stereochemistry was found to be the same. Lithium aluminium hydride reduction of isofenchone gives *endo*-isofenchol. [28,32] The carbinol hydrogen in the n.m.r. spectrum gives[28] a broad doublet centered at $\delta = 3.7$ ($J \simeq 9$ Hz). The reduction product of the monodeuterated isofenchone displayed a broad singlet at $\delta = 3.72$. This was interpreted as being consistent with compound 15. The disappearance of the large coupling constant indicates a *cis* arrangement, [28,33,34] and therefore *exo*-deuterium at C(3). Similarly,

camphor (7) was subjected[31] to various exchanges as shown in Scheme I-8. The carbinol hydrogen in isoborneol appears in the n.m.r. spectrum as a triplet centered around $\delta = 3.5$ p.p.m. The deuterated isoborneol 16 exhibited a doublet at $\delta = 3.53$, with $J = 8.5$ Hz. The magnitude of this coupling indicates a *cis* arrangement,[31,33,34] and therefore *endo-endo* coupling. The stereochemistry of the deuterium at C(3) is then *exo*. The isoborneol 17 exhibited a broad unresolved absorption at $\delta = 3.55$, the width of which at half height was about 5 Hz. This absorption was rationalized as a doublet with $J \simeq 2.5$ Hz, characteristic of *trans*-coupling,[31,33,34] establishing that the deuterium is *endo*.

At the onset of this work, no quantitative data were available on the rates of exchange of these bicyclic ketones. While the present work was in progress however, some kinetic data appeared in the literature. T.T. Tidwell and co-workers measured the rate of NaOD catalysed exchange of several bicyclic ketones in 66% dioxane-D_2O at 25°.[35-38] The kinetic procedure used was similar to that used in the present work, although the methods were developed independently. The data is listed in Table I-1.

Several conclusions were drawn:

1) The *exo*-selectivity observed in all these exchanges would have been predicted on steric grounds, but the magnitude of the selectivity is perhaps surprisingly large. This observation makes enolization of these ketones fall into H.C. Brown's classification[39,40,41,42] of non-cyclic reactions that are not very much affected sterically by 7,7-dimethyl substitution in the norbornyl system.

Scheme I-8

Stereochemistry of Exchange in Camphor [31]

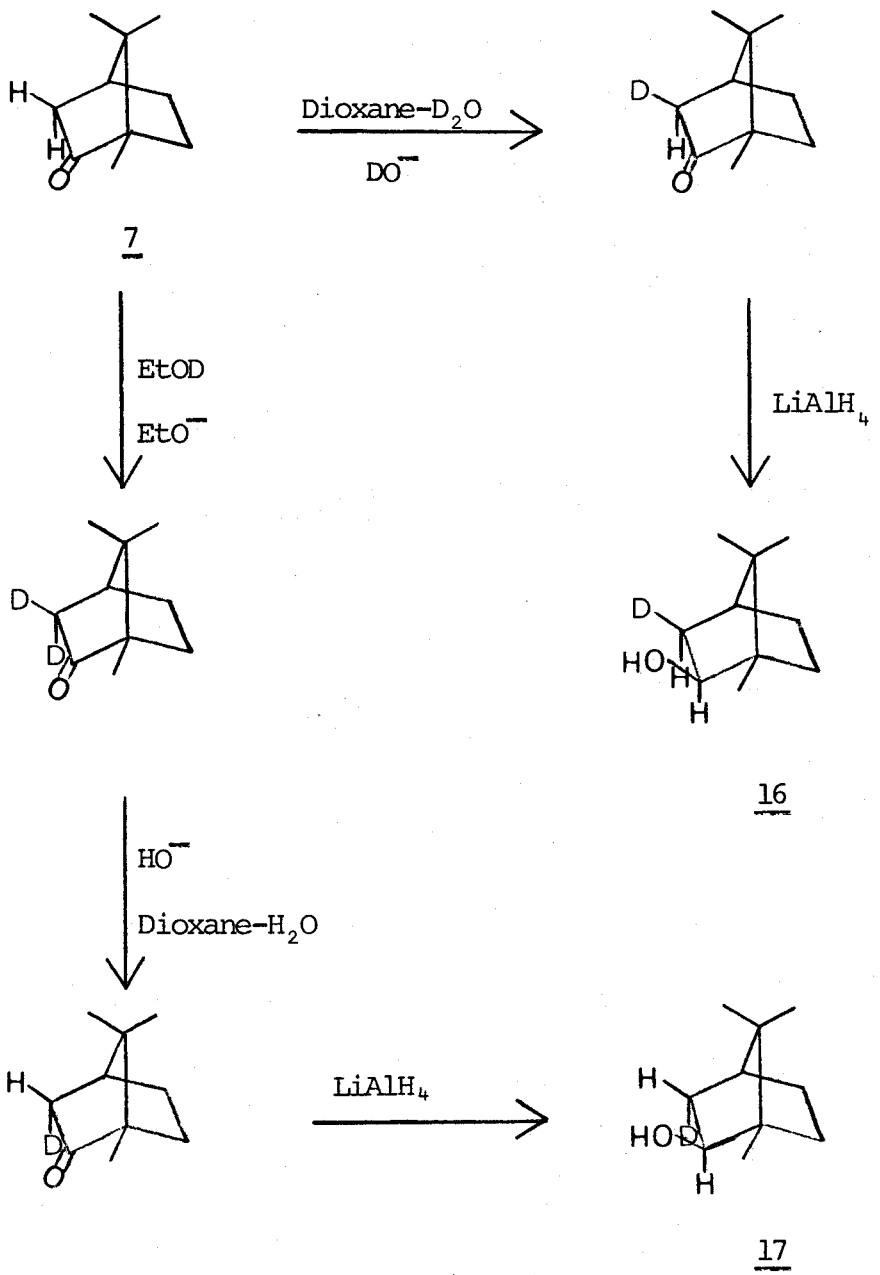


Table I-1

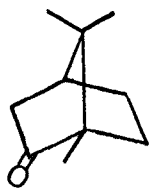
Second Order Rate Constants of NaOD-Catalyzed Deuterium Exchange in Ketones at 25° in 67% Dioxane-D_2O *

Ketones**		k_2 (l/mole·s)	Relative Rates		
			Exo	*Endo*	*Exo/endo*
13	*exo*	5.48×10^{-2}	1.0	-	715
	endo	7.67×10^{-5}	-	1.0	
7	*exo*	9.50×10^{-4}	0.017	-	21
	endo	4.46×10^{-5}	-	0.58	
14	*exo*	7.30×10^{-4}	0.013	-	120
	endo	6.06×10^{-6}	-	0.079	
18	*exo*	2.68×10^{-2}	0.49	-	595
	endo	4.50×10^{-5}	-	0.59	
19	*exo*	-	0.032	-	19
	endo	-	-	0.61	
20		-	1.1×10^{-4}	-	-
		-	-	0.080	
21		-	0.71	-	-
		-	-	510	

*References 35-48.
**Structures for these ketones will be found in Fig. I-1.

Fig. I-1

Structures for Compounds Listed in Table I-1



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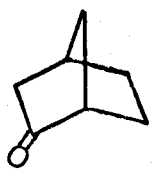

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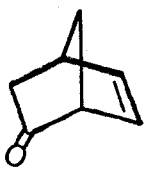
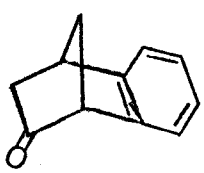
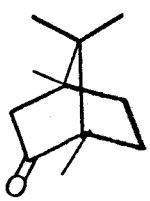


14



18



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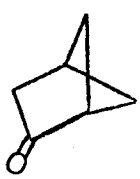

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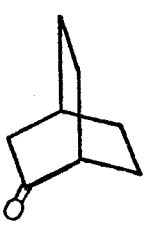
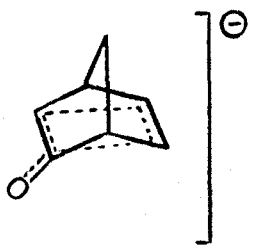


21

2) The low reactivity of 14 is contrary to previous report.[29]

3) The low reactivity of 14 and 18, relative to 13, and also the *exo-endo* rate ratios show that the steric effect of the *endo*-5,6-hydrogens in 13 is not the dominant factor in governing its reactivity relative to 14 and 18.

4) The results in 14 are contrary to expectation from the inductive effect of the double bond. Bishomoantiaromatic delocalization (structure 22, destabilizing) would however be consistent with the results.



22

5) Comparison of the rates of exchange in 7 and 19 show that torsional effects[23] are of minor importance. (This conclusion will be discussed in detail with some additional data in the Discussion).

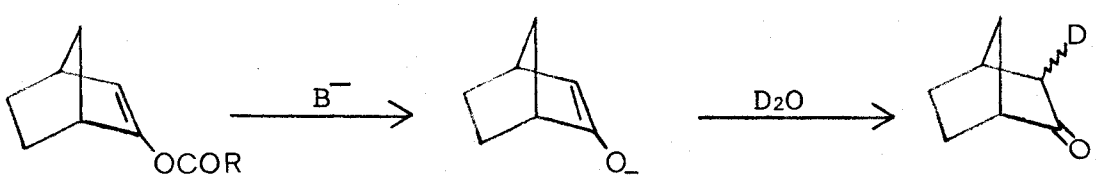
6) Angle strain (I-strain) and non-bonded van der Waals repulsion (F-strain) are major contributors to the rate differences in going from the {2.1.1.}system to the {2.2.1.} and {2.2.2.}systems.

7) Hybridization effects in going from the {2.1.1.}system to the {2.2.2.}system are not detected, but may still be operative. (This conclusion will be discussed further in the Discussion.)

W.O. Crain,[43,44] using d.m.r. spectroscopy, has also studied the stereochemistry of these exchange reactions. The rates of

isotopic exchange at C(3) in camphor (7) and in various deuterated camphors were measured in 60 % dioxane-D_2O (or dioxane-H_2O) at 34°. The results are shown in Table I-2.

In an attempt to determine whether or not the numbers shown in the table represented the true stereoselectivity of the exchange reaction, Crain measured the deuterium distribution in the hydrolysis of enol trifluoroacetates in DO^--D_2O. The argument was that the enol ester upon hydrolysis, gives rise in the rate determining step, to the enolate anion,[43,45,46] which upon deuteration, should give an *exo-endo* ratio that represents the true reactivity of the different stereochemical positions:



The enol trifluoroacetate was chosen because it is sufficiently reactive for the reaction to be complete before exchange with the medium can occur. The results are shown in Table I-3. The discrepency between these results and those obtained by the direct exchange of the ketone is large. Comments on these results are reserved until a later stage in this dissertation. Suffice it to say at this point that:

1) Hydrolysis of the enol ester gives rise to an enolate anion, which may not be the intermediate in the exchange reaction.

Table I-2

Pseudo-first Order Rate Constants for Exchange at *exo* and *endo* C(3) in Camphors in 0.2*N* Base in 60% dioxane-D_2O (or H_2O) at 34° [43]

Ketones	k_{exo} x 10^6 (min.$^{-1}$)	k_{endo} x 10^6 (min.$^{-1}$)	k_{exo}/k_{endo}
Camphor	240	13	18
Camphor-3,3-d_2	11	5.5	2
Camphor-*endo*-3-d_1	220	-	-
Camphor-*exo*-3-d_1	-	14	-

Table I-3

Relative Amounts of Deuterium Substitution into the *exo* and *endo* C(3) Positions from the Hydrolysis of Enol Trifluoroacetates of Various Bicyclo{2.2.1.}heptane-2-ones [43]

Compound	Source	*Exo*-D/*Endo*-D
Camphor-3-d_1	Enol trifluoroacetate of camphor, $D_2O/\overline{O}D$	8.2 ± 1.0
	Enol trifluoroacetate of camphor-3-d_1, $H_2O/\overline{O}H$	0.12 ± 0.01
Norcamphor-3-d_1	Enol trifluoroacetate of norcamphor, $D_2O/\overline{O}D$	60 ± 10
Isofenchone-3-d_1	Enol trifluoroacetate of isofenchone, $D_2O/\overline{O}D$	> 100

2) The transition state for protonation of the enolate from the ester hydrolysis may not be at the same position along the reaction coordinate as that in the exchange reactions.

Thus the present work shall deal with the mechanism of enolization in bicyclic ketones, in an attempt to determine what factors govern the reactivity of bicyclo{2.2.1.}heptanones under a particular enolization condition. It will constitute the initial study on the autoxidation mechanism. The factors that will be looked at will be:

1) Effect of hybridization changes at the α-carbon arising through strain in the {2.2.1.}skeleton.

2) Effect of various torsional interactions of the α-hydrogens.

3) Effect of additional strain, particulary strain of a second sp^2 center, in the {2.2.1.}skeleton.

4) Inductive effect and/or homoconjugative effect of a carbonyl group, placed 1,3 to an enolizable center.

II. RESULTS AND DISCUSSION

A. SYNTHESIS

In order to test the reactivity towards hydrogen-deuterium exchange of bicyclo{2.2.1.}heptanones, a number of monoketones, diones and enones were prepared. These are shown in Fig. II-1.

Monoketones

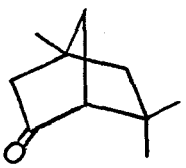
All the monoketones have been described in the literature. Norcamphor was available commercially.

6,6-Dimethyl-2-norbornanone (24) was obtained as shown in Scheme II-1. Cyclopentadiene and methylmethacrylic were condensed[47,48] in a Diels-Alder reaction to form a mixture of *exo* and *endo*-2-norbornene-5-methyl-5-carboxylic acid (32). Lithium aluminium hydride reduction of the mixture gave the corresponding mixture of carbinols (33).[49] Tosylation, followed by further reduction with lithium aluminium hydride gave the hydrocarbon camphenilene (34).[49] Epoxidation with perlauric acid gave only the *exo*-epoxide 35,[50,51,52] which when reduced with lithium aluminium hydride in diglyme at 100° gave stereospecifically *exo*-alcohol 36.[50] This compound was identical to an authentic sample kindly provided by Professor H.C. Brown of Purdue University, Lafayette, Indiana, U.S.A. Oxidation of alcohol 36 gave the desired 6,6-dimethyl-2-norbornanone (24).

Epiisofenchone (23) was prepared as shown in Scheme II-2. Fenchol (37) was dehydrated with fused $KHSO_4$ to a mixture of hydrocarbons.[53] The mechanism of the reaction is shown in Scheme II-3.[54] When this mixture of hydrocarbons is protonated (H_2SO_4) in acetic acid

Fig. II-1

Ketones of Interest in this Study



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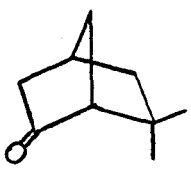

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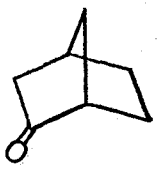

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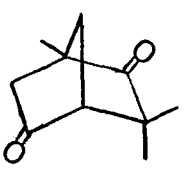

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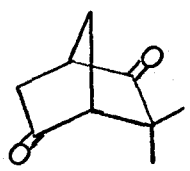

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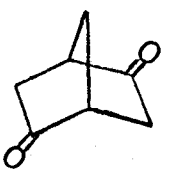

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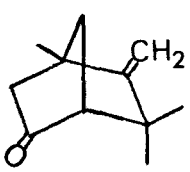

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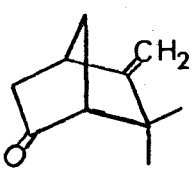

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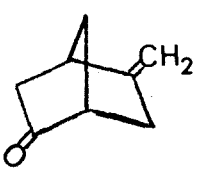

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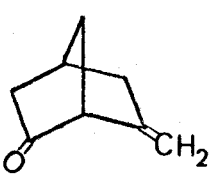
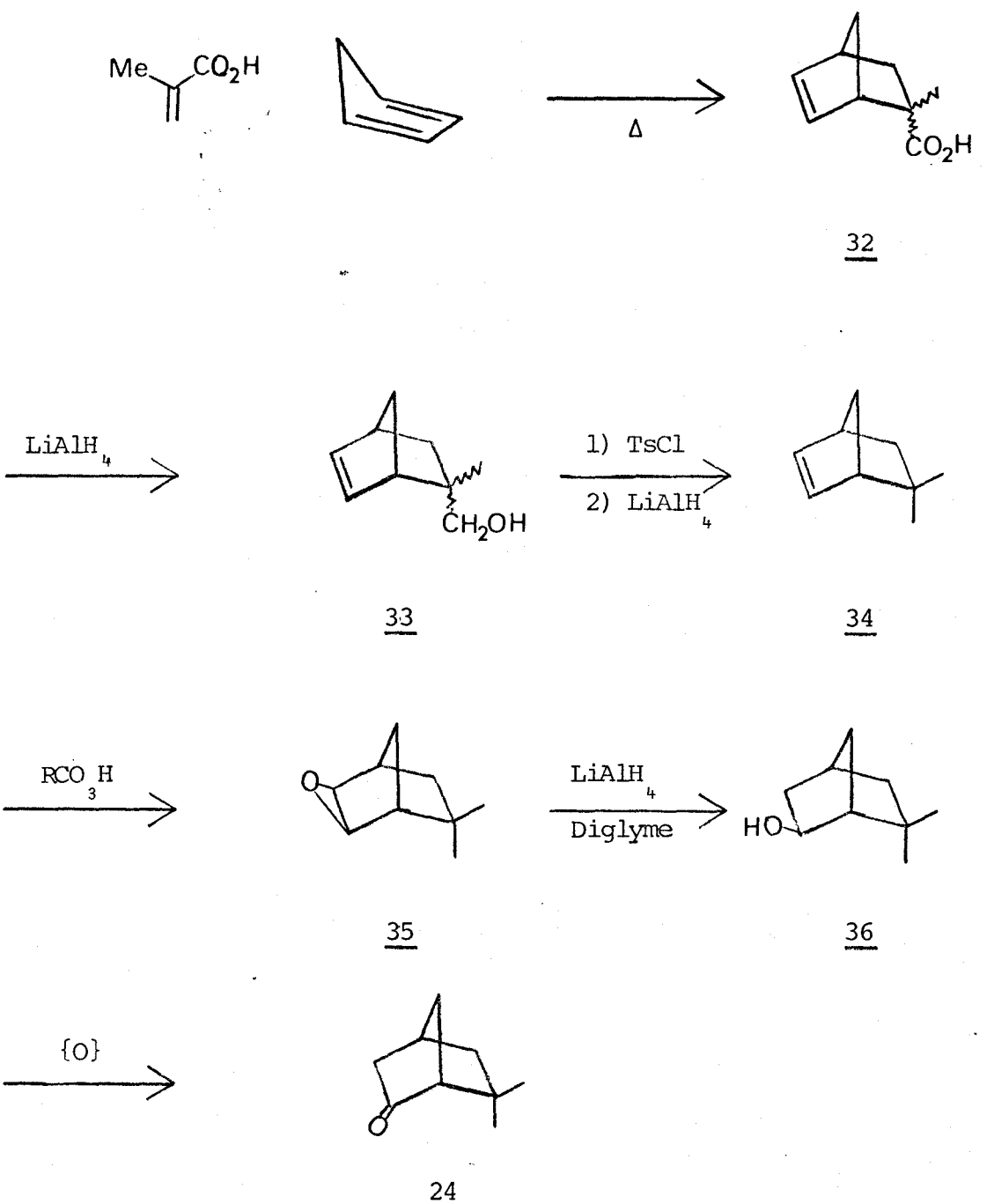


31

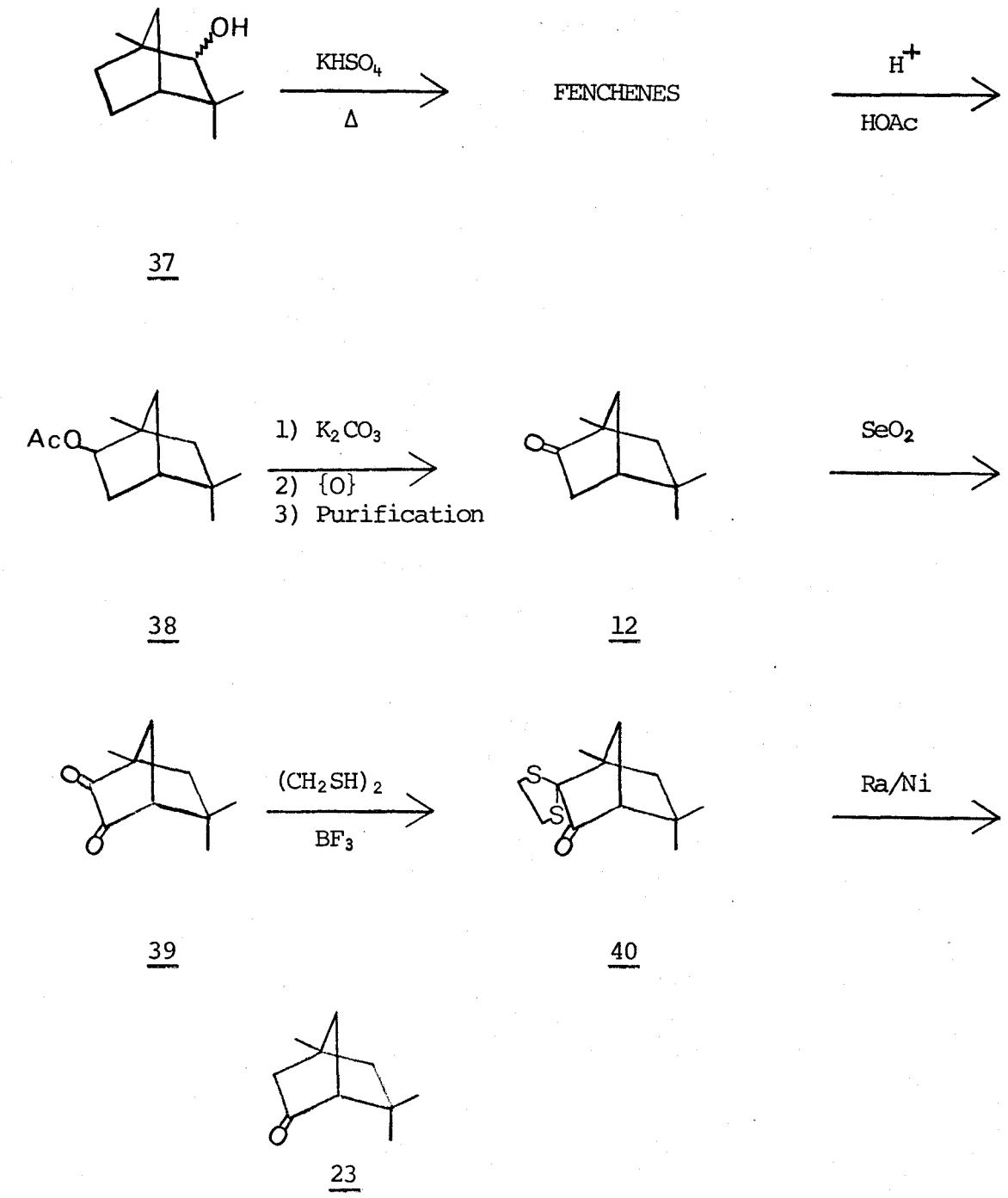
Scheme II-1

Preparation of 6,6-Dimethyl-2-norbornanone [47-52]



Scheme II-2

Preparation of Epiisofenchone (23) [53, 55-59]



37

38

12

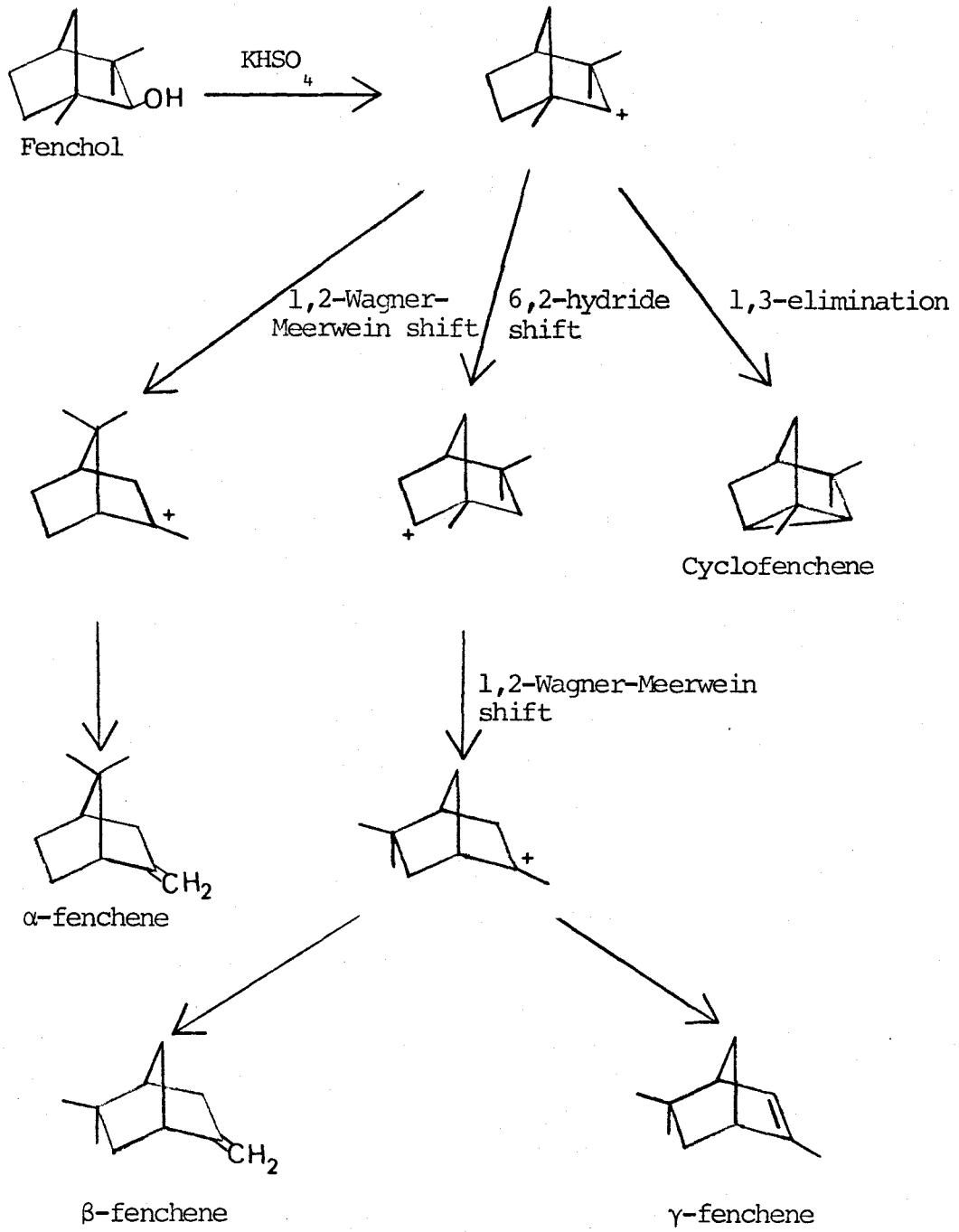
39

40

23

Scheme II-3

Dehydration of Fenchol [54]



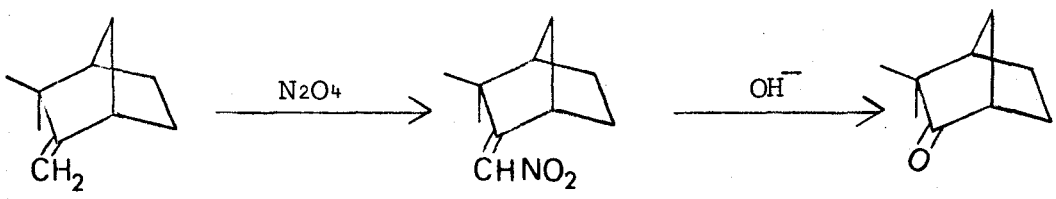
under thermodynamic conditions, isofenchyl acetate (38) predominates.[55] Hydrolysis of the acetate[56] followed by oxidation[57] gave isofenchone (12). Purification of this ketone was achieved by repeated recrystallization of the corresponding semicarbazone, followed by hydrolysis.[58] The ketone was identical in all respects with an authentic sample provided by Dr A.F. Thomas of the Laboratoires de Recherches, Firmenich et Cie, Geneva, Switzerland. Selenium dioxide oxidation of isofenchone (12) gave dione 39,[59] which upon thioketalization gave specifically dithioketal 40.[59] Desulfurization of the dithioketal (40) with Raney-Nickel gave epiisofenchone (23).[59]

Diones

Fenchane-2,5-dione (25) and 3,3-dimethylnorbornane-2,5-dione (44) were prepared from fenchone (41) and camphenilone (42) respectively. Camphenilone (42) was prepared by two methods:

a) Ozonolysis of camphene (43), followed by oxidative work up.[60]

b) Addition of dinitrogen tetroxide on camphene (43) followed by base cleavage:[61,62]

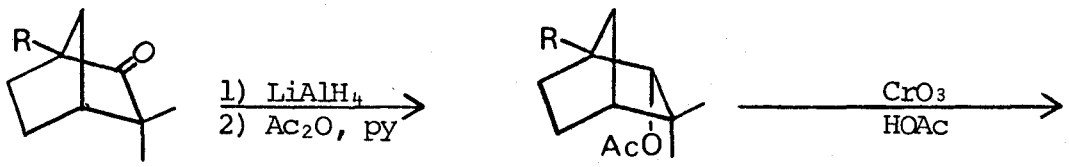


43 42

The preparation of the diones (25 and 26) is shown in Scheme II-4. Lithium aluminium hydride reduction of camphenilone (42) and

Scheme II-4

Preparation of Fenchane-2,5-dione (25) and 3,3-Dimethylnorbornane-2,5-dione (26)

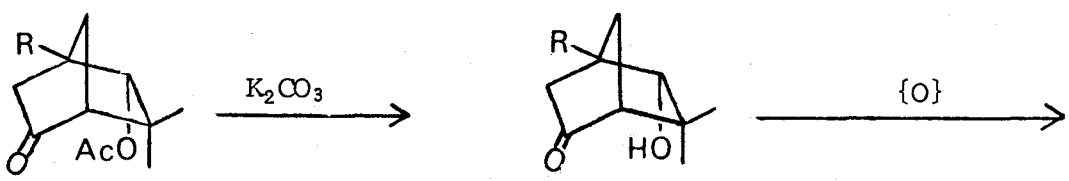


42 R = H

44 R = CH_3

45 R = H

46 R = CH_3

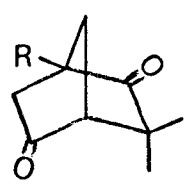


47 R = H

48 R = CH_3

49 R = H

50 R = CH_3



26 R = H

25 R = CH_3

fenchone (44), followed by acetylation gave the corresponding *endo*-acetates 45 and 46. Oxidation with CrO_3 in acetic anhydride / acetic acid gave the 5-ketoacetates 47 and 48,[56,63,64,65] which upon hydrolysis with aqueous K_2CO_3 yielded alcohols 49 and 50.[56,66] Spectral data and elementary analysis for previously unknown alcohol 49 were in agreement with the proposed structure (*cf.* EXPERIMENTAL).

The diones 26 and 25 were obtained by oxidation of the alcohols 49 and 50. Spectral data and melting point for fenchane-2,5-dione were in agreement with the published data.[66] Spectral data and elemental analysis for the previously unknown dione 26 were in agreement with the proposed structure. (N.m.r. is shown in Fig. II-8, and see discussion on page 55).

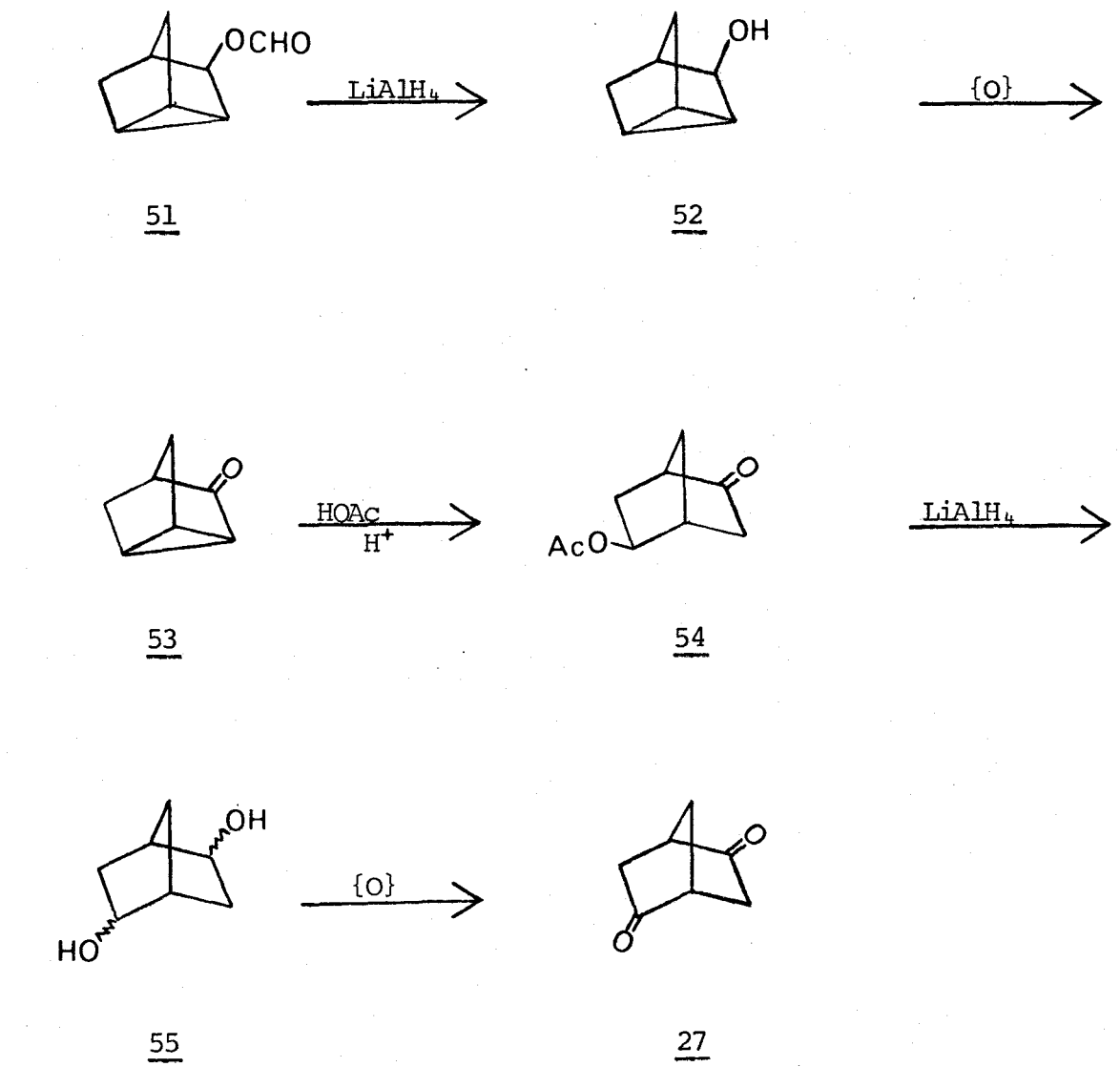
Norbornane-2,5-dione (27) was prepared by the known procedure shown in Scheme II-5.[67] Nortricyclyl formate (51) was reduced with lithium aluminium hydride to nortricyclanol (52) which upon oxidation gave the corresponding ketone (53). Treatment of this ketone with perchloric acid in HOAc gave the 2,5-ketoacetate (54). Reduction with lithium aluminium hydride followed by Jones' oxidation gave norbornane-2,5-dione (27), for which physical data were in agreement with the literature data.[67] (*Cf.* also DISCUSSION on page 46).

Enones

Previously unknown enones 28, 29 and 30 were prepared by the same procedure, starting from an intermediate in the synthesis of the corresponding diones. The synthesis of enone 28 is shown in

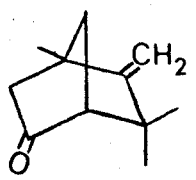
Scheme II-5

Preparation of Norbornane-2,5-Dione (27) [67]



51 52 53 54 55 27

Scheme II-6. Ketalization of 5-ketofenchyl acetate (48) gave the



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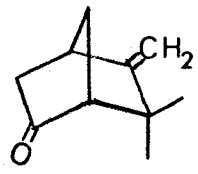

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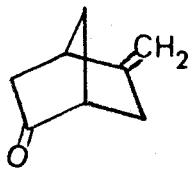
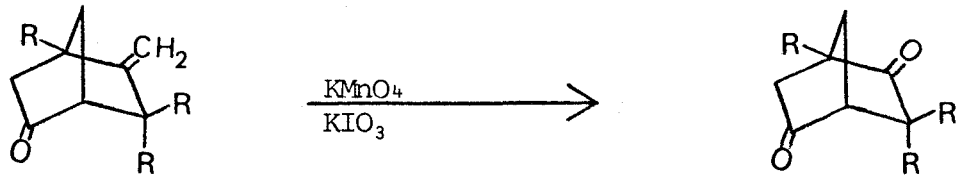


30

ketal 56. Reduction of the acetate with lithium aluminium hydride gave alcohol 57 which upon oxidation with CrO_3 in pyridine gave ketone 58. A Wittig reaction on ketone 58 gave the olefin 59, and subsequent hydrolysis of the ketal function yielded enone 28.

All the enones gave satisfactory elemental analysis or mass-spectral data, and their spectral data were in agreement with the proposed structures. They all could be transformed into the previously prepared corresponding dione by oxidation with $KMnO_4$ and KIO_3:

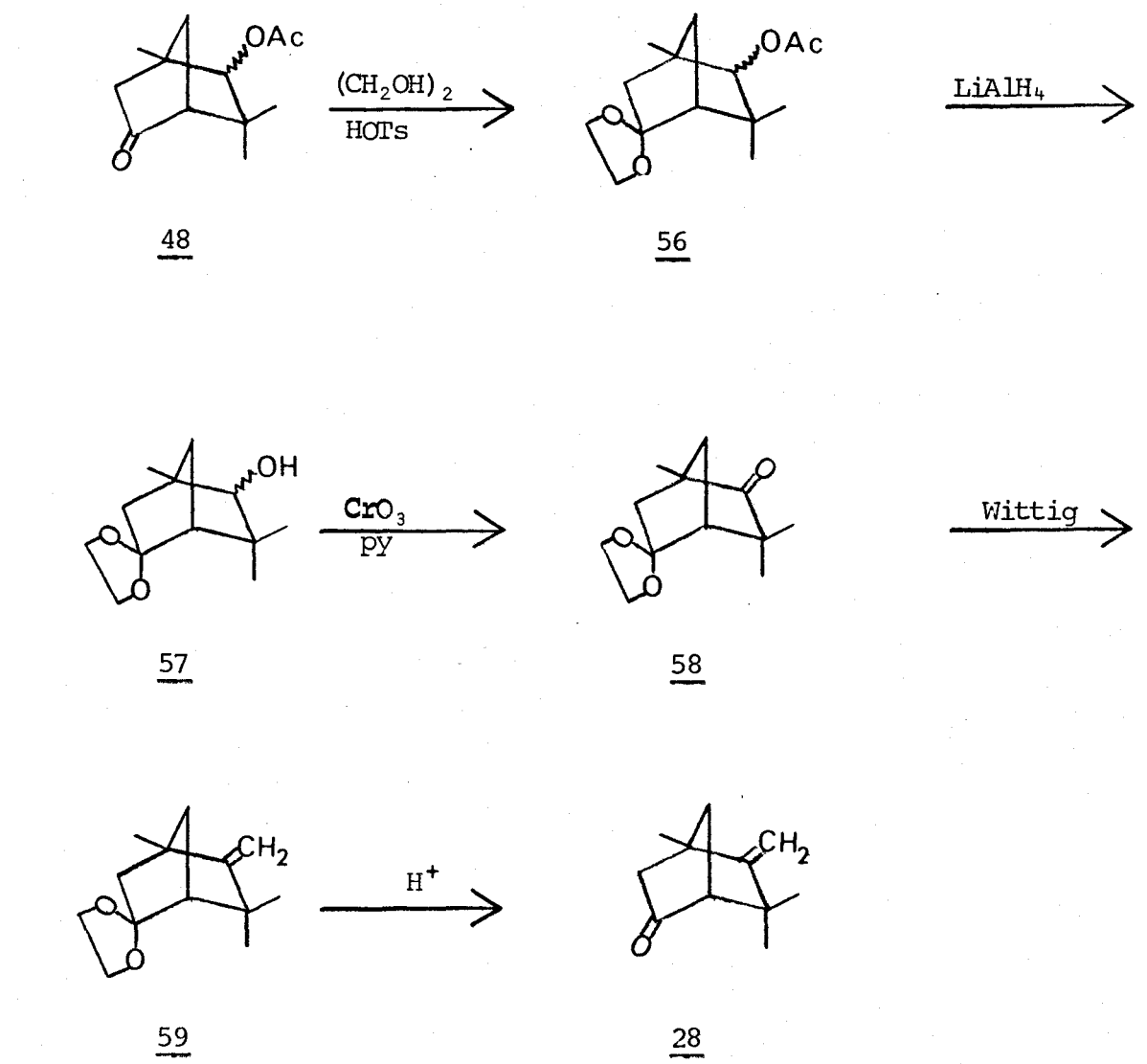


Also, all intermediates in the preparations gave satisfactory elemental analysis and the spectral data were in agreement with the proposed structure.

Previously unknown 6-methylene-2-norbornanone (31) was prepared

Scheme II-6

Preparation of 1-Methyl-5-Oxocamphene (28)

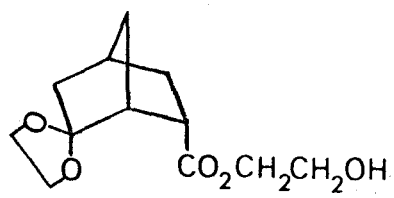


48 56

57 58

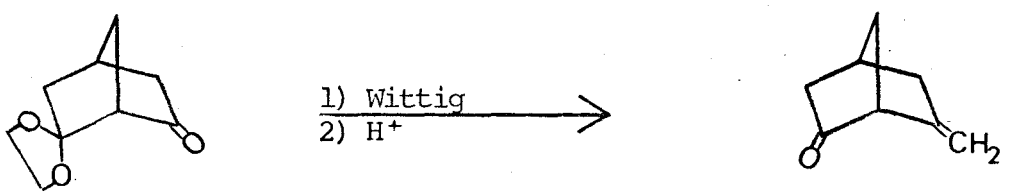
59 28

as shown in Scheme II-7. Treatment of acid 60 with iodine and KI afforded iodolactone 61[68,69] which upon base-catalyzed elimination of the iodine gave ketoacid 62.[68,70] Treatment of this ketoacid with ethylene glycol and acid gave a compound for which spectral evidence suggested that esterification as well as ketalization had occured:



Reduction with lithium aluminium hydride, followed by acetylation gave acetate 64. Pyrolysis of this acetate at 450-500°, followed by hydrolysis of the ketal function, gave 6-methylene-2-norbornanone (31). This compound gave a satisfactory elemental analysis, and the spectral data were in agreement with the proposed structure. Unlike the other enones, it could not be transformed into a known compound. For this reason, its n.m.r. spectrum is reproduced in Fig. II-2.

