HOMOENOLIZATION AND REARRANGEMENT OF BICYCLIC MONOKETONES AND DIKETONES

by

© SHAHIN YEROUSHALMI, M.SC.

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HOMOENOLIZATION AND REARRANGEMENT OF BICYCLIC MONOKETONES AND DIKETONES

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ABSTRACT

The H-D exchange and rearrangement of 3,3,6,6-tetramethyl[2.2.1]-heptane-2,5-dione (63a), 3,3,6,6-tetramethylbicyclo[2.2.1]heptan-2-one (63d) and 1,3,3-trimethylbicyclo[2.2.2]octane-2,5-dione (64) in 0.7 - 1.3 M K^+ t-BuO^-/t-BuOD(H) at 175°C were examined. Preliminary work on the dithione 63b and monothiomonoketone 63c has also been carried out.

The substrates 3,3,6,6-tetramethylbicyclo[2.2.1]heptan-2-one (63d), 3,3,6,6-tetramethyl-5-oxo-bicyclo[2.2.1]heptane-2-thione (63c), and 3,3,6,6-tetramethylbicyclo[2.2.1]heptane-2,5-dithione (63b), which have not been reported in the literature previously, were synthesized.

Approximate pseudo-first-order rate constants for the exchange at different sites were calculated from the H-D exchange data. The results suggested that the effect of the second carbonyl group in the exchange of the diones under homoenolization conditions, appeared to be due largely to an inductive and field effect, with small homoconjugative participation.

In addition, homoenolization of 3,3,6,6-tetramethylbicyclo[2.2.1]-heptane-2,5-dione (63a) resulted in rearrangement to 1,3,3-trimethylbicyclo-[2.2.2]octane-2,5-dione (64), via a novel β-homoenolate switch. This is the first report of such a rearrangement when the homoenolate is generated by deprotonation of a ketone. When dione 64 was treated under homoenolization conditions, it underwent unusually rapid H-D exchange of the hydrogens of the bridgehead methyl group. The facile exchange can be explained if a carbon analogue of the acyloin rearrangement is invoked, the first example of

such a rearrangement in a non-aromatic system. Monoketone 63d underwent H-D exchange at the bridgehead and the syn-H-7 position as well as at the hydrogens of the C-3 methyl group and the hydrogens of the endo-11-methyl group. It was also found that 1,3,3-trimethylbicyclo[2.2.1]heptan-2-one, (fenchone), (29), previously studied by others, also underwent exchange at the syn-7-position.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

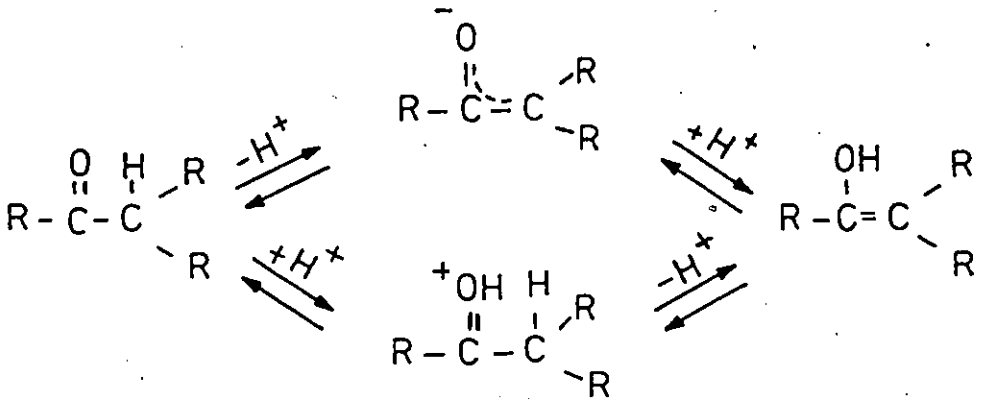
Homoenolization and Rearrangement of Bicyclic Monoketones and Diketones

CHAPTER 1

INTRODUCTION

1.1 Keto-Enol Equilibrium

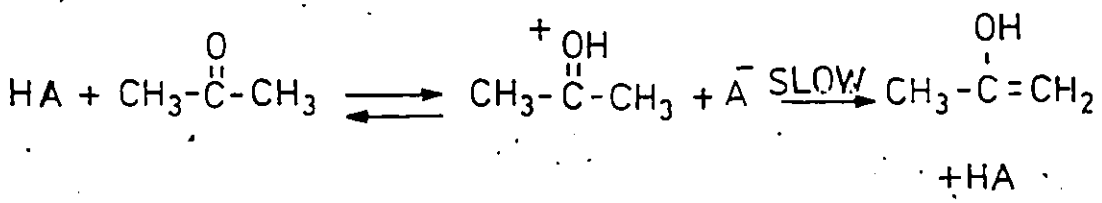
Almost all carbonyl containing compounds are enolizable, but the composition at equilibrium (enol ⇄ keto) depends on factors such as the structure of a monocarbonyl compound, the number of carbonyl groups in compounds having more than one, and on the relative positions of these carbonyl groups to each other. Extensive studies have been carried out to determine keto-enol equilibrium constants by chemical or physical methods (1-17). Scheme 1 shows the general mechanistic features of the interconversion of carbonyl compounds and enols.



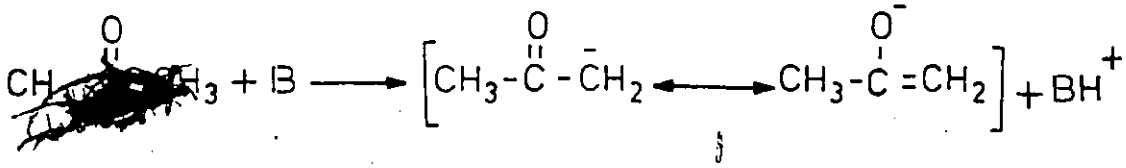
SCHEME 1

1.2 Mechanism of Enolization

Enolization of ketones can be catalyzed by both acid and base. Two distinct steps are believed to be involved in acid-catalyzed enolization (18). The first step is pre-equilibrium protonation of carbonyl oxygen. The second step, which is rate-determining, involves abstraction of an alpha-hydrogen by conjugate base A^-, to form the enol.

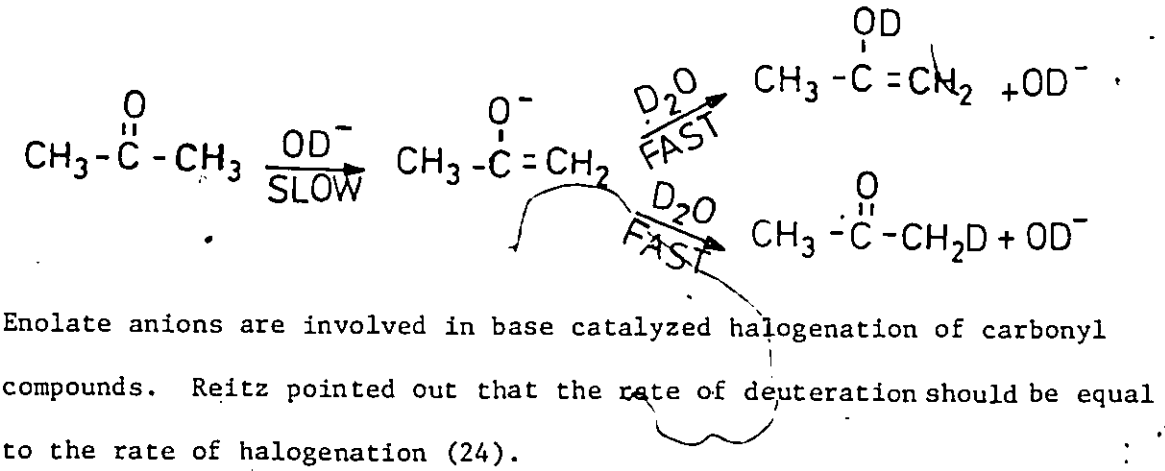


The reaction of ketone with base is simpler and the enolate ion is formed directly by proton abstraction.



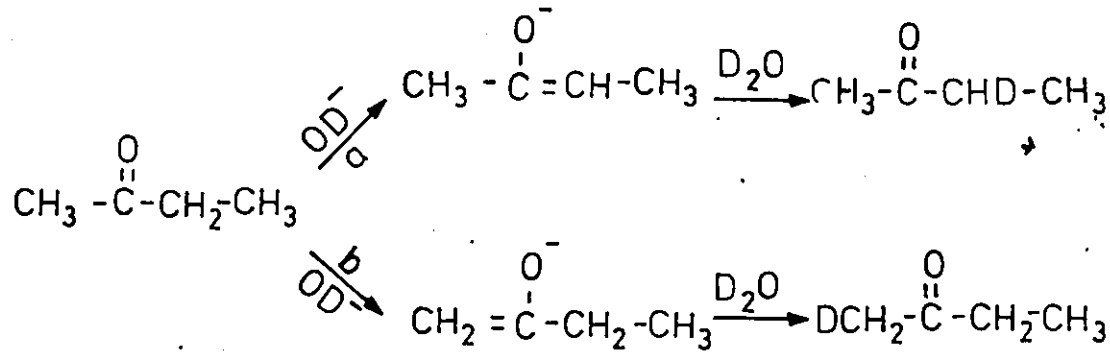
Since enolate ions can function as both carbon and oxygen nucleophiles (19-23), the name "enolate" is more suitable than simply "carbanion". Abstraction of a proton from a carbon alpha to the carbonyl is much easier than removal of a proton from a carbon further removed from the group because of the charge delocalization.

Hydrogen-deuterium exchange for acetone in basic solutions occurs via the enolate ion and the rate-determining step is enolate formation.



Enolate anions are involved in base catalyzed halogenation of carbonyl compounds. Reitz pointed out that the rate of deuteration should be equal to the rate of halogenation (24).

Substituent effects on the rates of enolization of ketones is one area which has been extensively examined recently. The simplest case that can be considered is 2-butanone where there are two sites containing alpha hydrogens as is shown in Scheme 2.



SCHEME 2

Are the exchange rates anticipated to be equal? This depends on the conditions under which the reaction is carried out. In OD^-/D_2O both sites are active (25,26). Under acidic conditions the methylene is exchanged preferentially. Radioactive iodine was used to study the rate of exchange of the hydrogens of the methyl and methylene groups in 2-butanone; progress of the reaction was followed by monitoring the activity of the iodoform and iodopropionic acid products (27). The results from these studies demonstrate that in basic media preferential enolization takes place at the methyl group but in acid media it occurs at the methylene group. Other substituents af-

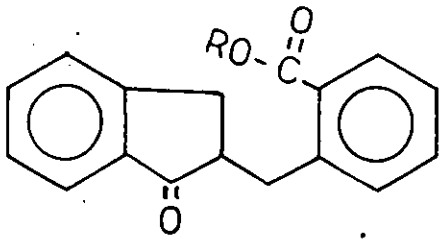
fect enolization rates by both steric and electronic effects. For each substituent each of the above factors will contribute differently and therefore it is difficult to predict the preferred site of enolization. For example, the effect of a halogen substituent on the enolization sites is complex (28,29).

1.3 Stereoelectronic, Inductive and Strain Effects

Maximum stabilization of an enolate anion is achieved when the four atomic centers bonded to the carbon-carbon double bond of the enolate ion are coplanar. Theoretical calculations by Wolfe and coworkers (30) on the acetaldehyde enolate anion show that the energy minimum for this anion occurs when all groups are co-planar. The C-C and C-O bond lengths were found to be consistent with the usual description. Using a non-empirical

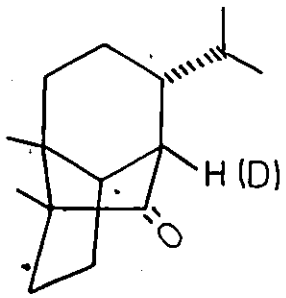
SCF-MO method, a conformation hypersurface was obtained using an STO-3G basis set, to obtain the C-C and C-O bond lengths as a function of rotation about the C-C bond. The rotation inversion surface was produced with an STO-4G basis set. Enolate stability was determined by conjugative and inductive effects. The calculations confirmed that (i) the conjugative effect dominates (a stabilization of greater than 30 kcal/mole based on the barrier to rotation) and any system which allows double bond formation would surely give a planar enolate and (ii) inductive effects are also important, and that (iii) when the orbital containing the lone pair is forced to be perpendicular to the carbonyl π-system (e.g., ring constraint) a pyramidal anion is favored

and there is a significant barrier to inversion. There has been only one case where a non-planar enolate was implicated. Ketone 1 is known to undergo halogenation at the α-carbon with retention of configuration (31-33). The degree of retention at the asymmetric centre depends on the solvent and halogenating reagent used.



1

In simple carbonyl compounds removal of an α-proton is usually facile, but exchange of the α-hydrogen at the bridgehead of a fused ring system requires vigorous alkaline conditions. For example, in order for the indicated bridgehead hydrogens in copacamphor 2 and in ent-17-norkauran-16-one 3 to undergo exchange, very strong base (K^+ t-BuO^-) and high temperature, 185°C for 2 (34) and 172°C for 3 (35), are required. In both of the above examples the bridgehead enolates involve a transoid double bond in a seven-membered ring. In contrast Nickon and coworkers (36) have



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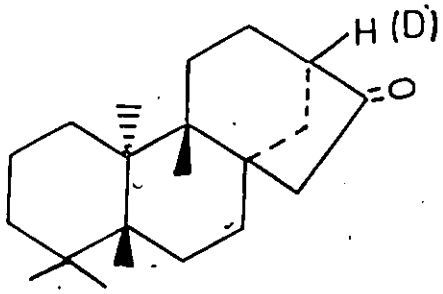
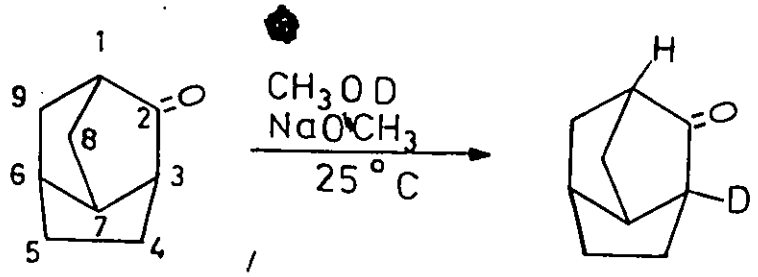


3

documented examples of unusually facile bridgehead enolizations, where the bridgehead enolates involved are transoid in a seven-membered ring (anti-Bredt-enolate). For example the bridgehead exchange at C-3 of brendan-2-one 4 occurs readily in $CH_3OD/NaOCH_2$ at 25°C (36).



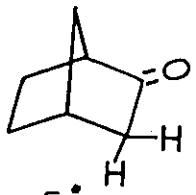
4

Differences in exchange rates can be the result of several factors in general: the degree of "s" character in the (C-H) carbon-hydrogen bonds (37-38), and the inductive stabilization of the carbanion by the carbonyl group (40).

The "s" character of the carbon hydrogen (C-H) bonds of cyclopropane is known to be greater than that of acyclic hydrocarbons (37-39, 41). Work by Shatenshtein (42) showed that the relative rates of hydrogen-deuterium exchange of some cyclopropanes in deuterated ammonia and base such as potassium amide, are greater than those of acyclic hydrocarbons.

In addition there are numerous examples of large rate differences in base-catalyzed hydrogen-deuterium exchange of endo and exo protons in bicyclic systems. The exchange rate differences can be explained in terms of either differing rates of exo and endo reprotonation of a planar anion or in terms of the formation of two non-planar anions. For example base

catalyzed hydrogen-deuterium exchange in 2-norbornanone, 5 was reported to be stereoselective (43).



5

Gassman and Zalar in 1966 (44) presented evidence showing that the inductive effect alone can change the acidity of a C-H bond. They examined a series of strained bicyclic and tricyclic ketones. These ketones were chosen in such a manner that in each case formation of an enolate (enolization) was not possible, since the geometrical requirement[1] for double bond formation at the bridgehead cannot be accommodated. It was demonstrated that the degree of acidity of the bridgehead hydrogen is due purely to the inductive effect of the carbonyl group. Two of these examples were the hydrogen-deuterium exchange in 7-norbornanone 6 and nortricyclanone 7 under forcing conditions. In t-butyl alcohol-OD containing potassium t-butoxide, 7-norbornanone 6 exchanges 25% of the hydrogens at

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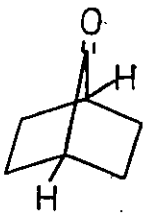
1 The most stable geometry for a double bond is that in which the axes of the two p orbitals are parallel and four groups attached to the ethylenic carbon lie in the same plane. If the orbitals are forced to lie at right angles no overlap can occur, and consequently none of the properties of a double bond may be expected for the system.



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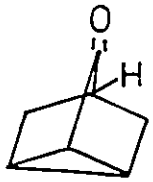
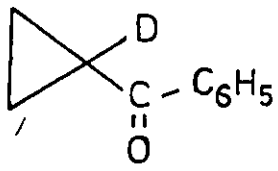


7

C-1 and C-4 in 48 hours at 200°C. Nortricyclanone 7 undergoes exchange more readily at several centers (36% after 24 h at 200°C). One other case that can be presented to illustrate the influence of steric strain on the enolization and isotopic exchange rate involves carbonyl compounds with cyclopropyl substituents. Introduction of a double bond exocyclic to a cyclopropane should be an energetically unfavourable process, because of the large deviation from the normal sp^2 bond angle. The results of several studies (45,15a) are in accord with this prediction. For example, the relative rates of enolization in compounds 8 and 9 are 1 and 170, respectively, even though the cyclopropane should have a lower pKa.



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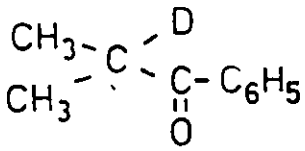

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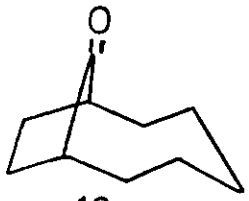
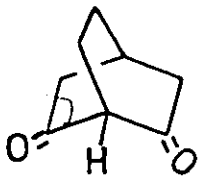
In the larger size rings normal reactivity has been observed. Ketone 10 exchanges readily at the bridgeheads in aqueous base (46).



10

In β-diketones a rate increase would be expected because of the increased acidity of the α-proton. However for effective resonance stabilization and facile proton abstraction, the coplanar requirement for stable anions must be met. For example, the hydrogen at the bridgehead carbon of the bicyclic β-diketone 11 exchanges much more slowly than the hydrogens of the monocyclic analogue 12 (47). In compound 11 formation of a stabilized enolate by abstraction of a proton from the bridgehead



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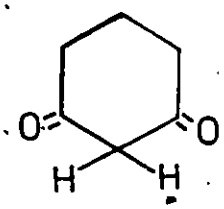
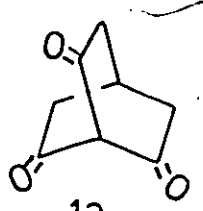


12

requires double bond character at the bridgehead. The strain energy of this process is adverse to the enolization.

A dramatic reduction in the acidity of an alpha proton relative to

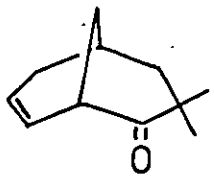
that in a monocyclic carbonyl compound is also observed in bicyclooctanetrione 13, which does not enolize detectably (48). There is no OH band in the infrared spectrum, it does not dissolve in base and when it is reacted



13

with diazomethane, no enol ether is formed nor is any methane discharged in a Zerewittenoff[2] determination.