The first approach to the preparation of 2,6-enone 31 had been intended to be as follows:

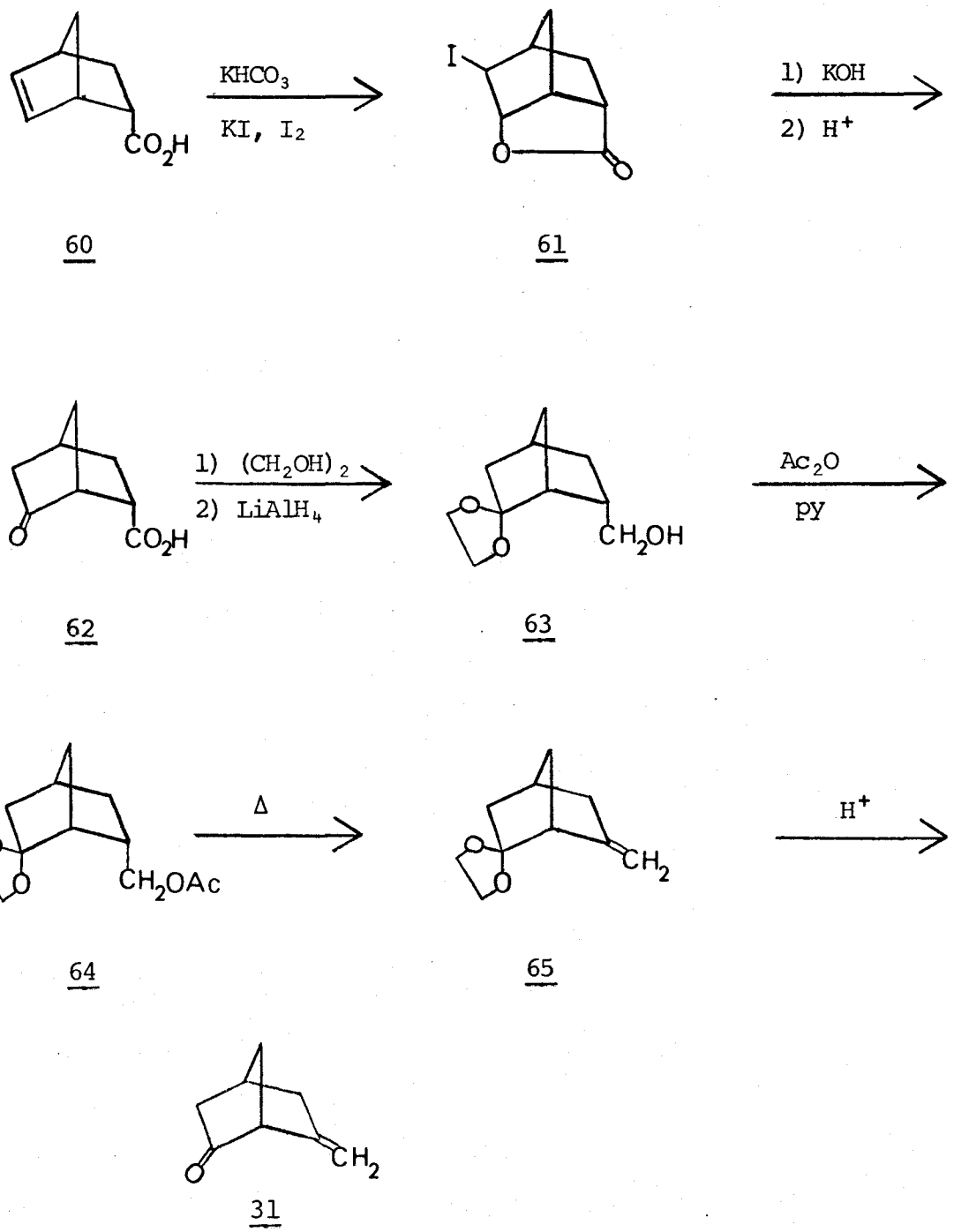


67 31

or

Scheme II-7

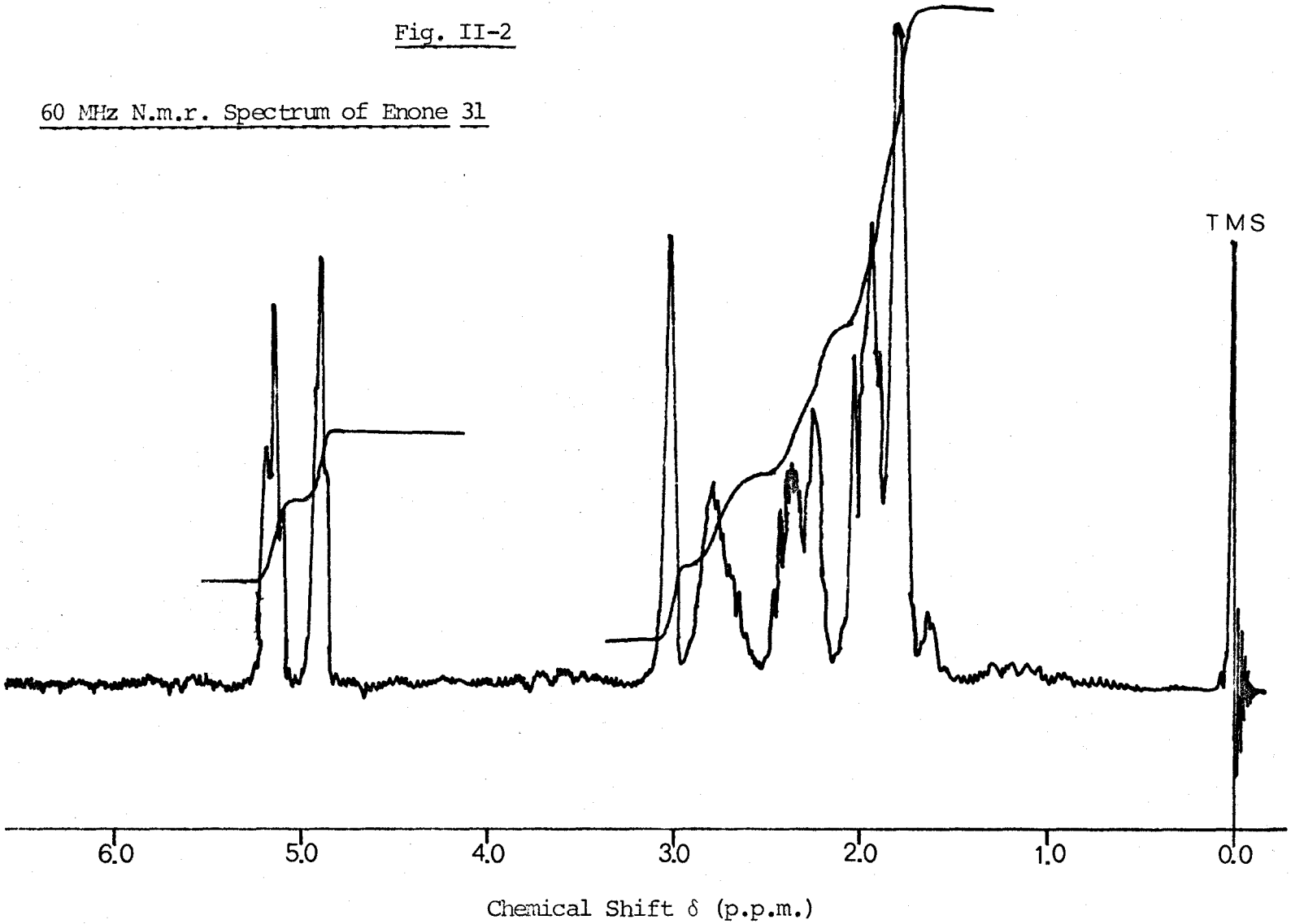
Preparation of 6-Methylene-2-norbornanone (31)

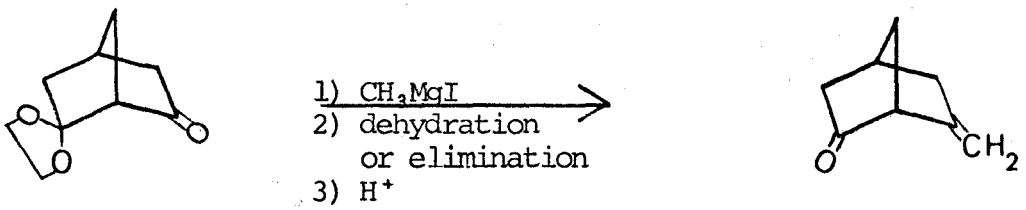


60 61 62 63 64 65 31

Fig. II-2

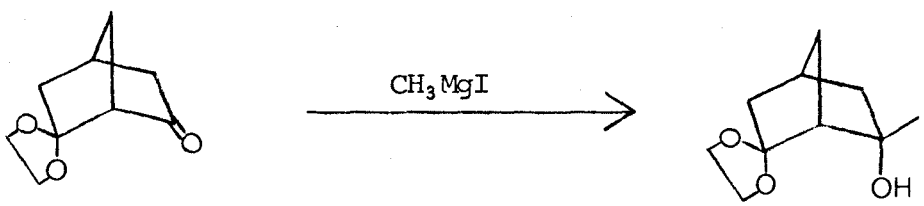
60 MHz N.m.r. Spectrum of Enone 31





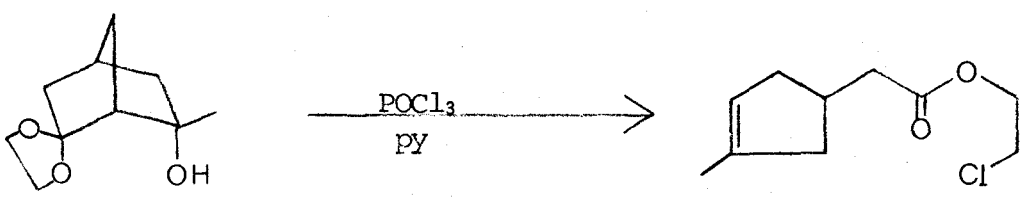
67 31

The preparation of ketoketal 67 is shown in Scheme II-8. The Wittig reaction did not succeed. Treatment of ketoketal 67 with a methyl Grignard gave ketalalcohol 68 which gave rise to an interesting rearrangement:



67 68

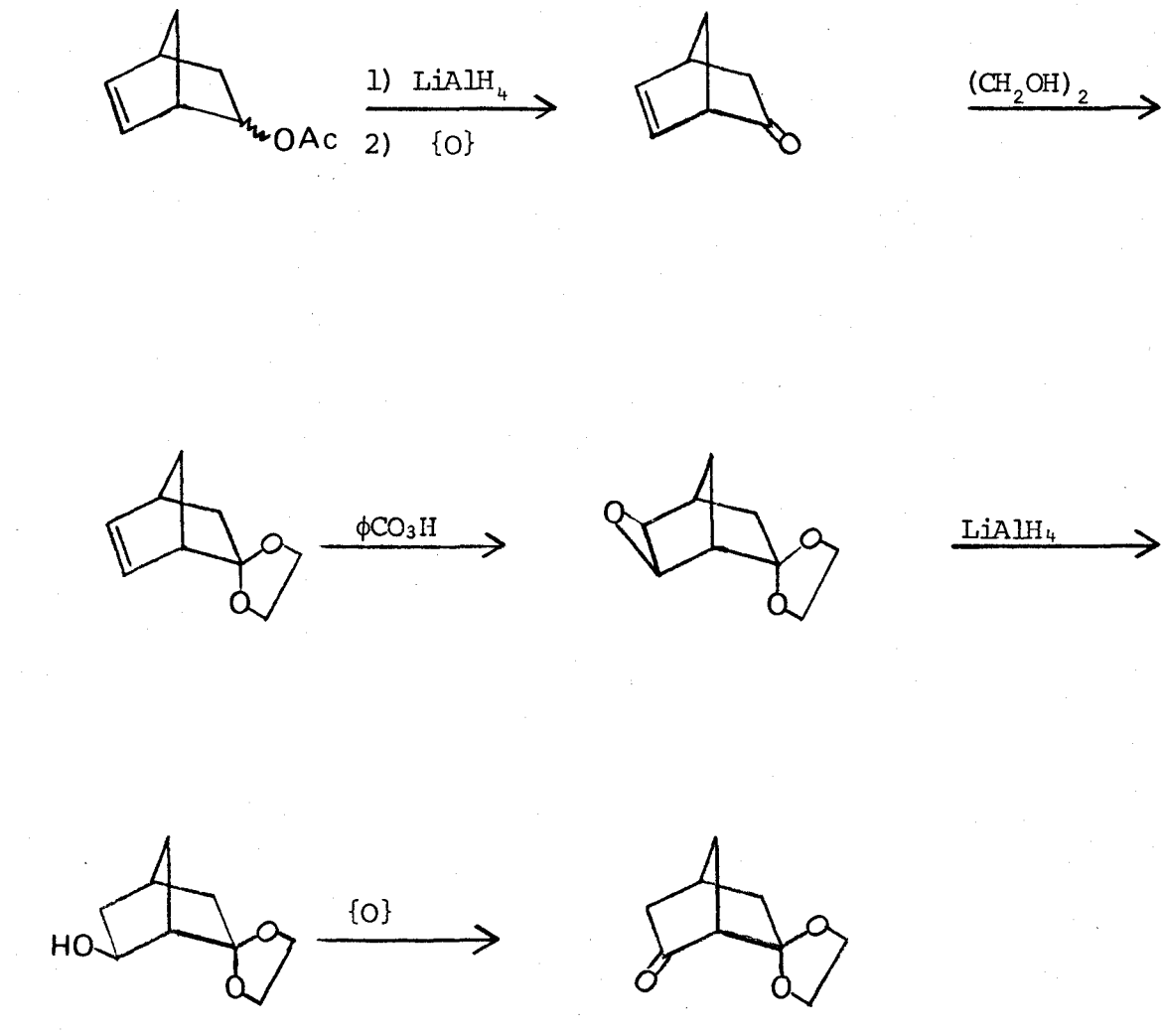
Dehydration of compound 68 with phosphoryl chloride gave as a major product (*ca.* 60 % of the mixture) the following compound (69):



68 69

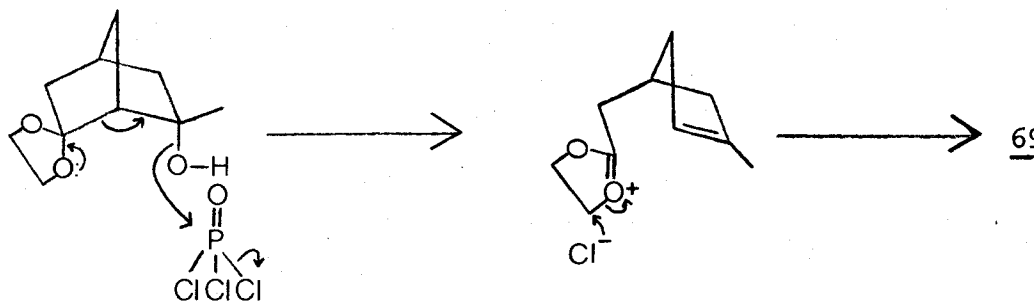
Scheme II-8

Preparation of 6-Ethylenedioxy-2-norbornanone (67) [71]



67

Compound 69 probably arises *via* the following mechanism:

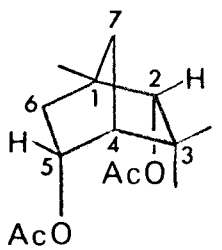


Attempts to eliminate the tosylate corresponding to 68 gave rise to solvolysis type products.

B. STEREOCHEMISTRY OF EXCHANGE AND CONFORMATION OF THE DIONES

The *exo*-stereoselectivity of the exchange reaction in the bicyclo{2.2.1.}heptanone system is well documented,[28-31, 35-38, 43] and was reviewed in the INTRODUCTION. Suffice it to say at this point that even in the case of camphor (7),[28-31, 36, 37, 44] where a 7-*gem*-dimethyl substituent is present, the preferred stereochemistry of exchange is still *exo*. That the preferred stereochemistry of exchange is also *exo* in the diones, was established as follows.

The n.m.r. spectrum of fenchane-2,5-di-*endo*-diacetate (70, n.m.r. # 88 A) exhibits a doublet at $\delta = 4.40$ for the C(2) hydrogen,

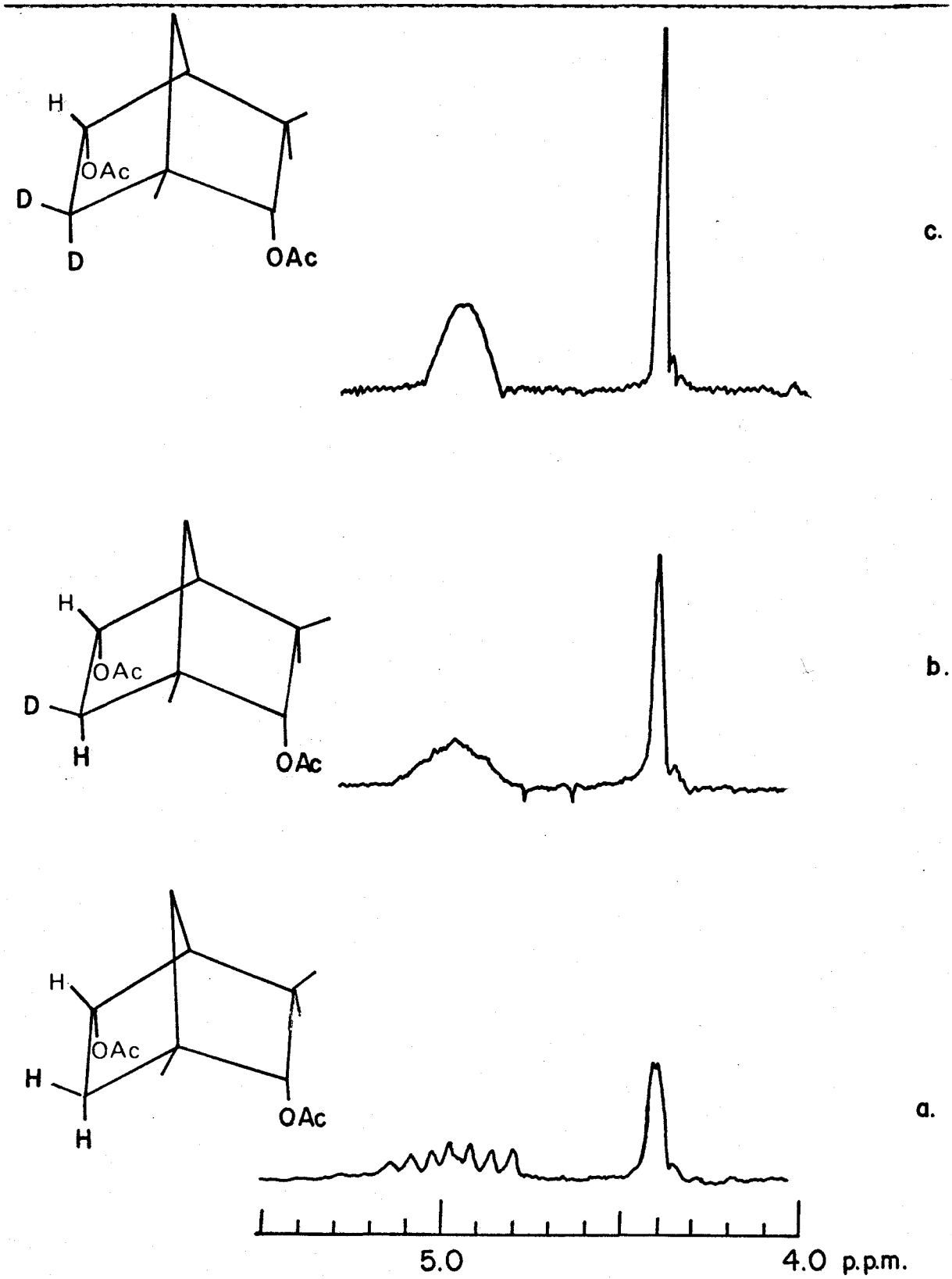


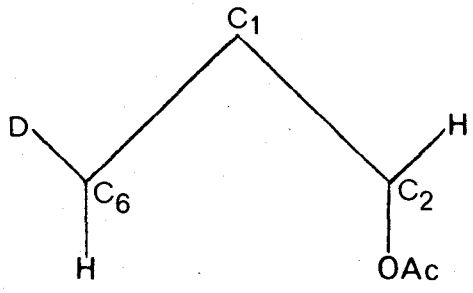
70

$J = 1.3$ Hz. The C(5) hydrogen absorption is a heptet centered at $\delta = 4.96$, with a signal width at half-height of about 22 Hz (*cf.* Fig. II-3-a). Fenchane-2,5-dione was subjected to monodeuteration conditions, and the resulting product was transformed into the corresponding di-*endo*-diacetate. Fig. II-3-b (n.m.r. # 88 C) shows the C(2) hydrogen as a sharp singlet ($\delta = 4.40$). This corresponds to the removal of "W" coupling:

Fig. II-3

60 MHz N.m.r. of Compound 70 and Various Deuterated Analogs





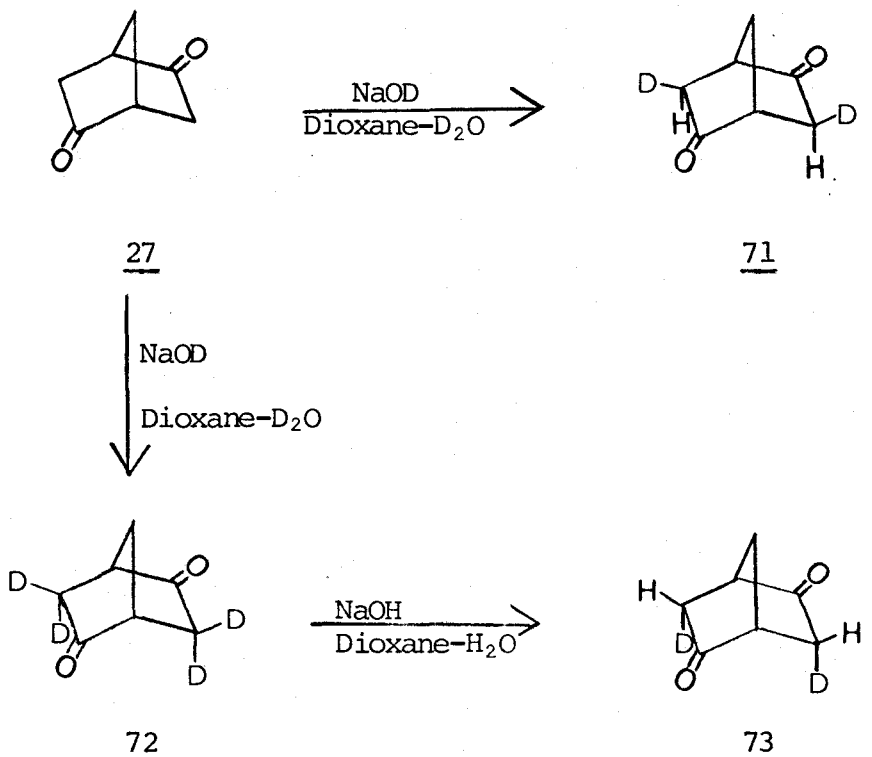
The C(5) absorption becomes a broad singlet of width at half-height of 11 Hz. This is consistent with the removal of a large coupling {$\frac{1}{2}$ (22-11) ≃ 5.5 Hz} and therefore, the removal of a *cis*-coupling[31, 33] *i.e.* *exo-exo*-coupling, thus establishing the C(5)-deuterium in an *exo*-position. The dideuterated material (n.m.r. # 88 b, Fig. II-3-c) shows the C(5) hydrogen absorption, the signal width at half-height of which is *ca.* 8.6 Hz. This is consistent with the further removal of a small coupling {$\frac{1}{2}$ (11-8.6) ≃ 1.2 Hz}, and therefore *trans*-coupling,[31, 33] or *exo-endo*-coupling. This further supports an *exo*-deuterium at C(5) in the monodeuterated species.

In the INTRODUCTION, it was stated that the conformation of the diones could have some importance in determining its reactivity towards hydrogen-deuterium exchange. N.m.r. analysis of these diones and some deuterated analogs can give some information about this.

Norbornane-2,5-dione (27) was subjected to various exchange reactions as shown in Scheme II-9. The n.m.r.(100 M Hz) spectrum

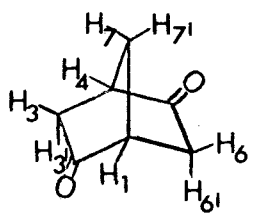
Scheme II-9

Stereospecific Deuteration of Norbornane-2,5-dione



27 71 72 73

(# 166 *d*) of the tetradeutero compound (72) is shown in Fig. II-4. This establishes the position of absorption of the bridgehead hydrogens {C(1) and C(4)} at δ = 272 Hz (2.72 p.p.m.) downfield from TMS, and the C(7) hydrogens at δ = 182 Hz (1.82 p.p.m.). The absorption due to the bridgehead hydrogens is not as well resolved because of line broadening due to deuterium coupling. That the two absorptions are coupled to each other was verified by double resonance experiments. Coupling constants are as follows:

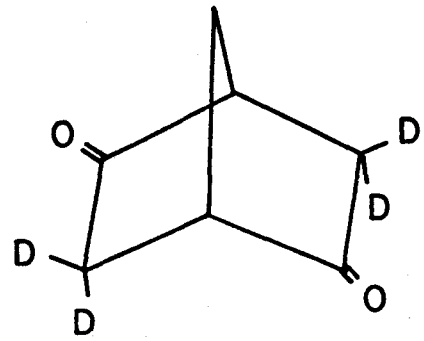


$J_{1,7'} = 1.8$ Hz
$J_{1,7} = 1.5$ Hz
$J_{4,7} = 1.5$ Hz
$J_{4,7'} = 1.8$ Hz

The spectrum (# 166 *e*) of the dideuterated species 73 is shown in Fig. II-5-a. Irradiation of the bridgehead hydrogens (δ = 272 Hz) collapses the C(7) signal to a singlet (Fig. II-5-b). The C(3) and C(6) hydrogens (δ = 208 Hz) then become a triplet. This triplet can only be interpreted as arising from geminal deuterium coupling, with $J_{H\text{-}D,\ geminal} = 2.8$ Hz. First order analysis of the multiplet at δ = 208 Hz of Fig. II-5-a then gives $J_{1,6} = J_{4,3} = 6.6$ Hz (Fig. II-6). An additional small coupling also appears to be present. That H_3 and H_6 (*exo*-protons) are involved is suggested by the magnitude of the coupling.[33] This conclusion is supported by the spectrum depicted in Fig. II-5-c. Irradiation at the C(3) and C(6) *exo*-hydrogens collapses the bridgehead hydrogen absorption to a singlet

Fig. II-4

100 MHz N.m.r. Spectrum of 72



72

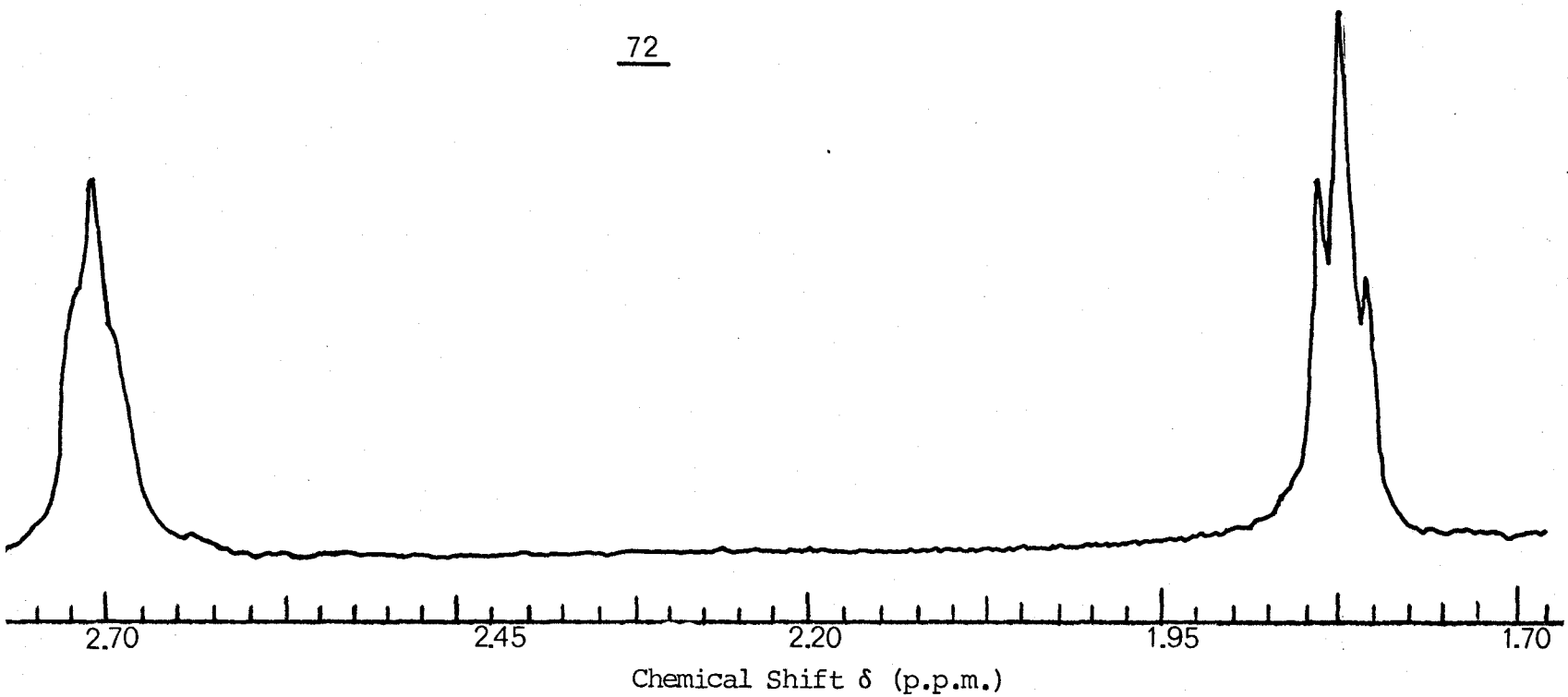
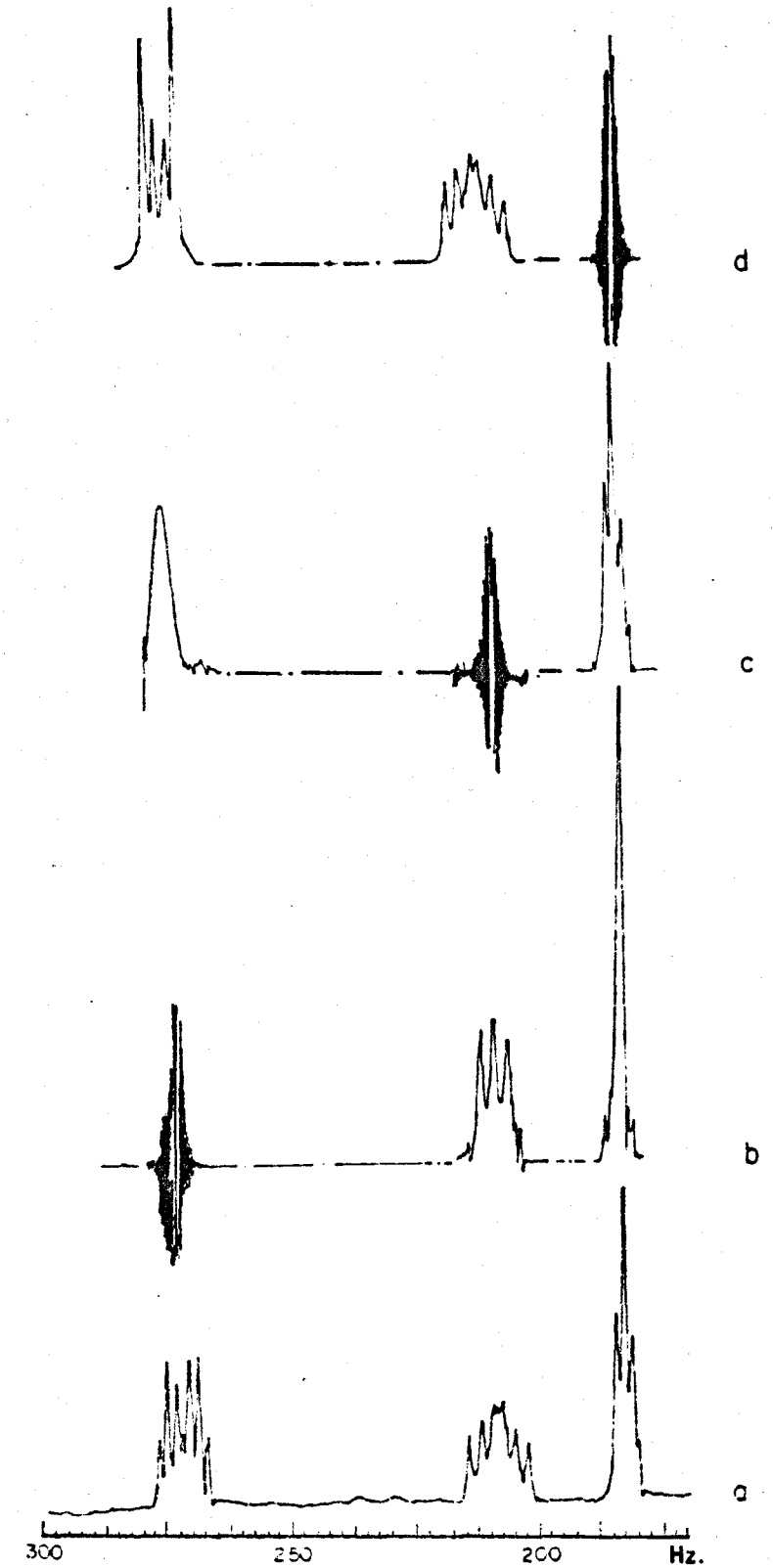
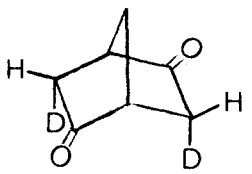


Fig. II-5

100 MHz N.m.r. Spectrum of 73; Double Irradiation Experiments



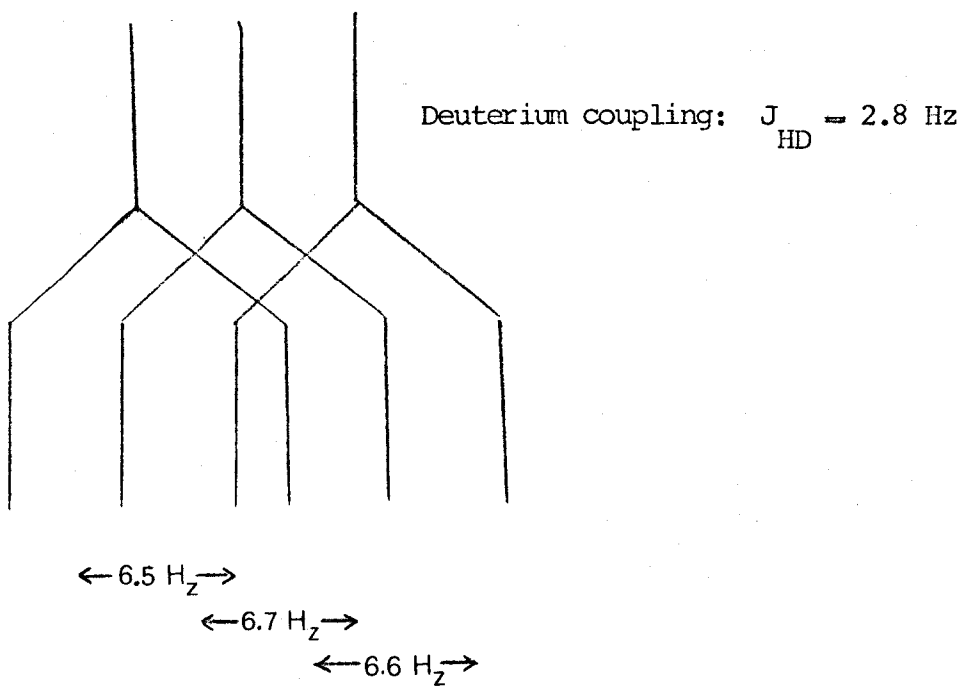


73

Fig. II-6

First Order Analysis of the C(3) and C(6) Hydrogens in Species **73**

(*cf.* Fig. II-3a)



(broadened by deuterium coupling), and leaves the C(7) hydrogen absorption unchanged. These hydrogens would have been coupled to $H_{3'}$ and $H_{6'}$ (*endo*-protons), *via* the "W" mechanism had there been protons rather than deuterons. This is also seen in Fig. II-5-d, where irradiation at the C(7) hydrogens does not give rise to any change at the C(3) and C(6) hydrogen absorption ($\delta = 208$ Hz). That the deuterium is in the *endo*-position in 73 is also consistent with spectrum of 71 (n.m.r. # 166 *e*, Fig. II-7), where the deuterium is in the *exo*-position and the protons appear at 180 Hz downfield from TMS.

The n.m.r. data for norbornane-2,5-dione is summarized in Table II-1. The vicinal coupling constant J is related to the dihedral angle ϕ by Karplus equation[72] (eq. 1),

$$J = 8.5 \cos^2\phi - 0.28 \text{ Hz} \qquad \text{eq. 1}$$

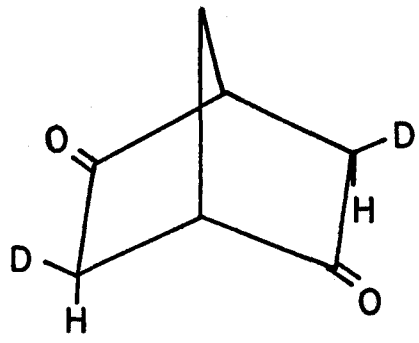
where $0° < \phi < 90°$. Using this equation , we can then obtain the dihedral angle ϕ between H_1 and H_6.* This angle turns out to be 26° ($J_{1,6} = 6.6$ Hz), as compared to norcamphor for which $J_{1,6} = 2$ Hz,[75] such that $\phi = 59°$. Also, the fact that $J_{1,7} \neq J_{1,7'}$ implies some degree twisting about the bridge. The dihedral angle difference between the two C(7)-H bonds and the C(1)-H bond is about 3°. In order that all these data be accomodated we must have that the {2.2.1.}skeleton be

---

*The equation has been shown experimentally to apply to a wide variety of compounds, including some compounds of the bicyclo{2.2.1.}system,[75] (camphane-2,3-diols). An electronegativity effect of the carbonyl might be operating, but it should be small.[74]

Fig. II-7

100 MHz N.m.r. Spectrum of 71

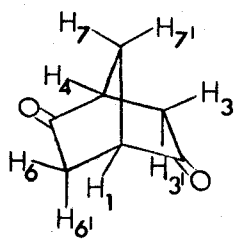


71

Chemical Shift δ (p.p.m.)

Table II-1

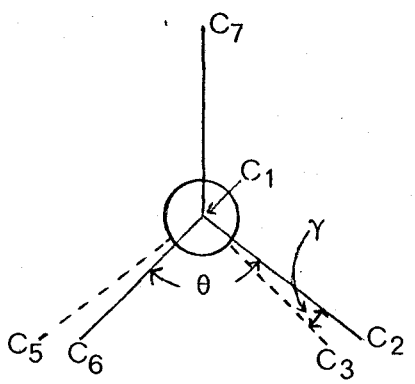
N.m.r. Data for Norbornane-2,5-Dione



27

Chemical Shifts (p.p.m.)				Coupling Constants (Hz)			
H_1	= H_4	=	2.72 (272 Hz)	$J_{1,7}$	= $J_{4,7'}$	=	1.8
H_3	= H_6	=	2.08 (208 Hz)	$J_{1,7'}$	= $J_{4,7}$	=	1.5
H_7	= $H_{7'}$	=	1.82 (182 Hz)	$J_{1,6}$	= $J_{3,4}$	=	6.6
$H_{6'}$	= $H_{3'}$	=	1.82 (182 Hz)				

twisted with a *synchro* twist,[76] *viz.*



where the two carbonyl groups {C(2) and C(5)} are pushed upwards, relative to C(3) and C(6), that are pushed downwards. This is in agreement with Santry's[77] calculations on this molecule from which a value of 80° was obtained for the angle θ, and a value of 21° for the angle γ. These calculations probably exaggerated the amount of twisting of the skeleton. Nevertheless, the real angle θ is probably closer to 90° than 109.5°. These conclusions are also in agreement with n.m.r. data on 3,3-dimethyl-norbornane-2,5-dione.

Extensive n.m.r. data were obtained[78] for 3,3-dimethylnorbornane-2,5-dione (26). The 100 MHz spectrum is shown in Fig. II-8, and the data are summarized in Tables II-2 and II-3. These data were obtained using partially deuterated compounds as before. Interatomic distances were calculated using Bell and Saunder's equation[78,79] (eq. 2)

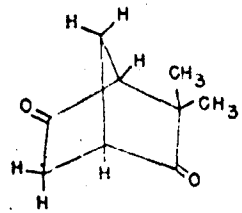
$$\frac{1}{\text{N.O.E.}} = A \; r_{AB}^{6} \qquad \text{eq. 2}$$

where N.O.E. = Nuclear Overhausser Effect

A = a constant

Fig. II-8

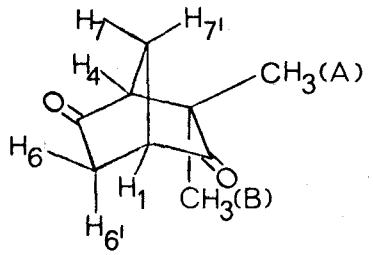
100 MHz N.m.r. Spectrum of 3,3-Dimethylnorbornane-2,5-Dione (26)



26

Table II-2

N.m.r. Data for 3,3-Dimethylnorbornane-2,5-Dione[78]



26

		Chemical Shifts (p.p.m.)	Coupling Constants (Hz)	
H_1		2.77	$J_{1,6}$	= 5.0
CH_3	(A)	0.98	$J_{1,6'}$	= 0.5
CH_3	(B)	1.10	$J_{1,7'}$	= 2.0
H_4		2.44	$J_{4,7}$	= 2.0
H_6		2.10	$J_{4,7'}$	= 1.2
$H_{6'}$		1.94	$J_{6',7'}$	= 4.0
H_7		2.06	$J_{7,7'}$	= 11.0
$H_{7'}$		1.71	$J_{1,7}$	= 1.1

Table II-3

Nuclear Overhausser Effect for Compound 26[78]

A) 3,3-Dimethylnorbornane-2,5-dione

Proton Irradiated	Proton Observed	Observed N.O.E. (%)	Calculated distance (Å)	Measured* distance (Å)
CH_3 (A)	H_4	15	2.96	2.85
CH_3 (B)	H_4	10	3.21	3.40
H_7	H_4	7	3.10	2.70
$H_{7'}$	H_4	8	3.03	2.70
H_7	H_1	8	3.03	2.70
$H_{7'}$	H_1	11	2.83	2.70
CH_3 (B)	$H_{6'}$	4	3.8	3.4

B) 6-*Exo*-deutero-3,3-dimethylnorbornane-2,5-dione

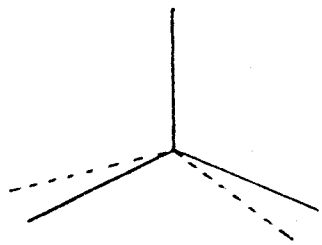
$H_{6'}$	H_1	20		2.65
CH_3	$H_{6'}$	4		3.4

* No twisting in the molecule.