The strain energy factor is also connected with the size of the ring. For example, some bridgehead olefins with eight carbons or more, which are generally stable, have been synthesized. In addition Marvell and coworkers (49) have observed bridgehead exchange in 14 under relatively



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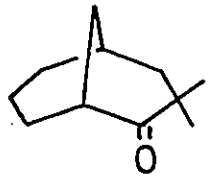


14

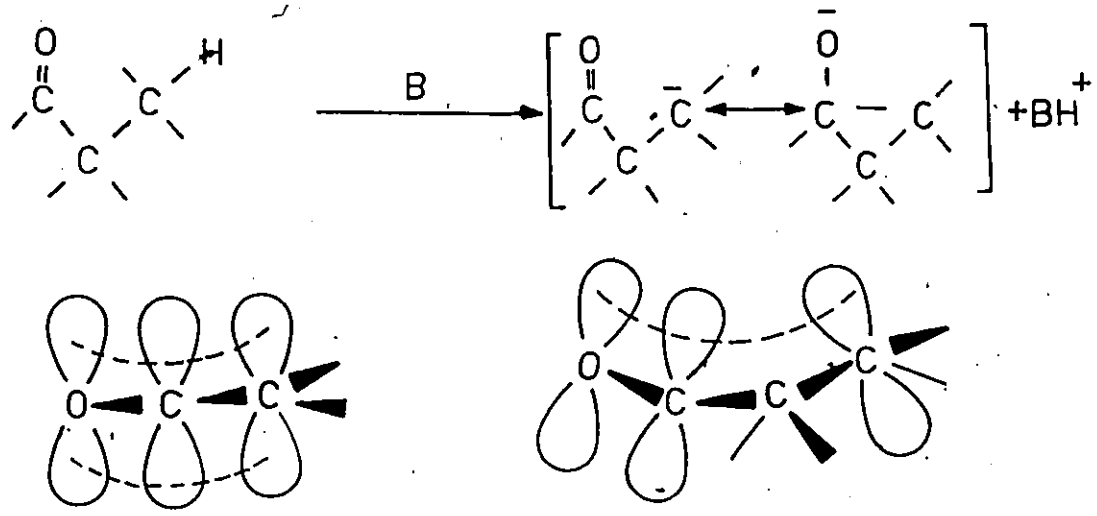
2 In the Zerewittenoff process the number of moles of active hydrogen in an unknown compound is determined by treatment of the compound with methyl magnesium bromide and measurement of the volume of methane evolved.

mild conditions (CH_3ONa/CH_3OD at 100.8°C) with a rate constant of exchange of 0.67×10^{-4} ℓ/mol. sec. However, in 15 the rate constant for exchange at the bridgehead is 30 times smaller, (1.96×10^{-6} ℓ/mol.sec), and this difference was attributed partly to conformational influences.

1.4 Homoenolization and Homoenolate Ions

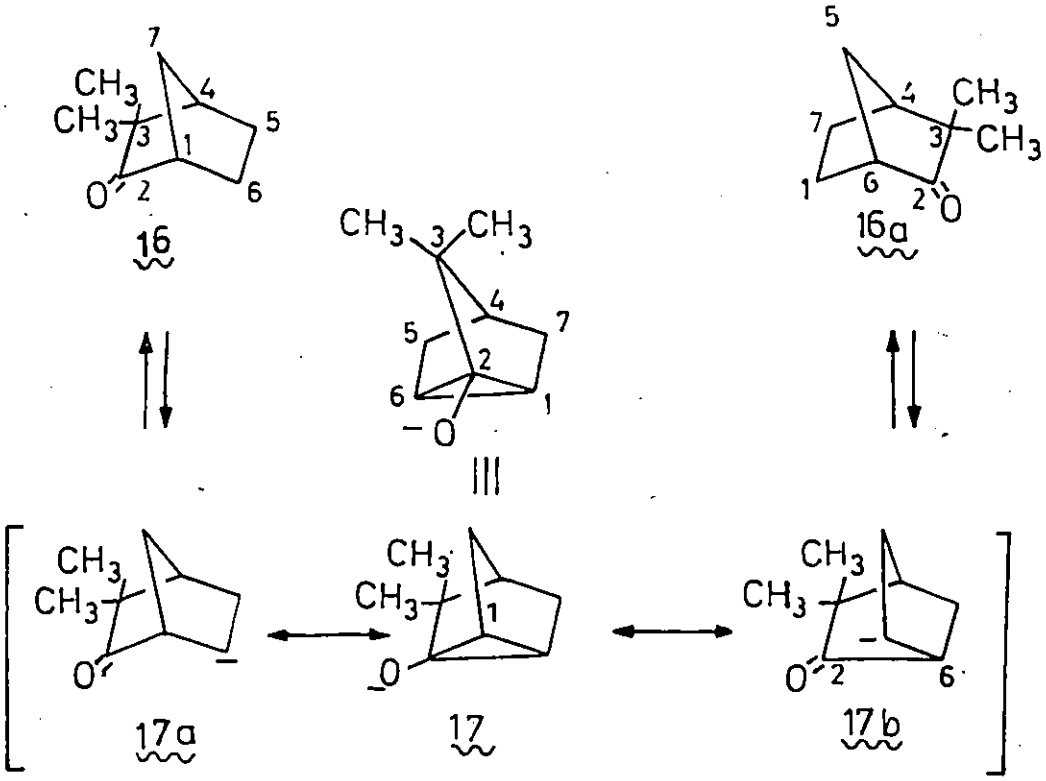
Removal of a proton from the α-position of a carbonyl compound leads to an α-enolate anion, whereas proton abstraction from a remote position leads to β-,γ-, or δ-enolates. This process is referred to as homoenolization. The relative orientations of the anionic centre and the π-system of the carbonyl group are expected to play a very important role in allowing sufficient overlap of orbitals. In the case of nonconjugated systems a ring structure provides the most favourable environment for orbital overlap, because the atoms have a fixed relative orientation.

Through homoallylic resonance, an anion can interact with a carbonyl group to form a homoenolate ion as shown in Scheme 3.



SCHEME 3

It was not until the early nineteen sixties that the first report of a study of the homoenolization of a bicyclic ketone was presented by Nickon and Lambert (50). A hydrogen alpha to a carbonyl group is acidic and its removal by base gives an anion which is stabilized by conjugation with the π-system of the carbonyl group. In the case of removal of a hydrogen β-, or γ-, to a carbonyl group, where stabilization occurs via homoconjugation, vigorous reaction conditions are required relative to a simple α-enolization. Nickon and Lambert (50,51) studied optically active camphenilone 16, and showed that at high temperatures (185°C) in 0.7 M potassium t-butoxide in t-butyl alcohol, (+)-camphenilone 16a racemized. To establish that loss of optical activity was not due to the elevated temperature, they showed that camphenilone does not racemize at 250°C in the absence of t-butoxide. The results were rationalized by the mechanism shown in Scheme 4.



SCHEME 4

A proton is abstracted from carbon 6 (C-6) and a symmetrical homoenolate anion 17 is formed. Ketonization of the symmetrical homoenolate leads to a racemization. Further evidence for the abstraction of a proton at the β-position was obtained when the same experiments were repeated using t-butoxide in t-butyl alcohol-OD at 185°C. The recovered material was racemized and had incorporated up to three atoms of deuterium per molecule. The deuterium content was determined mass spectrometrically. Uptake of up to three deuterium atoms can be explained in terms of the homoenolate anion 17, which allows exchange of two protons at C-6 and also the proton at C-1. When the ketone was treated for prolonged periods under homoenolization conditions, deuterium was incorporated into the methyl groups as well[3]. If the amount of racemization is compared to the extent of deuterium incorporation in camphenilone, more information is obtained about the homoenolate ion. From Table I it is evident that the percentage of racemization corresponds closely to the percentage of molecules containing deuterium. This correlation between racemization and deuterium incorporation means, according to Nickon and Lambert, "(a) that the first hydrogen exchanged is at a location that leads to a racemizable ion (this can only be at C-6), and (b) that the homoenolate ion formed by loss of a C-6 hydrogen racemizes before it can pick up deuterium from the solvent. Consequently, the homoenolate anion either has a symmetrical structure or, if it is unsymmetrical, it rearranges to its enantiomer faster than it reverts to ketone".

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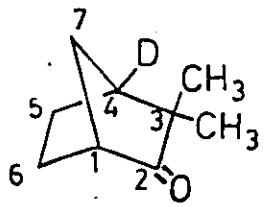
3 To exclude the possibility that the alkaline treatment was vigorous enough to exchange non-activated hydrogens, Nickon and coworkers (51) carried out an experiment using the corresponding hydrocarbon camphenilane. No significant incorporation was observed after 260 hours at 185°C.

TABLE I

Exchange and Racemization of Camphenilone in K^+ t-BuO$^-$/t-BuOD at 185°C (50)

Time (hours)	Percent species		Percent racemized
	No D	one or more D	
12	75	25	26
24	48	52	52
36	29	71	69
48	13	87	88

For clarification of the probable position of exchange in camphenilone, 18 and 19 were examined by treating them under the same conditions used to exchange camphenilone.



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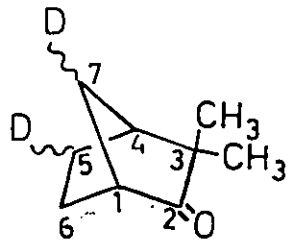


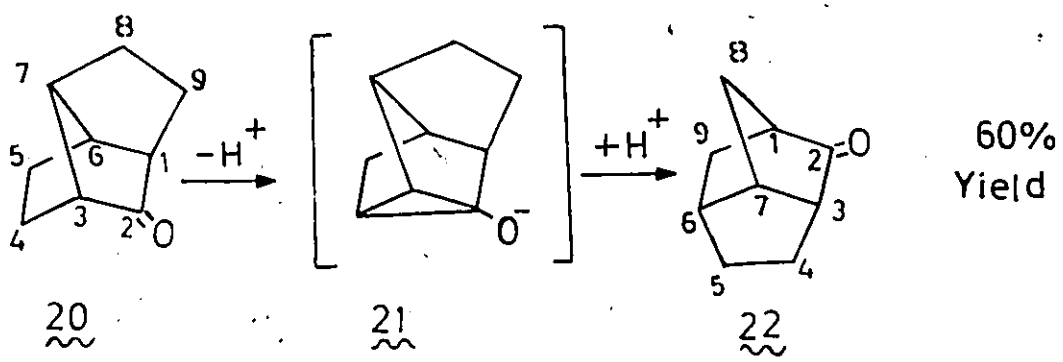
19

No detuerium loss was observed from C-4 of 18 or from C-5 and C-7 of 19. On this basis it was deduced that deuterium was incorporated into the methyl groups. It is noteworthy that C-1 and C-6 are scrambled via the homoenolate thereby precluding an accurate determination of the rate for bridgehead exchange in 16.

Subsequent to the first report of homoenolization by Nickon and Lambert (50), various acyclic and bicyclic carbonyl containing compounds have been investigated under homoenolization conditions. In the last decade several reviews on the preparation and reactions of homoenolate anions have appeared (52-55). Hence in the next three sections only a few examples of special interest will be cited for β- and γ-enolization. For completeness, the systems which have been studied, and the intermediates, are listed in Table II. In the last section a few examples of the reverse reaction, homoketonization, will be presented.

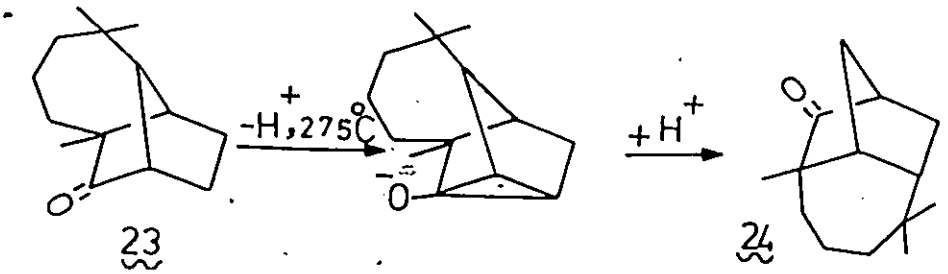
1.5 β-Enolization

One potential synthetic use of homoenolization is the construction of polycyclic systems which are difficult to prepare by direct synthetic routes. Such an example is the rearrangement of the tricyclic ketone brexan-2-one 20 to the isomeric ketone brendan-2-one 22 (56) when 20 is treated under homoenolization conditions (t-BuOH, K^+ t-BuO^- at 185°C). This transformation most likely proceeds through the homoenolate ion 21 which can be obtained by deprotonation at either C-4 or C-9. The authors concluded that the probable driving force in going from 20 to 22 is relief of strain, 22 presumably being more stable thermodynamically than 20. Coates

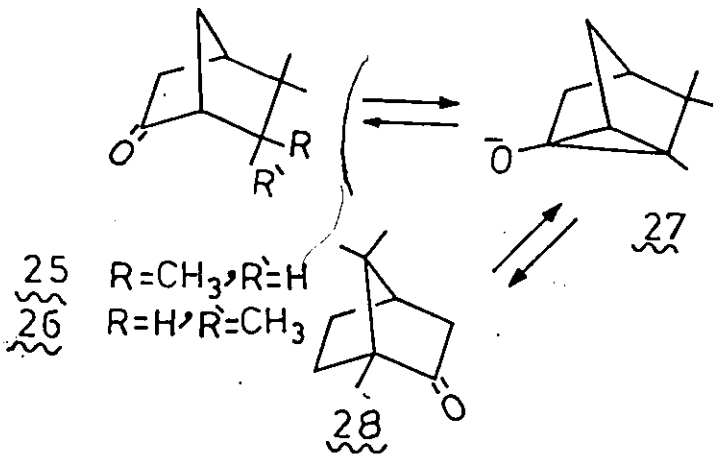


20 21 22

and Chen (46) have documented β-enolate formation in the equilibration of longicamphenilone 23 with the isomeric ketone 24, under homoenolization conditions.



In 1972 the first example of remote epimerization via homoenolate ion formation was reported by Hunter and coworkers (58), (see Scheme 5). A more detailed study by Nickon appeared in 1976 (59).

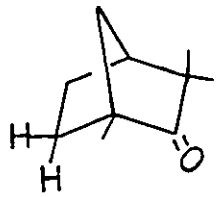


SCHEME 5

Treatment of ketones 25, 26, and 28 under homoenolization conditions (K^+ t-BuO^-/t-BuOH and 185-250°C range) showed that 25 and 26 were homoenolized about 59.5% (ratio of products 28:26 = 58:1.5) and 58% (ratio of products 28:25 = 22:36), respectively. Under similar conditions 26 produced a substantial amount of epimer 25, whereas 25 produced only 1.5% of its epimer 26. This is reasonable since protonation of the homoenolate ion 27 should be faster from the exo than from the endo direction in basic medium. There were no reports of exchange at the bridgehead or C-7 of 25 and 26. However in the case of camphor 28, even at prolonged reaction times, the extent of

homoenolization was significantly less than in the case of 25 or 26. For instance when camphor 28 was heated with K^+ t-BuO$^-$/t-BuOD initially for 667 h at 185°C and then at 220°C for an additional 142 h, only 2.5% rearrangement was observed. It was (59) suggested that this slow isomerization not only reflects the greater thermodynamic stability of 28 but also the relative difficulty of forming a β-enolate at C-6. The steric hindrance of the methyl groups and competitive α-enolization may be contributing factors to the low reactivity.

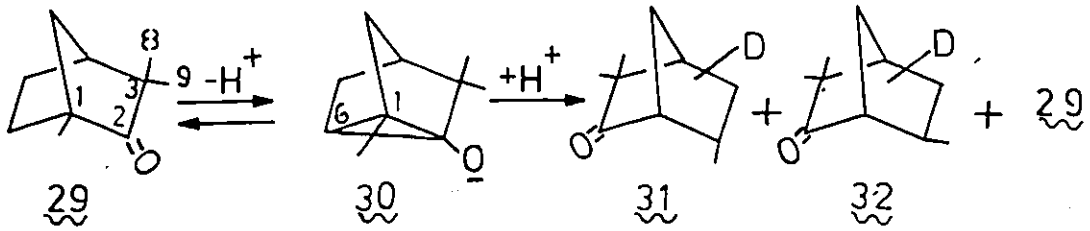
In view of the homoenolization studies to be discussed in later chapters it is important to consider the studies carried out with compounds that have similar structural features, such as fenchone, 29.



29

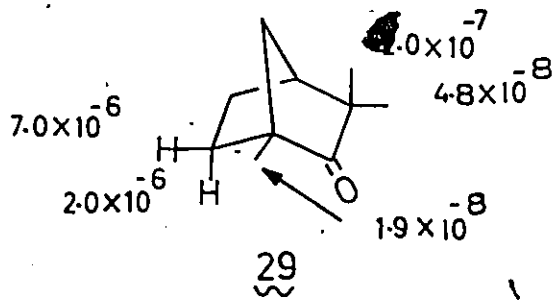
Preliminary work on fenchone 29, was carried out by J.L. Lambert (60). It was found that treatment of 29 under homoenolization conditions for a prolonged period of time resulted in a small amount of rearrangement (∿ 5%). When the reaction was carried out in a deuterated medium, the recovered starting material contained up to 6 excess atoms of deuterium per molecule. Reexamination of compound 29 by Johnson and coworkers (61) and analysis of the recovered starting material from the deuterated medium indicated the presence of deuterium only at C-6 and at the methyl groups of 29. A small amount (∿ 5%) of the rearranged products 31 and 32 in a ratio of 3:1 respectively was obtained. When 29 was heated in 0.7 M K^+ t-BuO$^-$/t-BuOD for 300 h,

1.94 excess atoms of deuterium were incorporated into the starting ketone 29. They were able to establish the amount of deuterium at different sites



29 30 31 32

by computer-fitting of $Pr(fod)_3$ shifted ^2H NMR spectral data. Exchange was 65% complete at exo-6-H, 64% at endo-6-H, 14% at the exo methyl group (C-8), 5.3% at the endo methyl group (C-9) and 2% at the bridgehead methyl group. However, as in the case of camphenilone, there was no indication of exchange at C-7, although β-enolization at C-7 might be expected. The pseudo-first-order rate constants for deuteration, obtained by one-point kinetic studies are shown below.

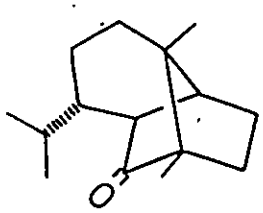


29

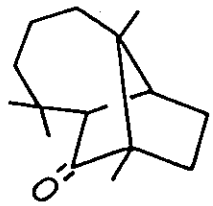
When a 3:1 mixture of 31 and 32 was subjected to homoenolization conditions for 200 h, a mixture of 29, 31 and 32 was obtained in a ratio of

75:2:20, suggesting that only 31 undergoes homoenolization or that 31 is the more reactive of the rearranged ketones obtained from fenchone, 29. It is interesting to note that in the ketone 29, the exchange of the exo proton at C-6 is 3.5 times faster than exchange of the endo proton. The same regioselectivity was also observed for the proton exchange at methyl groups C-8 and C-9;exo methyl exchanges faster than endo methyl. Deuterium exchange at the bridgehead methyl is the slowest since the formation of a highly strained "homoenolate" is required in that case.

Two other examples which were studied by Turnbull and coworkers (34) are copacamphor 2 and longicamphor 33. Compounds 2 and 33, which have the



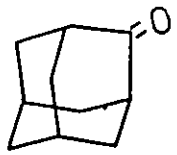
2



33

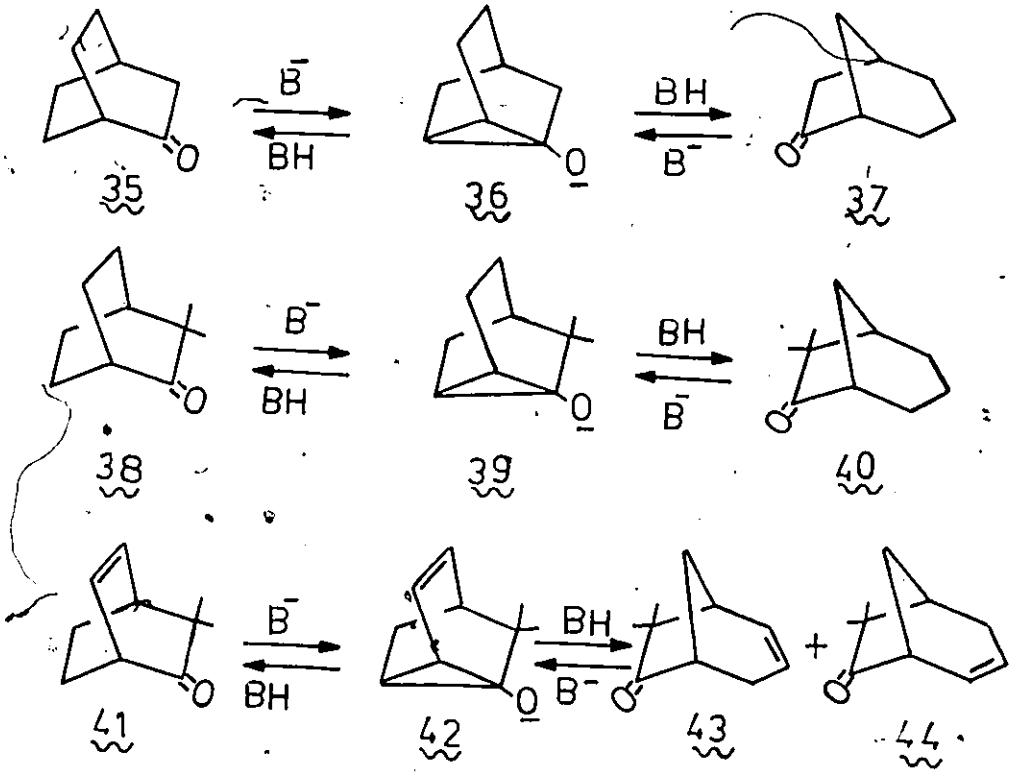
same basic [2.2.1] skeleton as fenchone and camphor, were treated under homoenolization conditions in an effort to incorporate deuterium via homoenolate anions. Exchange at remote sites of 2 was not observed whereas in compound 33 more than one proton was exchanged, but the location of deuterium incorporation was not accurately established. There was no report of any rearrangement product. In the light of the observation of exchange in fenchone and camphor it would be of interest to reexamine the homoenolization of 2 and 33. In the case of adamantanone 34, the first report (62)