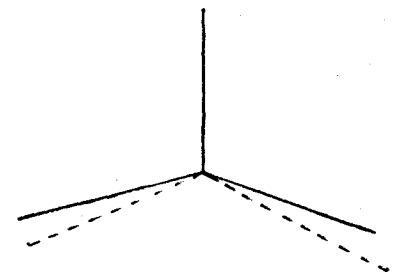
r_{AB} = Interatomic distance between proton A and proton B, or proton A and methyl group B (or *vice-versa*).

The "measured distances" are those found by using Dreiding models. Key features that are relevant to the structure are given below.

The large coupling between $H_{6'}$ and $H_{7'}$ (4.0 Hz) suggests that $H_{6'}$, C(6), C(1), C(7) and $H_{7'}$ form a planar "W".[78] To do this, it is necessary to move C(6) upwards. Then C(2) can twist either *synchro* or *contra*:[76]



synchro



contra

The value of the N.O.E.'s at H_4 when the CH_3(A) is irradiated relative to that when the CH_3(B) is irradiated, implies that the measured CH_3(A)-H_4 distance must increase and that of the CH_3(B)-H_4 distance must decrease. To do this we must push C(2) downwards, *i.e.* perform a *synchro* twist. This is also implied by the N.O.E. between CH_3(B) and $H_{6'}$. The measured distance must increase, and to do this we must push C(3) upwards, *i.e. synchro* twist.

The difference between $J_{1,7}$ and $J_{1,7'}$ is now considerable: 0.9 Hz as compared to 0.3 Hz in norbornane-2,5-dione. This gives rise to a difference in the calculated angle between the two C(7)-H bonds and

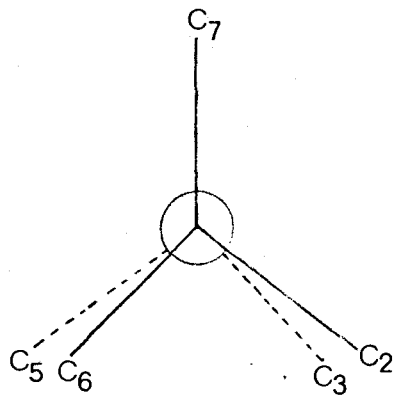
H_1, of about 10° (3° in norbornane-2,5-dione). This can be rationalized as follows: as C(2) is forced downwards and C(6) upwards, C(1) twists such that H_1 moves towards the C(2) carbonyl; and C(7) also moves in that direction, but not as much. Thus the H_1-$H_{7'}$ dihedral angle decreases, and so does the H_4-H_7 dihedral angle; but the H_4-H_7 distance increases. Thus the N.O.E. between H_4 and H_7 is less than that between $H_{1'}$ and $H_{7'}$.

The coupling constant $J_{1,6} = 5.0$ Hz. This corresponds to a dihedral angle 38°. The twist around C(1) described above, would account for this small angle.

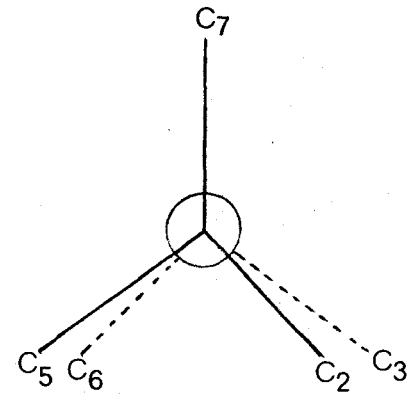
The data are also consistent with a small θ angle, as found for norbornane-2,5-dione. This is indicated by:

1) The small N.O.E. between CH_3 (B) and $H_{6'}$.
2) The large coupling constant $J_{6',7'}$.
3) The increase in the relative size of the N.O.E.'s from H_1 and $H_{7'}$ to H_1 and H_7.
4) The large N.O.E. between $H_{6'}$ and H_1.

In conclusion then, 3,3-dimethylnorbornane-2,5-dione, like norbornane-2,5-dione, exists in a *synchro* twist form.[76] But this *synchro* twist is a different one from that of norbornane-2,5-dione:

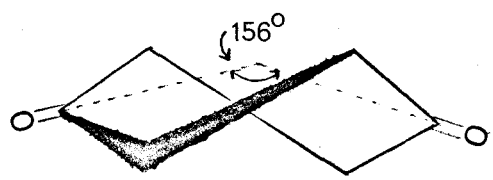


Norbornane-2,5-dione



3,3-Dimethylnorbornane-2,5-dione

The methyl groups at C(3) seem to have a dominant effect on the conformation. That the bicyclo{2.2.1.}heptane-2,5-dione skeleton may exist in such a twist form could perhaps be expected on the basis of the preferred conformation of cyclohexane-1,4-dione in solution or in the solid phase,[81-84]* which exists in a twist boat conformation:



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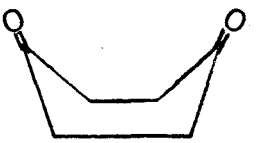
*In the gas phase, the molecule seems to exist in a non-polar chair form.[85]

However, recent calculations[80] have lead to a reinterpretation of the data, and may suggest another twist boat conformation, more or less distorted by pseudorotational motion:[80]



C. KINETICS

The rates of hydrogen-deuterium exchange in all the ketones under study are listed in Table II-4. The results for norcamphor (13) compare well with those independently found by Tidwell[35,36] (*cf.* INTRODUCTION, Table I-1, p. 19), if one takes into account the solvent difference: 60 % dioxane-D_2O in this study, and 67 % dioxane-D_2O in Tidwell's study.

The rate constants of Table II-4 were obtained by dividing the pseudo-first order rate constant by the base concentration. The pseudo-first order rate constant is the first order rate constant of incorporation of the first deuterium (*exo*) and the first order rate constant of incorporation of the second deuterium (*endo*), as followed by mass-spectrometry. All the reactions were carried at least once to close to 3 half-lives or more, and all showed good linearity (except for the special case of *endo*-exchange in the diones; *cf.* EXPERIMENTAL). The rate constants for *exo*-exchange in the diones were obtained as follows: since *exo*-exchange is very fast ($t_{\frac{1}{2}} \simeq 16$ sec.; $\{OD^-\} \simeq 0.02\ M$) $k_{2\ exo}$ was obtained by considering the extent of reaction $d_0 \longrightarrow d_1$ after 1-4 min., obtaining $t_{\frac{1}{2}}$, using the expression $t_{\frac{1}{2}} = ln\ 2/k$ and dividing the pseudo-first order rate constant by the base concentration.

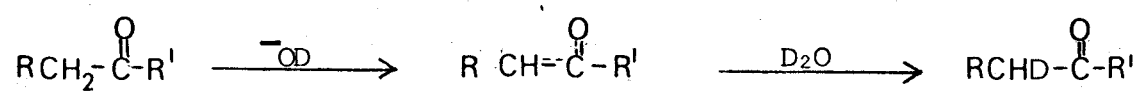
Generally, the enolization mechanism can be formalized as follows:[86]

Table II-4

Second Order Rate Constants of NaOD-Catalyzed Deuterium Exchange in ketones at 25° in 60 % Dioxane-D_2O

Ketones*		k_2 ($l.$ mole^{-1}sec.$^{-1}$)	Dev. (%)	Relative Rates		
				Exo	*Endo*	*Exo/Endo*
13	*exo*	3.85×10^{-2}	7.0	1.0	-	650
	endo	5.90×10^{-5}	1.9	-	1.0	
27	*exo*	4.7	36	130	-	130
	endo	3.54×10^{-2}	4.5	-	600	
30	*exo*	3.42×10^{-1}	0.3	8.9	-	2800
	endo	1.24×10^{-4}	1.6	-	2.1	
31	*exo*	6.97×10^{-2}	1.6	1.8	-	5300
	endo	1.32×10^{-5}	1.5	-	0.22	
24	*exo*	1.64×10^{-2}	6.1	0.4	-	630
	endo	2.62×10^{-5}	3.2	-	0.4	
26	*exo*	6.6	4.5	170	-	170
	endo	3.89×10^{-2}	5.1	-	660	
29	*exo*	1.31×10^{-1}	1.5	3.5	-	1800
	endo	7.48×10^{-5}	3.7	-	1.3	
23	*exo*	9.88×10^{-3}	0.5	2.6	-	390
	endo	2.53×10^{-5}	21.0**	-	0.4	
25	*exo*	2.0	18.5**	52	-	44
	endo	4.57×10^{-2}	6.8**	-	775	
28	*exo*	6.80×10^{-2}	11.5**	1.8	-	940
	endo	7.28×10^{-5}	0.4	-	1.2	

* Structure for these compounds will be found in Fig. II-1.
** Represents the standard deviation (3 results).



I II III

No charge is given to intermediate II to illustrate that enols or enolates can be the intermediate.[87] Also, the structure of II can vary considerably.[87] The rate determining step is the formation of II.[86] Two types of intermediates can be envisaged for the enolization of bicyclo{2.2.1.}heptanones. One will involve intermediate enols or enolates for which the hydrogen that is NOT removed will retain some characteristic of its stereochemistry; this is depicted in Scheme II-10.* The other will involve a planar enol or enolate as shown in Scheme II-11.** It is to be noted that if the equilibria between species 75 and 79 , and 77 and 81 (Scheme II-10) are very rapid, then the mechanism in Scheme II-10 is effectively the same as that in Scheme II-11, at least kinetically.

Consider Scheme II-10. The observed stereospecificity, *viz.* that an *exo*-deuterium is incorporated completely before the *endo*-hydrogen exchange occurs implies that the rate at which the equilibrium is reached.

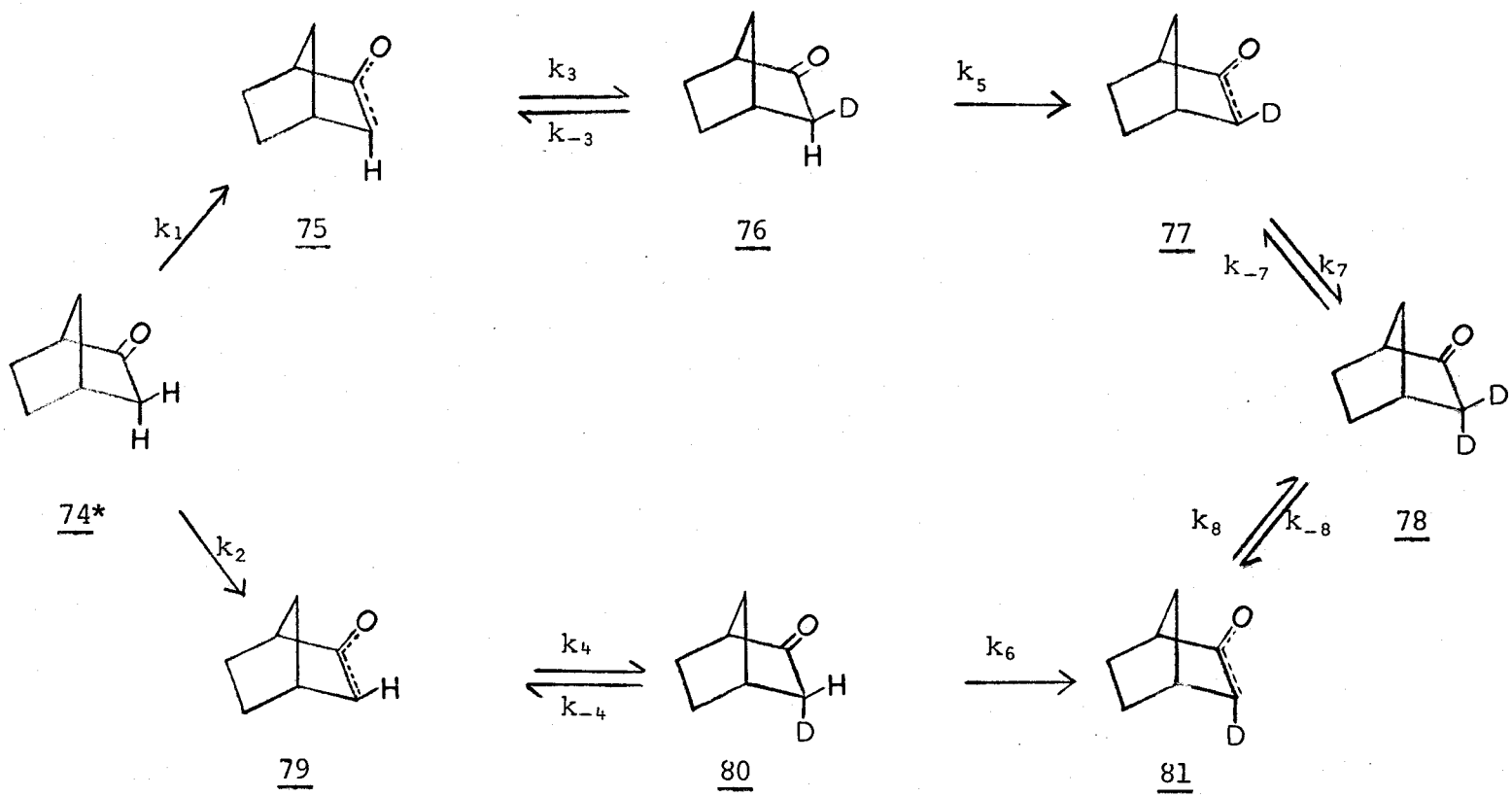
---

*Here again no charge is assigned to the intermediates to illustrate that enols or enolates can exist.

**A scheme such as this one was proposed by Crain.[43]

Scheme II-10

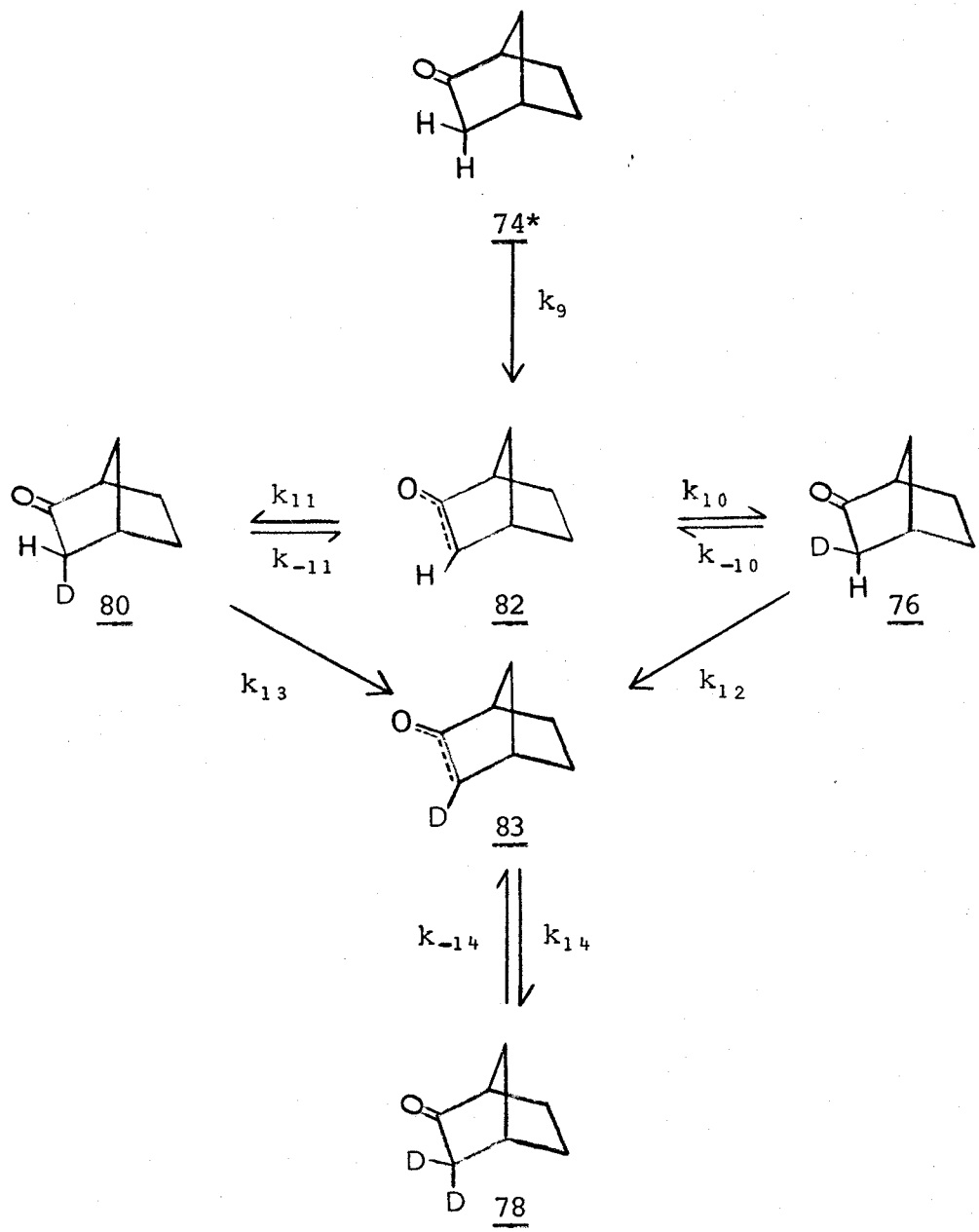
Kinetics of Enolization of Bicyclo{2.2.1.}heptanones, I



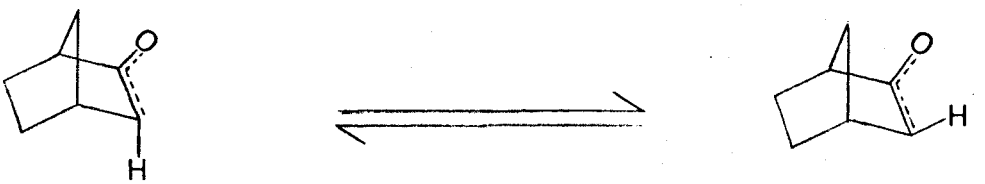
*This structure, as well as the others in this scheme, are meant to represent a generalized bicyclo {2.2.1.}heptanone system.

Scheme II-11

Kinetics of Enolization of Bicyclo{2.2.1.}heptanones, II



*This structure, as well as the others in this scheme, are meant to represent a generalized bicyclo{2.2.1.}heptanone system.



75 79

is either slow as compared to the overall exchange rate or non-existant. The same is presumably true for the equilibrium

$$\underline{77} \rightleftharpoons \underline{81}$$

Further, the steps described by k_1, k_2, k_5 and k_6 are effectively irreversible, because under the experimental conditions, there was a large excess of D_2O, such that $k_-\{DOH\} \simeq 0$, where k_- represents the rate constant for the reverse reaction. The equilibria k_7 / k_{-7} and k_8 / k_{-8} can be ignored since they do not change the final product concentration. This is also true for the equilibria k_3 / k_{-3} and k_4 / k_{-4}, involving the intermediate products 76 and 80. From all this, we must have for Scheme II-10:

$$k_1 = \text{measured } k_{exo}$$
$$k_5 = \text{measured } k_{endo}$$

And if the secondary isotope effect is small,* then

$$k_5 \simeq k_2 = k_{endo}$$
$$k_1 \simeq k_6 = k_{exo}$$

Similarly for Scheme II-11, this type of analysis can be made. The steps described by k_9, k_{12}, and k_{13} are effectively irreversible because of the large excess of D_2O. The equilibrium k_{14}/k_{-14} can be ignored because it does not affect the concentration of 78. Since the *exo/endo* rate ratio is large then $k_{10} >> k_{11}$, $k_{13} >> k_{12}$ and {82} ≃ 0. This means that 74 exchanges to give only 76 which in turn exchanges to give only 78; 80 is never formed. This implies that

$$k_9 = \text{measured } k_{exo}$$
$$k_{12} = \text{measured } k_{endo}$$

and if the secondary isotope effect is small, then

$$k_9 \simeq k_{13} = k_{exo}$$
$$k_{12} \simeq k_{endo}$$

The above discussion therefore, shows that the rate constants

---

*This assertion is reasonable as evidenced by the measured isotope effect of the NaOD-catalyzed exchange of bicyclo{2.2.2.}octanone in 50 : 50 dioxane-D_2O studied by Lamaty, Roques and Fonzes.[88] It was found that the secondary isotope effect of a deuterium was 0.99 ± 2%.

in Table II-4 represent the true reactivity of the hydrogen for which the rate of exchange was measured. These results will be discussed in terms of the possible effects listed in the INTRODUCTION, *viz.*

1) Hybridization effect.

2) Torsional effect.

3) Conformational effect.

4) Strain effect.

5) Inductive-homoconjugative effect.

D. DISCUSSION OF THE EFFECTS RELATED TO ENOLIZATION

1) Hybridization Effect

1.a. The Chemical Evidence

The more a molecule is strained, the more the C-C bonds have p-character, and correspondingly, the more the C-H bonds have s-character. An extreme example of this is cyclopropane where the C-C bonds are formed with orbitals approaching sp^5 hybridization[19,20] and correspondingly, the C-H bonds are formed with orbitals approaching sp^2 hybridization. Now the kinetic acidity of a C-H bond is known to depend qualitatively on the amount of s-character on the carbon bonding orbital.[89,90,91] That strain is an important factor in the kinetic acidities of hydrocarbons was shown by Streitwieser and Caldwell[91] who found the kinetic acidities of cycloalkanes to be as follows:

Cycloalkane	Relative Rate*
C_6	1.00
C_5	5.72
C_4	28
C_3	7.0×10^4

In the ketones presently under study, the strain introduced in the molecule by the presence of a second sp^2 center (diones and enones) could cause an increase in the kinetic acidities of the enolizable

---

* Relative rate of cesium cyclohexylamide-catalyzed tritium incorporation from N-tritiated cyclohexylamine.

hydrogens,and hence affect the rate of enolization. A test for these hybridization effects arising from strain was provided by Tidwell[38] in the series of compounds listed in Fig. II-9 (*cf.* also the INTRODUCTION). If the hybridization effects were important, one would expect the rate of exchange to decrease from 20 to 13 to 21, since strain decreases in that direction. The reverse is actually observed. Tidwell concluded[38] that angle-strain and non-bonded repulsions were the dominant factors* governing the reactivities in the above series of compound while hybridization effects were not detected. Thus, although these experiments do not evaluate quantitatively the effect of hybridization because of opposing effects, they tend to show, however, that the effect is not important in these exchange reactions.

1.b. The Spectroscopic Evidence: C.m.r. of Highly Substituted Bicyclo {2.2.1.}heptanes

^{13}C-n.m.r. spectroscopy (c.m.r.) is a powerfull method to study the electronic and molecular structure of molecules (*vide infra*). One advantage of ^{13}C shifts over, for example, proton shifts, is that the shifts range over 200 p.p.m.[92] Further, the shifts are sensitive to electronic and structural changes. Broad classification of chemical shifts can be made according to carbon type.[93,94] Generally, the shift sequence from low to high field is $sp^2 < sp < sp^3$. A general correlation is shown in Fig. II-10.

---

*Torsional effects are not important, as will be discussed in a later section.

Fig. II-9

Hybridization Effect, Chemical Evidence: Relative Rates of NaOD-Catalyzed Deuterium Exchange of Ketones at 25° in 2:1 Dioxane-D_2O [38]

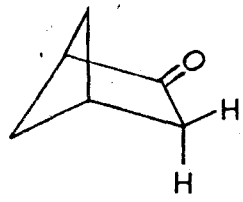
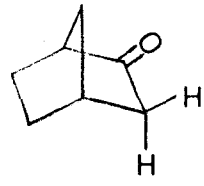
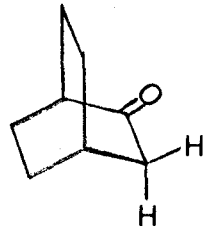
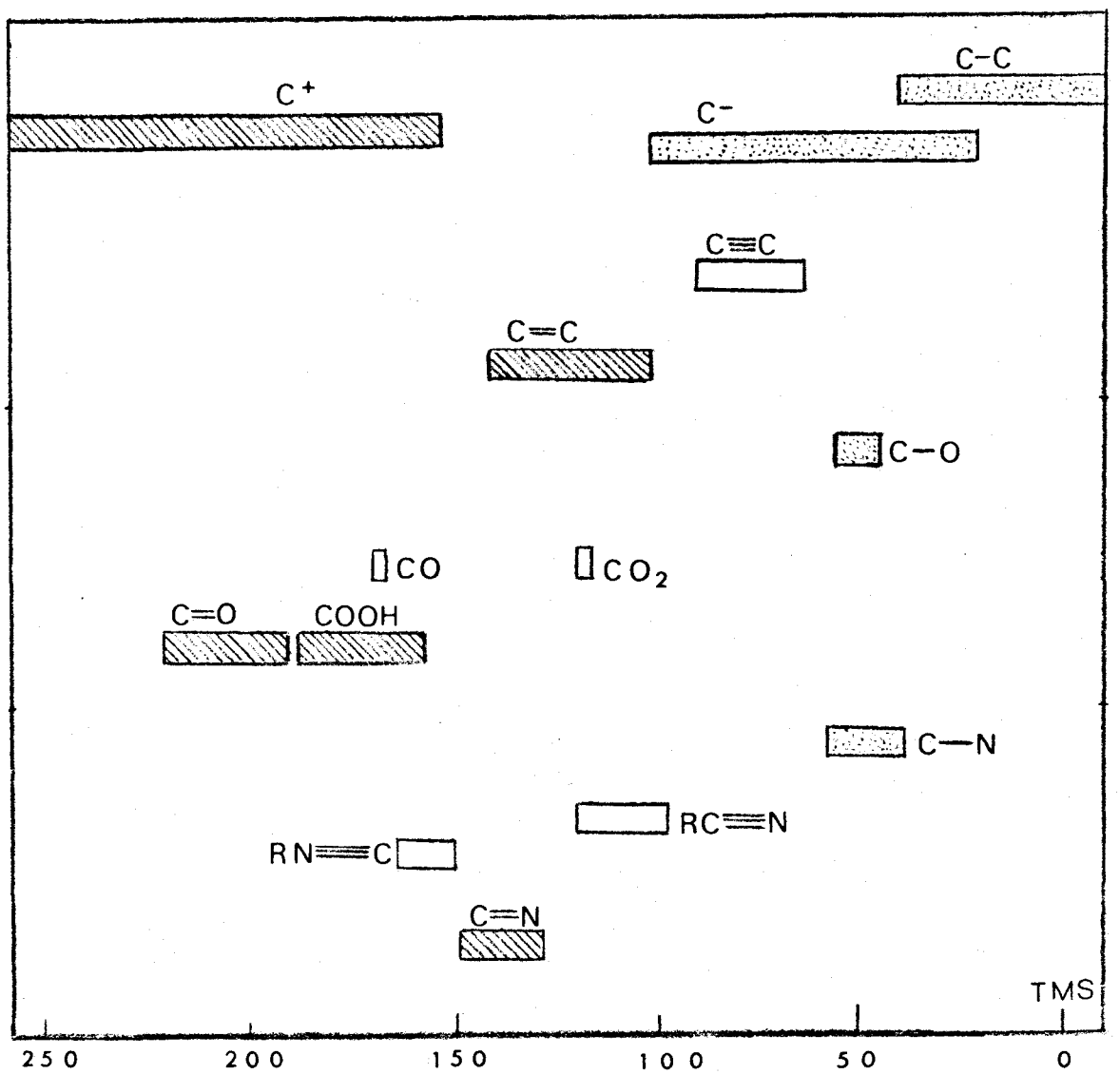
 20	0.080 0.080
 13	715 1.0
 21	510 510

Fig. II-10

Correlation Table of ^{13}C Chemical Shifts and Structural Type[94]



Very early in the development of c.m.r. spectroscopy, it was shown[95] that ^{13}C-schifts, on first order approximation, is a constitutive property for homologous series of compounds, just like, for example, molar refraction and polarization. In other words the chemical shift of any given carbon is to a great extent dependent on its immediate structural environment, and not on distant parts of the molecule. Thus it should be possible to obtain empirically a series of parameters that should enable us to predict the ^{13}C-shifts in any molecule. Also, significant deviations from immediate additivity would be expected to occur for molecules with unusual structural and / or electronic features. Numerous examples have appeared in the literature that illustrate this constitutive property. For example, alkanes have been studied[96] and the chemical shifts can be predicted using the formula:

$$\delta_C\ (k) = B - \Sigma\ A_l n_{kl} \qquad \text{eq. 3}$$

where δ_C (k) = The chemical shift of the k*th* carbon atom.

B = A constant, which is approximately the shift in methane.

A_l = Additive chemical shift parameter.

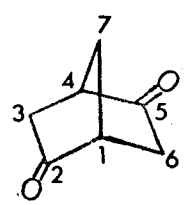
n_{kl} = Number of carbon atom in the *lth* position relative to the k*th* carbon.

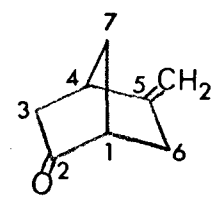
For structures more complex than alkanes however, such universal parameters do not apply, as specific electronic and structural effects start to play an important role. But still, it is possible to correlate chemical shifts, and define new sets of parameters that apply for a

particular series of compounds. Such was the case for example, for methylcyclohexanes,[97] cyclohexanols,[98] α,β-unsaturated acids,[99] and norbornyl derivatives.[100–102]

Lippmaa *et al.*[101] have made an extensive study of the norbornyl system using 51 simple derivatives. The shift parameters that were derived from that study are listed in Table II-5. With these parameters it should be possible to predict the chemical shift of every carbon atom in the {2.2.1.}system, provided that a shift parameter exist for the substituent.

As stated earlier, in the ketones presently under study, it is possible that the strain introduced in the molecule by the presence of a second sp^2 center (diones and enones), causes a change in hybridization at C(1), C(4), C(3) and C(6). Such a change at C(6) might affect





the rate of enolization in these ketones. In order to investigate this possibility, a study of the ^{13}C-shifts in the compounds under study was undertaken. The results are shown in Table II-6. Unless there is some special effect in these compounds, particularly the diones and enones, (such as a change in hybridization of the carbon atoms due to

Table II-5

Substituent Parameters for the Calculation of Approximate ^{13}C-Chemical Shifts of Norbornane and Norbornene Derivatives [101]

	Changes of chemical shifts of the carbon atom in the bicyclic ring system *								
	C_1	C_2	C_3	C_4	C_5	C_5	C_6	C_6	C_7
Substituent groups	sp^3	sp^3	sp^3	sp^3	sp^3	sp^2	sp^3	sp^2	sp^3
1-CH_3	-6.1	-6.5	-1.5	0	-1.5	0	-6.5	-5.3	-6.2
2-*exo*-CH_3**	-5.5	-8.3	-10.4	0	-0.3	-0.3	-1.0	-1.6	-3.0
2-*exo*-OH **	-6.5	-44.9	-10.8	-0.5	-1.5	-3.6	-2.3	-0.4	-3.0
2-*endo*-CH_3**	-6.3	-6.9	-8.5	-0.5	0	-1.2	-7.0	-3.1	-2.0
2-*endo*-OH**	-7.2	-45.7	-11.3	0	-0.2	-2.8	-8.1	-2.0	-1.5
7-CH_3***	-3.6	-2.5	-2.5	-3.6	-0.5		-0.5	-6.3	-5.5
2=CH	-8.0	-121.0	-8.6	-1.0	-1.0	0	-0.5	-1.7	-0.5
2=O	-12.0	-176.0	-11.7	-1.3	-2.2		-5.2		-0.7
C_5=C_6****	-5.5	-3.5	-3.5	-5.5		-109.0		-109.0	-11.0

* Shift differentials are added to the shift in norbornane.
**Introduction of methyl or hydroxyl groups into the 3-, 5- or 6- positions leads to symmetrical effects.
****Syn*- to the 2- and 3- positions.
*****Introduction of one double bond between C_5 and C_6.

Table II-6

^{13}C Chemical Shifts *

Compound***	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)
13	50.3	217.7	45.6	36.2	27.8	24.9	38.1				
27	47.4	213.7	36.4	47.4	213.7	36.4	33.8				
42	49.8	221.8	46.5	46.2	22.8	24.3	34.6	22.8	21.9		
24	35.9	440 @	35.6	61.7	216.0	43.8@	36.7	29.4	27.7		
26	48.5	217.9	44.8	60.2	213.6	38.6	32.6	21.6	21.6		
43	47.8	166.0	41.5	48.4	25.3	28.9	37.1	28.5	23.9	100.0	
29	43.4	162.0	39.1	62.0	215.1	42.3	33.8	24.8	23.7	100.0	
44	53.7	222.4	46.9	45.4	24.9	31.8	41.6	23.1	21.4	14.1	
25	52.8	220.0	45.6	60.0	213.3	45.1	39.1	21.6	21.6	14.4	
85	49.1	160**	42.7	47.6	25.4	35.6	44.3	29.4	25.9	18.1	97.3
28	48.6	160**	42.4	62.1	212.0	50.1	42.4	28.9	27.1	18.2	101.9
86	49.3	85.3	39.6	48.3	25.8	24.9	41.0	30.6	20.6	19.1	
50	47.7	83.1	40.6	63.1	219.4	38.7	42.6	20.7	21.1	18.1	
87	50.1	160**	43.4	52.6	75.4	44.5	43.1	31.8	27.5	18.7	

*In p.p.m. (±0.1) downfield from tetramethylsilane.

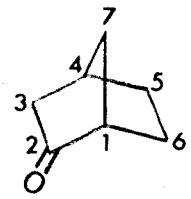
**Not determined, estimated from 43 and 29.

***Structures for these compounds are given in Fig. II-11.

@Assignments may be interchanged.

Fig. II-11

Structures for the Compounds Listed in Table II-6



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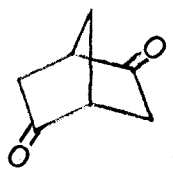

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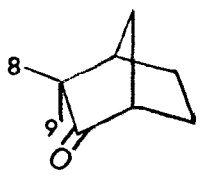

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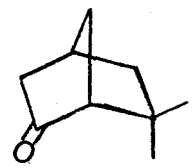

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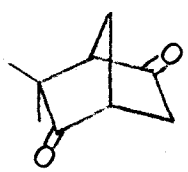

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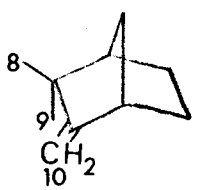

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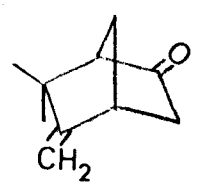

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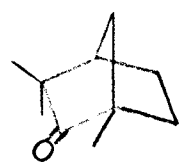

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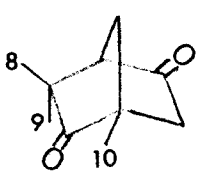

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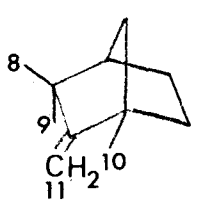

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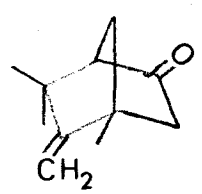

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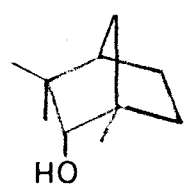

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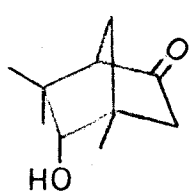

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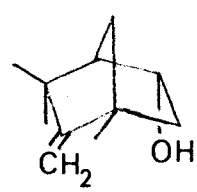


87

strain) it should be possible to predict quantitatively (within ± 4 p.p.m.) the chemical shift of the carbons in all of these compounds, using Lippmaa's shift parameters listed in Table II-5. The results of such predicted shifts for C(1), C(4), C(6) and C(7) are listed in Table II-7. The good agreement between the observed values and the predicted values tend to show that there is no unusual effect in these compounds.* In order words, Lippmaa's parameters account sufficiently for changes in hybridization which arise from distortion of the {2.2.1.} system, through incorporation of substituents; *i.e.* incorporation of a large number of substituents, especially a carbonyl group, only gives rise to the addition of effects of each single substituent, and not to an additional special effect. This conclusion is also consistent with the ^{13}C-H coupling constants in these compounds.

Bond hybridization is known to play an important role in directly bonded ^{13}C-H coupling constants.[103-110] Pople *et al.*[110] have made

*For compounds 26, 25, 29, and 28, C(4) and C(6) are consistently 2.0-2.6 and 1.6-2.7 p.p.m. downfield and C(7), 1.3-3.7 p.p.m. upfield, respectively, from the predicted positions. C(1) appears 1.0-1.6 p.p.m. upfield from the expected position in 27, 26, and 29 and at the exact position, within experimental error, in 25 and 28. Since no consistent upfield-downfield differentials are evident in the other compounds, with special attention drawn to the 2,5-systems 50 and 87, the shift differentials for 26, 25, 29, and 28 do perhaps indicate the operation of some effect not completely accounted for by the shift parameters. However, the trend, although consistent, is less in magnitude than the accuracy of the calculation (± 4 p.p.m.).

Table II-7

Predicted and Observed Shifts Differences

Compounds*	Substrate* use for prediction	Predicted shifts				Differences from observed shifts**			
		C(1)	C(4)	C(6)	C(7)	C(1)	C(4)	C(6)	C(7)
27	13	49.0	48.2	36.6	37.9	-1.6	-0.8	-0.2	-4.1
42	13	50.8	46.2	25.8	37.6	-1.0	0.0	-1.5	-3.0
26	42	49.5	58.2	37.5	36.9	-1.0	-2.0	-1.1	-4.3
29	43	45.7	60.3	40.6	36.4	-2.3	-1.7	-1.7	-2.6
44	42	56.9	46.2	32.3	43.8	-3.2	-0.8	-0.5	-2.2
25	13	55.6	60.0	42.8	36.4	-2.8	0.0	-2.3	-2.7
25	44	52.4	57.4	43.5	40.9	-0.4	-2.3	-1.6	-1.8
85	43	53.1	48.3	35.4	43.0	-3.2	-0.7	-0.2	-1.0
28	85	48.6	59.6	47.4	43.6	0.0	-2.5	-2.7	-1.2
50	86	48.0	60.3	36.6	40.3	-0.3	-2.8	-2.1	-2.3
87	MN***	52.2	56.0	47.2	45.9	-2.1	-3.4	-2.7	-2.8
87	85	49.9	54.8	46.9	45.8	-0.2	-2.2	-2.4	-2.7

*Structures corresponding to these compounds will be found in Fig. II-11.

**Plus and minus indicate upfield and downfield shifts relative to the expected position.

***2-Methylenenorbornane used as substrate.

considerable progress in the understanding of the coupling mechanism. The basis of this understanding lies in the following equation:[111]

$$J_{CH} = \frac{K S_C^2 S_H^2 P_{S_C S_H}^2}{\Delta E}$$

In this equation, K is a constant and is equal to

$$K = (4/3)^2 h \gamma_C \gamma_H \beta \qquad \text{eq. 5}$$

where β is the Bohr magneton; h, Plank's constant; and the γ's are the gyromagnetic ratios for carbon and hydrogen. S_C^2 is the carbon 2s orbital density at the carbon nucleus; S_H^2 is the hydrogen 1s orbital density at the hydrogen nucleus. $P_{S_C S_H}^2$ is the bond order between carbon and hydrogen. It is this term that caries information about the "carbon s-character".[110,112] ΔE is the summation over all the electronic excited states. The coupling constants for a large number of compounds (113) were calculated[110] and the results compared with experiments. The calculations were made holding the terms S_C^2, S_H^2, and ΔE constants.

The net result of this study was that prediction of J_{C-H} in this way had varying success, depending on the type of compounds. Reasonably accurate predictions were obtained for hydrocarbons, and hydrocarbons substituted with, in Pople and Gordon's terminology, a $-I^+$ group.[110,113]* For those compounds substituted with a $-I^-$ group* however, the calculated J_{C-H} was not nearly as accurate. It was

suggested that in the former class of compounds ($-I^+$ group), the bond order, or the "carbon s-character" accounted sufficiently for variations in J_{C-H}. For the other class of compounds ($-I^-$ group) however, it was suggested that inaccuracies arose from variation in the s-orbital density, *i.e.* the S_H^2 and S_C^2 terms in eq. 4. It was suggested further that the variation in the orbital density on hydrogen was dominant.** Such variation in these terms have also been used by Lichtman and Grant[115] in methanes substituted with halogens, and oxygens (acetals and orthoesters).

With those results in mind, the ^{13}C-H coupling constant in a number of compounds have been determined. The results are shown in Table II-8. In norbornane, $J_{C(1)-H} = J_{C(4)-H} = 142$ Hz. Introduction of a keto-group at C(2) (norcamphor) gives rise to an increase of *ca.* 10 Hz in $J_{C(1)-H}$, while $J_{C(4)-H}$ remains constant. Introduction of a

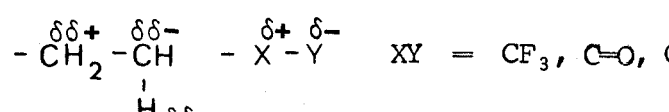
---

*Using a CNDO MO theory. Pople and Gordon[113] have calculated charge distributions in compounds substituted with polar groups. Two types of electron withdrawing groups were recognized:

1) $-I^+$:

X = F, OR, NR_2

2) $-I^-$:



XY = CF_3, C=O, C≡N, NO_2, CO_2R

***Cf.* also Ref. 114.

Table II-8

^{13}C-H Coupling Constants in Bicyclo{2.2.1.}heptane Derivatives

Compounds*	C(1)	C(3)	C(4)
88	142 ± 1	130 ± 2	142 ± 1
13	152 ± 1	134 ± 1	142 ± 2
27	157 ± 2	-	156 ± 1
89	142 ± 2	-	142 ± 1
14	153 ± 1	138 ± 1	155 ± 1
31	155 ± 1	130 ± 2	144 ± 2
43	145 ± 2	-	140 ± 1
42	152 ± 1	-	142 ± 2
24	-	-	150 ± 2
26	159 ± 1	-	159 ± 1
91**	155 ± 1	-	143 ± 2
92	-	134 ± 2	140 ± 2
53	-	-	159 ± 1
93**	143 ± 1	-	135 ± 1
94**	139 ± 2	-	-
90***	146 ± 0.5	-	146 ± 0.5

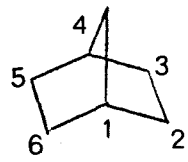
* Structures for these compounds will be found in Fig. II-12.