showed no exchange of β-hydrogen under homoenolization conditions, but reexamination (63) of the system showed that there was exchange of the α- and β-hydrogens. In addition, at the β-position exo exchange is faster than endo exchange by a factor of 15.



34

A number of compounds with a [2.2.2] skeleton have been examined. Stothers and coworkers (64,65) have studied the homoenolization of a series of bicyclo[2.2.2]octanones, shown in Scheme 6.



SCHEME 6

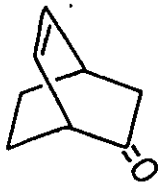
As is illustrated in Scheme 6, bicyclo[2.2.2]octanones and bicyclo[3.2.1]octanones, are interconvertible in strongly basic media through a common β-homoenolate intermediate. The rate of interconversion is very slow. For example in the conversion of 38 to 40, the ketone was recycled up to nine times, each cycle involving heating for 100 hours, before equilibrium was reached. The final mixture contained ∿ 60% of 40. When ketones 38 and 40 were isolated from the analogous reaction in a deuterated medium, the deuterium distributions in ketones 38 and 40 were determined initially by a ^{13}C NMR study (64) of the corresponding alcohols and later by ^{2}H NMR (65). It was established that exchange in ketone 38 occurred mainly at C-6, C-7, and at the methyl groups. Analysis of deuterated 40 revealed the presence of deuterium at exo-3-H, exo-4-H,H-5, and both methyl sites (exo and endo). Exchange of exo-3-H was observed only in the case of prolonged reaction times (400 - 500 h). The estimated rate constants for ^{2}H incorporation showed that exo exchange is preferred over endo exchange. The authors have qualitatively ordered the reactivity with respect to ^{2}H incorporation of several ketones as follows:

$$29 > 38 > 40 > 34$$

One major difference between 38 and 40 is the exchange rates of the hydrogens of the methyl groups. In 40 the exo methyl hydrogen exchange is 100 times faster than the corresponding endo exchange, and the endo exchange is comparable to the rate of methyl hydrogen exchange in ketone 38.

In contrast to the previous examples, equilibration of 41 with 43 and 44 is achieved fairly rapidly (half-life ≈ 7 h) under homoenolization

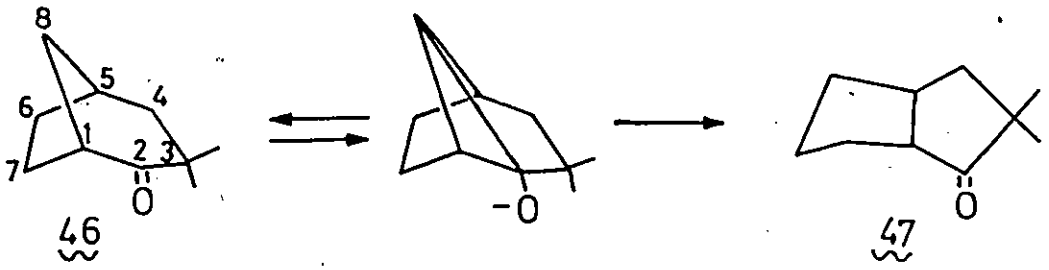
conditions. From the ratio of 8:44:48 for 41, 43, and 44 respectively it can be seen that the [3.2.1] skeleton is favored over the [2.2.2] skeleton. The rate of rearrangement of 41 is reported to be 100 times that of the saturated analogue 38. When the unsubstituted ketone 45 (67) was heated under homoenolization conditions, almost all the starting material was consumed. It was found that the product resulted mostly from self-condensation and



45

subsequent reactions, rather than from rearrangement.

The only other related bicyclic ketone which has been investigated is 3,3-dimethylbicyclo[3.2.1]octan-2-one 46 (68). On treatment under homoenolization conditions, 46 rearranged in high yield to 3,3-dimethylbicyclo[3.3.0]octan-2-one 47 via a β-enolate. Examination of a deuterated sample of 46 showed that exchange had occurred at C-1, at <u>exo</u> and <u>endo</u> C-7,

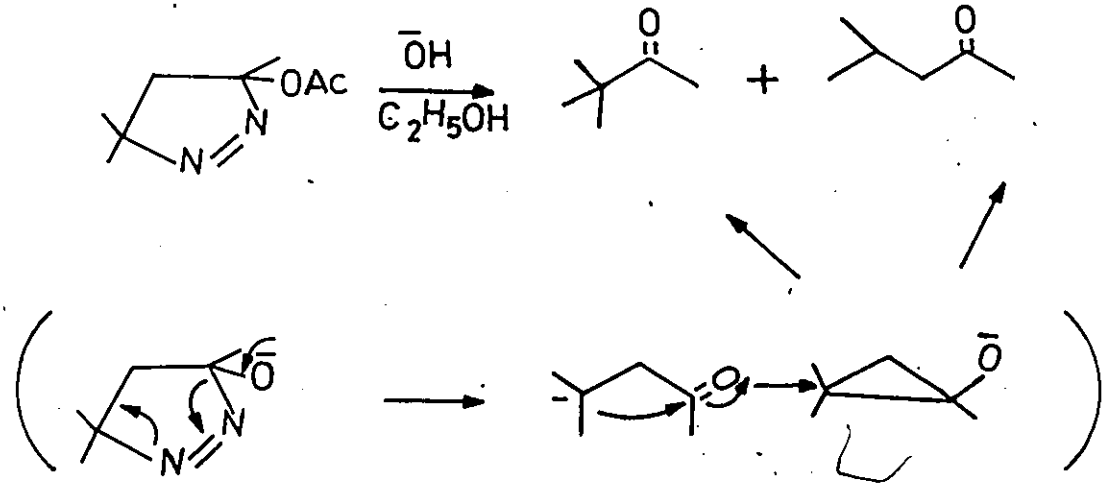


46 47

as well as at both methyl groups. The exo exchanges at C-7 and at the exo-methyl group were faster than the corresponding endo exchanges. Bridgehead exchange was very fast (> 90% in 1 h).

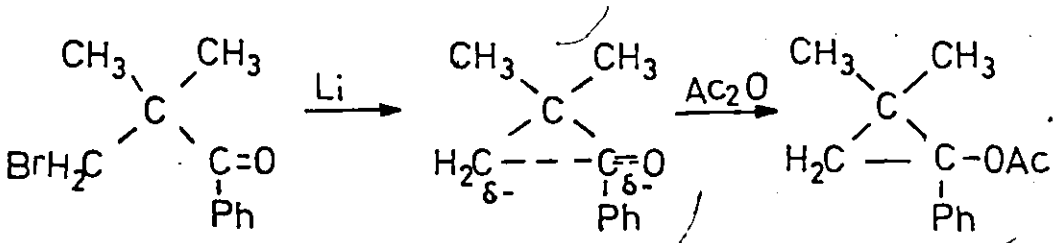
A few examples of β-enolization in acyclic carbonyl compounds have been reported (69) and are given in Table II.

Bicyclic compounds are not the only type of compound that undergo rearrangement via β-enolates. There are examples of rearrangements of other systems under basic conditions which confirm the formation of homoenolates as intermediates. Freeman and Plonka (70) studied the base-catalyzed hydrolysis of 3-acetoxy-Δ^1-pyrazolines and observed carbon skeleton rearrangement via a homoenolate ion as shown in Scheme 7. The same product ratio was obtained when 1,2,2-trimethylacetoxycyclopropane was hydrolysed.



SCHEME 7

A homoenolate ion is implicated as the intermediate (Scheme 8) in the formation of cyclopropylacetate 49 from bromoketone 48 (71).



SCHEME 8

The pKa of an homoenolizable methylene hydrogen in bicyclic systems has been estimated to be about 35 - 36, based on the assumption that there is a relationship between kinetic and thermodynamic acidities. Similar but somewhat milder conditions than the conditions used for homoenolization of bicyclic ketones are used to exchange the alpha and ring hydrogens of 2-phenylbutane, the methyl hydrogens in 2,4,4-trimethyl-2-pentene, and the ring hydrogens of various naphthalenes. This puts the pKa of homoenolizable protons of bicyclic ketones near that of propene (35.5), cumene (37), or benzene (37) on the MSAD[4] scale (72). Therefore, this ranks the pKa's of β-methylenes about half-way between those of normal methylenes (45 for cyclohexane) and those of alpha enolizable methylenes (21 for acetone).