** Ref. 117.

*** Ref. 116.

Fig. II-12

Structures for the Compounds Listed in Table II-8



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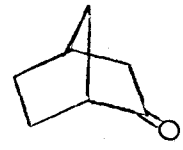

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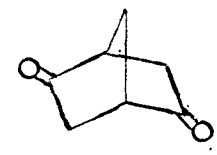

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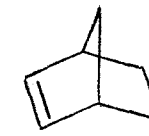

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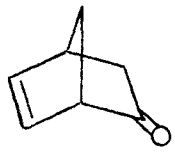

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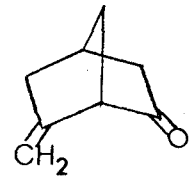

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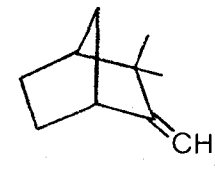

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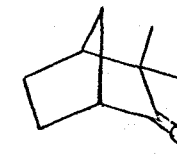

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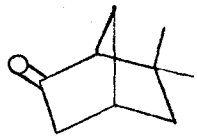

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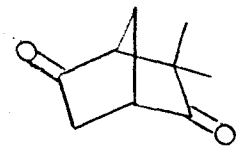

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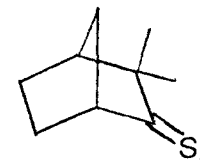

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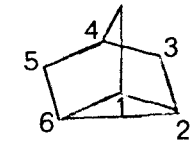

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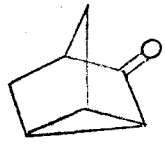

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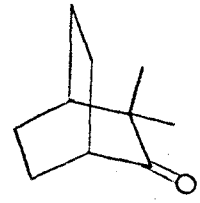

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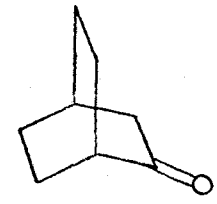
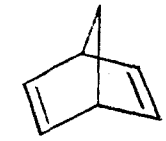


94



90

gem-dimethyl group at C(3) in camphenilone does not change the coupling any further. These results are in accord with the above discussion: a carbonyl group is a $-I^-$ group, and as such, J_{C-H} is well accounted for in the terms $P^2_{S_C S_H}$, S^2_H and S^2_C of eq. 4. On going to the diones however, J_{C-H} rises to 156-158 Hz, which is *ca.* 5Hz more than the expected 10 Hz as seen in norcamphor (13) and camphenilone (42).

It is not known, at this stage, whether or not this non-additive 5 Hz is significant; 5 Hz is only *ca.* 3% of the total coupling constant. Generally, J_{C-H} correlations have not this amount of accuracy. Nevertheless, the non-additive 5 Hz may be rationalized on a basis other than a hybridization change in the dione system. We suggest that the higher than expected value of J_{C-H} in the dione system is due to a decrease in the term ΔE in eq. 4. This decrease in ΔE would arise *via* a small 1,4-transanular interaction between the two carbonyl groups. That such an interaction is present is suggested by the U.V. spectra of these compounds.

Ferguson and Nnadi[118] have proposed as criteria for transanular interaction and homoconjugation, an enhanced ε value and a shift of λ_{max} to higher wavelength.* Data from the U.V. spectrum of some of the ketones are listed in Table II-9. The lower λ_{max} in norbornane-2,5-diones (27), as compared to 3,3-dimethylnorbornane-2,5-dione (24) and fenchane-2,5-dione (25), may be a result of the difference in conformation of these compounds. (*Cf.* Section II-B). The difference of *ca.*

**Cf.* also Ref. 119 and 120 for a discussion on the corresponding O.R.D. curves (homoconjugated ketones).

Table II-9

U.V. Spectra of Some Bicyclic Ketones

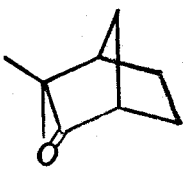
Compounds *	λ_{max}	ε	U.V. #
(13)	285	35	5
(42)	284	20	3
(44)	284 (s)	110	Ref. 121
(27)	286	48	4
(24)	292	48	2
(25)	295	52	Ref. 121
(31)	297	400	1
(89)	195	-	Ref. 122
(90)	211	-	Ref. 122

* Structures for these compounds will be found in Fig. II-13.

Fig. II-13

Structures for Compounds Listed in Table II-9

13



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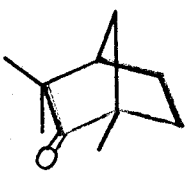

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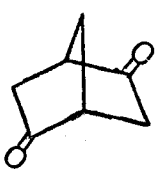

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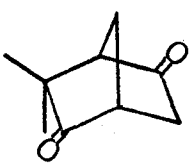

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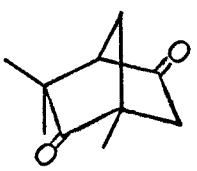

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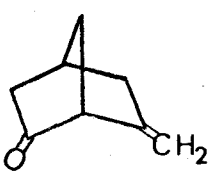

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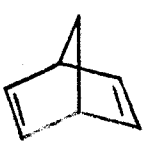
89



90

2 Hz in J_{C-H} of these compounds is also consistent with this. Since $\pi \longleftrightarrow \pi$ transitions are lower in energy than $\sigma \longleftrightarrow \pi$ transitions, then excitation energies will be more important for the latter transitions than the former.[123] Therefore the ΔE effect should be more important in the diones. The relative values of J_{C-H} for norbornene (89) and norbornadiene (90) also suggest this. (*Cf.* Table II-8)

Alternatively, the two carbonyl groups could interact *via* a three σ bonds conjugation, a phenomenon observed by Cookson[124] and described theoretically by Hoffmann.[125,126,127]

It should perharps be pointed out that the term ΔE of the J_{C-H} equation has been used in the interpretation of J_{C-H} in methanes substituted with halogens, CN, NO_2, OH and NH_2.[128,129]

This interpretation is also consistent with ^{13}C-chemical shifts of these compounds.* The dominant contributing term for this type of compound in the theory of chemical shifts, has been shown[130,131] to be the paramagnetic shielding constant σ_p of the carbon nucleus, and σ_p is related to the paramagnetic susceptibility χ_p:[127]

$$\sigma_p \propto \chi_p \qquad \text{eq. 6}$$

Also, the paramagnetic susceptibility in the *z*-direction of nucleus A is given by:[131]

---

*The discussion that follows is not meant to be evidence for the ideas presented above, but merely to point out that all the results are consistent with the interpretation given.

$$(\chi_p)_z^A = \frac{e^2 \hbar^2}{4m^2 c^2} \cdot \frac{1}{\Delta E} \cdot Q_A \qquad \text{eq. 7}$$

where $e^2\hbar^2/4m^2c^2$ are constants; ΔE is the energy sum over all electronic excited states, as before; and Q_A is a description of the bonding orbitals of A. Since the chemical shift δ can be written as:

$$\delta \propto \sigma_r - \sigma_s \qquad \text{eq. 8}$$

where σ_r and σ_s are the total shielding constants of the reference and sample respectively, then a decrease in ΔE (as postulated here) will cause an increase in σ_s and hence a decrease in δ. A close look at Table II-6 reveals that the carbonyl shifts in the diones are consistently at higher field (*i.e.* smaller δ values) than the corresponding monoketones.

An altogether different interpretation can be given to the observed coupling constant J_{C-H}. The interpretation given to $J_{C(1)-H}$ in ketones 13, 14, 42 and 24 and in thione 91, (as compared to 88) in term of variation in the terms $P^2_{S_C S_H}$, S_C^2 and S_H^2 of eq.4 (*vide supra*) is not entirely satisfactory because of the following reasons:

1) The coupling constants for ethane, acetone and acetophenone are 126, 127 and 127 Hz, respectively.[110, 132–135]

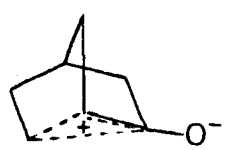
2) The coupling constants for cyclopropane, cyclobutane, and cyclopentane (161, 134.6, and 128.5 Hz, respectively) are, within experimental error, identical to the coupling constants for the C-H bond α to the carbonyl in 2,2-dimethylcyclopropanone, cyclobutanone, and cyclopenta-

none (160, 134.8, and 129.5 Hz respectively).[136]

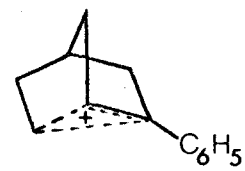
3) $J_{C(4)-H}$ for compounds 88, 89 and 92 are identical, within experimental error, yet, the strain energies are 18.4, 22.8 and 42.9 kcal/mole respectively.[137]

These facts however can be rationalized by the following interpretation. Here, we propose that the introduction of a carbonyl or a thiocarbonyl group into an appropriate system results in a hyperconjugative interaction between a C-C-single bond and the π system of the C=O or C=S. Both the hybridization and alignment of the bond with the π system would be important.

In norcamphor, contributing structures of the type 95 may be written resulting in a change in hybridization and electron density at C(1). Interestingly, Olah[138] has reported a $J_{C(1)-H}$ value of 152 ± 5 Hz for the 2-phenylnorbornyl cation (96). This suggests



95



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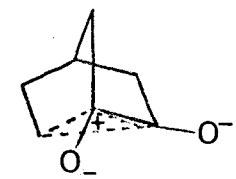
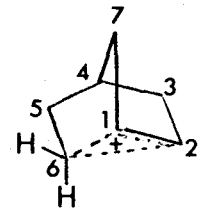


97

norcamphor is delocalized in the ground state to the same degree as the 2-phenylnorbornyl cation (96), contrary to earlier considerations.[139] That 95 is a viable species is supported by the unusual reactivity of 1-hydroxy-2-norbornanones,[140-142] the chemistry of which

must involve intermediates of the type 97.* Further, as expected, the $J_{C(1)-H}$ and $J_{C(4)-H}$ differential in the bicyclo{2.2.2.}octyl system (93 and 94) is smaller than norbornyl.**

The fact that there is a hybridizational change at C(1) in these ketones does not imply a similar change at C(6). Indeed, Olah[138] has estimated the $^{13}C(6)-H$ coupling constant in the norbornyl cation (100) to be 125 Hz, which is that expected for a sp^3 hybridized carbon. (*Cf.* the coupling constant in ethane).



100

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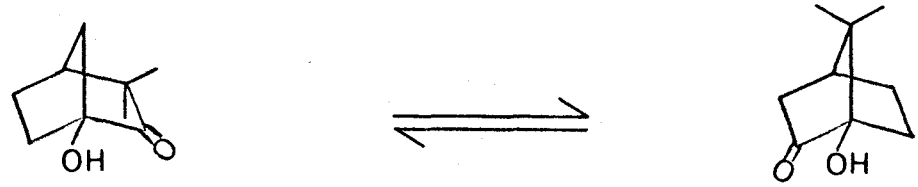
*A striking example of the unusual reactivity of 1-hydroxy-2-norbornanones is the following facile rearrangement of 1-hydroxy-camphenilone (98) into 7,7-dimethyl-1-hydroxy-2-norbornanone (99):[143]



98 99

**Further tests for these ideas are presently under investigation by Dr N.H. Werstiuk.

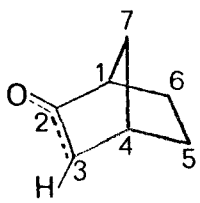
The higher than expected $J_{C(1)-H}$ in diones 26 and 27 could then be a result of improved hyperconjugative alignment of the C(1), C(6) and C(4), C(5) bonds, as a result of a *synchro*-twist. (*Cf.* Section II-B). Alternatively, as before, it could be due to a 1,4-transanular interaction or a three σ bond conjugation of the two carbonyl groups (*vide supra*).

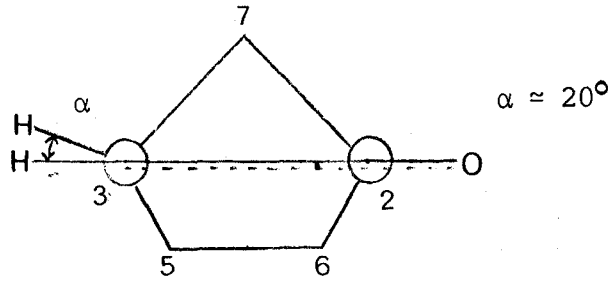
The data for norbornenone (14) are of special interest. While the effect on $J_{C(1)-H}$ of the introduction of the double bond into norcamphor is minimal as expected, $J_{C(3)-H}$ and $J_{C(4)-H}$ show dramatic increases. Certainly, some special effect, perhaps conjugative, operates in this case. The extra ground state stability in 14 gained as a consequence of the cyclic conjugation could contribute to its decreased reactivity in $^{-}$OD catalyzed deuterium-protium exchange α to the carbonyl group. (*Cf.* INTRODUCTION)

Although the J_{C-H} studies indicate that some visible effects are operating in the ground state of the diones, we present the shift data as evidence that there is no gross hybridization effect operating in the diones. This effect will be discussed further in the discussion on strain. More work must be carried out to evaluate the effects which give rise to the changes in the observed J_{C-H} as tabulated in Table II-8.

2) Torsional Effects

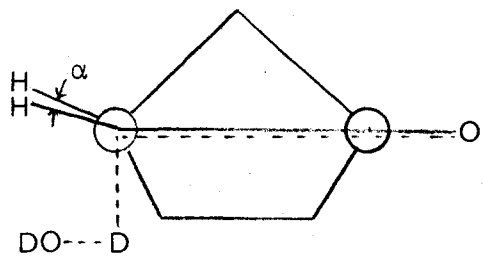
These effects were first formulated for the norbornane system in 1967 by Schleyer,[23] and since then they have been used in the interpretation of a variety of data.[144–150] They were intended to be one contributing factor to the high *exo*-stereoselectivity[151] observed in very many different reactions of the norbornyl system. Since the stereochemistry of enolization in bicyclic ketones was to a large extent the basis for the formulation of these effects, it is therefore important that they be looked at very closely. Consider the enol or enolate of norcamphor (IV):





IV

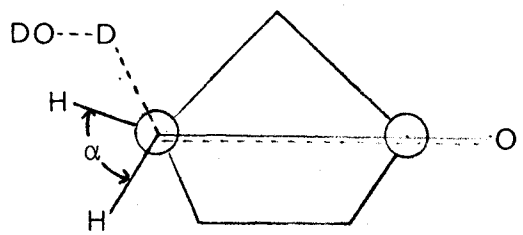
The dihedral angle between C(3)-H and C(4)-H is about 20° (obtained by consideration of models; *cf.* also Ref. 23). *Endo*-attack of D_2O on the molecule (IV) can be represented by structure V:



α < 20°

V

where the eclipsing interaction between H(3) and H(4) is increasing. On the other hand, *exo*-attack by D_2O gives structure VI:



α > 20°

VI

Here, the eclipsing interaction between the two hydrogens should decrease, thus accounting for the faster rate of exchange of the *exo*-protons.

In structure V, the maximum eclipsing energy should be approximately 1/3 of the rotational barrier in ethane (only one interaction is involved here while there are 3 in ethane), *i.e.* 0.96-0.98 kcal.[152 153]* If however the C(4) hydrogen is replaced by a methyl

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*This argument is used in Ref. 37.

group, then the interaction becomes the hydrogen-methyl eclipsing barrier, 1.43 kcal.[37,154]* The difference of 0.45 kcal represents a difference in rate of a factor of *ca.* 2. In other words, upon methyl substitution at C(4), the rate for *endo*-exchange should decrease (by a factor of *ca.* 2), and for *exo*-exchange, the rate should increase. Further the *exo-endo* rate ratio should increase upon methyl substitution. The rate data for several pairs of compounds are presented in Fig. II-14. In all cases shown, the expected rates are not seen. For *exo*-exchange, in all cases, the rate decreases (prediction: rate increase). For *endo*-exchange, the rate either remains constant or increases (prediction: rate decrease). And in all cases the *exo/endo* ratio decreases (prediction: increase). It therefore appears that torsional effects in enolization reactions of these systems are small or non-existant and not important.

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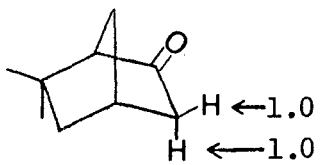
*Obtained by consideration of neopentane.

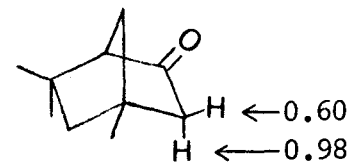
Fig. II-14

Investigation of Torsional Effects

A) Monoketones

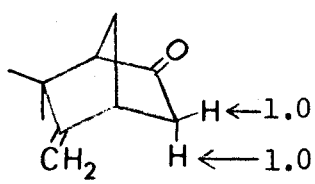


$\frac{exo}{endo}$ = 626

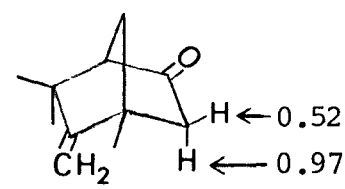


$\frac{exo}{endo}$ = 390

B) Enones

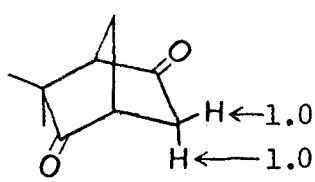


$\frac{exo}{endo}$ = 1800

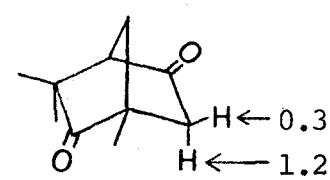


$\frac{exo}{endo}$ = 930

C) Diones



$\frac{exo}{endo}$ = 170

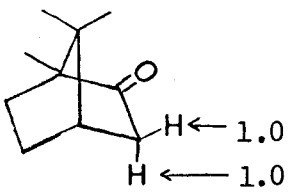


$\frac{exo}{endo}$ = 44

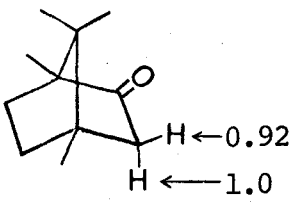
Fig. II-14 (continued)

Investigation of Torsional Effects

D) Tidwell's study, *cf.* Ref. 37 and Table I-1



$\frac{exo}{endo} = 21$



$\frac{exo}{endo} = 19$

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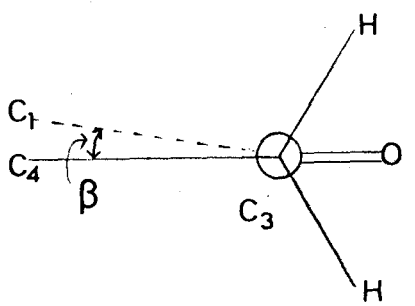
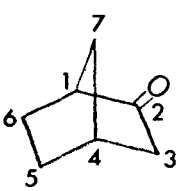
3) Conformational Effect

It has been suggested[21,22] that in enolization reactions, the α-proton is most readily removed when the carbon-hydrogen bond is perpendicular to the plane of the carbonyl group, *i.e.* parallel to the π-orbital of the carbonyl. Variation in the conformation of the α-hydrogens, through twisting of the norbornane skeleton, could then be of some importance in the rate of exchange of these ketones. Altona and Sundaralingam[76] have studied the effect of substitution on the conformation of the norbornane skeleton. Most instructive in this respect is the following angle β:



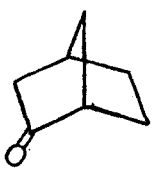
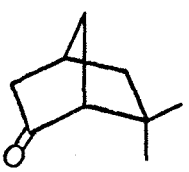
VII



Structure VII represents a view of the {2.2.1.}skeleton along the C(3)-C(2) axis. A *gem*-dimethyl substituent at C(6) was calculated[76] to cause an increase in the torsional angle β of 7°. This implies that the position of the hydrogens, α- to the ketone function {C(3) hydrogens}, relative to the plane of the carbonyl group, varies appreciably from norcamphor to 6,6-dimethyl-2-norbornanone. Table II-10 gives the relevant data. The conformation varies appreciably,

Table II-10

Conformational Effect

Compound	β'*	Relative Rate	
		exo	*endo*
 13	0°	1.0	1.0
 24	7°	0.4	0.4

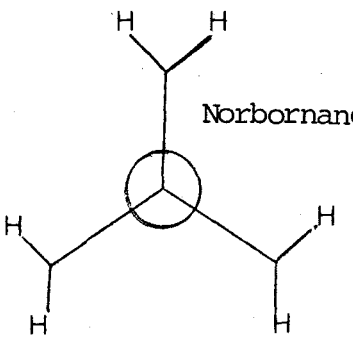
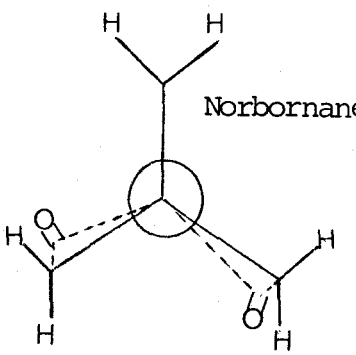
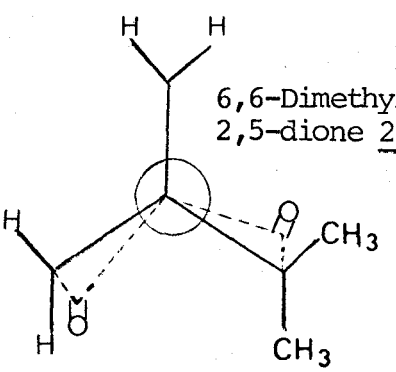
* β' is defined here as the increase in the torsional angle β when substituents are added; *cf.* text.

while the rate of exchange only changes by a factor of 2.5, thus suggesting the unimportance of this effect.

This is further supported by the rate of exchange in the diones. As was suggested earlier (Section II-B), norbornane-2,5-dione and 3,3-dimethylnorbornane-2,5-dione may exist in two different *synchro* twist forms. These are again represented in Fig. II-15, where a view of the skeleton is projected from the C(1)-C(4) axis. Here the conformation of the α-*endo*-hydrogen, relative to the plane of the π-electrons of the carbonyl, varies drastically, and yet, the rate of exchange remains essentially the same. The same is true for the *exo*-protons. It is therefore concluded that this effect is of minor importance in these exchange reactions.

Fig. II-15

Conformation of Diones

Rel. rate of exchange		Compounds
exo	*endo*	
-	-	 Norbornane
1.0	1.0	 Norbornane-2,5-dione 27
1.4	1.1	 6,6-Dimethylnorbornane-2,5-dione 26

4) Strain Effects

The strain introduced by the second carbonyl group could contribute to the enhanced reactivity of the diones over the monoketones. As models for strain, a number of enones were included in this study. That an exocyclicmethylene group is a good model for bond angle strain of ketones is supported by the following evidence:

a) Both carbonyl infra-red frequencies and olefin frequencies in $(CH_2)_n$ C=X (where X = CH_2 or O) have been correlated with bond angle strain.[155] Further, infra-red frequencies of ketones and exocyclic-methylene compounds have been correlated[156] with each other. This correlation included compounds in the bicyclo{2.2.1.}heptane system. Carbonyl frequencies for ketones in this study are listed in Table II-11.

b) The structure of 1,4-dimethylenecyclohexane was found to be similar to that of cyclohexane-1,4-dione.[82]

The rate data for 3 enones, compared to the corresponding monoketones are listed in Table II-12. As can be seen, there is no large apparent effect (*maximum:* 9). Before drawing any conclusion, the role of the double bond 1,3 to the enolizable center needs to be established. Fig. II-16 lists several examples of reactions involving a double bond 1,3 to a carbanion center. In all cases listed, the effect is not dramatic* (*maximum* effect: 10). However, in those cases as

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*The compound anti-7-cyano-2-norbornene (case C in Fig. II-16) may not be a good example, as it has been suggested[159] that the corresponding

well, a combination of effects may be operating; thus might be:

a) An accelerating effect:

- Inductive and/or homoconjugative effect of double bond.
- Hybridization effect.

b) A decelerating effect:

-Strain.

These effects might be counterbalancing each other. In this respect, the rates of deprotonation of nitro-compounds are most instructive (case B of Fig. II-16). Indeed, that such counterbalancing effects be exactly the same in the cyclohexyl, bicyclo{2.2.1.}heptyl, and bicyclo{2.2.2.}octyl systems, is not reasonably likely. Strain effects therefore are small and not important.

The compound 6-methylene-2-norbornanone (31) further supports this conclusion. The data is listed in Table II-13, together with the relevant comparisons. The strain in compound 30 should be the same as that in compound 31. Yet in 31, the inductive and/or homoconjugative effect 1,3 to the enolizable center is not present. The data show then that the effect of the double bond is almost entirely inductive, and does not give rise to a strain effect. If we assume that the effect of the double bond in 31 is entirely a strain effect, then strain causes an acceleration (!) of 1.8 for *exo*-exchange, and a deceleration of 5 for *endo*-exchange. Consequently the inductive/homoconjugative effect of the double bond in 30 would be an acceleration by a factor of 5 for *exo*-exchange and 10 for *endo*-exchange. In this line of

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anion be the destabilized bishomoantiaromatic delocalized anion.

Table II-11

Carbonyl Infrared Frequencies in some Ketones

Compounds*	$\nu_{C=O}$**
(25)	1757
(30)	1754
(27)	1766 (1731 s)
(31)	1750
(26)	1755
(24)	1748
(29)	1756
(13)	1751
(7)	1746

* Structures for these compounds will be found in Fig. II-1 and I-1.

** (± 2 cm^{-1}).

Table II-12

Effect of Strain in Enones; Relative Rate of Exchange of Enones as Compared to Ketones

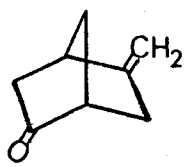
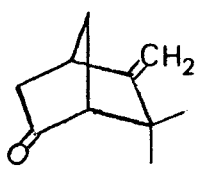
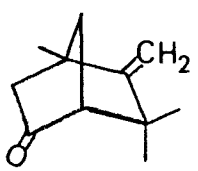
Compound	Rate Acceleration over the Corresponding Hydrogen in the Corresponding Ketone.
 30	*exo* : 9.0 *endo* : 2.1
 29	*exo* : 8.0 *endo* : 3.0
 28	*exo* : 7.0 *endo* : 3.0

Fig. II-16

Effect on the Reaction Rate, of a Double Bond, Placed 1,3- to an Incipient Anionic Reaction Center

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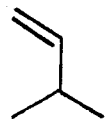
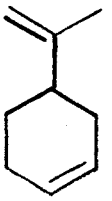
A. Relative rates of isomerization of olefins with *t*-BuOK in DMSO at 55°:[157]

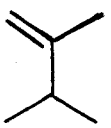
i)

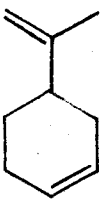




rel. rate: 1 2

ii)

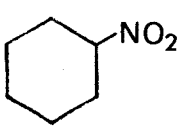


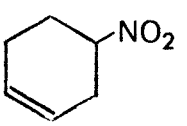


rel. rate: 1 1.4

B. Base-Catalyzed deprotonations of nitrocompounds at 28° in 50:50 dioxane-water:[158]

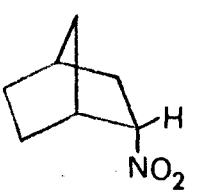
i)

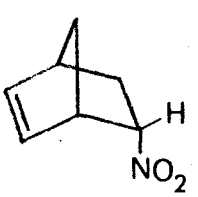




rel. rate: 1 0.4

ii)



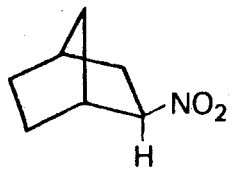


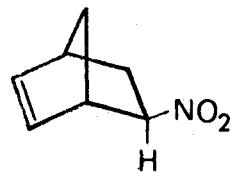
rel. rate: 1.0 1.7

Fig. II-16 (Continued)

B.

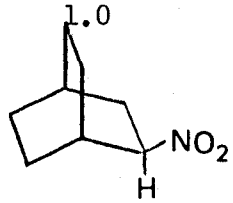
iii)

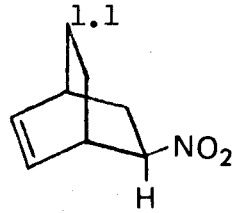




rel. rate: 1.0 1.1

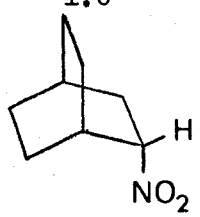
iv)

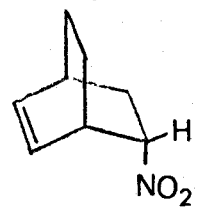




rel. rate: 1.0 0.80

v)

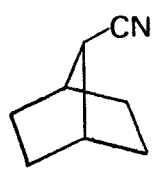


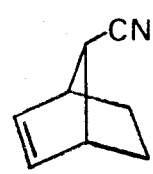


rel. rate 1.0 0.80

C. Relative rates of deprotonation of cyanocompounds with *t*-BuOK in *t*-BuOH at 65°:[159]

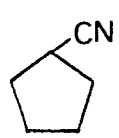
i)

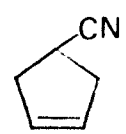




rel. rate: 1.0 1.4

ii)

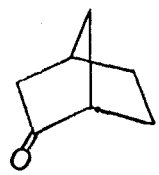
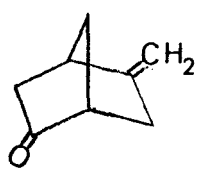
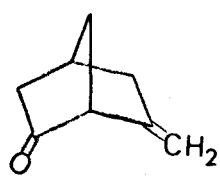




rel. rate: 1.0 10

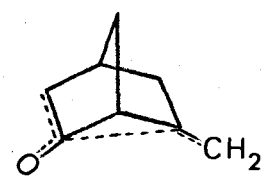
Table II-13

Effect of an Exocyclic methylene Group on the Exchange of Bicyclo{2.2.1.} Heptanones

Compound	Rel. Rate of Exchange	
	exo	*endo*
 13	1.0	1.0
 30	9.0	2.1
 31	1.8	0.2

thinking, the difference in the effect experienced by the *exo* and *endo*-hydrogens would probably be due to the same phenomenon as present in the diones where the same acceleration is not felt by the *exo* and *endo*-hydrogens. This will be discussed later on in connection with the discussion of the effect of the carbonyl.

It should be pointed out however that the above assumption, *viz.* that the effect of the double bond in 31 is entirely a strain effect, may not be a valid one. The U.V. data (*cf.* Table II-9) indicate that the enone system in 31 is homoconjugated. This might mean that the more delocalized structure (VIII),



VIII

in the enol or enolate-like transition state or intermediate, might be of some significance. The net effect of structure VIII would be to decrease the effect of strain and increase the inductive effect in 30. At any rate, the data presented above indicates that strain effects are not important.*

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*The fact that strain effects are not important further supports the unimportance of the conformational effect. Indeed, the orientation of the α-hydrogens with regards to the π-system of the carbonyl group,

5) Effect of the Carbonyl group

Inductive and Homoconjugative Effect

All the effects discussed so far have turned out to be small (*maximum* effect is 10). Then the large part of the rate acceleration in the exchange reaction of the diones must be due to the second carbonyl group itself. The rate data are listed in Table II-14. The acceleration then is due to either an inductive effect and/or a homoconjugative effect of the second carbonyl group.

Carbonyl compounds have a well known ability to activate α-hydrogens to produce keto-enol tautomerism. Activation of a β-hydrogen[160,161] or further removed hydrogens[162—164] have also been observed. The process of activation of a β-hydrogen sufficiently to be able to convert the compound to an anion and to stabilize it by conjugation with the carbonyl, has been termed homoenolization. This is represented in Fig. II-17. Evidence for homoenolization has been provided by Nickon and co-workers.[160,161] Camphenilone (42) was treated with base and was racemized. The mechanism for the racemization is depicted in Scheme II-12. When treated in deuterated medium, camphenilone could incorporate up to 9 deuteriums.[165] These were at positions 1, 6, 8 and 9. However position 6 was by far the easiest position for hydrogen abstraction.[160,161,165]

---

varies considerably in going from norcamphor to methyl-substituted norcamphors, to 1,4-enones, to methyl-substituted-1,4-enones, to 1,5-enones; yet, no appreciable effect is observed.

Table II-14

Effect of Carbonyl Group in Diones; Relative Rate of Exchange of Diones as Compared to Monoketones

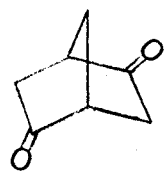
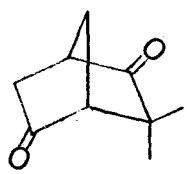
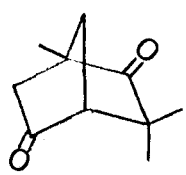
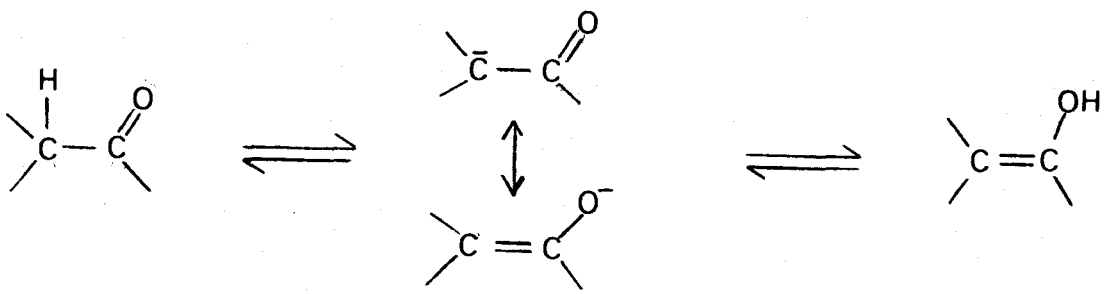
Compound	Rate Acceleration over the Corresponding Hydrogen in the Corresponding Monoketone.
 27	*exo* : 130 *endo*: 600
 26	*exo* : 210 *endo*: 1800
 25	*exo* : 400 *endo*: 1500

Fig. II-17

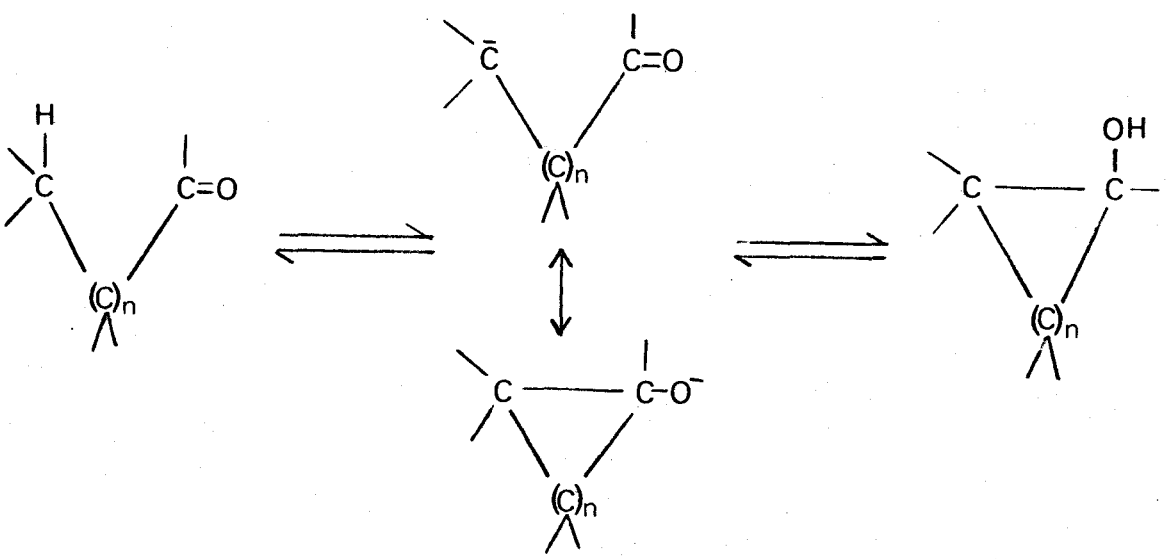
Activation of Hydrogens by Carbonyl Groups [160,161]

A) Enolization:



enolate enol

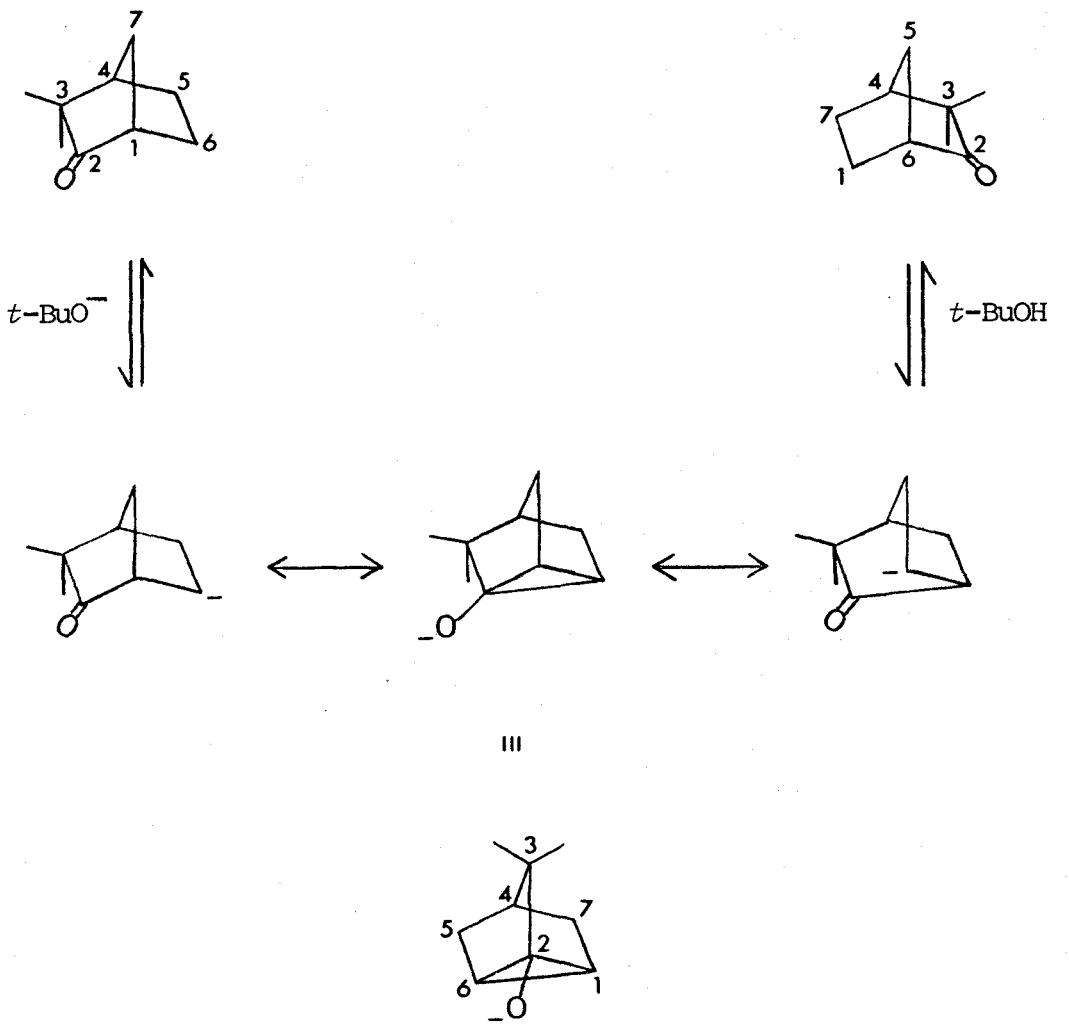
B) Homoenolization:

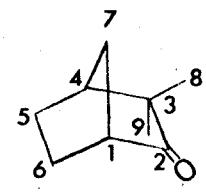


homoenolate homoenol

Scheme II-12

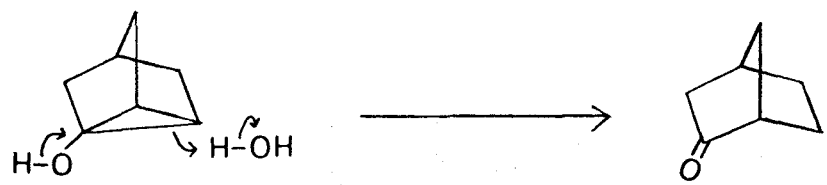
Racemization of Campheniloneone with KO-*t*-Bu in HO-*t*-Bu[160]





42

The stereochemistry of homoenolization at C(6) was also investigated[166] by a study of the reverse process, homoketonisation:

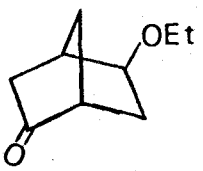


It was found that in acid medium, the preferred stereochemistry for deuterium incorporation at C(6) was *endo*. In basic medium, the preferred stereochemistry at C(6) was *exo*.

Thus in the present exchange reactions in the dione systems, the first expectation is that if the second carbonyl group participates by homoconjugation, then the *exo*-proton should experience a larger acceleration than the *endo*-proton. This is not observed (*cf.* Table II-14). In fact the situation seems a great deal more complicated (*vide infra*).

First we can attempt to separate the inductive and homoconjugative

contributions. To do this a model for the inductive effect is required. Such a model could be 5-ethoxy-2-norbornanone (101),



101

whose rate of exchange was recently measured by Tidwell,[167] and was found to be (67 % dioxane: D_2O, 25°):

$$k_{exo} = 1.3 \times 10^{-1}\ l.\ mole^{-1} sec.^{-1}$$
$$= 1.8 \text{ (rate of norcamphor)}$$

The effect of the ethoxy substituent should be a pure inductive effect since

1) no homoconjugation is possible,

2) no steric effect should be involved because the ethoxy substituent is *exo* and on the other side of the molecule.

A measure of the inductive effect will be given by Taft's polar substituent constant σ*.[168–170] What is required, is a σ* value for the group Et-O-CHR-CHR-. A close approximation to this is the group CH_3-O-CH_2-CH_2- which can be obtained as follows:[168–170]

Given that[168–170]**

$$\sigma^*_X = 2.5\ \sigma^*_{XCH_2} \qquad \text{eq. 9}$$

and

$$\sigma^*_{CH_3-O-CH_2} = 0.64 \text{ }^{168}$$

then

$$\sigma^*_{CH_3-O-CH_2-CH_2} = 0.64/2.5$$
$$= 0.26$$

Now

$$\log k_{rel.} = \rho^* \sigma^* \qquad \text{eq. 10}$$

then for 5-ethoxy-2-norbornanone (101)

$$\log 1.8 = \rho^*_{exo} \; 0.26$$

and

$$\rho^*_{exo} = 0.96$$

We can now predict the rate acceleration of the carbonyl group due to its inductive effect only:

Given that[168]

$$\sigma^*_{CH_3-CO-CH_2} = 0.60$$

then

$$\log (k_{rel.})^{exo}_{ind.} = \rho^*_{exo} \sigma^*$$
$$= 0.96 \times 0.60 = 0.58$$

**Slightly different "relay factors" (2.5 above) are obtained for different reaction series so that this equation may not hold exactly. This might particularly be true in the present situation since the insulating group is not a "CH_2" but a "-CHR". However, since norcamphor, the standard compound, has the same R group, the relation should be fairly good.

Cf. Ref. 170 for a discussion on this problem.

hence

$$(k_{rel.})^{exo}_{ind.} = 3.8$$

The observed acceleration for *exo*-exchange in norbornane-2,5-dione (27) is 130. Since the inductive effect of the second carbonyl is 3.8, then the non-inductive effect of the second carbonyl is 130/3.8 = 34.

This value of 34 for the non-inductive effect is a *minimum*, because there probably is a small strain effect in the dione without which the *exo*-acceleration in the dione would be larger than 130.

Unfortunately the same treatment for *endo*-exchange cannot be made as the rate data for *endo*-exchange in 5-ethoxy-2-norbornanone (101) is not available. Since the *exo-endo* rate ratios are to a large extent governed by steric factors, the ρ* value for *endo*-exchange will certainly not be the same as the ρ* value for *exo*-exchange. But it is still possible to obtain an approximate ρ* value for *endo*-exchange, if the compound 5-methylene-2-norbornanone (30) is used as the standard:

$$\sigma^*_{CH_2=CH} = 0.36\ ^{168}$$

$$\sigma^*_{CH_2=CH-CH_2} = 0.36/2.5 \simeq 0.14$$

then

$$\log k_{rel.} = \rho^* \sigma^* \qquad \text{eq. 10}$$

$$\log 2.1 = \rho^*_{endo}\ 0.14$$

and hence

$$\rho^*_{endo} = 2.3$$

The rate acceleration of the second carbonyl group due to its inductive effect is then,

$$\log (k_{rel.})^{endo}_{ind.} = 2.3 \times 0.60$$
$$= 1.4$$

hence

$$(k_{rel.})^{endo}_{ind.} \simeq 24$$

Now the observed $k_{rel.}$ for *endo*-exchange in norbornane-2,5-dione (27) is 600; then the non-inductive effect of the second carbonyl group is 600/24 = 25.

This calculation is considerably less reliable than the preceding one, because the standard compound, 5-methylene-2-norbornanone (30) is not as devoid of effects as 5-ethoxy-2-norbornanone (101), even though these effects are small.* These effects are:

1) A strain effect of the double bond.

2) A steric effect: there is no *endo*-5-hydrogen in 30, such that steric approach of base will be less hindered.

3) A homoconjugative effect of the double bond (?).

Now here, the observed $k_{rel.}$ (= 2.1) for 30 may be less than what would be expected for an inductive effect of a double bond, because of strain effects. However, these strain effects are partly cancelled by the other factors (steric and homoconjugative). Thus

$$\rho^*_{endo} \geq \rho^*_{endo\ actual}$$

In fact, if we calculate a ρ value for *exo*-exchange using 30 as the reference, we obtain $\rho^*_{exo} = 6.8$, compared to 0.96 using 101 as the standard compound.

then

$$(k_{rel.})^{endo}_{ind.} \geq 24$$

and

$$(k_{rel.})^{endo}_{homoconj.} \leq 25$$

i.e. the homoconjugative acceleration in the *endo* case is less than the homoconjugative acceleration in the *exo* case, in accord with what is known about homoconjugation (*vide supra*).

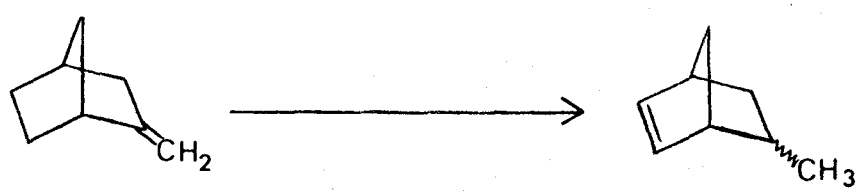
Thus it is evident that there is very little homoconjugative participation of the second carbonyl group. The rate acceleration is minor when compared to Miller's case[17] (10^6; *cf.* INTRODUCTION).

The observed acceleration in 3,3-dimethylnorbornane-2,5-dione (26) and fenchane-2,5-dione (25) (*cf.* Table II-14), is somewhat larger (factor of 2 to 3), yet, presumably, the inductive effect is the same as in norbornane-2,5-dione. This difference could arise *via* the conformational difference observed for these compounds (*cf.*Section II-B); in norbornane-2,5-dione, the orbitals would be less favourably aligned for participation.

In summary then, we have seen that the effect of the second carbonyl group in the exchange reactions of the diones, is largely inductive, with a small homoconjugative participation.

6) Discussion

It has been shown that hybridization effects, torsional effects, conformational effects and strain effects play a minor role in the exchange reactions of the bicyclo{2.2.1.}heptanone system. This might be considered as surprising, particularly the strain effects; this is illustrated by the relatively high heat of isomerization of methylenenorbornane (102) to methylnorbornene (103):[171]



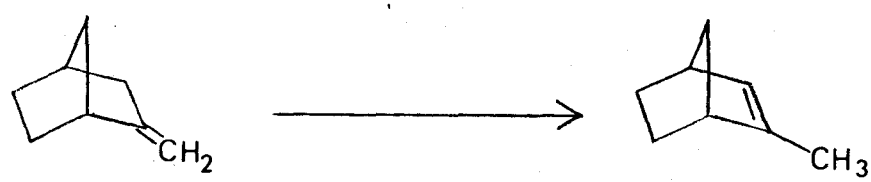
102 $\Delta H_{isom.} = 4.75$ kcal mole^{-1} 103

Further, in the diones, the observed acceleration due to the second carbonyl is largely inductive, with little homoconjugative participation. Thus, the exchange reactions of these ketones are quite insensitive to structural and electronic effects. This section then, will deal about the reasons why this might be so, and about what information it gives about the mechanism of enolization of these ketones.

The reason why there are no hybridization effects, is perhaps related to the structure of the diones. As we have seen, there is considerable amount of twisting in the skeleton of the diones. This presumably arises *in order that* there is no energetically costly[20] hybridization change in the molecule.

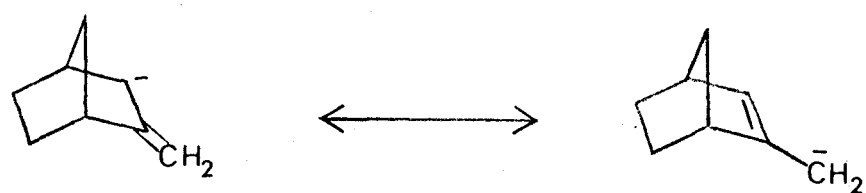
That torsional and conformational effects play a minor role in the exchange reactions, may be due to the position of the transition state, relative to ground state and enol or enolate intermediate. Torsional effects for a C(1) hydrogen were estimated to be of the order of 1 kcal/mole. And this represented a *maximum* effect. Obviously, the earlier the transition state along the reaction coordinate, the less important these effects will become.[37,149,150,172] Thus, the lack of sensitivity to these effects, tend to show a reactant-like transition state.

S. Bank *et al*[173] have studied the rate of isomerization of cyclic and bicyclic olefins {including the isomerization of methylenenorbornane (102) to 2-methyl-2-norbornene (104)}. They recognized two types of strain that were important in those isomerization reactions:
1) Bond angle strain, which is the strain introduced by the fact that a sp^2 carbon strives for an angle of 120°, while the rigid bicyclic structure does not allow it.
2) Torsional strain of the type discussed above. The energies of these two types of strain were estimated and correlated with the rates of isomerization from an exocyclic double bond to an endocyclic one. It was found that a plot of log $k_{\text{exocyclic} \longrightarrow \text{endocyclic}}$ *vs* bond angle strain energies had a least-square correlation coefficient of 0.03 (a random array of points would give 0.0, and a perfect correlation would give 1.0). On the other hand, a plot of log $k_{\text{exocyclic} \longrightarrow \text{endocyclic}}$ *vs* torsional strain energies, gave a least-square correlation coefficient of 0.82. These data are for an isomerization of the type, for example,



102 104

The intermediate in this reaction is, of course, a resonance stabilized allyl anion (IX):

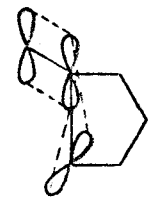


IX

The data cited above indicate that the main factor governing the rate of isomerization is a torsional strain effect. Further, the rate-determining step in the reaction is the formation of the anion.[174] Now for ketones, the rate-determining step in hydrogen-deuterium exchanges, halogenations and racemization reactions is the formation of enols or enolates.[175,176] Thus isomerization of exocyclic olefins and enolization of ketones are quite similar reactions. Indeed, the rate of isomerization of exocyclic olefins has been correlated to the rate of bromination of the corresponding ketone by a linear free-energy relationship.[177] So that factors influencing the isomerization of

olefins should also influence the enolization of the corresponding ketone.

In the work on the isomerization of olefins,[173] it was concluded that the strained allylic anion formed was not planar, but resembled structure X:



X

This also implies that the transition state is even more reactant-like. Now the strain effect we are talking about in the present work is a secondary effect. We are considering a strain effect introduced by a sp^2 center in a "remote" part of the molecule, such that these effects should be attenuated. Thus, it now becomes reasonable that the strain effect arising from the second sp^2 center is not important. Also, torsional strain effects, which were the main effect governing the isomerization of olefins *(vide supra)*, have been examined here separately, and have been found to be of minor importance. This further suggests a very early transition state.

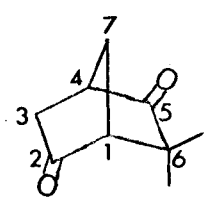
That the additional strain arising from a second sp^2 center in the diones and enones is small is also suggested by the calculated[80] strain energy difference of 0.64 kcal/mole between 2-norbornanone and

norbornane (compared to 1.04 for cyclohexanone-cyclohexane).

Thus, the lack of sensitivity to hybridization, conformational torsional and strain effects, of the exchange reactions of bicyclic ketones is not only reasonable, but also indicates the transition state leading to enol or enolate intermediates is reached relatively early along the reaction coordinate.

It now remains to discuss what information will the effect of the second carbonyl group give, about the mechanism of enolization.

The fact that there is very little homoconjugative participation of the second carbonyl group, compared to Miller's case[17] (10^6) implies that there is very little negative charge developed at C(3) in the transition state leading to enol or enolate intermediate.



This would be best accounted for by an enol intermediate, where as a proton is being remove at C(3) the oxygen atom is being protonated. The calculated ρ^* value should give more information on this problem.

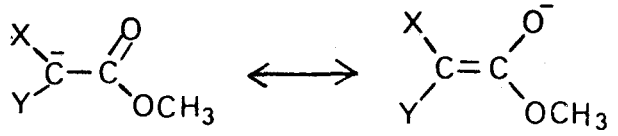
A review of the literature reveals that there are few examples of ρ^* correlations for enolization-type reactions. Hine *et al.*

have reported a ρ^* value of 1.78 for the methoxide-catalyzed hydrogen-deuterium exchange of α-hydrogens in methyl esters:[178]

$$XYCHCO_2CH_3 \longrightarrow XYCCO_2CH_3 \longrightarrow XYCDCO_2CH_3$$

XI

The intermediate here (XI) is the following resonance stabilized anion:

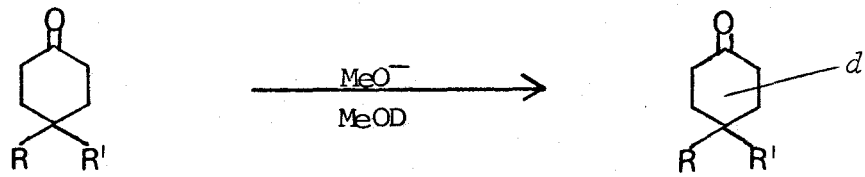


XI

Also, a ρ^* value of 1.59 has been reported[179] for acetate-catalyzed bromination of aryl ketones in water.**

Perhaps a better standard ρ^* value will be found by looking at Bordwell's data[181] on the enolization of 4,4 -disubstituted-cyclohexanones:

** The ρ^* value was calculated[139] from data reported in Ref. 180 (Evans and Gordon, 1938) where no definite conclusions are reached about the problem at hand.



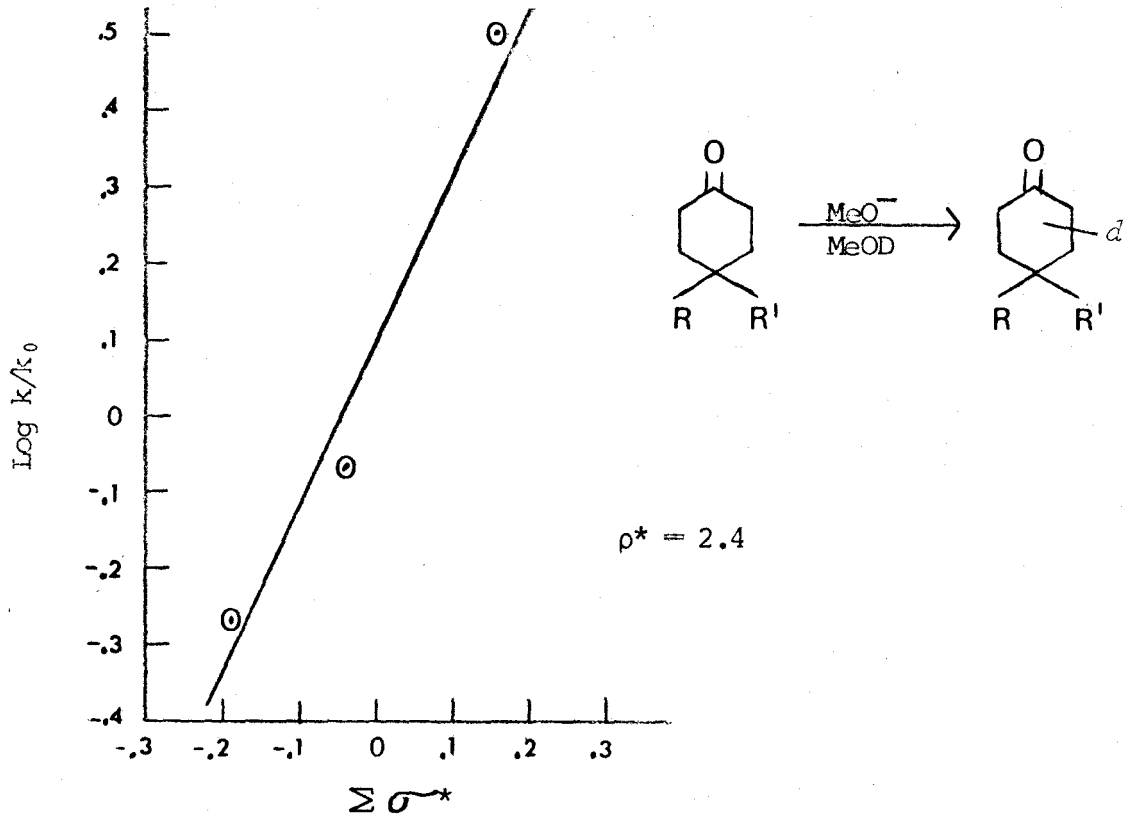
The data are listed in Fig. II-18 together with the ρ* correlation. Here, the strongly basic conditions most certainly give rise to an enolate anion as the intermediate.[25–27, 181] The large ρ* value found here (2.4), compared to the value found for *exo*-exchange in the present work (0.96) suggests that very little negative charge is developed in the transition state, and hence an *enol* intermediate.**

In support of these conclusions, are Crain's results on the hydrolysis of enol-trifluoroacetates of some bicyclo{2.2.1.}heptane-2-one (*cf.* Table I-3).[43, 44] The difference between these results and those found by the direct exchange method would indicate a different intermediate. The enol ester, upon hydrolysis, gives rise in the rate determining step, an *enolate* anion.[43, 45, 46] An early transition state and an *enol* intermediate in the direct exchange reaction, would explain the different *exo-endo* ratios obtained by the two methods.

** For reasons given in Section II-D-5, the calculated ρ* value for *endo*-exchange is not reliable enough to permit comparison with ρ* values listed here.

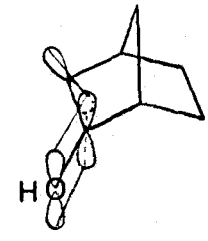
Fig. II-18

Inductive Effect[181]



R	R'	Σ σ*[168]	k(M^{-1}sec.$^{-1}$)	log k/k_0
H	H	-	1.05 x 10^{-1}	-
ϕ	ϕ	0.16	3.4 x 10^{-1}	0.50
ϕ	Me	-0.04	0.89 x 10^{-1}	-0.07
Me	Me	-0.19	0.57 x 10^{-1}	-0.27

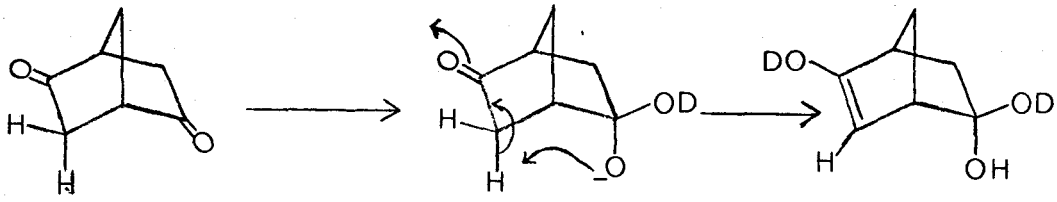
Further, in the discussion on the strain effect (*vide supra*), the similarity between the exchange reaction and the isomerization reaction of an exocyclic double bond to an endocyclic one was pointed out. In the latter reaction a strained allylic anion was claimed as the intermediate (structure X). If we consider an enol as a *protonated-enolate*, then we could have, as the intermediate in the enolization reaction of bicyclic ketones a strained enol (structure XII):



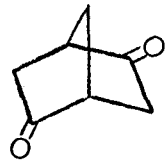
XII

Protonation of such an intermediate would be by far easier from the *exo*-side. Thus the surprisingly large *exo-endo* ratios[36] observed in these reactions (*cf.* Table II-4 and Table I-1) would be explained.

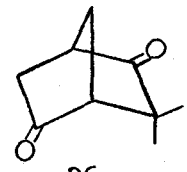
Finally, one more comment should be made concerning the non-inductive participation of the second carbonyl group in the exchange of the dione systems. Base-catalyzed hydration of ketones is known to be rapid.[182] Then, the following mechanism, conceivably, could contribute to the overall exchange acceleration in the dione systems:



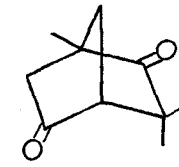
However the fact that the rate of exchange in diones 27, 26 and 25 do not differ appreciably (*cf.* Table II-1), while the rate of



27



26



25

nucleophilic attack on the carbonyl should decrease drastically because of increasing methyl substitution, indicates that the above mechanism is not important. Also, proton transfer from solvent to $-O^-$ should be almost instantaneous[182] (diffusion controlled) and should compete favourably with the transfer from the other carbon.

E. CONCLUSION

In summary then base-catalyzed enolization reactions of bicyclo{2.2.1.}heptanones have the following general characteristics:

1) They generally lack sensitivity to steric-strain and electronic effects.

2) A carbonyl group, placed 1,3- to an enolizable center, gives rise to little homoconjugative participation (factor of 25-30).

3) The reaction gives a small ρ^* value.

These evidences lead to a mechanism of enolization that involves a transition state that occurs relatively early along the reaction coordinate, and a transition state that leads to an enol intermediate. Further, the high *exo-endo* ratios observed in these reactions are consistent with a strained enol intermediate.

III. EXPERIMENTAL

A. GENERAL

All melting points were taken on a Kofler Hot Stage melting point apparatus with calibrated thermometers. They are uncorrected. Boiling points are uncorrected and refer to the pressure indicated in parentheses after the letters "b.p." For example, b.p., 98-100° (12 mm), denotes the boiling point range to be 98-100°C, at a pressure of 12 mm of mercury.

Deuterium oxide was obtained from Columbia Organic Chemicals Ltd, or Merk Sharp & Dohme of Canada Ltd. Deuterochloroform was obtained from Stohler Isotope Chemical Co. Nitrogen and helium gases were obtained from Canadian Liquid Air Ltd.

Infrared spectra were recorded on two instruments: a Perkin-Elmer 337 Grating Spectrometer, and a Beckman I.R. 5 instrument, equipted with sodium chloride optics. All absorptions are in reciprocal centimeters, and calibrated with a polystyrene film. The infrared spectrum will be denoted as follows: I.R. (# 10, CCl_4). This represents spectrum # 10, using CCl_4 as solvent. The main absorption bands will follow this notation. Carbonyl frequencies (Table II-11) were obtained using a Perkin-Elmer model 521 instrument.

Nuclear magnetic resonance spectra were recorded on Varian Associates Inc. model HA-60, model T-60 and model HA-100 n.m.r. spectrometers. The spectra from the model HA-100 were recorded by

B.G. Sayer. The spectra will be denoted as follows: n.m.r. (# 82, CCl_4/TMS, T-60); this represents spectrum # 82, recorded on the T-60 using CCl_4 as solvent and tetramethylsilane as an internal standard. This will be followed by the main chemical shifts which will be reported as "δ" values (p.p.m. downfield from TMS).

^{13}C nuclear magnetic resonance spectra were recorded by B.G. Sayer with a Varian Associates HA-100 spectrometer at 23.5 kG and 25.1 MHz. The operating probe temperature was 55°C. Field frequency stabilization was achieved by use of an external (1.5 mm capillary) $^{13}CS_2$ lock and chemical shift measurements were made initially relative to internal dioxane, benzene, and then to internal tetramethylsilane. A sample volume of 0.1-0.3 ml was used in a 5 mm o.d. sample tube, with dioxane as solvent where necessary. Normally a signal accumulation of 4 to 16 scans with a Varian Associates C-1024 time averaging computer was sufficient to give an adequate signal to noise enhancement. Proton decoupling was carried out using a Varian Associates V-3512-1 noise decoupler. Carbon atom assignments were accomplished by examination of off-resonance decoupled spectra which were obtained by accumulation of 100-300 scans. For ^{13}C-H coupling constants, a signal accumulation of 300-500 scans was necessary . J_{C-H} was obtained from the doublets and triplets by drawing an envelope for each absorption (broadened by long range coupling) and using the center (at half the peak width at half height) of the Gaussian curves. Each value quoted is the mean of 3-4 determinations. The technique was calibrated in two ways. Our value of

142 ± 1 for J_{C_1-H} in norbornane is identical to that obtained from satellite studies!^{117} Furthermore, our value of J_{C_1-H} for 31 was identical to that obtained on an XL-100 FT system.^{204}

Mass spectra were recorded on a Perkin-Elmer Hitachi mass spectrometer, model RMU 6 A. Deuterium assay measurements were done at 14 *e*V. Deuterium percentages were obtained as described in Ref. 205.

Ultra-violet spectra were recorded by M. McClory using a Carry-14 spectrometer. The solvent used was distilled 95% ethanol.

Analytical gas-liquid chromatograms were recorded using a Varian Associates "Aerograph" instrument, model 204. Preparative scale gas-liquid chromatography was performed with a Varian Associates "Aerograph" instrument, model A-90-P-3, with manual sample collection. Analytical columns used were $^1/_8$ inch in diameter and the carrier gas (helium) flow rate was normally 20-30 ml/min. Preparative columns were $^3/_8$ or $^1/_4$ inch in diameter and the carrier gas (helium) flow rate was normally 60 ml/min. Chromosorb W (Chromatographic Specialties Ltd) of mesh size 60/80 was used in all cases as the solid phase. Liquid phases were various and will be denoted as follows: V.p.c. (# 160, 5% SE-30, 10', 225°). This denotes chromatogram # 160; 5% SE-30 on chromosorb W liquid phase; the column was 10 feet long; and the analysis was carried out at 225°.

Micro analyses were performed by A.B. Gygli of 329 St George Street in Toronto, Ontario.

B. KINETICS

Purification of dioxane [201]

Dioxane (1 litre, reagent grade) was refluxed for *ca.* 20 hours with hydrochloric acid (conc., 14 ml) and water (100 ml). A slow stream of nitrogen was passed throughout to entrain the acetaldehyde formed. After cooling, potassium hydroxide pellets were added until they no longer dissolved, and until a second layer separated. The dioxane was decanted into fresh potassium hydroxide pellets to dry further. It was then decanted into a clean flask and refluxed for *ca.* 15 hours with sodium. It was then distilled and stored under nitrogen.

Preparation of the buffer solution (pH 7)

A NaOD solution was prepared by adding sodium metal (186 mg) in D_2O (25 ml).

Disodium hydrogen phosphate (725 mg) was dissolved in D_2O and 9.5 ml of the NaOD solution was added. The solution was diluted to *ca.* 90 ml with D_2O. The pD was then adjusted to 7 using a pH-meter, and acetic acid-O-*d*.

Test of Buffer solution

A buffer solution was required to quench sample for analysis from the kinetic runs (*Cf.* below). This buffer solution-quenching method was checked to determine whether or not exchange occured.

Fenchane-2,5-dione (74.6 mg) was dissolved in dioxane (1.2 ml),

and the solution was diluted to 2.00 ml with D_2O. The buffer solution (2.0 ml) was added to the solution, and the solution was left standing for 45 minutes. The solution was then extracted twice with ether, then saturated with sodium chloride, and extracted again with ether. The combined extracts were dried ($MgSO_4$) and evaporated. The mixture, still containing some dioxane, was reduced with lithium aluminium hydride (2 ½ hours). (*Cf.* below for check that there is no deuterium loss during reduction stage). Recrystallization of the solids from pentane-ether mixtures gave fenchane-2,5-diols (43.4 mg, 58 % yield) melting at 110-120°.

Mass spectral results are shown in Table III-1. The "Natural abundance" sample refers to a sample of fenchane-2,5-dione reduced with lithium aluminium hydride. The "Treated sample" refers to the above sample. The invariance in the intensities of the molecular ions shows that there is no deuterium incorporation during the quenching stage.

General procedure for kinetic runs

A stock solution of sodium hydroxide-O-*d* in D_2O of convenient normality was prepared by adding an appropriate amount of sodium metal to D_2O (usually *ca.* 10 ml). This solution was standardized just before use with standard hydrochloric acid (BDH Canada Ltd volumetric solution of appropriate normality) using phenolphthalein as an indicator.

The ketone solution was prepared in a volumetric flask by

TABLE III-1

Test of Buffer Solution

M/e	Mass Spectral Intensities: Natural Abundance (M.S. # 14)	Mass Spectral Intensities: Treated Sample (M.S. # 15 A)
170	100.%	100.%
171	13.1	12.8
172	1.2	1.4

dissolving the ketone {enough to make the final solution 0.11 to 0.36*M* (typically 0.2*M*) in the ketone} in dioxane (60% of the total volume). For example, if the total volume of the reaction mixture at $t = 0$, was 2.00 ml, then the ketone was dissolved in 1.20 ml of dioxane.

The NaOD stock solution, the ketone solution, and D_2O were placed in a constant temperature bath at 25.0° for at least one hour for thermal equilibration. At time $t = 0$, the appropriate amount of NaOD was added (usually 0.30 to 0.50 ml) and the solution was quickly diluted to volume. The solution was then flushed for a few seconds with dry nitrogen. The volumetric flask was stoppered with a rubber septum. Samples (usually 0.2-0.3 ml) were removed for analysis with a syringe. The final normality of the NaOD ranged from 0.006*N* to 0.17*N*. Samples removed at convenient times for analysis were worked up as follows:

The sample was quenched in 1.5-2 ml of buffer solution. The aqueous solution was immediatly extracted with anhydrous ether (2 x 5-10 ml). The aqueous phase was then saturated with solid sodium chloride, and extracted again with ether (5-10 ml). The combined ether extracts were dried ($MgSO_4$ or Na_2SO_4). After filtration, the solution was concentrated and the sample isolated by preparative v.p.c., using a 20% SE-30 column, 5' x ¼''. The sample was collected in 1/16'' o.d. glass tubing, and the mass-spectrum recorded.

Kinetic procedure for norbornane-2,5-dione (27) and fenchane-2,5-dione (25)

Exchange of the *exo*-proton in norbornane-2,5-dione (27) and fenchane-2,5-dione (25) occured within the mass spectrometer. The diones were thus converted to the corresponding diacetates *via* a lithium aluminium hydride reduction, followed by acetylation of the diols with acetic anhydride in pyridine. The mass spectra of the diols gave a weak parent peak such that it was not entirely satisfactory for deuterium assay.

After the concentration of the ether extracts of the diones (*vide supra*), the solution was added to a slurry of lithium aluminium hydride in ether. The mixture was refluxed for 2-3 hours. The excess lithium aluminium hydride was then destroyed with sodium hydroxide (10%) and water. After filtration of the inorganic salts and drying ($MgSO_4$), the ether solution was evaporated to dryness. The crystalline diol was recrystallized from pentane-ether mixtures.

The diol was then dissolved in acetic anhydride (1.5 ml) and pyridine (2.5 ml). After standing at room temperature for *ca.* 24 hours, the solution was poured onto ice. After the ice melted, the solution was diluted to *ca.* 80 ml and extracted with ether (3 x *ca.* 25 ml). The ether extracts were then washed with water (*ca.* 25 ml), hydrochloric acid (dil., *ca.* 25 ml), bicarbonate (sat., *ca.* 25 ml), water (*ca.* 25 ml), and finally, sodium chloride (sat., *ca.* 25 ml). After drying ($MgSO_4$ or Na_2SO_4), the solution was concentrated and the diacetate was isolated by preparative v.p.c.

Lithium aluminium hydride reduction of diones

To check if there was any deuterium loss during the lithium aluminium hydride reduction of norbornane-2,5-dione (27) and fenchane-2,5-dione (25), the latter was reduced with lithium aluminium deuteride, and the mass spectrum (M.S. # 12) of the recrystallized product was recorded. Deuterium content was found to be as follows:

M/e	% Deuterium
170 (d_0)	0.0
171 (d_1)	7.9
172 (d_2)	92.1
173 (d_3)	0.0
174 (d_4)	0.0

The absence of any d_3 species shows that exchange does not occur during the reduction.

Control experiments on deuterium analysis

As stated above, some deuterium was lost during the handling of norbornane-2,5-dione (27) and fenchane-2,5-dione (25). And this was corrected for by a modification in the procedure, as described above. It then needed to be established that no such losses occured during the handling of the other ketones-monoketones, enones and particularly, 3,3-dimethylnorbornane-2,5-dione (26). Since the above experiment shows that lithium aluminium hydride reduction does not entrain any deuterium losses, then deuterium assay on the corresponding acetate should provide a check on the deuterium analysis. The experi-

ments described below establish that:

1) No deuterium losses occur while the sample is standing awaiting analysis (analysis is random with time-experiment A below).

2) No deuterium losses occur during the purification step by preparative v.p.c.

Reduction and acetylation of the samples were done immediately after exchange.

A) Epiisofenchone (23)

A solution was prepared by dissolving epiisofenchone (43.1 mg) in dioxane (0.6 ml). A NaOD solution (0.4 ml, prepared by adding 31 mg of sodium in 10 ml of D_2O) was added, and the solution was reacted for 1 $\frac{3}{4}$ hour at room temperature. After the usual work up, the ether solution was divided into two parts.

The first part was concentrated and the ketone was isolated by preparative v.p.c. (# 180, 20 % SE-30, 5', 120°). Three different samples (3 different injections) were isolated in this way at different times and the mass spectra were recorded. The results are shown in Table III-2.

The second part was concentrated and reduced with lithium aluminium hydride to the corresponding alcohol. This alcohol was acetylated in acetic anhydride and pyridine. Isolation and purification by preparative v.p.c. (#180, 20% SE-30, 5', 120°) gave a sample for mass spectral analysis. The results are shown in Table III-2.

Table III-2

Control Experiment in Deuterium Analysis of Epiisofenchone (23)

	% Deuterium			
	KETONE			ACETATE
Species	immediately after exchange (M.S. # 72)	3 days after exchange (M.S. # 74)	(M.S. # 75)	(M.S. # 80)
d_0	9.1	9.5	9.6	13.5
d_1	91.0	90.5	90.5	86.5
d_2	0.0	0.0	0.0	0.0

B) 1-Methyl-oxocamphene (28)

A similar experiment as above was performed using 40.6 mg of 1-methyl-5-oxocamphene, 0.9 ml dioxane, 0.4 ml of 0.14*N* NaOD and 0.2 ml D_2O. The results are shown in Table III-3.

C) 3,3-Dimethylnorbornane-2,5-dione (26)

A similar experiment as above was performed using 39.0 mg of 3,3-dimethylnorbornane-2,5-dione, dissolved in 0.6 ml dioxane. NaOD (0.3 ml, 0.103*N*) was added and the solution was diluted with D_2O to 1.00 ml. The results are shown in Table III-4.

The above experiments show that the deuterium analysis done on the ketones themselves does not entrain any deuterium losses.

Rate fall-off in kinetics of diones

It was found that in the kinetics of the diones (norbornane-2,5-dione, 3,3-dimethylnorbornane-2,5-dione and fenchane-2,5-dione) there was a rate decrease with time. This rate decrease could be correlated with a decrease in the base concentration. To obtain the rate constant for these compounds, the following correction to the deuterium analysis was applied:

Under similar conditions (ketone concentration, NaOD concentration) as those used in the kinetic runs, the change in base concentration was followed with time, and plotted as per Fig. III-1 (fenchane-2,5-dione). Since at time $t = t$ the base concentration has been lowered by x %, then because of the linear equation,

Table III-3

Control Experiment in Deuterium Analysis of 1-Methyl-5-Oxocamphene (28)

Species	% Deuterium	
	KETONE (M.S. # 95)	ACETATE (M.S. # 97)
d_0	5.7	9.0
d_1	94.3	90.9
d_2	0.0	0.0

Table III-4

Control Experiment in Deuterium Analysis of 3,3-Dimethylnorbornane-2,5-dione (26)

Species	% Deuterium		
	DIONE (M.S. # 161)	DIACETATE (M.S. # 162)	
		M^+ peak	M^+-Ac peak
d_0	4.1 %	5	4.5
d_1	91.3 %	89	88.7
d_2	4.6 %	5	5.3

$$\text{rate} = k_2 [\text{ketone}] [\text{NaOD}] \qquad \text{eq. 11}$$

A correction can be made by augmenting the ketone concentration by x %. For example, for 3,3-dimethylnorbornane-2,5-dione, the change in base concentration at time t = 30 min. is 5.7 % (from Fig. III-1). The measured % d_2 is 51.4 % (*cf.* Section IV). Then a corrected % d_2 is found as follows:

$$\text{corrected \% } d_2 = \frac{\% \, d_2 \, (100 + \% \text{ change in base conc.})}{100} \qquad \text{eq. 12}$$

$$= \frac{51.4 \, (100 + 5.7)}{100}$$

$$= 54.3$$

The experimental details are given in Section IV, with the kinetic results. An example of the rate fall-off together with the correction is shown in Fig. III-2.

Fig. III-1

Correction to the Base Concentration in the Kinetics of the Diones

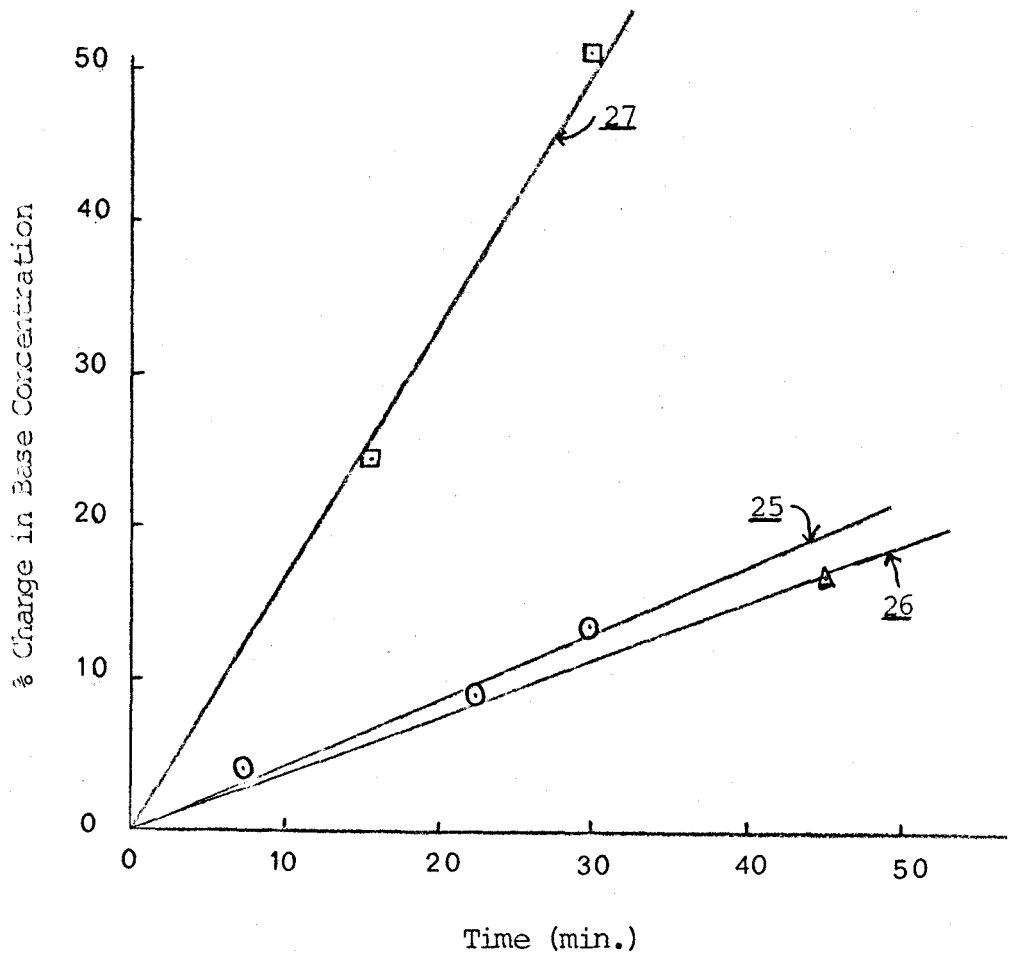
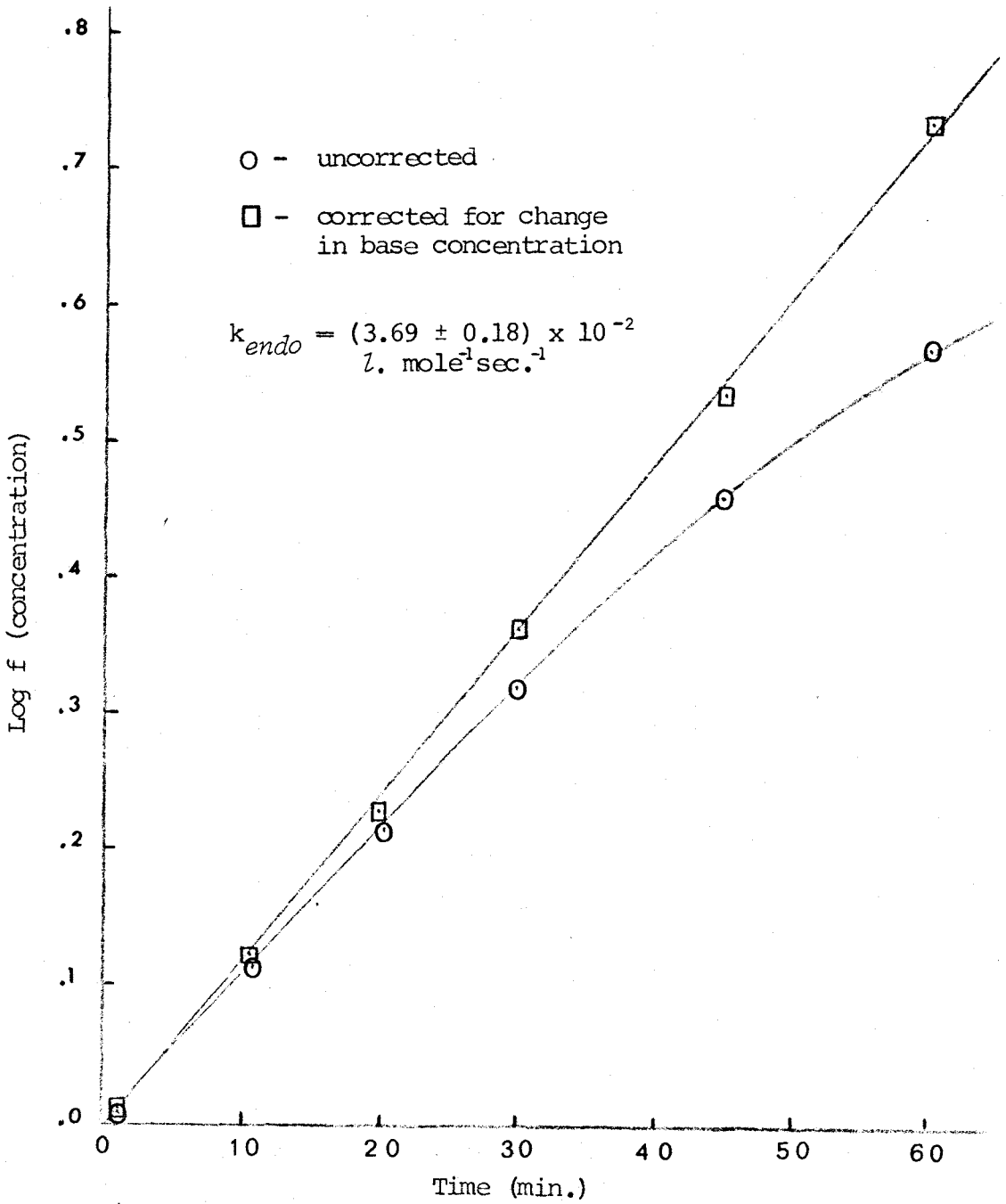


Fig. III-2

Kinetics for *Endo* Exchange on 3,3-Dimethyl-norbornane-2,5-Dione, Run 1



C. SYNTHESIES

1) Preparation of 5-Oxofenchol (50) (Scheme II-4)

Reduction of Fenchone (44)

All glassware was oven dried before use, and the ether was distilled from lithium aluminium hydride.

In a 2 *l*. 3-necked flask, fitted with condenser (with a $CaCl_2$ drying tube) and adding funnel, was placed a slurry of lithium aluminium hydride (25 g) in ether (500 ml). Fenchone (Eastman Chemicals Co., technical, 100 g, 0.66 mole) dissolved in ether (300 ml) was slowly added over a period of one hour. The mixture was then refluxed for two hours.

The reaction was then cooled in an ice-water bath and stirred magnetically. Sodium hydroxide (10 %, 50 ml) was slowly added, followed by water (35 ml). The resulting white precipitate was filtered and washed several times with ether. The filtrate was dried ($MgSO_4$) and evaporated to yield fenchol (90.1 g, 90 % yield): m.p., 26-30° (*exo*-fenchol, m.p., 6.3°; *endo*-fenchol m.p., 38-39°).[183] Less than 5 % of *exo*-fenchol was detectable by n.m.r. N.m.r. (# 91, CCl_4/TMS, A-60): $\delta = 0.80$, 0.92, 1.01 (3s., 3H each, methyl groups); $\delta = 3.15$ (d., 1H, *exo*-C_2-H); $\delta = 1.50$ (s., 1H, OH). I.R. (# 84, neat): 3400 cm^{-1} (OH). V.p.c. (# 175, 5 % SE-30, 10', 150°): fenchol (r.t. 1.3 min., *ca.* 94 %) and a minor component (r.t. 2.0 min., *ca.* 6 %).