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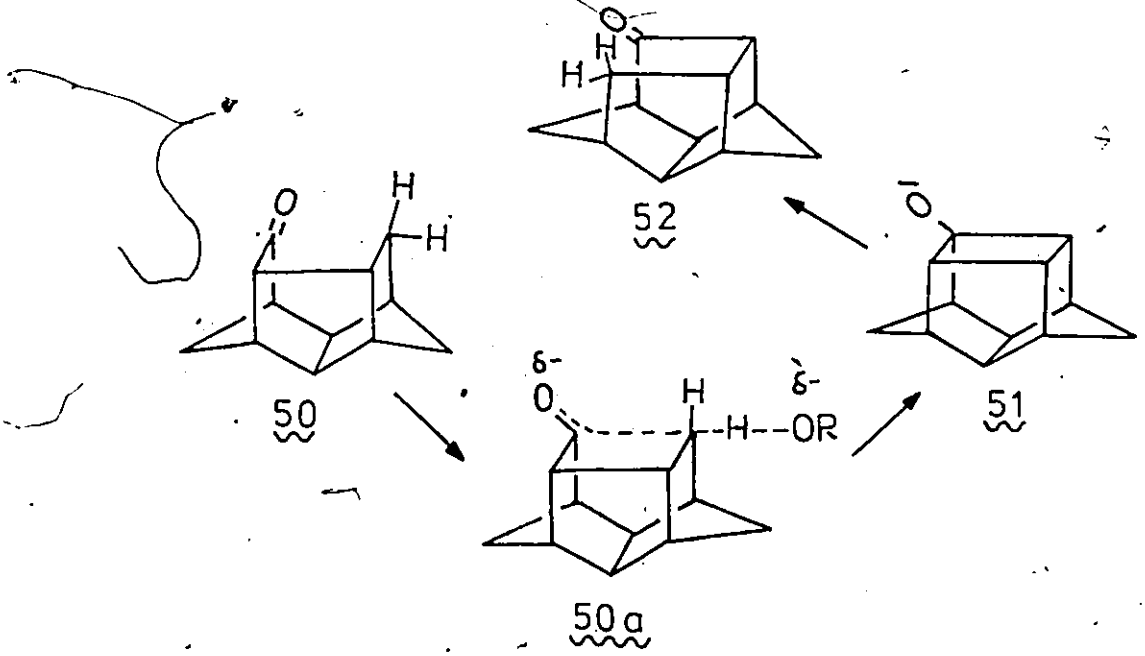
4. The MSAD scale is for measurement of very weak acids (pKa above ∿ 17). It is named in recognition of the work of McEwan, Streitwieser, Applequist, and Dessy, who made advances in this area.

1.6 γ-Enolization

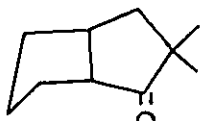
The first example of rearrangement via homoenolization involving γ-hydrogen abstraction was reported concurrently by Fukunaga (73), and Howe and Winstein (74,75). The half-cage ketone 50 was converted to the less strained half-cage ketone 52. The available data implies that isomerization occurs via γ-homoenolate anion 51, as shown in Scheme 9.



SCHEME 9

The carbonyl group assists the proton abstraction step by delocalizing the developing negative charge. Although no definitive proof of stereochemistry was given in the original work, a subsequent study by Crow and Borden (76) showed that the homoketonization step proceeded by retention of configuration as is the case for almost all γ-homoenolate homoketonizations.

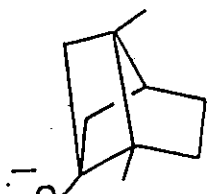
3,3-Dimethylbicyclo[3.3.0]octan-2-one 47, which has a relatively flexible carbon skeleton, was the second example of γ-proton abstraction



47

under homoenolization conditions. Compound 47 was obtained by rearrangement of 3,3-dimethylbicyclo[3.2.1]octan-2-one 46 (68). When a non-deuterated sample of 47 was treated under homoenolization conditions in deuterated media, the study of the ^2H NMR spectra of recovered and deuterated 47 showed that at least eight sites underwent exchange. Using $Pr(fod)_3$ to increase the dispersion of ^2H resonances, the eight signals were resolved, revealing exchange at C-1, C-6, C-7, C-8 and at the methyl groups.

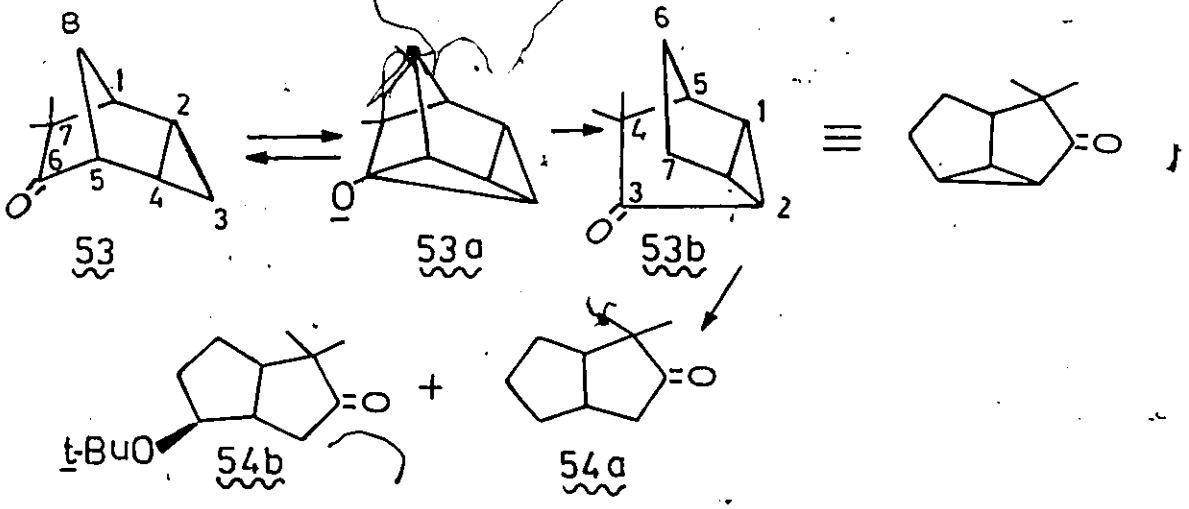
Nickon and coworkers (59) studied the homoenolization of two isomers of isocamphenone, 25 and 26, in conjunction with camphor 28. It was found that camphor 28, homoenolizes more slowly than the other bicyclo[2.2.1]-heptan-2-ones. Even though deuterium incorporation in ketone 28 was slow and required high temperature (185°C) and long reaction times (667 h), deuterium incorporation was observed at C-8 (methyl group), which implicated a γ-enolate 28a as an intermediate. This is the only known example of γ-enolization of



28a

a methyl group. The corresponding homoenol has been prepared by Dadson and Money (77) from reduction of 8-bromocamphor using Mg/THF or Ca/NH_3. Treatment of this homoenol under homoenolization conditions produced only 8-deuteriocamphor.

In a recent communication (78) it was reported by Stothers and coworkers, that 7,7-dimethyltricyclo[3.2.1.$0^{2,4}$]octan-6-one 53 homoenolizes and rearranges via a γ-enolate to 4,4-dimethyltricyclo[3.3.0.$0^{2,4}$]octan-3-one 53b. However 53b was unstable under the reaction conditions and slowly transformed to a mixture of the bicyclic octanone 54a and its exo-6-t-butoxy derivative 54b.



The most striking feature of this case is that H/D exchange at C-3 of the outside hydrogen is faster than exchange of the inside one. This implies that homoketonization of the γ-enolate proceeds with inversion of configuration. In all the previous cases, γ-homoketonizations occurred via retention of configuration. Scheme 10 illustrates mechanisms suggested by the authors for the conversion of 53b to 54a and 54b.

Table II

Summary of Examples of Homoenolic Rearrangements in Bicyclic, Tricyclic and Acyclic Systems in K^+ t-BuO^-/t-BuOH