Acetylation of fenchol

The above fenchol (95 g, 0.58 mole) was dissolved in pyridine (400 ml) and acetic anhydride (250 ml). The solution was left standing at room temperature for 24 hours, after which it was poured into 1500 ml of crushed-ice. After the ice melted, the solution was diluted to 1.6 *l*. with water. It was then extracted with ether (3 x 200 ml). The combined ether extracts were washed with water (100 ml), hydrochloric acid (10 %, 100 ml) until free of pyridine, water (2 x 100 ml), a bicarbonate solution (sat., 100 ml) and finally, a sodium chloride solution (sat., 100 ml). After drying ($MgSO_4$), solvent evaporation yielded fenchyl acetate (46) (105 g, 96 % yield). N.m.r. (# 92, CCl_4/TMS, A-60): $\delta = 0.70, 0.98, 1.03$ (3s., 3H each, methyl groups); $\delta = 1.92$ (s., 3H, acetate methyl); $\delta = 4.25$ (d., 1H, *exo*-C_2H). I.R. (# 85, neat): 1740 cm^{-1} (C=O); 1250 cm^{-1} (acetate). V.p.c. (# 176, 5 % SE-30, 10', 150°): fenchyl acetate (r.t. 1.9 min., *ca*. 97 %) and a minor component (r.t. 2.4 min., *ca*. 3 %).

5-Oxofenchyl acetate (48)[63]

Fenchyl acetate, 46, (50 g, 0.25 mole) was dissolved in Ac_2O (175 ml) and acetic acid (175 ml), and was placed in a 1 *l*. 3-necked flask, fitted with a condenser and a mechanical stirrer. The solution was brought to reflux and was stirred vigorously. Solid chromium trioxide (70 g) was then added over a period of 1½ hour, after which the mixture was further refluxed for 2 hours. After cooling, the mixture was diluted with water to *ca*. 1.5 *l*. and extracted with ether (3 x 200 ml). The combined ether extracts were washed with water (100 ml), a bicarbonate solution (sat., 100 ml) until free of acetic acid, and a

sodium chloride solution (sat., 100 ml). Drying ($MgSO_4$) and solvent evaporation yielded 43.2 g of oil. The unreacted fenchyl acetate (22.8 g) was distilled through a vacuum-jacketed Vigreux column. V.p.c. analysis (# 177, 5 % SE-30, 5', 140°) on the residue (20.3 g, 35 % yield): 5-oxofenchyl acetate, 48 (r.t. 3.4 min., *ca.* 90 %), a higher boiling component (r.t. 6.6 min., *ca.* 10 %), traces of fenchyl acetate (r.t. 1.8 min.) and some other compounds (r.t. 5.1 min.). N.m.r. (# 93, CCl_4/TMS, A-60): δ = 0.70, 1.18, 1.22 (3s., 3H each, methyl groups); δ = 2.02 (s., 3H, acetate methyl); δ = 4.50 (d., 1H, *exo*-C_2-H). I.R. (# 86, CCl_4): 1750 cm^{-1} (C=O); 1240 cm^{-1} (acetate).

5-Oxofenchol (50)[56,66]

The above ketoacetate 48 (20 g) was transfered using a little ethanol to a flask containing potassium carbonate (37 g) dissolved in water (300 ml). The mixture was refluxed overnight. After cooling, the solution was extracted with ether (2 x 200 ml). The aqueous phase was then saturated with ammonium chloride and extracted again with ether (2 x 100 ml). The combined ether extracts were washed with a sodium chloride solution (sat., 2 x 75 ml). After drying ($MgSO_4$), evaporation of solvent gave 13.9 g of crude 5-ketofenchol, 50 (87 % yield). I.R. (# 87, CCl_4): 3640, 3450 cm^{-1} (OH); 1745 cm^{-1} (C=O). Purification was achieved by recrystallization from pentane: m.p., 75-76° (reported, [66] 76-77.5°). N.m.r. (# 12, 56, CCl_4/TMS, T-60, A-60): δ = 0.74, 1.04, 1.15 (3s., 3H each, methyl groups); δ = 3.52 (d., 1H, *exo*-C_1-H).

2) Preparation of fenchane-2,5-dione (25)[57]

The oxidizing reagent was prepared by dissolving $K_2Cr_2O_7$ (16.1 g) in concentrated sulfuric acid (12.5 ml), and diluting to 82 ml with water.

Crude 5-ketofenchyl alcohol, 50, (27.5 g, 0.16 mole) was dissolved in ether (65 ml, previously treated with the oxidizing reagent), and placed in a 3-necked flask, fitted with a condenser, an adding funnel, and a magnetic stirrer. The reagent was added slowly over a period of 20 minutes, maintaining the temperature around 25°. The mixture was then stirred for 2 hours. The two layers were then separated. The aqueous layer was extracted twice with ether, and the combined ether layers were washed twice with a bicarbonate solution. The combined aqueous layers were saturated with sodium chloride and extracted twice with ether. The combined ether solutions were dried ($MgSO_4$) and evaporated to give 26.1 g of oil (90 % yield). Crystallization in pentane and sublimation gave a solid melting at 43° (reported:[66] m. p., 41-42°). N.m.r. (# 14, 57, CCl_4/TMS, T-60, A-60): δ = 0.90, 1.04, 1.12 (3s., 3H each, methyl groups); δ = 1.90 {m. (narrow), 4H}; δ = 2.40 (broad s., 1H, bridgehead). I.R. (# 17, CCl_4): 3500 cm^{-1} (overtone to carbonyl); 1757 cm^{-1}* (C=O).

3) Preparation of 1-methyl-5-oxocamphene (28) (Scheme II-6)

5-Ethylenedioxyfenchol

Crude 5-ketofenchol, 50), (5.3 g, 31 mmoles) was dissolved in

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* Perkin-Elmer 521.

benzene (530 ml, previously distilled from lithium aluminium hydride). Ethylene glycol (8 ml) and *p*-toluenesulfonic acid (0.53 g) were added and the solution was refluxed for 20 hours, with magnetic stirring and a Dean-Stark water separator. After cooling, the benzene solution was quenched with a bicarbonate solution (sat., 100 ml). The benzene solution was then washed with a sodium chloride solution (sat.) and dried ($MgSO_4$). Evaporation of the benzene gave 6.6 g of oil (100 % yield). V.p.c. analysis (# 111, 5 % SE-30, 10', 175°): 5-ethylenedioxyfenchol (r.t. 7.1 min., *ca.* 90 %) and starting material (r.t. 3.9 min., *ca.* 10 %). Purification by preparative v.p.c. (# 114, 20 % SE-30, 5' x ¼", 175°), followed by bulb to bulb distillation gave an analytical sample:

	C	H
Found :	67.97 %	9.62 %
Calculated:	67.89 %	9.50 %

N.m.r. (# 58, CCl_4/TMS, T-60): $\delta = 1.06$ (s., 6H, methyl groups); $\delta = 1.10$ (s., 3H, methyl group); $\delta = 3.24$ (d., 1H, C_2-H); $\delta = 3.85$ (m., 4H, ketal). I.R. (# 110, CCl_4): 3620, 3500 cm^{-1} (OH).

5-Ethylenedioxyfenchone (58)[184,185]

The oxidizing reagent was prepared by adding pyridine (72 ml) to chromium trioxide (7.2 g, 72 mmoles) dissolved in water (7.2 ml) in an ice bath. The reagent was added to the alcohol (4.4 g, 25 mmoles) and the mixture was left standing at room temperature for 17 hours. The mixture was then diluted with water to 800 ml and was extracted with ether (4 x 100 ml). The combined ether extracts were washed with water (6 x 50 ml) to remove as much pyridine as possible, and then

with a sodium chloride solution (sat., 50 ml). After drying ($MgSO_4$), the ether was evaporated, and the remaining pyridine was distilled under vacuum. There remained 4.1 g of ketone 58 (94 % yield). V.p.c. analysis (# 113, 5 % SE-30, 10', 175°): ketone 58 (r.t. 6.1 min., *ca.* 85-90 %), starting material (r.t. 6.9 min., *ca.* 2 %) and another component, probably fenchane-2,5-dione (r.t. 2.4 min., *ca.* 10 %). Purification by preparative v.p.c. (# 115, 20 % SE-30, 5' x ¼", 175°) followed by bulb to bulb distillation, gave the following analytical sample:

	C	H
Found :	68.49 %	8.88 %
Calculated:	68.54 %	8.62 %

N.m.r. (# 60, 44, CCl_4/TMS, T-60, A-60): δ = 3.98 (m., 4H, ketal); δ = 1.08, 1.01, 0.98 (3s., 3H each, methyl groups). I.R. (# 59, CCl_4): 1750 cm^{-1} (C=O).

1-Methyl-5-ethylenedioxycamphene (59)[186]

A flow of dry nitrogen was passed through the reaction mixture during the preparation of the ylide. *n*-Butyl lithium (2.54 g, in 5 ml hexane, 20 mmoles) was added to a mixture of triphenylmethylphosphonium bromide (7.2 g, 20 mmoles) in hexane (70 ml, purified as follows: reagent grade hexane was treated with concentrated sulfuric acid, then with permanganate. After washing with water, the hexane was filtered through a column of alumina and then distilled). The mixture was stirred magnetically for 4 hours. 5-Ethylenedioxyfenchone 58 (4.1 g, 20 mmoles) in hexane (30 ml, purified as above) was then slowly added, and the resulting mixture was refluxed for 24 hours. After cooling, the

solids were filtered and the hexane solution was washed with water until neutral. Drying ($MgSO_4$), and evaporation of solvent yielded 3.3 g (80 %) of 1-methyl-5-ethylenedioxycamphene (59).
V.p.c. analysis (# 117, 5 % SE-30, 10', 170°): compound 59 (r.t. 3.8 min.) was *ca.* 95 % pure. Purification by preparative v.p.c., followed by bulb to bulb distillation, gave the following analytical sample:

	C	H
Found :	74.07 %	9.91 %
Calculated:	74.25 %	9.59 %

N.m.r. (# 61, CCl_4/TMS, T-60): δ = 1.02, 1.12, 1.26 (3s., 3H each, methyl groups); δ = 3.88 (m., 4H, ketal); δ = 4.60 (d., 2H, olefin).
I.R. (# 64b, neat): 3070 cm^{-1} (C-H olefinic); 1650 cm^{-1} (C=C); 880 cm^{-1} (C=C).

1-Methyl-5-oxocamphene (28)

1-Methyl-5-ethylenedioxycamphene (59) (0.3 g, 1.4 mmole) was dissolved in aqueous acetone (90 %, 10 ml), and one drop of concentrated hydrochloric acid was added. The solution was stirred magnetically at room temperature for *ca.* 24 hours. The reaction mixture was then diluted with water to 50 ml, and 3-4 drops of sodium hydroxide (10 %) were added. The solution was saturated with sodium chloride, and then extracted twice with ether. The combined ether extracts were washed once with water and once with a sodium chloride solution (sat.). After drying ($MgSO_4$), 0.1 g of oil was obtained (45 %). V.p.c. analysis (# 105, 5 % SE-30, 10', 160°): 1-methyl-5-oxocamphene 28 (r.t. 3.1 min., *ca.* 90 %) and starting material (r.t. 6.5 min., *ca.* 10 %).

Purification by preparative v.p.c. (# 115, 20 % SE-30, 5', 150°) gave the following sample: M.S. (# 94). Parent peak M/e = 164 as per the molecular weight for this compound. N.m.r. (# 64, CCl_4/TMS, T-60): δ = 1.02, 1.10, 1.28 (3s., 3H each, methyl groups); δ = 4.82 (d., 2H, olefin). I.R. (# 61, neat): 3060 cm^{-1} (C-H olefinic); 1750 cm^{-1} (C=O); 1640 cm^{-1} (w., C=C); 880 cm^{-1} (C=C).

Confirmation of structure of 1-methyl-5-oxocamphene (28)

Oxidation[187] to fenchane-2,5-dione (25)

1-Methyl-5-oxocamphene (150 mg, 0.9 mmole) was dissolved in acetone-water (50 %, 10 ml). Potassium periodate (4 g) was added and the mixture was cooled in an ice-water bath. Potassium permanganate (0.2 g) in water (*ca.* 3 ml) was added, with magnetic stirring, dropwise over a period of 10 minutes. The reaction mixture was then stirred for 4 hours at room temperature. The mixture was then filtered, and the filtrate was diluted to 100 ml with water and extracted with ether (3 x 25 ml). The combined ether extracts were washed with water, and a solution of sodium chloride (sat.). Drying ($MgSO_4$) and evaporation gave a compound which was identified to be fenchane-2,5-dione by comparison with an authentic sample (v.p.c. # 127, I.R. # 69, 70).

4. Preparation of epiisofenchone (23) (Scheme II-2)

Dehydration of fenchol (37)[53]

Potassium hydrogen sulfate was fused in a vacuum oven at 200° and at aspirator pressure.

Fenchol (Pfaltz and Bauer Inc., 75 g, 0.49 mole) was carefully

mixed with fused grounded potassium bisulfate (225 g). The mixture was transfered to a 500 ml 3-necked flask, and the flask was placed in an oil bath. A stream of nitrogen swept the reaction mixture throughout. The oil bath was very slowly heated, allowing the hydrocarbons produced to distill. After 5 hours, the oil bath temperature had reached 230° and the reaction was stopped.

The distillate was dissolved in pentane (50 ml), and the solution was washed with a sodium hydroxide solution (dil., 20 ml), water (20 ml), and a sodium chloride solution (sat., 20 ml), and was dried ($MgSO_4$).

After cooling, the potassium bisulfate residue was extracted with pentane (500 ml). This pentane solution was filtered with sodium hydroxide (dil., 75 ml), water (75 ml) and sodium chloride (sat., 75 ml). After drying ($MgSO_4$), most of the pentane was removed with the aspirator.

The two pentane solutions were combined and distilled at atmospheric pressure through a 4" vacuum-jaketed Vigreux column. The hydrocarbon portion (35.7 g, 54 % yield) boiled between 147° and 171°. V.p.c. analysis (# 133, 10 % Carbowax, 10', 80-190°): *ca.* 95 % of 7 low boiling components and *ca.* 5 % of higher boiling components (alcohols).

Reaction of the fenchenes with acid[188]

A mixture of the fenchenes (71 g, 0.5 mole) was dissolved in acetic acid (glacial, 500 ml). Sulfuric acid (50 %, 40 ml) was added and the solution was stirred at room temperature for 24 hours. The solution was then diluted with water to 1.8 *l.*, and extracted with pentane(3 x 200 ml). The combined pentane extracts were washed with

bicarbonate (sat., 2 x 100 ml), with water (100 ml), and a solution of sodium chloride (sat., 100 ml). After drying ($MgSO_4$), the pentane was evaporated, and the mixture of acetates distilled through a 4" vacuum-jacketed Vigreux column to yield 81.9 g (82 %) of acetates: b.p., 122-130°(50mm). V.p.c. analysis (# 135, 10 % Carbowax, 10', 150°): a mixture of *ca.* 5 compounds, one of which consisting of *ca.* 60 % of the mixture.

Hydrolysis of the acetates[56]

The mixture of acetates (81 g, 0.4 mole) was dissolved in methanol (80 %, 1.2 *l.*) containing potassium carbonate (160 g). After refluxing for 12 hours, the solution was diluted to 3.5 *l.* The solution was then divided into two and each portion was extracted with pentane (3 x 200 ml). The combined pentane extracts were washed with water (2 x 200 ml), and with a sodium chloride solution (sat., 200 ml). After drying ($MgSO_4$) the pentane was removed over the aspirator to yield 74 g of a mixture of compounds. V.p.c. analysis (# 137, 10 % Carbowax, 10', 150°): one major peak (r.t. 10.5 min., *ca.* 85 %).

Oxidation[57] of the alcohols

The oxidizing reagent was prepared by dissolving $Na_2Cr_2O_7 \cdot 2H_2O$ (40 g) in sulfuric acid (conc., 40 ml), and diluting the solution with water to 200 ml. The ether was treated with the reagent, washed with water, dried ($MgSO_4$) and distilled before use.

The above mixture of alcohols (74 g, 0.48 mole) was dissolved in ether (160 ml) and placed in a 500 ml 3-necked flask, fitted with

condenser, mechanical stirrer and adding funnel. The oxidizing reagent (200 ml) was added over a period of 30 minutes, maintaining the temperature at *ca.* 20° (tap water temperature). The reaction mixture was stirred for another 3 hours at room temperature. The ether layer was then separated, and the aqueous layer was extracted with ether (2 x 50 ml). The combined ether solutions were washed with bicarbonate (sat., 2 x 75 ml), with water (75 ml), and with a sodium chloride solution (sat., 75 ml). After drying ($MgSO_4$), the ether was evaporated to yield 70 g (95 %) of a mixture. V.p.c. analysis (# 139, 10 % Carbowax, 10', 150°): a mixture of 6 compounds, one of which (r.t. 6.4 min.) accounts for *ca.* 60% of the mixture.

Semicarbazone[58] of isofenchone (12)

A stock solution of semicarbazide hydrochloride was prepared by dissolving the compound (55.5 g) in water (250 ml) and filtering. One ml of the solution contains 2 mmoles of semicarbazide hydrochloride.

The above mixture of ketones (65 g) was added to the semicarbazide hydrochloride solution (215 ml). Enough ethanol was added to make the solution clear and homogeneous. Pyridine (35 ml) was added and the solution was warmed on the steam bath until some crystals started to form. The solution was then cooled in ice and 49.5 g of crystals were collected (m.p., 211-215°). The crystals were recrystallized 5 times from ethanol-water mixtures. There resulted 18 g of crystals melting at 225-227°. For the semicarbazone of isofenchone, m.p., 217-218°,[189] or m.p., 222°.[190] I.R. (# 76, $CHCl_3$): 3520, 3400,

3375, 2910, 2860, 1675, 1560 and 1080 cm^{-1}. N.m.r. (# 80, 81, d_6-DMSO, T-60): δ = 6.25 (broad s., 2H, NH_2); δ = 1.31, 1.20, 1.06 (3s., 3H each, methyl groups).

Isofenchone (12)

The semicarbazone (16.5 g, 0.09 mole) was dissolved in benzene (500 ml). Dilute hydrochloric acid (2.4 *N.*, 100 ml) was added and the mixture was refluxed with stirring for 24 hours. After cooling, the layers were separated. The benzene layer was washed with bicarbonate (sat., 2 x 75 ml), with water (75 ml) and with a sodium chloride solution (sat., 75 ml). After drying ($MgSO_4$), evaporation of solvent and distillation gave 10.0 g (73 %) of isofenchone. V.p.c. analysis (# 155, 10 % Carbowax, 10', 155°) indicated the purity to be *ca.* 95 %. N.m.r. (#79, benzene/TMS, A-60): δ = 0.95, 1.01, 1.10 (3s., 3H each, methyl groups). I.R. (# 79, CCl_4): 1750 cm^{-1} (C=O). All spectra compared with those of an authentic sample[191] (v.p.c. # 155, n.m.r. # 63, I.R. # 80).

Isofenchoquinone (39)[59]

Isofenchone (10.0 g, 66 mmoles) was dissolved in glacial acetic acid (200 ml). Selenium dioxide (8 g) was added and the mixture was refluxed for 48 hours. The solution was then cooled, filtered, and diluted to 1.5 *l.* with water. It was extracted with ether (3 x 200 ml). The combined ether extracts were washed with bicarbonate (sat.) until the ether layer was free of acetic acid, with water (100 ml) and with a solution of sodium chloride (sat., 100 ml). After drying ($MgSO_4$), evaporation of solvent gave 11.4 g of a semi-

solid. V.p.c. analysis (# 158, 5 % SE-30, 10', 190°): quinone 39 (r.t. 2.9 min., *ca.* 90 %), starting material (r.t. 2.1 min., *ca.* 5 %), and some other impurity (r.t. 3.4 min., *ca.* 5 %). N.m.r. (# 82, CCl_4/TMS, T-60): δ = 1.0, 1.1, 1.2 (3s., methyl groups). I.R. (# 78, neat): 1745 cm^{-1} (C=O).

Dithioketal 40[59]

The above mixture (11.4 g) was dissolved in ethane-dithiol (7.2 ml). Boron trifluoride etherate (72 ml) was added, and the solution was left standing for 10 hours. Water (100 ml) was then added, and the resulting mixture was decanted. The aqueous solution was extracted with ether (2 x 100 ml). The combined ether extracts were washed with sodium hydroxide (1 *N.*, 50 ml) until alkaline, with water (50 ml), and finally with a sodium chloride solution (sat., 50 ml). After drying ($MgSO_4$), the ether was removed to yield 9.6 g of oil. V.p.c. analysis (# 159, 5 % SE-30, 10', 227°) showed 3 products in the following ratio: 4 % (r.t. 1.3 min.); 49 % (r.t. 5.1 min.); and 48 % (r.t. 7.1 min.). Filtration on alumina (Fisher Scientific Co., Brockman activity 1, 80-200 mesh, 200 g) and eluting with petroleum ether, then ether, gave as a second fraction, 4.3 g of a white solid, m.p., 74-75° (reported,[59] m.p., 96°). V.p.c. analysis (# 160, 5 % SE-30, 10', 225°): dithioketal 40 (r.t. 4.0 min.), *ca.* 98 % pure. N.m.r. (# 83, CCl_4/TMS, A-60): δ = 1.05, 1.10, 1.30 (3s., 3H each, methyl groups); δ = 3.35 (m., 4H, dithioketal). I.R. (# 81, CCl_4): 1745 cm^{-1} (C=O).

Preparation of Raney-Nickel (W-4)[192,193]

Sodium hydroxide (64 g) was dissolved in water (250 ml) and placed in an erlenmeyer flask, which was placed in a water bath at 50°. The nickel-aluminium alloy (50 g) was added with magnetic stirring, keeping the temperature at 50 ± 5°. After the addition, the alloy was digested for 50 minutes at 50 ± 2°.

The mixture was then transfered to a 500 ml graduated cylender. The aqueous phase was decanted and the cylinder was filled with distilled water. This procedure was repeated until the water was neutral. The Raney-Nickel was then rinsed in the same manner, several times with absolute ethanol. The Raney-Nickel thus prepared, was stored in the refregerator, under absolute ethanol.

Epiisofenchone (23)[59]

The dithioketal 40 prepared above (4.3 g, 18 mmoles), was dissolved in absolute ethanol (70 ml), and 3 spoonfulls of Raney-Nickel were added. The mixture was refluxed for 19 hours. After cooling, the solution was filtered and diluted to 200 ml with water. It was then extracted with pentane (3 x 50 ml). The combined pentane extracts were washed with water (50 ml) and a solution of sodium chloride (sat., 50 ml). Drying ($MgSO_4$), and evaporation of solvent gave 1.7 g (62 %) of epiisofenchone. V.p.c. analysis (# 162, 10 % Carbowax, 10', 125°): epiisofenchone 23 (r.t. 8.8 min.), 97 % pure, with some 2.5 % of isofenchone (r.t. 9.3 min.). There was no fenchone present (r.t. 7.6 min.). I.R. (# 82, neat): 1750 cm^{-1} (C=O); 1405 cm^{-1} (CH_2 α to C=O). N.m.r. (# 84, CCl_4/TMS, T-60): δ = 1.02,

1.19, 1.30 (3s., 3H each, methyl groups); δ = 1.30-2.30 (m., 7H).

5. Preparation of 5-oxocamphenilol (49) (Scheme II-4)

Camphenilone (42); method A[61, 62]

Camphene (43) (Aldrich Chemical Co., 79 % camphene, 21 % tricyclene, 150 g, 0.88 mole of camphene) was dissolved in ether (2 *l.*) and placed in a 3*l.* 3-necked flask, fitted with a pressure equalizing funnel with drying tube, a mechanical stirrer, and a gas inlet tube. Nitrogen swept the reaction mixture throughout the reaction time. The flask was placed in an ice-water bath. Dinitrogen tetroxide (Matheson Co., 0°, 100 ml), dissolved in ether (500 ml), was added dropwise, with stirring, over a period of 3 hours. The reaction mixture was then stirred for another 2 hours at 0°. Sodium bicarbonate (sat., 500 ml) was then added, and after stirring for a few minutes, the two phases were separated. The ether layer was washed with water and dried ($MgSO_4$). Evaporation of solvent yielded 233 g of oil.

The oil was dissolved in ethanol (500 ml), and was added to a solution of sodium hydroxide (250 g) in water (2 *l.*). The resulting mixture was gently refluxed for 2½ hours. The solution was then steam distilled and the distillate was extracted with pentane. Evaporation of the dried pentane solution, followed by distillation, gave 69 g (57 %) of camphenilone (42): b.p., 49-51° (2.5 mm); m.p., 34-37° (reported,[61, 62] m.p., 38-38.5° or 38-39°). V.p.c. analysis (# 3, 10 % Carbowax, 5', 175°) showed the purity to be *ca.* 95 %. I.R. (# 2, neat): 1745 cm^{-1} (C=O).

Camphenilone (42); method B[60]

Camphene (43) (Aldrich Chemical Co., 79 % camphene, 21 % tricyclene, 100 g, 0.58 mole of camphene) was dissolved in absolute methanol (600 ml) and placed in a 1 *l.* 3-necked flask, fitted with a mechanical stirrer, a drying tube ($CaCl_2$) and a gas inlet tube. The flask was placed in a dry-ice-acetone bath, and ozone (3 % by weight in oxygen) was bubbled through for 5 hours, until the solution turned blue. Ozone was produced using a Welsbach Ozonizer, Model T-408. The excess ozone was removed by passing oxygen through the solution. The cold solution was then added to sodium iodide (300 g) in methanol (500 ml) and glacial acetic acid (115 ml). The mixture was then warmed to room temperature, and aqueous thiosulfate was added to reduced the iodine produced. The resulting solution was diluted to *ca.* 3.5 *l.* with water, and was divided into two parts. Each part was extracted with pentane (3 x 100 ml). The combined pentane extracts were washed with a bicarbonate solution (sat., 100 ml), water (100 ml) and a solution of sodium chloride (sat., 100 ml). After drying ($MgSO_4$), the pentane was evaporated and the mixture was distilled through a 5" Vigreux column, using an air-cooled condenser, to give 40.4 g of camphenilone (42) (50 %): b.p., 49-51° (2.5 mm); m.p., 35-37° (reported,[61,62] m.p., 38-38.5° or 38-39°). V.p.c. analysis (# 136, 5 % SE-30, 10', 165°): camphenilone (42), better than 95 % pure. I.R. (# 71, CCl_4): 1745 cm^{-1} (C=O). N.m.r. (# 70, CCl_4/TMS, A-60): δ = 0.95, 0.99 (2s., 3H each, methyl groups).

Camphenilol

All glassware was oven dried before use. The ether was distil-

led from lithium aluminium hydride.

Camphenilone (90 g, 0.65 mole) was dissolved in ether (300 ml) and was slowly added to a slurry of lithium aluminium hydride (50 g) in ether (150 ml). The mixture was then refluxed for 1½ hour. The reaction vessel was then put in an ice-water bath, and water (300 ml) was slowly added, as well as some ether to compensate for evaporation losses. Hydrochloric acid (10 %, 300 ml) was then added to dissolve the inorganic salts. The layers were separated. The aqueous layer was extracted with ether, and the dried solvent was evaporated to give 86.3 g (95 %) of a solid melting at 68-71° (reported,[194] m.p., 76°). V.p.c. analysis (# 5, 5 % Carbowax, 5', 175°): Camphenilol (r.t. 1.0 min.), better than 95 % pure. I.R. (# 4, CCl_4): 3630, 3470 cm^{-1} (OH); no carbonyl absorption. N.m.r. (# 1, CCl_4/HDMS, A-60): δ = 0.78, 0.90 (2s., 3H each, methyl groups); δ = 2.18, 2.56 (2 broad s., 1H each, bridgeheads); δ = 3.52 (broad s., 1H, C<u>H</u>OH).

<u>Camphenilyl acetate</u> (<u>45</u>)

Camphenilol (89 g, 0.63 mole) was dissolved in pyridine (400 ml) and acetic anhydride (250 ml). The solution was left standing at room temperature for 28 hours. The reaction mixture was then added to crushed ice (200 ml), and it was extracted several times with ether. The combined ether extracts were washed free of pyridine with dilute hydrochloric acid. They were then washed with bicarbonate (sat.) and water. After drying ($MgSO_4$), evaporation of solvent gave 100 g (87 %) of camphenilyl acetate (<u>45</u>): b.p., 70-74° (4 mm). V.p.c. analysis (# 9, 10 % Carbowax, 5', 150°): the acetate <u>45</u> was *ca.* 95 % pure. I.R.

(# 5, neat): 1740 cm^{-1} (C=O); 1250 cm^{-1} (acetate). N.m.r. (# 2, CCl_4/TMS, A-60): δ = 0.81, 0.99 (2s., 3H each, methyl groups); δ = 1.90 (s., 3H, acetate); δ = 4.45 (d., 1H, *exo*-C_2H).

5-Ketocamphenilyl acetate (47)[56,64,65]

Camphenilyl acetate (39 g, 0.21 mole) was dissolved in acetic acid (300 ml), and was placed in a 1 *l*. 3-necked flask, fitted with a condenser and a mechanical stirrer. The solution was brought to reflux and stirred vigorously. Solid chromium trioxide (100 g) was added over a period of 50 minutes, and the mixture was refluxed for another 2 hours. After cooling, the mixture was diluted to *ca.* 1.6 *l*. with water, and was extracted with ether (4 x 200 ml). The combined ether extracts were washed with water (200 ml), sodium hydroxide (dil., 200 ml), water (2 x 200 ml) and finally, with sodium chloride (sat., 200 ml). After drying ($MgSO_4$) and solvent evaporation, the unreacted camphenilyl acetate was distilled under vacuum. The residue was recrystallized from pentane. There resulted 9.6 g (24 %) of crystals melting at 62-64° (reported,[64] m.p., 65.0-65.5°). V.p.c. analysis (# 143, 5 % SE-30, 10', 165°): 5-ketocamphenilyl acetate (r.t. 7.1 min.) was essentially pure with traces of camphenilyl acetate (r.t. 3.5 min.). I.R. (# 74, CCL_4): 1740 cm^{-1} (C=O); 1240 cm^{-1} (acetate); 1055, 1020 cm^{-1}. N.m.r. (# 74, CCl_4/TMS, T-60): δ = 0.8, 1.2 (2s., 3H each, methyl groups); δ = 2.0 (s., 3H, acetate); δ = 4.8 (d., 1H, *exo*-C_2H).

5-Oxocamphenilol (49)[56]

5-Ketocamphenilyl acetate (9.8 g, 50 mmoles) was added to a solution of potassium carbonate (24 g) in water (200 ml). The solution

was stirred vigorously for one hour in a boiling water bath. After cooling, the yellow-brown mixture was extracted 3 times with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to 7.0 g of oil (90 %). Crystallization in ether-petroleum ether afforded crystals melting at 68-71°. V.p.c. analysis (# 17b, 10 % Carbowax, 5', 175°) showed 5-oxocamphenilol to be *ca.* 90 % pure. Purification of an analytical sample by preparative v.p.c. (# 305, 20% SE-30, 5', 120°), followed by sublimation gave a solid melting at 139-139.5°. Analysis:

	C	H
Found :	70.06 %	9.10 %
Calculated:	70.10 %	9.15 %

N.m.r. (# 90, CCl_4/TMS, A-60): $\delta = 3.88$ (d. of d., 1H, *exo*-C_2H); $\delta = 3.20$ (s., broad, 1H, OH); $\delta = 2.60$ (unresolved m., 1H, C_1H); $\delta = 1.10$, 0.82 (2s., 3H each, methyl groups). I.R. (# 65): 3400 cm^{-1} (OH); 1740 cm^{-1} (C=O).

6. Preparation of 5-oxocamphenilone (26)

Oxidation[57] of 5-oxocamphenilol (49)

The ether was treated with the reagent before use. The oxidizing reagent was prepared by dissolving potassium dichromate (5 g) in water (22 ml) and adding sulfuric acid (conc., 3.8 ml). Crude 5-oxocamphenilol (6.7 g, 34 mmoles) was dissolved in ether (20 ml). The reagent was added with magnetic stirring over a period of 30 minutes, maintaining the temperature of the reaction mixture at 25°. The reaction mixture was then stirred at room temperature for another 3 hours. The layers were then separated and the aqueous phase was extracted several times with ether. The combined ether layers were washed with bicarbonate

(sat.), then water. After drying ($MgSO_4$), the solvent was evaporated to yield 4.8 g of material. V.p.c. analysis (# 18, 10 % Carbowax, 5', 175°) indicated the dione to be *ca.* 90 % pure. This material was then chromatographed on silica gel (Davidson Chemicals, grade 923) to yield 3.1 g (60 %) of white crystals. V.p.c. analysis (# 21, 10 % Carbowax, 5', 175°) indicated the dione to be better than 95 % pure. Sublimation gave crystals melting at 55-58°. Analysis:

	C	H
Found :	71.36 %	7.67 %
Calculated:	71.03 %	7.95 %

N.m.r.: *cf.* Fig. II-8. I.R. (# 9, CCl_4): 3500 cm^{-1} (overtone to C=O); 1750 cm^{-1} (C=O).

7. Preparation of 5-oxocamphene (29)

Preparation of 5-ethylenedioxycamphenilol

Crude 5-oxocamphenilol (49) (5 g, 32 mmoles) was dissolved in benzene (500 ml, previously distilled from lithium aluminium hydride). Ethylene glycol (7.5 ml) and *p*-toluenesulfonic acid (0.5 g) were added, and the mixture was refluxed for 15 hours, using a Dean-Stark water separator. After cooling, the mixture was added to sodium bicarbonate (sat., 200 ml). The benzene solution was then washed with water (200 ml) and sodium chloride (sat., 200 ml). Drying ($MgSO_4$) and evaporation of solvent gave 4.5 g of oil (74 %). V.p.c. analysis (# 148, 5 % SE-30, 10', 175°): only one peak (r.t. 13.2 min.). N.m.r. (# 78, CCl_4/TMS, A-60): $\delta = 3.30$ (s., 1H, OH); $\delta = 3.80$ (m., 4H, ketal); $\delta = 1.02$ (s., 6H, methyl groups). I.R. (# 77, CCl_4): 3620, 3460 cm^{-1} (OH). Purification by preparative v.p.c. (# 147, 20 % SE-30, 5', 175-180°), followed

by bulb to bulb distillation, gave an analytical sample:

	C	H
Found :	66.38 %	9.12 %
Calculated:	66.64 %	9.15 %

5-Ethylenedioxycamphenilone

The oxidizing reagent[184,185] was prepared by adding chromium trioxide (6.1 g) in water (61 ml), to ice-cold pyridine (288 ml). This solution was added to the above alcohol (4 g, 21 mmoles). The resulting solution was left standing at room temperature for *ca.* 24 hours. It was then added to ice (500 ml) and the mixture was diluted to 1.5 l. with water. This solution was extracted with ether (3 x 200 ml). The ether extracts were washed with water (200 ml), dilute hydrochloric acid (200 ml) until free of pyridine, water (200 ml), bicarbonate (sat., 200 ml), and finally, water again (200 ml). After drying ($MgSO_4$), evaporation of solvent gave 3.5 g of oil (85 %). V.p.c. analysis (# 157, 5 % SE-30, 10', 185°) showed the ketoketal (r.t. 6.2 min.) to be better than 95 % pure. N.m.r. (# 85, CCl_4/TMS, A-60): $\delta = 3.87$ (m., 4H, ketal); $\delta = 1.18$, 1.05 (2s., 3H each, methyl groups). I.R. (# 83, neat): 1750 cm^{-1} (C=O). Purification by preparative v.p.c. (# 163, 30 % SE-30, 5', 190-200°), followed by bulb to bulb distillation gave the following analytical sample:

	C	H
Found :	67.23 %	8.19 %
Calculated:	67.32 %	8.22 %

5-Oxocamphene (29)

The ylide was prepared[186] using triphenylmethyl phosphonium bromide (3.6 g) in hexane (20 ml, dried by filtration on alumina). A

stream of nitrogen swept the reaction mixture throughout. Butyllithium (2.8 ml *ca.* 1.5 *M.* in hexane) was added and the mixture was stirred at room temperature for 4 hours. The above ketone (1.5 g), in hexane (20 ml) was then added and the mixture was refluxed overnight. The solids were then filtered, and the hexane solution was washed with water until neutral. After drying ($MgSO_4$), the solvent was evaporated, and the compound was hydrolysed.

The above reaction products were added to aqueous acetone (90 %, 75 ml) and hydrochloric acid (conc., 5 drops) was added. The mixture was stirred at room temperature for 1½ day. It was then diluted with water and extracted with ether. The ether extracts were dried and concentratred. 5-Oxocamphene was isolated by preparative v.p.c. (# 216, 20 % SE-30, 120-125°), m.p., 61-63°. N.m.r. (# 97, CCl_4/TMS, T-60): δ = 4.85 (d., 2H, methylene group); δ = 3.05 (broad s., 1H, bridgehead); δ = 2.4-1.5 (m., 5H); δ = 1.12, 1.07 (2s., 3H each, methyl groups). I.R. (# 90, CCl_4): 3050 cm^{-1} (CH, olefin); 1745 cm^{-1} (C=O); 890, 1650 cm^{-1} (C=C). M.S. (# 214): parent peak at M/*e* = 150, as per the molecular weight of this compound.

Confirmation of structure of 5-oxocamphene (29)

Oxidation[187] to 5-oxocamphenilone (26)

5-Oxocamphene (63 mg) was dissolved in aqueous acetone (50 %, 7 ml) and KIO_4 (2 g) was added to the solution. The mixture was cooled in ice-water and was stirred magnetically. $KMnO_4$ (100 mg) in water (*ca.* 2 ml) was added dropwise over a period of 10 minutes, after which the mixture was warmed to room temperature and stirred for an additio-

nal 6 hours. It was then diluted to 100 ml with water, and extracted with ether (3 x 25 ml). The ether extracts were washed with water (2 x 25 ml), sodium chloride (sat., 25 ml), and dried ($MgSO_4$). After evaporation of solvent, the following v.p.c. analysis was performed (# 217, 5 % SE-30, 130°):

- 5-oxocamphene (29) : r.t. 7.8 min.
- 5-oxocamphenilone (26) : r.t. 10.4 min.
- oxidation product (above) : r.t. 10.5 min.
- 5-oxocamphene & 5-oxocamphenilone : 2 peaks: r.t. 7.9 & 10.4
- oxidation product & 5-oxocamphenilone: 1 peak : r.t. 10.6 min.

Purification of the oxidation product by preparative v.p.c. (# 218, 20 % SE-30, 5', 120°) gave a compound whose I.R. (# 91) was superimposable on that of an authentic sample of 5-oxocamphenilone (I.R. # 92).

8. Preparation of 6,6-dimethyl-2-norbornanone (24) (Scheme II-1)

2-Norbornene-5-methyl-5-carboxylic acid (32)[47,48]

Methylmethacrylic acid (Matheson, Coleman and Bell Co.) was distilled {b.p., 73.5-74° (35 mm)} through a 4" vacuum jacketed Vigreux column. Cyclopentadiene was obtained from bicyclopentadiene (Eastman Chemicals Co.) by distillation through a 12" vacuum jacketed Vigreux column.

Two sealed tubes, each containing methylmethacrylic acid (17.2 g, 0.2 mole), freshly distilled cyclopentadiene (13.2 g, 0.2 mole), hydroquinone (*ca.* 0.1 g) and toluene (25 ml), were heated for 2 hours at *ca.*

160°. The two tubes were opened and combined, and solvent and excess methylmetacrylic acid were removed by distillation. The crystalline products were then recrystallized from 50 % acetic acid, to yield 43.3 g (71 %) of a mixture of *exo* and *endo*-2-norbornene-5-methyl-5-carboxylic acid (32).

5-Methyl-5-hydroxymethyl-2-norbornene (33)[49]

The ether was distilled from lithium aluminium hydride before use.

The above carboxylic acids 32, (43.3 g, 0.28 mole) were dissolved in ether (150 ml), and were slowly added to a slurry of lithium aluminium hydride (18 g), during a period of 3 hours. The mixture was then stirred at room temperature for 7½ hours, and then refluxed for an additional 2 hours. The mixture was then cooled in an ice-water bath, and the excess lithium aluminium hydride was destroyed by adding water (100 ml), followed by hydrochloric acid (20 %, 500 ml). The aqueous layer was separated, and extracted with ether (2 x 150 ml). The combined ether solutions were washed with sodium hydroxide (10 %, 2 x 150 ml), water (2 x 150 ml), and a solution of sodium chloride (sat., 150 ml ml). After drying ($MgSO_4$), the solvent was evaporated to yield 25.6 g (66 %) of epimeric alcohols 33.

Camphenilene (34)[49]

The above alcohols 33 (25.6 g, 0.18 mole) were dissolved in pyridine (100 ml) and cooled in ice. Tosyl chloride (35.5 g) dissolved in pyridine (75 ml) and cooled in ice, was added. The solution was left standing in ice for 2 hours, then at room temperature, for an additional

10½ hours. The solution was then added to 400 ml of crushed ice. The resulting solution was diluted with water to 1 *l.* and extracted with ether (3 x 200 ml). The combined ether extracts were washed with water (100 ml), hydrochloric acid (10 %, 3 x 200 ml), sodium bicarbonate (sat., 100 ml), water (100 ml) and finally, with a solution of sodium chloride (100 ml). After drying ($MgSO_4$), evaporation of solvent yielded 48.4 g of oil.

Without purification, the tosylate was dissolved in ether (250 ml, previously distilled from lithium aluminium hydride), and was added over a period of 1 hour, to a slurry of lithium aluminium hydride (15 g) in ether (250 ml, as above). The mixture was refluxed with magnetic stirring for 33 hours. The excess lithium aluminium hydride was then destroyed by slowly adding to the ice-cold mixture, sodium hydroxide (10 %, 30 ml), followed by water (35 ml). After filtration of the inorganic salts, and drying ($CaSO_4$), the solvent was removed by distillation through a 8" vacuum jacketed Vigreux column. Distillation through the same column gave 10.6 g (47 % from the carbinol) of very low melting crystals: b.p., 130-131° (760 mm) {reported,[49] m.p., 27-28°, b.p., 128-131° (760 mm)}. V.p.c. analysis (# 198, 5 % SE-30, 10', 115°): camphenilene (r.t. 1.2 min.), *ca.* 98 % pure. N.m.r. (# 94, CCl_4/TMS, A-60): δ = 0.84, 1.16 (2s., 3H each, methyl groups); δ = 2.22 (m., 1H, bridgehead); δ = 2.72 (broad s., 1H, bridgehead); δ = 6.01 (t., 2H, olefin). I.R. (# 88, CCl_4): 3070 cm^{-1} (CH, olefin); 1610 cm^{-1} (w., C=C); 700 cm^{-1} (C=C).