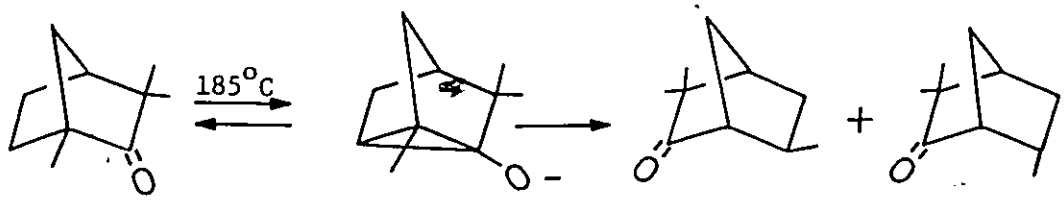
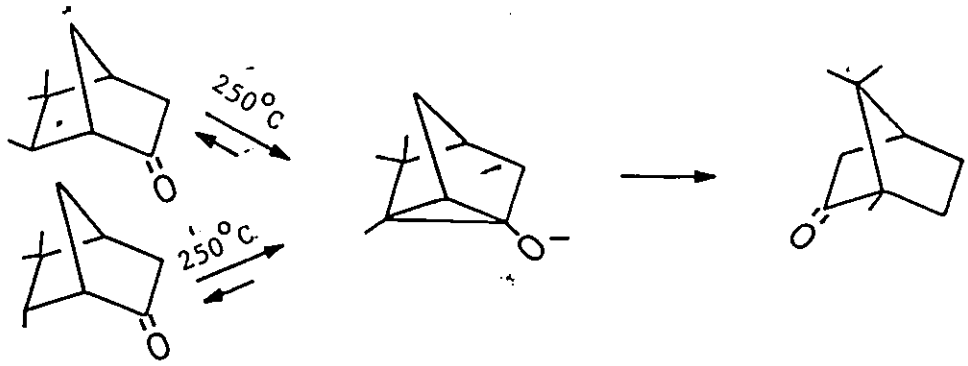
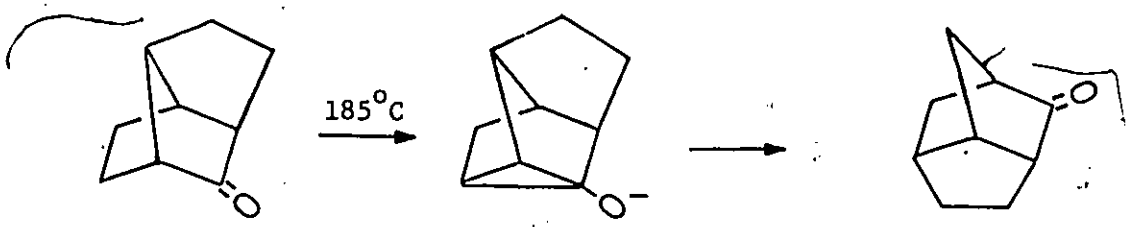
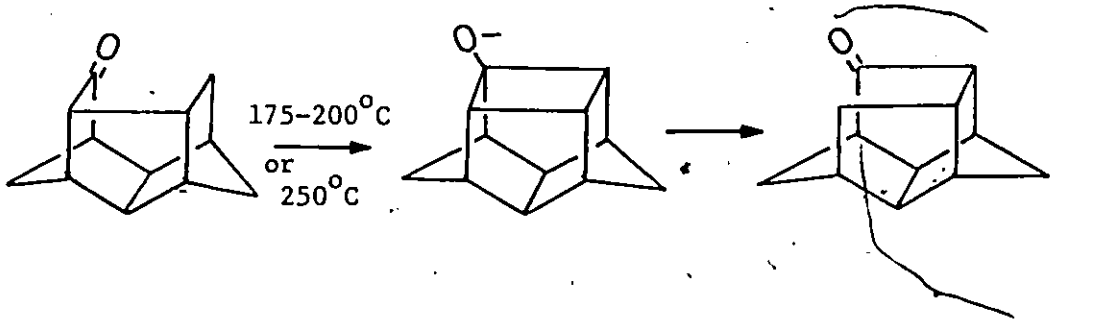
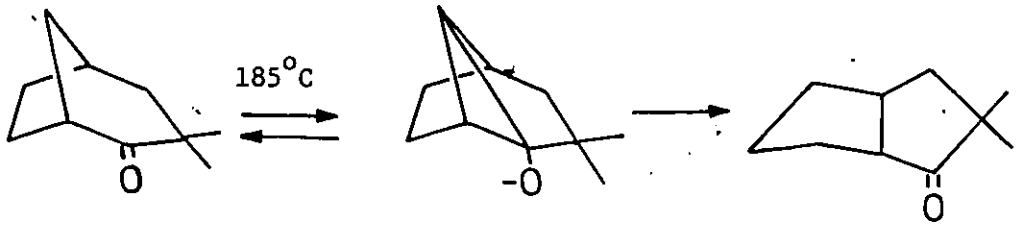
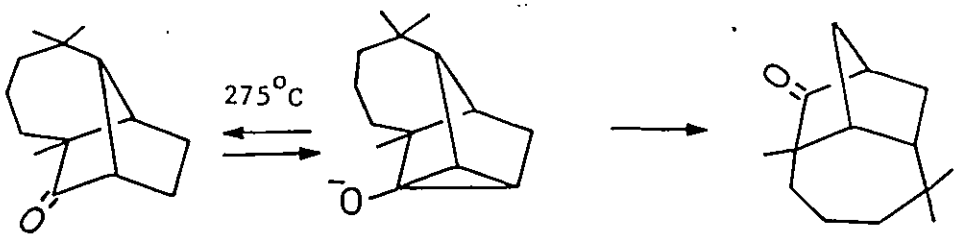
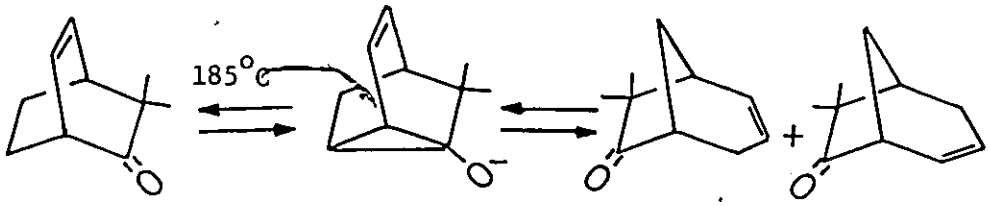
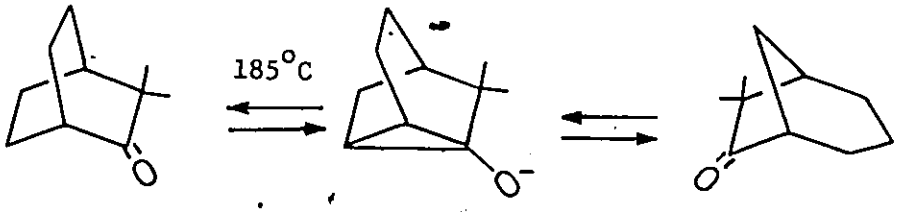
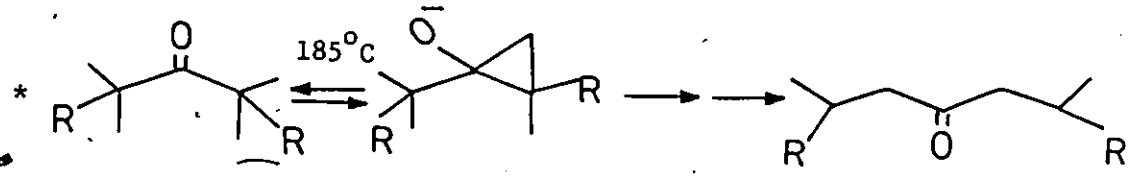
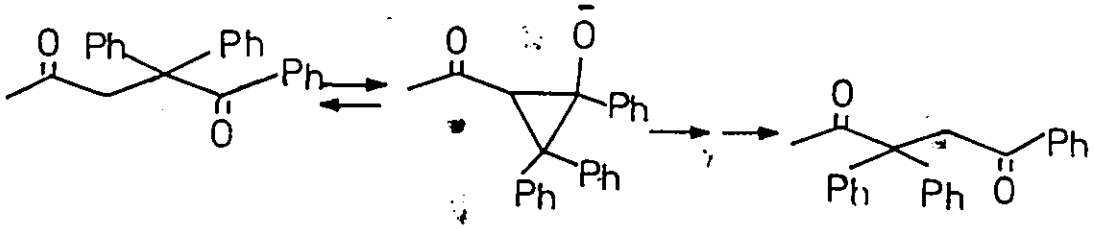
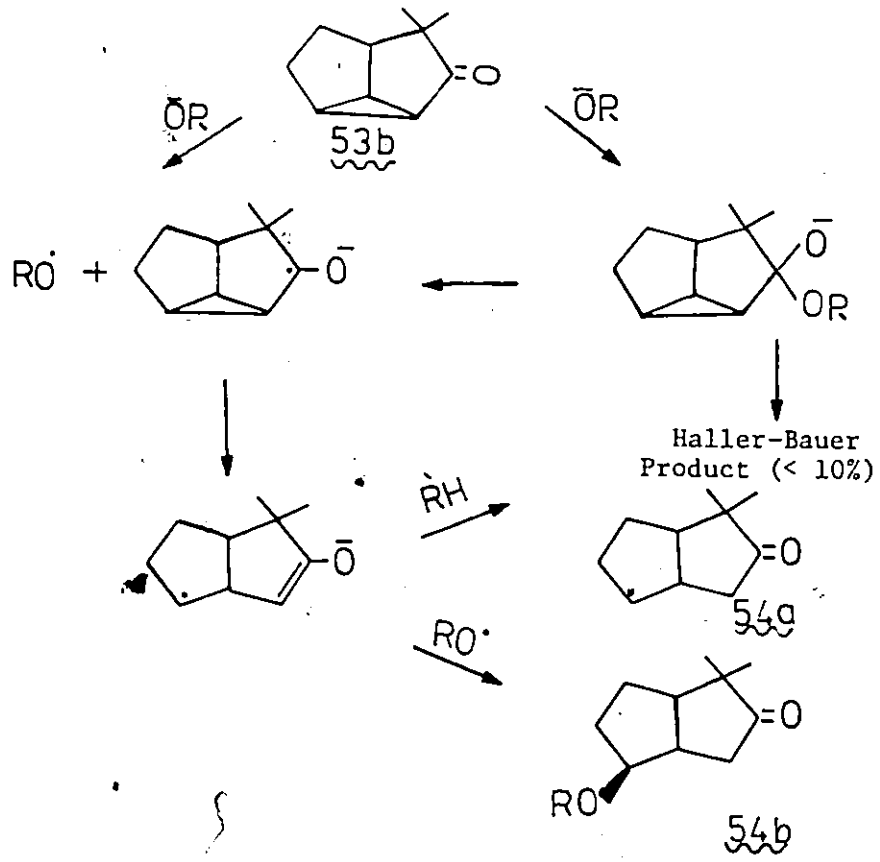
Substrate	Homoenolate	Product	Ref.
			(58,61)
			(58)
			(56)
			(73,74,76)
			(68)

Table II (cont.)

Substrate	Homoenolate	Product	Ref.
			(57)
			(64)
			(65)
			(69)
			(79,80)

*This rearrangement involves more than one intermediate.



SCHEME 10

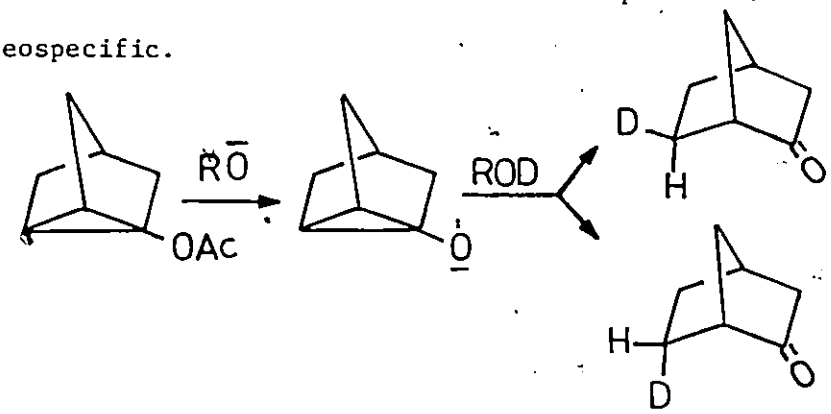
1.7 Homoketonization

The reverse process of homoenolization is homoketonization. Investigation of this process has focussed mainly on three areas - the regiochemistry of ring opening (see Scheme 11), the stereoselectivity of protonation on ring opening (see Scheme 12), and on the reaction mechanism.

Homoketonization has been examined under basic and acidic conditions (76,81-84); since this study involves basic conditions, only the basic process will be considered. In general, for base catalyzed β-homoketonization, it has been found that the regiochemistry of ring opening follows the expected order of stability of the incipient carbanion (i.e. $1^{o}>2^{o}>3^{o}$ etc. (54)) as shown in Scheme 11. This suggests that the cleavage involves develop-

ment of substantial negative charge on the carbon in the transition state.