Preparation of perlauric acid[195]

Lauric acid (Eastman Chemicals Co., 30 g, 0.15 mole) was dissolved in sulfuric acid (conc., 64.5 g), and was placed in a beaker cooled in an ice bath. The solution was stirred mechanically. Hydrogen peroxide (50 %, 15.3 g, 0.2 mole) was added dropwise during a period of *ca.* 10 minutes. The temperature during the course of the addition did not exceed 30°. The mixture was then stirred for an additional 50 minutes. Ice-water was then added to dilute the mixture to 800 ml. The aqueous mixture was extracted with ether (3 x 200 ml), and the ether solution was washed with water until free of peroxide and acid. After drying ($MgSO_4$), evaporation of solvent yielded 36.3 g of a waxy solid, 82 % of peracid (thiosulfate titration).

2,2-Dimethyl-5,6-epoxynorbornane (35)[50-52]

Camphenilene (34) (4.8 g, 39 mmoles) was dissolved in ether (100 ml), and cooled in the refrigerator. Perlauric acid (11.2 g, 75 % peracid) was added. The resulting solution was left standing in the refrigerator (*ca.* 5°) for 12 days. The solution was then extracted several times with bicarbonate (sat.) to remove some of the lauric acid. After drying ($MgSO_4$), the ether was evaporated, and the epoxide was distilled to yield 3.7 g (69 %) of crystals, m.p., 99-101° (no melting point has been reported[50-52] for this compound). V.p.c. analysis (# 144, 5 % SE-30, 10', 125°): only one peak (r.t. 5.2 min.). N.m.r. (# 75, CCl_4/TMS, A-60): δ = 1.00, 1.05 (2s., 3H each, methyl groups); δ = 1.88 (d., 1H, bridgehead); δ = 2.35 (broad s., 1H, bridgehead); δ = 3.02 (q., 2H, 5,6-*endo*-hydrogens); (reported,[50] δ = 1.01, 1.05,

1.90, 2.35 and 3.03). I.R. (# 73, CCl_4): 855 cm^{-1} (epoxide).

6,6-Dimethyl-*exo*-norborneol (36)[50]

A slurry of lithium aluminium hydride (0.7 g) in diglyme (10 ml, freshly distilled from lithium aluminium hydride) was placed in a 50 ml 3-necked flask fitted with a condenser and an adding funnel. 2,2-Dimethyl-5,6-epoxynorbornane (35) (2.0 g, 16 mmoles) in diglyme (6 ml, as above) was added dropwise, and the mixture was stirred magnetically at 100 ± 3° for 5 days. The mixture was then cooled in ice-water, and sodium hydroxide (10 %, 0.7 ml), followed by water (0.7 ml), were slowly added. After filtration of the white precipitate, the solution was diluted with pentane to *ca.* 75 ml. The pentane-diglyme solution was then washed with water (10 x 25 ml). Drying ($MgSO_4$), and evaporation of solvent gave 1.7 g (76 %) of alcohol 36. V.p.c. analysis (# 166d, 10 % Carbowax, 10', 160°): 6,6-dimethyl-*exo*-norborneol (r.t. 7.1 min.), *ca.* 94 % pure, with some 6 % of starting epoxide (r.t. 3.4 min.). I.R. (# 111, neat): 3350 cm^{-1} (OH). N.m.r. (# 129, CCl_4/TMS, A-60): δ = 0.92 (s., 6H, methyl groups); δ = 1.68 (broad s., 1H, bridgehead); δ = 2.14 (broad s., 1H, bridgehead); δ = 3.91 (s., 1H, OH); δ = 4.06 (d., 1H, *endo*-C_2H). All spectra were identical in all respect to those of an authentic sample[196] (v.p.c. # 166a, I.R. # 112, n.m.r. # 130).

6,6-Dimethyl-2-norbornanone (24)[57, 50-52]

The oxidizing reagent was prepared as follows: $Na_2Cr_2O_7 \cdot 2H_2O$ (2.0 g) was dissolved in water (5 ml). Sulfuric acid (conc., 1.5 ml) was added, and the solution was diluted to 100 ml.

The above alcohol 36 (1.7 g, 12 mmoles) was dissolved in ether (10 ml), and was placed in a 50 ml 3-necked flask, fitted with a condenser and a dropping funnel. The flask was placed in a water bath at room temperature. The oxidizing reagent was added over a period of 10 minutes, and the reaction mixture was stirred magnetically for 3 hours. The layers were then separated, and the ether layer was washed with water, bicarbonate and water again. After drying ($MgSO_4$), evaporation of solvent yielded 1.5 g (90 %) of colourless liquid. V.p.c. analysis (# 209, 10 % carbowax, 10', 135°): 6,6-dimethyl-2-norbornanone (r.t. 5.7 min.), *ca.* 95 % pure. I.R. (# 113, neat): 1748 cm^{-1} (C=O). N.m.r. (# 131, CCl_4/TMS, A-60, T-60): δ = 0.89, 0.98 (2s., 3H each, methyl groups); δ = 2.50 (broad s., 1H, bridgehead).

9. Preparation of 5-ketonorbornyl acetate (54) (Scheme II-5)
Preparation of nortricyclanone (53)

The nortricyclyl formate (51) was prepared by R.R. MacDonald[197] and was *ca.* 63 % pure {by n.m.r. (# 109)}. The balance was norbornenyl formate.

The mixture of formates (41 g) was dissolved in ether (250 ml), and was added at room temperature over a period of 3 hours, to a slurry of lithium aluminium hydride (11 g) in ether (1.2 *l.*). The mixture was then refluxed for 3 hours. It was then cooled in an ice-water bath, and sodium hydroxide (10 %, 30 ml), followed by water (15 ml), were added. The mixture was stirred overnight. The white precipitate was then filtered and washed with ether. Most of the ether was then evaporated through a Vigreux column. V.p.c. analysis (# 244, 10 % carbowax, 10',

130°) showed two compounds in the approximate ratio of 2:1, (n.m.r. # 114). Complete removal of the ether being difficult, oxidation[57] was performed without purification.

The oxidizing reagent was prepared as follows: sodium dichromate (50 g) was dissolved in water (100 ml) and sulfuric acid (conc., 37.5 ml) was added. The solution was diluted to 250 ml with water.

The above alcohols (52) were dissolved in ether (120 ml, previously treated with the reagent) and the oxidizing reagent (250 ml) was slowly added. The mixture was then stirred at room temperature for 7½ hours.

The layers were then separated. The aqueous layer was extracted with ether (2 x 75 ml). The combined ether solutions were washed with water (100 ml), bicarbonate (sat., 100 ml), and again with water (2 x 100 ml). After drying ($MgSO_4$), the solvent was evaporated through a Vigreux column to give 20.3 g of material (traces of ether present). V.p.c. analysis (# 246, 10 % Carbowax, 10', 115°) showed two products in the ratio of *ca.* 4:1 (r.t. 5.3 and 3.6 min.). Traces of two other compounds were also present (r.t. 4.8 and 7.6 min.). N.m.r. (# 115, ether/TMS, T-60) showed nortricyclanone to be the major product (complex structure at δ = 1.0-2.2).

5-Ketonorbornyl acetate (54)[67]

The above nortricyclanone (20.3 g, 0.19 mole) was dissolved in acetic acid (glacial, 60 ml) and perchloric acid (70 %, 3 ml) was added. The solution was heated on the steam bath for 4 hours. After cooling,

the solution was added to an ice-cold solution of sodium hydroxide (10 %, 100 ml). It was then neutralized with solid bicarbonate, and extracted with ether (5 times for a total of 500 ml). After washing with bicarbonate (sat.) and drying (Na_2SO_4), the solvent was removed and the residue distilled, to yield as a second fraction 13.9 g (44 %) of 5-ketonorbornyl acetate (54); b.p., 94-97° (0.6 mm) {reported,[67] b.p., 88-90° (1.2 mm)}. V.p.c. analysis (# 248, 10 % Carbowax, 10', 190°) showed the compound to be *ca.* 90 % pure (r.t. 6.4 min.). N.m.r. (# 116, CCl_4/TMS, T-60): δ = 1.98 (s., 3H, acetate); δ = 2.45 (d., 1H, C_1H); δ = 2.65 (broad s., 1H, C_4H); δ = 4.78 (q., 1H, *endo*-C_2H). I.R. (# 100, neat): 1750 cm^{-1} (C=O); 1250 cm^{-1} (acetate).

10. Norbornane-2,5-dione (27) (Scheme II-5)

Norbornane-2,5-diol (55)[67]

5-Ketonorbornyl acetate (54) (5.8 g, 35 mmoles) was dissolved in ether (previously distilled from lithium aluminium hydride), and was added to a slurry of lithium aluminium hydride (5 g) in ether (200 ml, as above), over a period of one hour. The mixture was refluxed for 8½ hours. The solution was then cooled in an ice-bath. Sodium hydroxide (10 %, 7 ml), followed by water (9 ml) were added dropwise. Filtration of the inorganic salts and evaporation of solvent gave 3.6 g (80 %) of diols 55. V.p.c. analysis (# 259. 10 % carbowax, 10', 175°): only one broad peak (r.t. 12.5 min.). N.m.r. (# 124, D_2O): δ = 3.7-4.4 (complex structure, CHOH); δ = 0.5- 2.4 (complex structure). I.R. (# 107, $CHCl_3$): 3575, 3400 cm^{-1} (OH); no carbonyl absorption around 1750 cm^{-1}.

Norbornane-2,5-dione (27)[67]

The oxidizing reagent was prepared as follows: chromium trioxide (8 g) was dissolved in water (20 ml). Sulfuric acid (conc., 12.8 g) was added and the solution was diluted with water to 40 ml.

The mixture of diols (3.4 g, 26 mmoles) was dissolved in acetone (325 ml). The reagent (20 ml) was added slowly with mechanical stirring, over a period of ½ hour. After stirring at room temperature for 3 hours, the solution was filtered through a sintered glass funnel (fine porosity). Evaporation of solvent gave 2 g (62 %) of dione. V.p.c. analysis (# 259, 10 % Carbowax, 10', 175°) showed the dione (r.t. 4.6 min.) to be *ca.* 95 % pure. A sublimed sample melted at 139-141° (reported,[67] m.p., 141.5-143°). N.m.r. (# 122, CCl_4/TMS, T-60): δ = 1.7-2.7 (m., 6H); δ = 2.9 (broad s., 2H, bridgeheads). I.R. (# 105, CCl_4): 1766, 1731 (s.) cm^{-1} (C=O).

11. Preparation of 5-methylenenorcamphor (30)

5-Ethylenedioxy-2-norbornyl acetate

5-Ketonorbornyl acetate (10 g, 60 mmoles) was dissolved in benzene (500 ml, previously distilled from lithium aluminium hydride). *Para*-toluenesulfonic acid (1 g), and ethylene glycol (20 ml) were added and the solution was refluxed for 24 hours, with magnetic stirring and with a Dean-Stark water separator. The solution was then quenched with bicarbonate (sat., 100 ml), and the layers were separated. After drying (Na_2SO_4), the benzene was removed to yield 11.0 g (87 %) of ketal. V.p.c. analysis (# 249, 10 % Carbowax, 10', 200°) showed the ketal (r.t. 6.3 min.) to be *ca.* 90 % pure. Purification by preparative

v.p.c. (# 270, 20 % SE-30, 5', 162°), followed by bulb to bulb distillation, gave an analytical sample:

	C	H
Found :	62.25 %	7.52 %
Calculated:	62.25 %	7.60 %

I.R. (# 101, CCl_4): 1745 cm^{-1} (C=O); 1245 cm^{-1} (acetate). N.m.r. (# 117, CCl_4/TMS, T-60); δ = 1.95 (s., 3H, acetate); δ = 3.80 (m., 4H, ketal); δ = 4.60 (q., 1H, *endo*-C_2H).

Reduction of the acetate

The glassware was oven dried before use and the ether was distilled from lithium aluminium hydride.

5-Ethylenedioxynorbornyl acetate (10 g, 47 mmoles) dissolved in ether (150 ml) was added over a period of one hour, at room temperature, to a magnetically stirred slurry of lithium aluminium hydride (3.6 g, 94 mmoles) in ether (200 ml). The mixture was refluxed for 10 hours. The excess lithium aluminium hydride was then destroyed as usual, and solvent evaporation gave 5.8 g (73 %) of alcohol. V.p.c. analysis (# 250b, 10 % Carbowax, 10', 200°) showed the 5-ethylenedioxynorbornyl alcohol to be *ca.* 80 % pure (major impurity may be the *endo*-alcohol). I.R. (# 102, neat): 3400 cm^{-1} (OH); no absorption around 1750 cm^{-1}. N.m.r. (# 118, CCl_4/TMS, T-60): δ = 3.8 (m., ketal.).

5-Ethylenedioxy-2-norbornanone

The oxidizing reagent[184,185] was prepared as follows: chromium trioxide (10 g) was dissolved in water (10 ml) and the solution was added to ice-cold pyridine (100 ml). 5-Ethylenedioxy-2-norborneol (5.4 g, 32 mmoles) was added, and the solution was left standing at

room temperature for 16 hours. The solution was then diluted to 300 ml with ice-water, and the mixture was filtered through celite. The precipitate was washed with water (30 ml) and methylene chloride (3 times for a total of 100 ml). The aqueous layer was extracted with methylene chloride (5 x 100 ml). The combined methylene chloride solutions were filtered through celite. The solvent was then concentrated to *ca.* 100 ml. It was then washed with very dilute sulfuric acid until acid, then with bicarbonate (sat.). After drying, evaporation of solvent gave 3.4 g (63 %) of ketone. V.p.c. analysis (# 251, 10 % carbowax, 10', 180°) indicated the 5-ethylenedioxy-2-norbornanone (r.t. 6.8 min.) to be *ca.* 95 % pure. Purification by preparative v.p.c. (# 275, 20 % SE-30, 5', 170°), followed by bulb to bulb distillation gave an analytical sample:

	C	H
Found :	64.27 %	7.30 %
Calculated:	64.27 %	7.19 %

N.m.r. (# 119, CCl_4/TMS, T-60): $\delta = 3.8$ (m., 4H, ketal); $\delta = 1.4$-2.6 (m., 8H). I.R. (# 103, neat): 1745 cm^{-1} (C=O).

5-Methylene-2-norbornanone (30)

A flow of dry nitrogen was passed through the reaction mixture during the preparation of the ylide.[186] *n*-Butyl lithium (*ca.* 1.5 *N.*, 25 ml, 0.04 mole) was added to a mixture of triphenylmethyl phosphonium bromide (10.5 g, 0.04 mole) in ether (150 ml, previously distilled from lithium aluminium hydride). The mixture was stirred magnetically for 4 hours at room temperature. 5-Ethylenedioxy-2-norbornanone (3.2 g, 0.04 mole) dissolved in ether (125 ml) was slowly added and the mixture was refluxed for $10\frac{1}{2}$ hours. The solids were then filtered and

the ether solution was washed with water until neutral. The solvent was evaporated through a Vigreux column, leaving a small amount of ether and traces of ϕ_3PO. V.p.c. analysis (# 252, 10 % Carbowax, 10', 175°) indicated the olefin (r.t. 1.8 min.) to be *ca.* 90 % pure. N.m.r. (# 120, hexane/TMS, T-60): δ = 3.7 (m., 4H, ketal); δ = 4.7 (d., 2H. olefin). With no attempt to purify, the mixture was hydrolysed immediately

The above mixture was dissolved in a mixture of ethanol (75 ml) and water (35 ml). Acetic acid (1 ml) and hydrochloric acid (50 %, 5 drops) were added and the mixture was stirred at room temperature for 3 days. It was then diluted to 400 ml with water and extracted with ether (3 times for a total volume of 350 ml). The ether solution was washed with water (100 ml) and bicarbonate (sat., 100 ml). After drying ($MgSO_4$), most of the solvent was evaporated through a Vigreux column. Purification by preparative v.p.c. (# 253, 20 % SE-30, 5', 110°), followed by bulb to bulb distillation gave an analytical sample:

	C	H
Found :	78.59 %	8.25 %
Calculated:	78.65 %	8.25 %

I.R. (# 104, CCl_4): 3080 cm^{-1} (CH, olefin); 1754 cm^{-1} (C=O); 1660, 890 cm^{-1} (C=C). N.m.r. (# 121, CCl_4/TMS, T-60): δ = 4.9 (d., 2H, olefin); δ = 3.05 (broad s., 1H, bridgehead); δ = 2.65 (broad s., 1H, Bridgehead).

Confirmation of structure of 5-methylenenorcamphor (30)

Oxidation[187] to norbornane-2,5-dione (27)

5-Methylenenorcamphor (45 mg, 0.37 mmole) was dissolved in

aqueous acetone (50 %, 7 ml), containing potassium periodate (2 g). The solution was cooled in ice-water, and a solution of potassium permanganate (0.1 g in 3 ml of water) was added dropwise over a period of 10 minutes. The resulting mixture was warmed to room temperature and stirred for 5 hours. The solution was then filtered through a medium porosity cintered glass funnel, and it was diluted to 100 ml. It was extracted with methylenechloride (3 x 50 ml), and the extracts were washed with water (25 ml). After drying (Na_2SO_4), solvent evaporation gave a compound whose v.p.c. (# 260, 10 % Carbowax, 10', 160°, r.t. 6.3 min.; r.t. of enone, 1.6 min.), I.R. (# 160, CCl_4) and n.m.r. (# 123, CCl_4/TMS, T-60) spectra were identical to those of an authentic sample of norbornane-2,5-dione (v.p.c. # 260, I.R. # 105, n.m.r. # 122).

12. Preparation of 6-methylenenorcamphor (31) (Scheme II-7)

Preparation of iodolactone 61

Method A[68,69]

Bicyclo{2.2.1.}hept-5-ene-2-carboxylic acid (60) (Aldrich Chemical Co., 20 g, 0.14 mole, mixture of *exo* and *endo*) was dissolved in an aqueous solution of sodium bicarbonate (870 ml of 0.5 *N*.). Potassium iodide (145 g, 0.87 mole) was added, followed by iodine (73.6 g, 0.29 mole). The solution was left standing for *ca.* 20 hours at room temperature. A dilute solution of potassium thiosulfate was then added to reduce the excess iodine. The solution was then extracted several times with methylene chloride (total volume of 500 ml). After drying, solvent evaporation yielded 35 g (95 %) of yellow crystals; m.p., 53-54°. (No melting point is reported in Ref. 68)

Method B[68,69]

A solution of iodine (1 *M.*) in potassium iodide (3 *M.*) was prepared (127 g of iodine and 249 g of KI in 500 ml of water).

Bicyclo{2.2.1.}hept-5-ene-2-carboxylic acid (60) (20 g, 0.14 mole) was dissolved in potassium bicarbonate (360 ml, 1 *M.*). This solution was titrated with the iodine solution until excess iodine was present. The solution was then extracted several times with methylene chloride (total volume of 600 ml). After washing with water and thiosulfate, the organic layer was dried ($MgSO_4$) and evaporated to yield 37.5 g (98 %) of crystals.

The combined iodolactone crystals (from methods A and B) were recrystallized from ethylacetate-petroleum ether mixtures to yield yellowish crystals melting at 55-56.5°. V.p.c. analysis (# 279, 5 % SE-30, 10', 195°) showed only one peak (r.t. 10.4 min.). I.R. (# 118, CCl_4): 1790 cm^{-1} (lactone). N.m.r. (# 137, CCl_4/TMS, T-60): $\delta = 5.05$ (d., 1H, ICH); $\delta = 3.92$ (d., 1H, OCH).

Bicyclo{2.2.1.}heptan-6-one-2-carboxylic acid (62)[68,70]

The iodolactone 61 (70 g, 0.38 mole) was dissolved in methanol (90 %, 700 ml), and potassium hydroxide (35 g) was added. The solution was refluxed for 7 hours. Most of the methanol was then steam-distilled and the resulting aqueous solution was neutralized with dilute sulfuric acid (20 %). The solution was made slightly alkaline, and was filtered. After acidification, the aqueous solution was extracted with methylene chloride (4 x 100 ml). Evaporation of the solvent gave 22.5 g of white

crystals.

The aqueous layer was then subjected to continuous extraction for *ca.* 24 hours with ether. After drying ($MgSO_4$), evaporation of solvent gave 14.9 g of crystals. Combined yield was 37.4g (92 %); m.p. 95-101°. Recrystallization from ethylacetate-petroleum ether mixtures gave, after drying under vacuum, white crystals, m.p., 95-97°. (Reported,[70] m.p., 103-104°). 2,4-Dinitrophenylhydrazone, m.p., 166-167° (reported,[70] m.p., 167-168°). I.R. (# 119, $CHCl_3$): 3000 cm^{-1} (broad, acid OH); 1710, 1745 cm^{-1} (C=O, acid and ketone). N.m.r. (# 119, $CDCl_3$/TMS, T-60): δ = 10.3 (broad s., 1H, COOH); δ = 3.4-1.6 (m., 9H).

6-Ethylenedioxybicyclo{2.2.1.}hept-*endo*-2-carbinol (63)

The above ketoacid 62 (32.3 g, 0.21 mole) was dissolved in benzene (300 ml, previuosly distilled from lithium aluminium hydride). Ethylene glycol (100 ml, freshly distilled) and *p*-toluenesulfonic acid (1 g) were added and the mixture was refluxed for *ca.* 20 hours with a Dean-Stark water separator. After cooling, the layers were separated. The ethylene glycol layer was extracted with benzene (20 ml). The ethylene glycol layer was then diluted with sodium bicarbonate (sat., 100 ml) and was extracted with methylene chloride (3 x 75 ml). The extracts were washed with water (50 ml) and dried ($MgSO_4$).

The combined organic layers were evaporated to 45.5 g of oil. I.R. (# 120, neat): 3500 cm^{-1} (OH); 1750, 1200 cm^{-1} (ester). N.m.r. (# 139, $CDCl_3$/TMS, T-60): δ = 4.2 (m., 2H); δ = 3.7 (m., 4H); δ = 2.7 (broad s., 1H). These data suggest that esterification, as well as

ketalization occured to give ketalester 66. Without purification the compound was reduced.

All glassware was oven dried before use, and the ether was distilled from lithium aluminium hydride.

The above oil (45 g) was dissolved in ether (300 ml) and was added to lithium aluminium hydride (10 g) in ether (200 ml), over a period of 2 hours. The mixture was then refluxed overnight. After cooling, sodium hydroxide (10 %, 10 ml), and water (10 ml) were added and the mixture was stirred for 6 hours at room temperature. Filtration of the inorganic salts, and evaporation of solvent gave 36.1 g (93 %) of oil. Distillation of this oil under reduced pressure gave a colourless liquid. I.R. (# 122, neat): 3500 cm^{-1} (OH); no absorption around 1700 cm^{-1}. N.m.r. (# 141, CCl_4/TMS, T-60): δ = 3.8 (d., 4H, ketal); δ = 3.7 (m., 5H, OH, CH_2OH, $CH\ CH_2OH$). Purification by preparative v.p.c. (# 307, 20 % SE-30, 5', 150°), followed by bulb to bulb distillation, gave an analytical sample:

	C	H
Found :	65.17 %	8.92 %
Calculated:	65.17 %	8.76 %

Acetylation

The above alcohol 63 (12 g, 78 mmoles) was dissolved in pyridine (40 ml) and acetic anhydride (20 ml). The solution was left standing at room temperature for *ca.* 20 hours. The solution was then diluted to 400 ml with ice-water, and was extracted with ether (3 x 100 ml). The ether solution was washed with water (80 ml), dilute hydrochloric acid (5 %, 2 x 80 ml), water (80 ml), bicarbonate (80 ml), and finally, water

again (80 ml). After drying ($MgSO_4$), evaporation of solvent gave 13.9 g (81 %) of oil. I.R. (# 141, neat): no absorption around 3500 cm^{-1}; 1745 cm^{-1} (acetate). N.m.r. (# 156, CCl_4/TMS, T-60): δ = 4.2 (m., 2H, CH_2OAc); δ = 3.8 (m., 4H, ketal); δ = 2.0 (s., 3H, acetate). Purification by preparative v.p.c. (# 306, 20 % SE-30, 10', 180°), followed by bulb to bulb distillation gave an analytical sample:

	C	H
Found :	63.72 %	8.16 %
Calculated:	63.70 %	8.02 %

6-Methylenenorcamphor (31)

A glass column, packed with glass helices, was placed vertically in a pyrolysis oven heated at 450-500°. A flow of nitrogen (1 ml $min.^{-1}$) was maintained throughout the experiment to entrain the products. 6-Ethylenedioxybicyclo{2.2.1.}hept-*endo*-2-carbinyl acetate (64) was added very slowly dropwise (*ca.* 3 drops per 5 minutes) to the packed column. The products of the reaction were trapped at the end of the column in a flask in a dry-ice-acetone bath. After the addition to the column is completed the flask was warmed to room temperature and the content was dissolved in ether. The ether solution was washed with bicarbonate (sat.) and dried ($MgSO_4$). Evaporation of solvent, and distillation gave in *ca.* 5% yield, the ethylene ketal of 6-methylenenorcamphor. The balance of the reaction mixture was starting material which could be recycled. N.m.r. (# 160, CCl_4/TMS, T-60): δ = 4.7 (d., 2H. methylene group); δ = 3.9 (narrow m., 4H, ketal); δ = 2.5 (broad s., 1H, bridgehead); δ = 2.3 (m., 1H, bridgehead). M.S. (# 326): molecular ion at *M/e* = 166 in accordance with the molecular

weight of this compound.

Without purification, the compound was hydrolysed to the ketone. In a typical experiment, the ketal (200 mg) was added to water (7 ml) containing one drop of concentrated hydrochloric acid. The mixture was stirred at room temperature for 2 hours. Solvent extraction and purification by preparative v.p.c. (# 297, 10 % UKON, 10', 155-160°) gave a colourless liquid. N.m.r. (# 162, CCl_4/TMS, T-60): $\delta = 5.05$ (d. of t., 2H, methylene group); $\delta = 3.05$ (s., 1H, $C_1\underline{H}$); $\delta = 2.80$ (unresolved m., 1H, $C_4\underline{H}$); $\delta = 2.6$-1.6 (m., 6H). I.R. (# 142, CCl_4): 3490 cm^{-1} (w., overtone of carbonyl); 3080 cm^{-1} (CH, olefin); 1750 cm^{-1} (C=O); 1650 cm^{-1} (C=C); 890 cm^{-1} (C=C). Bulb to bulb distillation of a sample gave an analytical sample:

	C	H
Found :	78.57 %	8.43 %
Calculated:	78.65 %	8.25 %

13. Preparation of 6-ethylenedioxy-*exo*-norborneol (Scheme II-8)

Norbornenol

Norbornenyl acetate was obtained from N.H. Werstiuk, and was better than 95 % pure (v.p.c. # 238, 5 % SE-30, 10', 135°, r.t. 2.9 min.). All glassware was oven dried before use, and the ether was distilled from lithium aluminium hydride.

Norbornenyl acetate (40 g, 0.26 mole) was dissolved in ether (200 ml), and was added over a period of 2½ hours, to a slurry of lithium aluminium hydride (10 g) in ether (1 ℓ.). The mixture was then refluxed for 3 hours with magnetic stirring. After cooling the mixture in an ice-water bath, sodium hydroxide (10 %, 15 ml), followed by water

(15 ml), and again sodium hydroxide (10 %, 15 ml), were slowly added. The mixture was then stirred for two hours at room temperature. The white precipitate was then filtered, and the ether was removed by distillation through a column packed with glass helices. There resulted 28 g (97 %) of norbornenol. V.p.c. analysis (# 238, 5 % SE-30, 10', 135°) showed the norbornenol (r.t. 1.8 min.) to be better than 95 % pure. N.m.r. (# 107, CCl_4/TMS, T-60): $\delta = 6.1$ (m., 2H, olefin); $\delta = 4.4$ (m., 1H, C_2HOH); $\delta = 2.8$ (2 unresolved peaks, 2H, bridgeheads). I.R. (# 97, CCl_4): 3650, 3525 cm^{-1} (C-H olefin); 1600 cm^{-1} (C=C).

Preparation of aluminium *t*-butoxide[198]

Aluminium foil (64 g, 2.37 moles), *t*-butanol (254 ml, 2.7 moles), aluminium *i*-propoxide (Eastern Chemical Co., 7 g) were placed in a 2 *l*. flask, fitted with a condenser and a drying tube. The mixture was heated to boiling on the steam bath, and mercuric chloride (0.4 g) was added. The mixture was then stirred vigorously, and then heated on the steam bath for 1½ hour. *t*-Butanol (309 ml, 3.3 moles) and benzene (200 ml, previously distilled from lithium aluminium hydride) were then added. After heating for a few minutes on the steam bath, the reaction flask was set aside for 2 hours. It was then refluxed on the steam bath for 19 hours.

The benzene and the unreacted *t*-butanol were then removed by distillation, getting the last traces with the aspirator pump. Dry ether (1 *l*., previously distilled from lithium aluminium hydride) was added, and the aluminium *t*-butoxide was dissolved by refluxing over the steam bath for a few minutes. After cooling, wet ether (35 ml) was

added. After standing for 1½ hour, the mixture was centrifuged for 30 minutes at 1700 r.p.m. Wet ether was added again, and after standing for 2 hours, the mixture was centrifuged again. Evaporation of solvent gave 292 g (60 %) of a grayish solid.

Dehydronorcamphor[199]

Norbornenol (20 g, 0.18 mole) and *p*-benzoquinone (101 g, 0.94 mole) were dissolved in benzene (2.6 *l.*); 0.8 *l.* of the benzene was distilled from the reaction mixture. After cooling, aluminium *t*-butoxide (34.6 g, 0.14 mole) dissolved in benzene (300 ml, previously distilled from lithium aluminium hydride) was added to the magnetically stirred solution over a period of several hours. After stirring for 6 days at room temperature, water (10 ml) was added and the mixture was warmed on the steam bath. It was then filtered through a coarse porosity cintered glass funnel. The solution was then washed several times with sodium hydroxide (5 %) until clear, then with water. After drying ($MgSO_4$), the solution was distilled through a vacuum jacketed Vigreux column, using biphenyl (3 g) as a chaser, to yield 13.8 g (70 %) of dehydronorcamphor: b.p., 97-98° (91 mm). V.p.c. analysis (# 240b, 10 % Carbowax, 10', 130°) showed the product to be *ca.* 95 % pure (r.t. 4.1 min.). N.m.r. (# 108, CCl_4/TMS, T-60): $\delta = 6.3$ (m., 2H, olefin); $\delta = 3.1$ (m., 1H bridgehead); $\delta = 2.8$ (m., 1H, bridgehead); $\delta = 1.7$-2.4 (m., 4H). I.R. (# 114, neat): 3075 cm^{-1} (w., CH, olefin); 1750 cm^{-1} (C=O).

Dehydronorcamphor ethyleneketal[71]

Dehydronorcamphor (13 g, 0.12 mole) was dissolved in benzene

(200 ml, previously distilled from lithium aluminium hydride) and *p*-toluenesulfonic acid (0.65 g) and ethylene glycol (150 ml, freshly distilled) were added. The mixture was refluxed for 14 hours with magnetic stirring and with a Dean-Stark water separator. The solution was then quenched with bicarbonate (sat., 100 ml). After drying ($MgSO_4$), most of the benzene was removed by distillation through a Vigreux column. The resulting benzene solution contained 16 g (88 %) of ketal (as determined by n.m.r., #111). V.p.c. analysis (# 241, 10 % Carbowax, 10', 135°) indicated the dehydronorcamphor ethyleneketal (r.t. 4.8 min.) to be better than 95 % pure. Complete removal of the benzene gave a sample having the following spectra: n.m.r. (# 112, CCl_4/TMS, T-60): $\delta = 6.2$ (m., 2H, olefin); $\delta = 3.8$ (s., 4H, ketal); $\delta = 2.65$ (broad s., 1H, bridgehead); $\delta = 2.50$ (broad s., 1H, bridgehead). I.R. (# 99, neat): 3060 cm^{-1} (CH, olefin); no absorption around 1750 cm^{-1}.

Preparation of perbenzoic acid[200]

Sodium peroxide (24 g, 0.31 mole) was slowly added to ice-cold water (405 ml) such that the temperature did not reach 10°. The suspended solids were then filtered through a fine porosity fritted glass funnel, keeping the filtrate in an ice bath to keep cool. The filtrate was then placed in a 3 *l*. beaker, and was stirred magnetically; the beaker was kept in an ice-water bath. Ethanol (95 %, 540 ml) was then added, followed by a solution of $MgSO_4 \cdot 7H_2O$ (1.5 g, in 20 ml of water), such that the temperature did not reach 10°. Benzoyl chloride (34.8 ml, 0.30 mole) was then added dropwise over a period of 45 minutes, keeping the temperature below 8°. After filtration through a coarse porosity

fritted glass funnel, the solution was acidified with sulfuric acid (20 %), always keeping the temperature below 10°. The solution was then extracted 5 times with benzene using a total volume of 1 ℓ. The benzene was dried ($MgSO_4$) and was stored in the refrigerator. Yield: 25 g (65 %), as determined by iodimetric titration.

Exo-2,3-epoxy-5-ethylenedioxybicyclo{2.2.1.}heptane[71]

The above ene-ketal (13.2 g, 87 mmoles) was added to a solution of perbenzoic acid (19 g, 125 mmoles) in benzene (800 ml). The solution was kept in the refrigerator (*ca.* 5°) for 4 days. The benzene solution was then washed with sodium hydroxide (5 %, 3 x 100 ml), and water (100 ml). After drying (Na_2SO_4), evaporation of solvent gave 14.0 g (96 %) of epoxyketal. N.m.r. (#126, CCl_4/C_6H_6/TMS, T-60): δ = 3.68 (s., 4H, ketal); δ = 3.18 (m., 2H, *endo*-2,3-H); δ = 2.3 (m., 2H, bridgeheads); δ = 1.8-1.0 (m., 4H). I.R. (#115, neat): 1085, 855, 725 cm^{-1}.

6-Ethylenedioxybicyclo{2.2.1.}heptan-*exo*-2-ol (67)[71]

The above epoxyketal (14.0 g, 83 mmoles) was added to a slurry of lithium aluminium hydride (3.0 g) in N-ethylmorpholine (150 ml, previously distilled from lithium aluminium hydride), and the mixture was heated with magnetic stirring, for 6 days at 110-115°. After cooling in ice, sodium hydroxide (10 %, 5 ml), followed by water (5 ml), were slowly added with stirring. Filtration of the inorganic salts followed by distillation through a 4" vacuum jacketed Vigreux column gave 4.4 g (32 %) of alcohol 67; b.p., 140° (2 mm). V.p.c. analysis (# 271, 5 % SE-30, 5', 150°) showed the compound to be better than 98 % pure

(r.t. 4.4 min.). N.m.r. (# 127, CCl_4/TMS, T-60): δ = 4.13 (d., 1H, *endo*-C_2H); δ = 3.8 (s., 4H, ketal); δ = 3.6 (s., 1H, OH); δ = 2.25 (m., 1H, bridgehead); δ = 2.05 (m., 1H, bridgehead); δ = 2.0-1.2 (m., 6H). I.R. (# 108, neat): 3600-3500 cm^{-1} (OH); 1075, 955, 840 cm^{-1}.

14. Rearrangement of ketalalcohol 68 to chloroester 69

6-Ethylenedioxy-2-*exo*-methyl-*endo*-norborneol (68)[202]

Magnesium metal (220 mg, 10 mmoles) and methyl iodide (freshly distilled, 1.4 g, 10 mmoles) in ether (*ca.* 5 ml) were stirred at room temperature for a few minutes. Ketoketal 67 (500 mg, 2.7 mmoles) was slowly added, and the mixture was stirred at room temperature for 24 hours. It was then added to crushed-ice (*ca.* 2 ml) and the aqueous solution was extracted with ether (2 x 10 ml). The combined ether extracts were washed with water, dried ($MgSO_4$), and evaporated. There resulted 440 mg of oil (81 %). V.p.c. analysis (# 276, 10 % Carbowax, 10', 190°): ketalmethylalcohol 68 (r.t. 5.8 min.), *ca.* 80 % pure. N.m.r. (# 133, CCl_4/TMS, T-60): δ = 4.40 (s., 1H, OH); δ = 3.9 (m., 4H, ketal); δ = 1.18 (s., 3H, methyl group). I.R. (# 116, CCl_4): 3500 cm^{-1} (OH); absorption at 1750 cm^{-1} had almost completly disappeared.

Dehydration[202] of alcohol 68

The above alcohol (440 mg, 2.4 mmoles) was dissolved in pyridine (4 ml), and phosphoryl chloride (1.4 ml) was added. The solution was stirred at 40-50° for one hour. It was then cooled in ice and water (0.5 ml) was slowly added. Sodium hydroxide (10 %, 30 ml) was then added and the mixture was extracted with ether (2 x 20 ml). The ether extracts

were washed with dilute acid (10 ml) until acid, sodium hydroxide (5 %, 10 ml), and water (10 ml). After drying ($MgSO_4$), evaporation of solvent gave a mixture of compounds. V.p.c. analysis (# 277, 10 % Carbowax, 10', 190°): chloroester 69 (r.t. 4.6 min., *ca.* 60 %). Purification by preparative v.p.c. (# 278, 20 % SE-30, 10', 195°) gave a sample having the following spectra: n.m.r. (# 135, CCl_4/TMS, T-60): $\delta = 5.20$ (broad s., 1H, olefin); $\delta = 4.28$ (t., 2H, $\underline{CH_2}Cl$); $\delta = 3.60$ (t., 2H, $O\underline{CH_2}$); $\delta = 1.70$ (broad s., 3H, methyl group); $\delta = 2.8\text{-}1.8$ (m., 8H). I.R. (# 117, CCl_4): 3050 cm^{-1} (CH, olefin); 1750 cm^{-1} (C=O, ester); 1650 cm^{-1} (C=C). M.S. (# 303): parent peak at $M/e = 202$ and 204 in accord with the molecular weight of 69; $M/e = 123$, loss of $ClCH_2CH_2O\cdot$; $M/e = 107$, further loss of CO.

IV. APPENDICES

A. GENERAL

This section lists the kinetic data for all the exchange reactions, treated on a *pseudo*-first-order basis. The second-order rate constant was obtained by dividing the *pseudo*-first-order constant by the base concentration. In the tables below (Section C), log f (c) is defined as follows:

$$f_1\ (c) = \frac{100 - d_{0_\infty}}{100 - d_{0_\infty} - d_1} \qquad \text{eq. 13}$$

$$f_2\ (c) = \frac{100 - d_{0_\infty}}{100 - d_{0_\infty} - d_2} \qquad \text{eq. 14}$$

$$f_3\ (c) = \frac{100 - \frac{1}{2}\ (d_{0_\infty} + d_{1_\infty})}{100 - \frac{1}{2}(d_{0_\infty} + d_{1_\infty}) - (d_3 + d_4)} \qquad \text{eq. 15}$$

where d_{0_∞} = % of d_0 species at infinite time.

d_x = % of d_x species at time t.

The rate constants found for norbornane-2,5-dione was divided by 2 for statistical correction.

Slopes and standard deviations were obtained using a computer program for the CDC 7040. The program is included in Section IV-Appendix D.

B. CALCULATION OF THE ERROR

The results listed in Section-IV, Appendix C below, quotes an error in the measurements made. This was found as follows:

1) Slope

The standard deviation of the slope was taken as the error in the slope.

2) NaOD concentration

a) Error in standard HCl solutions

The HCl solution used was D.D.H. Standard Solution of normality 1.00 ± 0.01. The following dilutions were made:

$0.1N$: 10 ml diluted to 100 ml

$0.5N$: 25 ml diluted to 50 ml

$0.05N$: 5 ml diluted to 100 ml

Errors in volumetric equipment were taken as the permissible deviations given in Ref. 203. Below, the symbols "δ" will denote the relative error and "Δ" the absolute error. The dilution formula is

$$N_x = \frac{N_1 V_1}{V_x} \qquad \text{eq. 16}$$

then,

$$\delta N_x = \{(\delta N_1)^2 + (\delta V_1)^2 + (\delta V_x)^2\}^{\frac{1}{2}} \qquad \text{eq. 17}$$

Typically, for

$$N_x = 0.1N$$

$$V_1 = 10.00 \pm 0.02 \text{ ml}$$

$$V_x = 100.00 \pm 0.08 \text{ ml}$$

then

$$\delta N_{01} = \left[\left(\frac{0.01}{1.00} \times 100\right)^2 + \left(\frac{0.02}{10} \times 100\right)^2 + \left(\frac{0.08}{100} \times 100\right)^2\right]^{\frac{1}{2}}$$

$$= 1.02 \%$$

Table IV-1 summarizes the error in the standard HCl solutions. Below, the error will be taken as ± 1.0 %.

b) Error in final NaOD concentration (N_{NaOD})

The formula used to calculate the final NaOD concentration was

$$N_{NaOD} = \frac{(\text{Titer})\ N_{HCl}}{V_{NaOD,\ S}} \cdot \frac{V_{NaOD}}{V_T} \qquad \text{eq. 18}$$

Each term is explained below together with its error. Total error in N_{NaOD} was found as usual.

$V_{NaOD,\ S}$: Volume of NaOD solution used for standardization. Volumetric pipettes were used (1.00 or 2.00 ml) and the error was ± 0.006.[203]

N_{HCl} : Normality of the standard HCl solution. Error was taken as ± 1.0 % (*vide supra*).

Table IV-1

Error in the Normality of the Standard HCl Solutions Used

N_{HCl}	δN_{HCl}
1.00	1.00 %
0.100	1.02 %
0.500	1.01 %
0.0500	1.02 %

V_{NaOD} : Volume of standardized NaOD solution used in kinetic runs. A measuring pipette was used and the error was ± 0.01.

V_T : Total volume of the final reacting solution. The reaction was carried out in a standard flask, usually 2.00 ± 0.01 ml

Titer : A 5 ml micro-burette was used and the error was ± 0.02 ml.[203]

C. KINETIC DATA

1) Norcamphor, *exo* (13)

Run 1

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	143	100.0	0.0	0.0	0.000
3.2	144	93.5	6.5	0.0	0.029
6.0	145	87.7	12.3	0.0	0.069
12.5	146	77.2	22.8	0.0	0.124
20.0	147	63.1	36.9	0.0	0.223
30.0	148	50.0	50.0	0.0	0.342
∞	149	8.2	91.8	0.0	-

v.p.c. #	:	194
ketone conc. (molar)	:	0.320
NaOD conc. (molar)	:	$(1.22 \pm 0.05) \times 10^{-2}$
slope ($min.^{-1}$)	:	1.14×10^{-2}
standard deviation	:	2.64×10^{-4}
intercept	:	-6.90×10^{-3}
standard deviation	:	2.67×10^{-3}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(3.58 \pm 0.16) \times 10^{-2}$

Run 2

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	143	100.0	0.0	0.0	0.000
3.0	154	88.8	11.8	0.0	0.053
9.0	155	75.2	24.8	0.0	0.127
20.0	156	51.6	48.4	0.0	0.299
36.0	157	32.0	68.0	0.0	0.525
50.0	158	20.7	79.3	0.0	0.737
∞	159	2.9	97.1	0.0	-

v.p.c. #	:	197
ketone conc. (molar)	:	0.358
NaOD conc. (molar)	:	$(1.36 \pm 0.05) \times 10^{-2}$
slope ($min.^{-1}$)	:	1.47×10^{-2}
standard deviation	:	1.3×10^{-4}
intercept	:	2.05×10^{-3}
standard deviation	:	2.43×10^{-3}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(4.12 \pm 0.15) \times 10^{-2}$

Averages Run 1 and Run 2

k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	3.85×10^{-2}
deviation	:	0.27×10^{-2} (7.0 %)
average error	:	0.16×10^{-2} (4.1 %)

2) Norcamphor, *endo* (13)

Run 1

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	281	100.0	0.0	0.0	0.000
5.5	282	1.3	86.5	12.1	0.057
13.0	285	1.1	73.4	25.6	0.130
22.2	286	1.0	59.4	39.4	0.221
34.8	287	1.3	44.7	54.0	0.344
47.0	291	1.6	34.0	64.4	0.459

d_{0_∞}	:	average of 1.3; 1.1; 1.0; 1.3; 1.6.
v.p.c. #	:	266
ketone conc. (molar)	:	0.231
NaOD conc. (molar)	:	0.104 ± 0.004
slope (hr^{-1})	:	9.77×10^{-3}
standard deviation	:	5.49×10^{-5}
intercept	:	2.42×10^{-3}
standard deviation	:	8.99×10^{-4}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(6.06 \pm 0.22) \times 10^{-5}$

Run 2

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	293	100.0	0.0	0.0	0.000
6.5	294	8.8	77.7	13.4	0.064
15.5	295	3.7	66.2	30.0	0.159
27.0	296	4.6	50.7	44.7	0.265
38.8	297	1.6	39.3	59.1	0.401
53.8	298	1.8	27.7	70.3	0.548
72.0	299	2.2	19.4	78.4	0.698

d_{0_∞}	:	average of 1.6; 1.8; 2.2.
v.p.c. #	:	267
ketone conc. (molar)	:	0.198
NaOD conc. (molar)	:	0.109 ± 0.004
slope (hr^{-1})	:	9.86×10^{-3}
standard deviation	:	0.19×10^{-3}
intercept	:	4.31×10^{-3}
standard deviation	:	4.59×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(5.79 \pm 0.23) \times 10^{-5}$

Averages Run 1 and Run 2

k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	5.90×10^{-5}	
deviation	:	0.11×10^{-5}	(1.9 %)
average error	:	0.22×10^{-5}	(3.7 %)

3) Norbornane-2,5-dione, *endo* (27)

Change in base concentration

A NaOD solution was made by dissolving *ca.* 9.5 mg of sodium in 8 ml D_2O. The solution was equilibrated for one hour in the constant temperature bath at 25 . Norbornane-2,5-dione (73.2 mg) was dissolved in 1.8 ml dioxane and placed in a 3.0 ml volumetric flask. The solution was equilibrated at 25° for one hour. Then 0.9 ml of base was added to the dioxane solution, and the solution was diluted with D_2O (equilibrated at 25°) to 3.0 ml. A 1.0 ml aliquot was immediatly removed ($t = 0$ min.) and titrated. Other aliquots were removed and titrated at $t = 30$ min. and at $t = 60$ min. The results are shown in the table below:

t (min.)	Aliquot (ml)	Titer (ml)	Titer for 1 ml aliquot (ml)	% Change in base conc.*
0	1.0	0.826	0.826	0
30	0.5	0.314	0.628	24
60	1.0	0.404	0.408	51

$$* \text{ \% Change in base conc.} = \frac{0.826 - (\text{titer})_{t=t}}{0.826} \qquad \text{eq.17}$$

The results are shown in graphical form in Fig. III-1. A blank run was made using 1.8 ml dioxane, 0.9 ml base and diluting the solution to 3.0 ml. The titer at $t = 0$ was 0.857 ml and that at $t = 60$ min. was 0.828, showing no significant change in the base concentration.

Corrections in deuterium concentration were made as discussed in the EXPERIMENTAL using the following formula:

$$\text{corrected \% } (d_3 + d_4) = \frac{(d_3 + d_4)\ (100 + \text{\% change in base})}{100} \qquad \text{eq. 18}$$

3) Norbornane-2,5-dione, *endo* (27)

Run 1

Time (min.)	M.S. #	% d_0	% d_1	% d_2	% d_3	% d_4
0.0	274	100.0	0.0	0.0	0.0	0.0
1.0	275	5.2	4.2	85.2	5.2	0.0
5.0	276	3.2	4.6	65.7	24.8	1.8
11.0	277	5.4	5.4	45.9	34.8	8.5
20.0	278	3.0	4.0	33.0	43.0	17.1
40.0	279	2.2	3.4	18.5	44.1	31.8
60.0	280	2.3	3.5	14.8	37.8	41.6

Time (min.)	% (d_3 + d_4)	% change in base conc.	Corrected % (d_3 + d_4)	log f_3 (c)
0.0	0.0	0.0	0.0	0.000
1.0	5.2	0.5	5.2	0.024
5.0	26.6	4.0	27.6	0.146
11.0	43.3	9.4	47.4	0.292
20.0	60.1	16.8	70.2	0.560

d_{0_∞}	:	av. of 3.2; 5.4; 3.0; 2.2; 2.3.
d_{1_∞}	:	av. of 4.6; 5.4; 4.0; 3.4; 3.5.
v.p.c. #	:	263
ketone conc. (molar)	:	0.203
NaOD conc. (molar)	:	$(1.58 \pm 0.05_5) \times 10^{-2}$
slope ($min.^{-1}$)	:	2.78×10^{-2}
standard deviation	:	$0.05_6 \times 10^{-2}$
intercept	:	-1.54×10^{-3}
standard deviation	:	4.17×10^{-4}
k_{endo} (stastistically corrected	:	$(3.38 \pm 0.13) \times 10^{-2}$ $l.\ mole^{-1} sec.^{-1}$

Run 2

Time (min.)	M.S. #	% d_0	% d_1	% d_2	% d_3	% d_4
0.0	274	100.0	0.0	0.0	0.0	0.0
1.0	283	3.7	5.1	86.0	5.3	0.0
4.0	284	2.9	5.1	72.1	18.6	1.2
8.0	288	3.6	5.8	57.6	29.4	3.6
15.0	289	2.9	5.6	42.9	39.6	9.1
22.0	290	3.0	6.2	33.2	43.2	14.4

Time (min.)	% (d_3 + d_4)	% change in base conc.	Corrected % (d_3 + d_4)	log f_3 (c)
0.0	0.0	0.0	0.3	0.000
1.0	5.3	0.5	5.3	0.025
4.0	19.8	3.2	20.4	0.104
8.0	33.0	6.6	35.2	0.199
15.0	48.7	12.6	54.7	0.369
22.0	57.6	18.4	68.2	0.543

d^0_∞	:	av. of 2.9; 3.6; 2.9; 3.0.
d_{1_∞}	:	av. of 5.1; 5.8; 5.6; 6.2.
v.p.c. #	:	265
ketone conc. (molar)	:	0.204
NaOD conc. (molar)	:	$(1.27 \pm 0.04) \times 10^{-2}$
slope ($min.^{-1}$)	:	2.46×10^{-2}
standard deviation	:	$0.01_2 \times 10^{-2}$
intercept	:	1.74×10^{-3}
standard deviation	:	9.77×10^{-4}
k_{endo} (statistically corrected)	:	$(3.71 \pm 0.13) \times 10^{-2}$ ($l.\ mole^{-1} sec.^{-1}$)

Averages Run 1 and Run 2

k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	3.54×10^{-2}	
deviation	:	0.16×10^{-2}	(4.5 %)
average error	:	0.13×10^{-2}	(3.7 %)

4) 5-Methylenenorcamphor, *exo* (30)

Run 1

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	244	100.0	0.0	0.0	0.000
3.0	245	62.5	37.5	0.0	0.206
8.0	246	30.0	70.0	0.0	0.534
15.0	247	10.5	89.5	0.0	1.017
25.0	248	3.0	97.0	0.0	1.696
∞	249	1.0	97.4	1.6	-

v.p.c. #	:	255
ketone conc. (molar)	:	0.196
NaOD conc. (molar)	:	$(7.63 \pm 0.28) \times 10^{-3}$
slope ($min.^{-1}$)	:	6.78×10^{-2}
standard deviation	:	$0.02_5 \times 10^{-2}$
intercept	:	-1.32×10^{-2}
standard deviation	:	2.21×10^{-2}
k_{exo} ($l. mole^{-1} sec.^{-1}$)	:	$(3.41 \pm 0.13) \times 10^{-1}$

Run 2

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	244	100.0	0.0	0.0	0.000
3.1	250	62.3	37.7	0.0	0.208
6.0	251	42.2	57.8	0.0	0.373
12.0	252	18.8	81.2	0.0	0.747
20.0	253	7.1	92.8	0.0	1.210
30.0	254	2.7	97.3	0.0	1.791
∞	255	1.1	97.2	1.7	-

v.p.c. #	:	256
ketone conc. (molar)	:	0.212
NaOD conc. (molar)	:	$(6.66 \pm 0.26) \times 10^{3}$
slope ($min.^{-1}$)	:	5.94×10^{-2}
standard deviation	:	0.053×10^{-2}
intercept	:	1.72×10^{-3}
standard deviation	:	5.53×10^{-3}
k_{exo} ($l.$ $mole^{-1}sec.^{-1}$)	:	$(3.42 \pm 0.14) \times 10^{-1}$

Averages Run 1 and Run 2

k_{exo} ($l.$ $mole^{-1}sec.^{-1}$)	:	3.42×10^{-1}	
deviation	:	0.01×10^{-1}	(0.3 %)
average error	:	0.14×10^{-1}	(4.0 %)

5) 5-Methylenenorcamphor, *endo* (30)

Run 1

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	256	100.0	0.0	0.0	0.000
5.5	257	1.4	74.4	24.3	0.123
12.0	258	2.6	50.8	46.6	0.279
15.5	259	1.6	44.8	53.6	0.340
26.0	260	1.4	27.8	70.6	0.549
39.0	261	1.1	16.5	82.5	0.791

v.p.c. #	:	257
d_{0_∞}	:	av. of 1.4; 2.6; 1.6; 1.4; 1.1.
ketone conc. (molar)	:	0.204
NaOD conc. (molar)	:	0.106 ± 0.004
slope ($min.^{-1}$)	:	2.02×10^{-2}
standard deviation	:	$0.05_1 \times 10^{-2}$
intercept	:	1.72×10^{-2}
standard deviation	:	6.56×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(1.22 \pm 0.06) \times 10^{-4}$

Run 2

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	262	100.0	0.0	0.0	0.000
5.0	263	1.1	75.7	23.1	0.114
11.5	264	0.8	55.2	43.9	0.255
22.5	265	1.4	32.2	66.5	0.486
28.5	266	1.0	22.2	76.8	0.652
35.0	267	1.1	18.1	80.8	0.740
46.8	268	1.1	11.9	87.1	0.927

d_{0_∞}	:	av. of 1.1; 0.8; 1.4; 1.0; 1.1; 1.1.
v.p.c. #	:	258
ketone conc. (molar)	:	0.226
NaOD conc, (molar)	:	0.104 ± 0.004
slope ($min.^{-1}$)	:	2.03×10^{-2}
standard deviation	:	$0.07_8 \times 10^{-2}$
intercept	:	2.07×10^{-2}
standard deviation	:	1.22×10^{-2}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(1.25 \pm 0.06) \times 10^{-4}$

Averages Run 1 and Run 2

k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	1.24×10^{-4}	
deviation	:	0.02×10^{-4}	(1.6 %)
average error	:	0.06×10^{-4}	(5.0 %)

6) 6,6-Dimethyl-2-norbornanone, *exo* (24)

Run 1

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	182	100.0	0.0	0.0	0.000
5.0	189	85.5	14.6	0.0	0.070
15.0	190	61.5	38.4	0.0	0.215
30.0	191	39.2	60.8	0.0	0.422
60.0	192	16.1	83.9	0.0	0.842
120.0	193	3.7	96.2	0.0	1.736
∞	194	2.0	96.1	1.9	-

v.p.c. #	:	211
ketone conc. (molar)	:	0.258
NaOD conc. (molar)	:	0.0359 ± 0.0016
slope ($min.^{-1}$)	:	1.44×10^{-2}
standard deviation	:	0.01×10^{-2}
intercept	:	-5.80×10^{-3}
standard deviation	:	4.65×10^{-3}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(1.54 \pm 0.07) \times 10^{-2}$

Run 2

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	182	100.0	0.0	0.0	0.000
5.0	195	84.9	15.1	0.0	0.073
15.0	196	60.4	39.6	0.0	0.227
30.0	197	36.6	63.4	0.0	0.458
60.0	198	13.8	86.3	0.0	0.947
∞	200	2.7	94.6	2.5	-

v.p.c. #	:	212
ketone conc. (molar)	:	0.236
NaOD conc. (molar)	:	0.0347 ± 0.0015
slope ($min.^{-1}$)	:	1.58×10^{-2}
standard deviation	:	$0.01_6 \times 10^{-2}$
intercept	:	-6.65×10^{-3}
standard deviation	:	3.42×10^{-3}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(1.75 \pm 0.08) \times 10^{-2}$

Averages Run 1 and Run 2

k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	1.64×10^{-2}	
deviation	:	0.10×10^{-2}	(6.1 %)
average error	:	0.08×10^{-2}	(4.9 %)

7) 6,6-Dimethyl-2-norbornanone, *endo* (24)

Run 1

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	182	100.0	0.0	0.0	0.000
10.0	201	0.7	85.1	14.2	0.067
23.0	202	0.8	69.0	30.2	0.158
40.0	203	0.8	52.9	46.4	0.267
58.0	204	1.0	36.4	62.5	0.422
80.0	205	1.5	26.4	72.1	0.522

d_{0_∞}	:	av. of 0.7; 0.8; 0.8; 1.0; 1.5.
v.p.c. #	:	213
ketone conc. (molar)	:	0.137
NaOD conc. (molar)	:	0.167 ± 0.06
slope (hrs^{-1})	:	7.01×10^{-3}
standard deviation	:	0.16×10^{-3}
intercept	:	-2.26×10^{-3}
standard deviation	:	4.50×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(2.68 \pm 0.12) \times 10^{-5}$

Run 2

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	182	100.0	0.0	0.0	0.000
10.0	207	0.3	85.3	14.3	0.067
25.5	208	0.4	67.3	32.4	0.168
39.5	209	0.4	53.9	45.6	0.267
59.0	210	0.4	39.1	60.5	0.406
82.5	211	0.6	28.5	70.8	0.539
104.5	212	0.6	21.0	78.5	0.676

d_{0_∞}	:	av. of 0.3; 0.4; 0.4; 0.4; 0.6; 0.6.
v.p.c. #	:	214
ketone conc. (molar)	:	0.123
NaOD conc. (molar)	:	0.162 ± 0.06
slope (hrs^{-1})	:	6.50×10^{-3}
standard deviation	:	0.10×10^{-3}
intercept	:	5.09×10^{-3}
standard deviation	:	3.58×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(2.56 \pm 0.10_5) \times 10^{-5}$

Averages Run 1 and Run 2

k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	2.62×10^{-5}	
deviation	:	0.06×10^{-5}	(3.2 %)
average error	:	0.11×10^{-5}	(4.2 %)

8) 5-Oxocamphene, *exo* (29)

Run 1

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	214	100.0	0.0	0.0	0.000
3.0	215	75.0	25.0	0.0	0.126
8.0	216	46.6	53.3	0.0	0.334
15.0	217	24.2	75.8	0.0	0.625
25.0	218	9.8	90.2	0.0	1.038
35.0	219	4.1	95.8	0.0	1.453
∞	220	0.7	96.6	2.7	-

v.p.c. #	:	219
ketone conc. (molar)	:	0.215
NaOD conc. (molar)	:	0.0122 ± 0.0005
slope ($min.^{-1}$)	:	1.31×10^{-2}
standard deviation	:	3.6×10^{-5}
intercept	:	1.36×10^{-3}
standard deviation	:	4.41×10^{-4}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(1.31 \pm 0.05) \times 10^{-1}$

Run 2

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	214	100.0	0.0	0.0	0.000
2.0	222	83.8	16.2	0.0	0.077
5.0	223	64.3	35.8	0.0	0.195
10.0	224	41.3	58.7	0.0	0.391
20.0	225	17.1	82.8	0.0	0.785
∞	227	1.0	98.0	1.0	-

v.p.c. #	:	221
ketone conc. (molar)	:	0.218
NaOD conc. (molar)	:	$0.0111 \pm 0.0004_5$
slope ($min.^{-1}$)	:	3.93×10^{-2}
standard deviation	:	5.4×10^{-5}
intercept	:	-1.06×10^{-3}
standard deviation	:	3.87×10^{-4}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(1.35 \pm 0.05_5) \times 10^{-1}$

Averages Run 1 and Run 2

k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	1.33×10^{-1}	
deviation	:	0.02×10^{-1}	(1.5 %)
average error	:	0.05×10^{-1}	(3.9 %)

9) 5-Oxocamphene, *endo* (29)

Run 1

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	214	100.0	0.0	0.0	0.000
7.5	228	0.4	79.0	20.6	0.100
16.0	229	0.7	60.1	39.2	0.218
25.5	230	0.5	45.1	54.4	0.344
33.5	231	0.5	35.6	63.9	0.447
47.0	232	0.7	23.4	76.0	0.627

d_{0_∞}	:	av. of 0.4; 0.7; 0.5; 0.5; 0.7.
v.p.c. #	:	222
ketone conc. (molar)	:	0.173
NaOD conc. (molar)	:	0.117 ± 0.005
slope (hrs^{-1})	:	1.33×10^{-2}
standard deviation	:	6.3×10^{-5}
intercept	:	1.52×10^{-3}
standard deviation	:	9.89×10^{-4}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(7.20 \pm 0.29) \times 10^{-5}$

Run 2

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	214	100.0	0.0	0.0	0.000
6.0	233	0.0	83.6	16.4	0.079
13.5	234	1.1	64.8	34.2	0.184
22.5	235	0.3	49.9	49.8	0.303
32.5	236	1.1	36.5	62.4	0.431
46.5	237	0.9	23.6	75.5	0.622
58.5	238	1.1	17.0	81.9	0.759

d_{0_∞}	:	av. of 0.0; 1.1; 0.3; 1.1; 0.9; 1.1.
v.p.c. #	:	223
ketone conc. (molar)	:	0.158
NaOD conc. (molar)	:	0.107 ± 0.004
slope (hrs^{-1})	:	1.31×10^{-2}
standard deviation	:	1.4×10^{-4}
intercept	:	4.33×10^{-3}
standard deviation	:	2.75×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(7.76 \pm 0.33) \times 10^{-5}$

Averages Run 1 and Run 2

k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	7.48×10^{-5}	
deviation	:	0.28×10^{-5}	(3.7 %)
average error	:	0.31×10^{-5}	(4.1 %)

10) 3,3-Dimethyl-5-oxo-2-norbornanone, *endo* (26)

Change in base concentration

The procedure was the same as that use for norbornane-2,5-dione, described in Set of Data # 3. 3,3-Dimethyl-5-oxo-2-norbornanone (78.1 mg) was dissolved in dioxane (1.2 ml). NaOD (0.3 ml, $N \simeq 0.07$) was added and the solution was diluted to 2.0 ml. Results of the titrations of the different aliquots with hydrochloric acid (0.0100N) are shown in the table below:

t (min.)	Aliquot (ml)	Titer (ml)	Titer for 1 ml aliquot (ml)	% Change in base conc.*
0.0	0.5	0.481	0.962	0
90.0	1.0	0.798	0.798	17

* Calculated using eq. 17 (Set of Data # 3).

The results are shown graphically in Fig. III-1. A blank run was made using 1.2 ml dioxane, 0.3 ml NaOD and diluting the solution to 2.0 ml. The liter at t = 0 was 0.960 (1 ml aliquot) and at t = 90 min., the liter was 0.478 ml (0.5 ml aliquot, *i.e.* titer = 0.956 ml for a 1.0 ml aliquot), showing no signifiant change in base concentration.

Corrections in deuterium concentration were made as discussed in the EXPERIMENTAL Section using the following formula:

$$\text{corrected \% } d_2 = \frac{\text{\% } d_2 \ (100 + \text{\% change in base conc.})}{100} \qquad \text{eq. 19}$$

10) 3,3-Dimethyl-5-oxo-2-norbornanone, *endo* (26)

Run 1

Time (min.)	M.S. #	% d_0	% d_1	% d_2	% Change in base conc.	Corrected % d_2	log f_2(c)
0.0	164	100.0	0.0	0.0	0.0	0.0	0.000
0.75	170	5.4	92.3	2.3	0.4	2.3	0.010
10.2	171	3.4	73.5	23.1	2.1	23.6	0.124
20.0	172	2.9	58.4	38.7	3.7	40.0	0.226
30.0	173	1.7	46.9	51.4	5.7	54.3	0.348
45.0	174	1.5	33.9	64.6	8.5	70.1	0.540
60.0	175	1.4	26.2	72.3	11.3	80.5	0.737

d_{0_∞}	:	av. of 1.7; 1.5; 1.4.
v.p.c. #	:	204
ketone conc. (molar)	:	0.267
NaOD conc. (molar)	:	$(1.14 \pm 0.05) \times 10^{-2}$
slope ($min.^{-1}$)	:	1.22×10^{-2}
standard deviation	:	1.9×10^{-4}
intercept	:	-5.03×10^{-3}
standard deviation	:	3.90×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(3.69 \pm 0.18) \times 10^{-2}$

Run 2

Time (min.)	M.S. #	% d_0	% d_1	% d_2	% Change in base conc.	Corrected % d_2	log f_2(c)
0.0	164	100.0	0.0	0.0	0.0	0.0	0.000
1.0	176	2.7	95.3	2.1	0.2	2.1	0.009
10.0	177	2.4	77.5	20.2	1.9	20.6	0.102
20.0	178	2.0	61.6	36.4	3.7	37.7	0.209
30.0	179	1.7	48.1	51.1	5.8	52.9	0.334
45.0	180	1.3	36.7	61.9	8.5	67.1	0.497
60.0	181	1.5	29.0	69.5	11.3	73.9	0.602

d_{0_∞}	:	av. of 1.7; 1.3; 1.5.
v.p.c. #	:	205
ketone conc. (molar)	:	0.267
NaOD conc. (molar)	:	$(1.08 \pm 0.04) \times 10^{-2}$
slope ($min.^{-1}$)	:	1.04×10^{-2}
standard deviation	:	3.0×10^{-4}
intercept	:	2.65×10^{-3}
standard deviation	:	6.39×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(4.09 \pm 0.21) \times 10^{-2}$

Averages Run 1 and Run 2

k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	3.89×10^{-2}	
deviation	:	0.20×10^{-2}	(5.1 %)
average error	:	0.20×10^{-2}	(5.1 %)

11) Epiisofenchone, *exo* (23)

Run 1

Time	M.S. #	% d_0	% d_1	% d_2	log $f_1(c)$
0.0 min.	60	100.0	0.0	0.0	0.000
2.0 min.	61	96.7	3.2	0.0	0.017
11.0 min.	62	83.6	16.5	0.0	0.083
30.0 min.	63	64.3	35.8	0.0	0.210
60.0 min.	64	43.1	56.9	0.0	0.412
105.0 min.	65	24.6	75.5	0.0	0.725
5.01 hrs	66	7.4	91.1	1.5	-
10.00 hrs	67	6.4	91.0	2.7	-
20.50 hrs	68	6.8	87.6	5.6	-
34.75 hrs	69	6.4	85.6	8.3	-
82.00 hrs	70	7.8	79.6	12.6	-

d_{0_∞}	:	av. of 7.4; 6.4; 6.8; 6.4; 7.8.
v.p.c. #	:	178
ketone conc. (molar)	:	0.312
NaOD conc. (molar)	:	$(5.35 \pm 0.10) \times 10^{-2}$
slope ($min.^{-1}$)	:	6.86×10^{-3}
standard deviation	:	0.03×10^{-3}
intercept	:	3.21×10^{-3}
standard deviation	:	1.29×10^{-3}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(9.83 \pm 0.20) \times 10^{-3}$

Run 2

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	71	100.0	0.0	0.0	0.000
5.0	77	86.4	13.6	0.0	0.064
15.0	78	66.6	33.4	0.0	0.182
30.0	79	42.2	57.8	0.0	0.394
60.0	80	22.6	77.4	0.0	0.695
100.0	81	10.5	89.5	0.0	1.111
∞	82	3.0	95.3	1.8	-

v.p.c. #	:	181
ketone conc. (molar)	:	0.307
NaOD conc. (molar)	:	$(4.30 \pm 0.12) \times 10^{-2}$
slope ($min.^{-1}$)	:	1.11×10^{-2}
standard deviation	:	0.03×10^{-2}
intercept	:	1.95×10^{-2}
standard deviation	:	1.05×10^{-2}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(9.92 \pm 0.39) \times 10^{-3}$

Averages Run 1 and Run 2

k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	9.88×10^{-3}	
deviation	:	0.05×10^{-3}	(0.5 %)
average error	:	0.30×10^{-3}	(3.0 %)

12) Epiisofenchone, *endo* (23)

Run 1

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	71	100.0	0.0	0.0	0.000
7.0	83	3.0	89.1	8.0	0.037
15.0	84	2.9	79.5	17.5	0.086
37.5	85	2.1	60.6	37.2	0.207
120.0	87	1.5	24.3	74.3	0.619

d_{0_∞}	:	av. of 3.0; 2.9; 2.1; 1.5.
v.p.c. #	:	182
ketone conc. (molar)	:	0.204
NaOD conc. (molar)	:	0.166 ± 0.005
slope (hrs^{-1})	:	5.14×10^{-3}
standard deviation	:	0.07×10^{-3}
intercept	:	5.30×10^{-3}
standard deviation	:	3.15×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(1.98 \pm 0.07) \times 10^{-5}$

Run 2

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	71	100.0	0.0	0.0	0.000
9.0	89	3.0	82.7	14.2	0.068
21.5	90	2.8	68.5	28.6	0.152
41.5	91	2.2	50.8	47.1	0.288
56.5	92	3.5	39.4	57.1	0.386

d_{0_∞}	:	av. of 3.0; 2.8; 2.2; 3.5.
v.p.c. #	:	183
ketone conc. (molar)	:	0.115
NaOD conc. (molar)	:	0.168 ± 0.006
slope (hrs^{-1})	:	6.80×10^{-3}
standard deviation	:	0.07×10^{-3}
intercept	:	3.93×10^{-3}
standard deviation	:	1.53×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(2.59 \pm 0.10) \times 10^{-5}$

Run 3

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	102	100.0	0.0	0.0	0.000
10.0	103	2.4	87.1	10.6	0.049
24.0	104	2.1	73.5	24.4	0.124
50.0	105	1.3	54.2	44.5	0.262
87.0	106	2.0	35.7	62.4	0.438
119.0	107	1.3	26.2	72.5	0.582

d_{0_∞}	:	av. of 2.4; 2.1; 1.3; 2.0; 1.3.
v.p.c. #	:	186
ketone conc. (molar)	:	0.112
NaOD conc. (molar)	:	0.104 ± 0.005
slope (hrs^{-1})	:	4.92×10^{-3}
standard deviation	:	0.08×10^{-3}
intercept	:	4.57×10^{-3}
standard deviation	:	3.35×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(3.02 \pm 0.14) \times 10^{-5}$

Averages Run 1, Run 2 and Run 3

k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	2.53×10^{-5}	
Standard deviation	:	0.54×10^{-5}	(21 %)
average error	:	0.10×10^{-5}	(4 %)

13) 1-Methyl-5-oxocamphene, *exo* (28)

Run 1

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	94	100.0	0.0	0.0	0.000
2.1	136	89.4	10.7	0.0	0.053
5.0	137	76.2	27.3	0.0	0.124
9.4	138	60.1	40.0	0.0	0.238
14.0	139	47.6	52.3	0.0	0.350
20.3	140	35.0	65.0	0.0	0.505
∞	142	5.4	94.6	0.0	-

v.p.c. #	:	193
ketone conc. (molar)	:	0.234
NaOD conc. (molar)	:	$(1.41 \pm 0.06) \times 10^{-2}$
slope ($min.^{-1}$)	:	2.49×10^{-2}
standard deviation	:	1.22×10^{-4}
intercept	:	1.23×10^{-3}
standard deviation	:	0.86×10^{-3}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(6.76 \pm 0.30) \times 10^{-2}$

Run 2

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	94	100.0	0.0	0.0	0.000
2.1	130	90.4	9.5	0.0	0.045
5.0	131	79.1	21.0	0.0	0.111
9.0	132	65.7	34.2	0.0	0.196
14.0	133	51.0	49.1	0.0	0.320
20.0	134	37.9	62.0	0.0	0.467
∞	135	5.9	92.7	1.5	-

v.p.c. #	:	192
ketone conc. (molar)	:	0.212
NaOD conc. (molar)	:	$(1.18 \pm 0.05) \times 10^{-2}$
slope ($min.^{-1}$)	:	2.33×10^{-2}
standard deviation	:	3.50×10^{-4}
intercept	:	-4.84×10^{-3}
standard deviation	:	9.57×10^{-3}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(7.58 \pm 0.33) \times 10^{-2}$

Run 3

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	94	100.0	0.0	0.0	0.000
3.0	126	81.8	18.1	0.0	0.093
9.2	127	70.6	29.5	0.0	0.161
14.0	128	56.3	43.7	0.0	0.267
20.0	129	43.7	56.3	0.0	0.391
∞	130	4.9	95.0	0.0	-

v.p.c. #	:	191
ketone conc. (molar)	:	0.222
NaOD conc. (molar)	:	$(1.18 \pm 0.05) \times 10^{-2}$
slope ($min.^{-1}$)	:	1.86×10^{-2}
deviation standard	:	0.13×10^{-4}
intercept	:	0.10×10^{-3}
deviation standard	:	9.57×10^{-3}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(6.05 \pm 0.25) \times 10^{-2}$

Avearges Run 1, Run 2 and Run 3

k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	6.80×10^{-2}	
standard deviation	:	0.77×10^{-2}	(11.5 %)
average error	:	0.27×10^{-2}	(4.0 %)

14) 1-Methyl-5-oxocamphene, *endo* (28)

Run 1

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	94	100.0	0.0	0.0	0.000
9.0	114	2.9	72.8	24.3	0.124
21.5	115	2.2	48.4	49.4	0.305
27.0	116	3.5	40.0	56.5	0.377
34.0	117	3.1	33.2	63.6	0.459
42.0	118	1.6	25.8	72.6	0.592
51.0	119	1.9	21.3	76.7	0.671

d_{0_∞}	:	av. of 2.9; 2.2; 3.5; 3.1; 1.6; 1.9.
v.p.c. #	:	188
ketone conc. (molar)	:	0.162
NaOD conc. (molar)	:	0.118 ± 0.005
slope (hrs^{-1})	:	1.34×10^{-2}
standard deviation	:	$0.03_4 \times 10^{-2}$
intercept	:	7.33×10^{-3}
standard deviation	:	5.61×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(7.25 \pm 0.34) \times 10^{-5}$

Run 2

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	94	100.0	0.0	0.0	0.000
4.5	120	2.7	85.5	11.9	0.057
13.5	121	2.5	64.4	33.2	0.179
19.5	122	1.6	51.7	46.7	0.281
30.0	123	1.3	37.5	61.2	0.425
42.0	124	1.4	27.3	71.3	0.564

d_{0_∞}	:	av. of 2.7; 2.5; 1.6; 1.3; 1.4.
v.p.c. #	:	189
ketone conc. (molar)	:	0.153
NaOD conc. (molar)	:	0.120 ± 0.005
slope (hrs^{1})	:	1.37×10^{-2}
standard deviation	:	$0.03_4 \times 10^{-2}$
intercept	:	9.27×10^{-4}
standard deviation	:	4.87×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(7.30 \pm 0.34) \times 10^{-5}$

Averages Run 1 and Run 2

k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	7.28×10^{-5}	
deviation	:	0.03×10^{-5}	(0.4 %)
average error	:	0.34×10^{-5}	(4.7 %)

15) Fenchane-2,5-dione, *endo* (25)

Change in base concentration

The procedure was the same as that use for norbornane-2,5-dione (Set of Data # 3) and 3,3-dimethyl-5-oxo-2-norbornanone (Set of Data # 10). Fenchane-2,5-dione (304 mg) was dissolved in dioxane (4.2 ml). Sodium hydroxide (11.7 mg) in D_2O) (2.8 ml) was added at $t = 0$. The titers of the different aliquots (1 ml) are shown in the table below and in a graphical form in Fig. III-1.

Time (min.)	Titer (ml)	% Change in* base conc.
0.0	0.580	0.0
15.0	0.556	4.1
45.0	0.529	8.6
60.0	0.503	13.3

* Calculated using eq. 17 (Set of Data # 3).

In a blank run using 12.6 mg NaOH, 4.2 ml dioxane and 2.8 ml D_2O, the titers of the different aliquots were as follows:

Time (min.)	Titer (ml)
0	0.839
18	0.830
30	0.845
45	0.825
60	0.830

These results show no significant change in base concentration. Corrections in deuterium concentration were made as discussed in the EXPERIMENTAL using eq. 19 (Set of Data # 10).

13) Fenchane-2,5-dione, *endo* (25)

Run 1

Time (min.)	M.S. #	% d_0	% d_1	% d_2	% Change in base conc.	Corrected % d_2	log f_2 (c)
0.0	37	100.0	0.0	0.0	0.0	0.0	0.000
1.0	38	10.8	84.4	5.3	0.2	5.3	0.021
4.0	39	5.4	75.2	19.3	0.9	19.4	0.097
11.2	40	4.9	51.9	43.2	2.4	44.2	0.267
20.0	41	4.0	35.2	61.4	4.3	64.1	0.490
30.0	42	1.8	24.8	73.6	6.5	78.5	0.736

d_{0_∞}	:	av. of 5.4; 4.9; 4.0; 1.8.
v.p.c. #	:	172
ketone conc. (molar)	:	0.268
NaOD conc. (molar)	:	$(2.12 \pm 0.10) \times 10^{-2}$
slope ($min.^{-1}$)	:	2.46×10^{-2}
standard deviation	:	$0.01_4 \times 10^{-2}$
intercept	:	-2.94×10^{-3}
standard deviation	:	1.57×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	4.45×10^{-2}

Run 2

Time (min.)	M.S. #	% d_0	% d_1	% d_2	% Change in base conc.	Corrected % d_2	log f_2 (c)
0.0	43	100.0	0.0	0.0	0.0	0.0	0.000
1.0	44	8.9	86.5	4.8	0.2	4.8	0.021
4.2	45	8.2	79.2	12.6	0.9	12.7	0.061
11.1	46	5.6	69.4	24.9	2.4	25.5	0.134
20.0	47	4.9	58.4	36.6	4.3	38.2	0.223
30.0	48	3.8	49.1	47.1	6.5	50.2	0.322
42.0	49	3.1	41.3	55.5	9.1	60.6	0.436

d_{0_∞}	:	av. of 5.6; 4.9; 3.8; 3.1.
v.p.c. #	:	173
ketone conc. (molar)	:	0.266
NaOD conc. (molar)	:	$(8.28 \pm 0.15) \times 10^{-3}$
slope ($min.^{-1}$)	:	1.02×10^{-2}
standard deviation	:	0.02×10^{-2}
intercept	:	1.26×10^{-2}
standard deviation	:	3.11×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(4.72 \pm 0.12) \times 10^{-2}$

Run 3

Time (min.)	M.S. #	% d_0	% d_1	% d_2	% Change in base conc.	Corrected % d_2	log f_2 (c)
0.0	56	100.0	0.0	0.0	0.0	0.0	0.000
1.1	57	5.4	87.2	7.4	0.2	7.4	0.033
4.0	58	3.3	72.4	24.4	0.8	24.6	0.127
11.5	59	1.9	45.0	53.2	2.4	54.5	0.352
30.0	60	1.2	18.1	80.6	6.7	86.0	0.915

d_{0_∞}	:	av. of 3.3; 1.9; 1.2.
v.p.c. #	:	174
ketone conc. (molar)	:	0.267
NaOD conc. (molar)	:	$(2.56 \pm 0.13) \times 10^{-2}$
slope ($min.^{-1}$)	:	3.05×10^{-2}
standard deviation	:	$0.01_0 \times 10^{-2}$
intercept	:	1.63×10^{-3}
standard deviation	:	1.08×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(4.54 \pm 0.23) \times 10^{-2}$

Averages Run 1, Run 2 and Run 3

k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	4.57×10^{-2}	
standard deviation	:	0.31×10^{-2}	(6.8 %)
average error	:	0.18×10^{-2}	(4.0 %)

16) 6-Methylene-2-norbornanone, *exo* (31)

Run 1

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	333	100.0	0.0	0.0	0.000
10.0	340	67.1	32.8	0.0	0.176
20.0	341	46.4	53.6	0.0	0.340
30.0	342	32.8	67.3	0.0	0.497
40.0	343	23.6	76.4	0.0	0.644
50.0	344	17.2	82.7	0.0	0.788
∞	345	1.2	95.8	3.0	-

v.p.c. #	:	303
ketone conc. (molar)	:	0.204
NaOD conc. (molar)	:	$(8.79 \pm 0.39) \times 10^{-3}$
slope ($min.^{-1}$)	:	1.57×10^{-2}
standard deviation	:	2.99×10^{-4}
intercept	:	1.46×10^{-2}
standard deviation	:	5.11×10^{-3}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(6.86 \pm 0.32) \times 10^{-2}$

Run 2

Time (min.)	M.S. #	% d_0	% d_1	% d_2	log f_1 (c)
0.0	333	100.0	0.0	0.0	0.000
7.0	346	76.5	23.4	0.0	0.118
15.0	347	58.0	42.0	0.0	0.228
25.0	348	41.7	58.2	0.0	0.391
35.0	349	30.4	69.6	0.0	0.539
46.0	350	22.2	77.8	0.0	0.688
∞	351	2.1	94.1	3.9	-

v.p.c. #	:	304
ketone conc. (molar)	:	0.210
NaOD conc. (molar)	:	$(8.14 \pm 0.36) \times 10^{-3}$
slope ($min.^{-1}$)	:	1.50×10^{-2}
standard deviation	:	2.27×10^{-4}
intercept	:	7.40×10^{-3}
standard deviation	:	3.60×10^{-3}
k_{exo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(7.08 \pm 0.33) \times 10^{-2}$

Averages Run 1 and Run 2

k_{exo} ($l.\ mole^{-1} sec.^{-1}$) : 6.97×10^{-2}

deviation	:	0.11×10^{-2}	(1.6 %)
average error	:	0.32×10^{-2}	(4.6 %)

17) 6-Methylene-2-norbornanone, *endo* (31)

Run 1

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	313	100.0	0.0	0.0	0.000
5.0	327	1.8	74.2	23.8	0.121
8.5	328	1.6	61.1	37.1	0.204
11.9	329	1.0	51.1	47.9	0.288
15.0	330	1.0	43.0	55.9	0.364
22.5	331	1.1	28.4	70.5	0.544
26.5	332	1.3	22.9	75.8	0.634

d_{0_∞}	:	av. of 1.8; 1.6; 1.0; 1.0; 1.1; 1.3.
v.p.c. #	:	301
ketone conc. (molar)	:	0.194
NaOD conc. (molar)	:	0.115 ± 0.004
slope (hrs^{-1})	:	2.40×10^{-2}
standard deviation	:	1.10×10^{-4}
intercept	:	1.21×10^{-3}
standard deviation	:	9.55×10^{-4}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(1.34 \pm 0.05) \times 10^{-5}$

Run 2

Time (hrs)	M.S. #	% d_0	% d_1	% d_2	log f_2 (c)
0.0	333	100.0	0.0	0.0	0.000
3.0	334	3.4	81.2	15.4	0.074
8.0	335	1.8	62.5	35.7	0.196
13.0	336	2.1	48.4	49.5	0.303
22.0	337	1.1	29.4	69.4	0.529
27.0	338	1.0	22.6	76.4	0.647
33.0	339	1.1	17.5	81.5	0.761

d_{0_∞}	:	av. of 1.8; 2.1; 1.1; 1.0; 1.1.
v.p.c. #	:	302
ketone conc. (molar)	:	0.186
NaOD conc. (molar)	:	0.115 ± 0.004
slope (hrs^{-1})	:	2.34×10^{-2}
standard deviation	:	3.34×10^{-4}
intercept	:	4.69×10^{-3}
standard deviation	:	3.87×10^{-3}
k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	$(1.31 \pm 0.05) \times 10^{-5}$

Averages Run 1 and Run 2

k_{endo} ($l.\ mole^{-1} sec.^{-1}$)	:	1.32×10^{-5}	
deviation	:	0.02×10^{-5}	(1.5 %)
average error	:	0.05×10^{-5}	(3.7 %)

D. LEAST-SQUARE PROGRAM FOR CDC 7040

```
C-----LEAST SQUARES PROGRAM.
      DIMENSION X(40), Y(40)
  100 READ 1, N
      IF(N.EQ.0) GO TO 101
    1 FORMAT(I3)
      DO 2 J = 1,N
    2 READ 3, X(J), Y(J)
    3 FORMAT(2F10.0)
      A = N
      SIGX = 0.0
      SGDXY = 0.0
      SGDX2 = 0.0
      SIGY = 0.0
      SIGY2 = 0.0
      SIGXY = 0.0
      DO 4 I = 1,N
    4 SIGX = SIGX + X(I)
      XBAR = SIGX/A
      DO 5 L = 1,N
      DELX = X(L) - XBAR
      SGDXY = SGDXY + Y(L)*DELX
      SGDX2 = SGDX2 + DELX**2
      SIGY2 = SIGY2 + Y(L)**2
      SIGY = SIGY + Y(L)
      SIGXY = SIGXY + X(L)*Y(L)
    5 CONTINUE
      SLOPE = SGDXY/SGDX2
      SYDX2 = (SIGY2 - ((SIGY**2)/A) - SLOPE*SIGXY + (SLOPE*SIGX*SIGY/A)
     1)/(A - 2.0)
```

```
      SB = SQRT(SYDX2/SGDX2)
      YBAR = SIGY/A
      CEPT = YBAR - SLOPE*XBAR
      SA = SQRT(SYDX2/A)
      PRINT 6, SLOPE, SB
    6 FORMAT(1H0,4X,8HSLOPE  =,E14.6,5X,20HSTANDARD DEVIATION =,E13.6)
      PRINT 7, CEPT, SA
    7 FORMAT(1H0,12HINTERCEPT  =,E14.6,5X,20HSTANDARD DEVIATION =,E13.6)
      PRINT 8
    8 FORMAT(1H0,15X,10H**********)
      GO TO 100
  101 CALL EXIT
      END
        6400 END OF RECORD
```

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