Early work by Nickon and coworkers demonstrated the general stereoselectivity of β-homoketonization. An example is their investigation of the homoketonization of acetoxynortricyclene (81) under mild basic hydrolytic conditions. Protonation of the homoenolic species was found to be highly stereospecific.



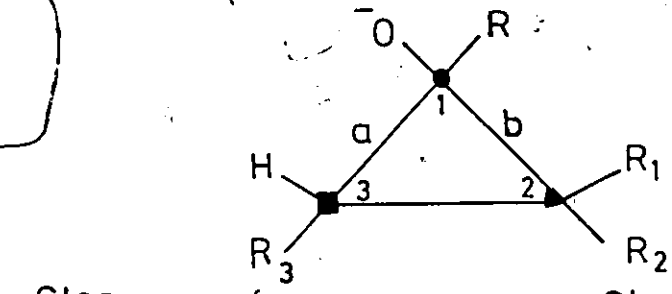
The authors concluded that in basic medium the preferred transition state involves exo protonation, resulting in inversion of configuration (see Scheme 12). In acidic media, homoketonization results in retention of configuration (82). Table III illustrates the effect of acidic and basic media at room temperature.

Table III

Effect of Media on Deuterium Configuration (81)

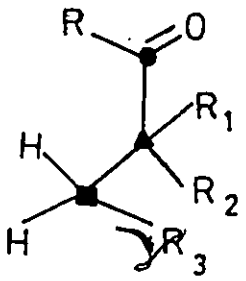
	Medium	Deuterium Configuration
1	K^+ t-BuO^- in t-BuOD	94.5% exo (inversion)
2	K^+MeO^- in MeOD	94.5% exo (inversion)
3	K^+MeO^- in MeOD/Dimethyl sulfoxide (1/1)	94.5% exo (inversion)
4	$(CH_3)_4N^+OD^-$ in t-BuOD	94.5% exo (inversion)
5	D_2SO_4 in $DOAc/D_2O$(1.2/1)	90.0% endo (retention)
6	D_2SO_4 in $DOAc/D_2O$(1.7/1)	90.0% endo (retention)

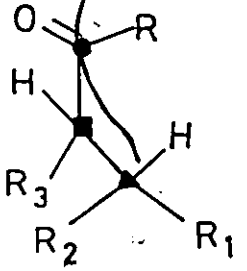
Regiochemistry of β-Ketonization



Cleavage of bond a

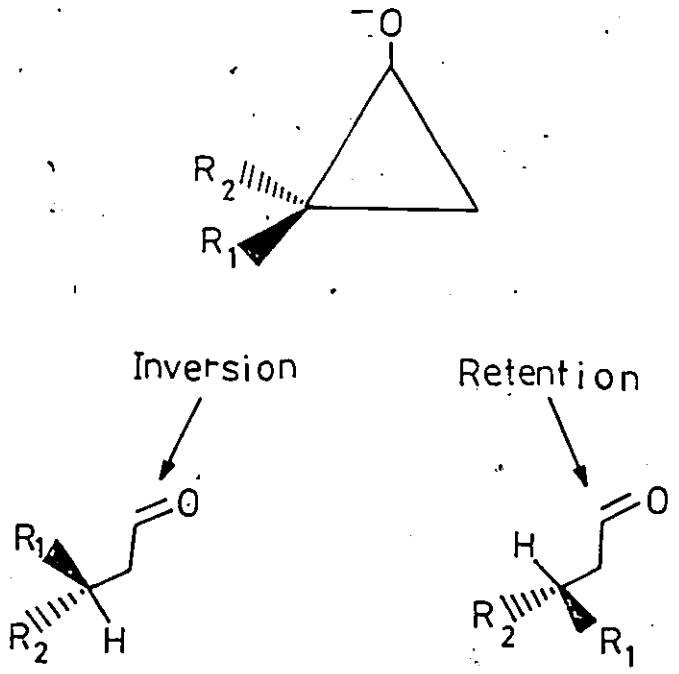
Cleavage of bond b





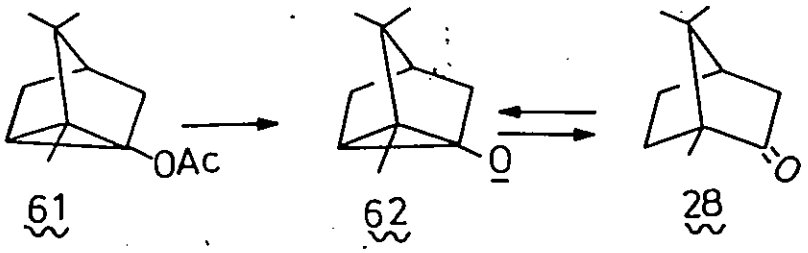
SCHEME 11

Stereochemistry of β-Ketonization



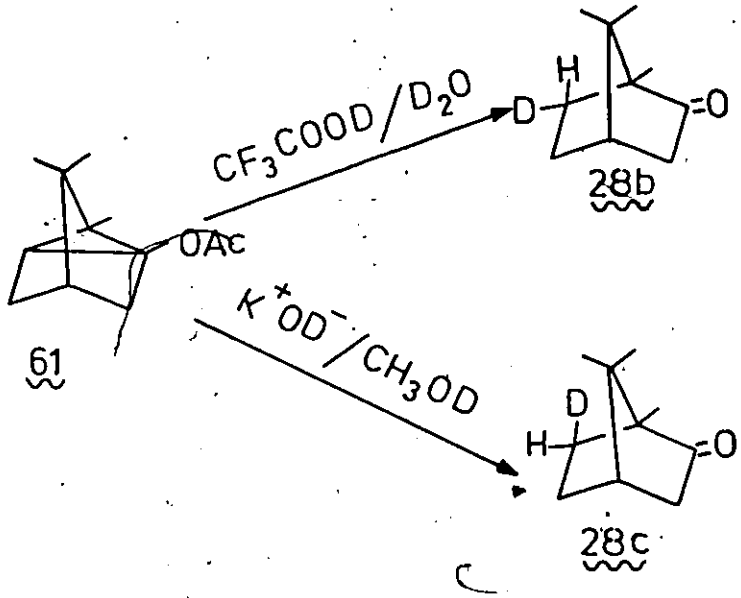
SCHEME 12

Homoketonization also has been observed when acetate 61 was treated with t-butyl alcohol and potassium t-butoxide at room temperature (58).



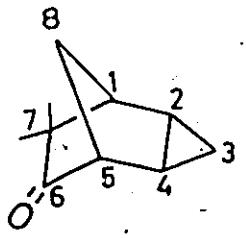
61 62 28

Based on the findings of Nickon and coworkers (82), Joshi and Warnhoff (85) were able to stereoselectively deuterate compound 61 (1-acetoxynortricyclene). Acid hydrolysis of 61 using CF_3COOD/D_2O yielded camphor-6-endo-d_1 28b, while basic hydrolysis with K^+OD^-/MeOD gave camphor-6-exo-d_1 28c



61

Although β-enolates usually open with inversion of configuration under basic conditions, γ-enolates normally open with retention. Exceptions to both of these are known (55). For example compound 53 (66) was reported to undergo γ-ketonization via inversion of configuration at C-3.



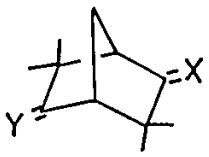
53

The best experimental information on an homoenolization mechanism is presented by Thibblin and Jencks (86), who have demonstrated that the base catalyzed ring opening of a series of 1-phenylcyclopropanols is subject to general acid catalysis. They also observed a primary deuterium isotope effect, thus showing that proton transfer is involved in the rate determining step. This is an indication that the ring opening and protonation occur in a concerted manner without formation of an intermediate carbanion. At the present time, there is not enough information to draw definite conclusions on the general reaction mechanism. Further work is required for a comprehensive understanding of the homoketonization mechanism.

1.8 Objectives of Present Study

Over two decades there has been a steady increase in the number of publications dealing with the homoenolization of polycyclic monoketones, and some progress has been made as regards the factors which control the site of homoenolization and rearrangement of polycyclic monoketones via

homoenolate anions. However, there were no reports of studies of the homoenolization of polycyclic polyketones prior to the report in 1975 (87) on the homoenolization and rearrangement of 3,3,6,6-tetramethylbicyclo[2.2.1]-heptane-2,5-dione 63a.



63

a, X = Y = O
b, X = Y = S
c, X = O; Y = S
d, X = O; Y = H_2

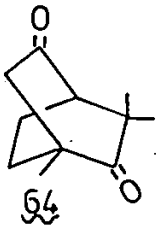
As a continuation of the research in the general area of base-catalyzed H-D exchange and rearrangement of polycyclic polyketones, we were interested in establishing the rate enhancement of base-catalyzed β- or γ-enolization by one or more carbonyl groups or thiocarbonyl groups located β or γ to an enolizable site. Resolution of any rate enhancement into homoconjugative and inductive components was another objective.

We chose to study the K^+ t-BuO^--catalyzed H-D exchange of 3,3,6,6-tetramethylbicyclo[2.2.1] heptane-2,5-dione 63a, 3,3,6,6-tetramethylbicyclo-[2.2.1]heptane-2,5-dithione 63b, 3,3,6,6-tetramethyl-5-oxo-bicyclo[2.2.1]-heptane-2-thione 63c, and 3,3,6,6-tetramethylbicyclo[2.2.1]heptan-2-one 63d. The hydrogens at C-7 of 63a are β to both carbonyl groups, so enolization

results in a β,β enolate. A study of the H-D exchange of dithione 63b would establish the relative homoenolizabilities of ketones and thiones and 63c would be used for intramolecular competitive exchange experiments. In order to quantify the effect of the second carbonyl group of 63a and the rate of H-D exchange at all sites - the methyls, the bridgeheads and C-7 - it was necessary to study the homoenolization of monoketone 63d.

Another objective was to establish the propensity for bridgehead exchange of 63a. While exchange data were available for several bicyclo-[2.2.2]octan-2-ones, bicyclo[2.2.2]oct-2-ene-5-one, bicyclo[3.2.1]octanones, and bicyclo[3.2.1]octanones (66), no rate data were available for bridgehead exchange alpha to the carbonyl group of bicyclo[2.2.1]heptan-2-one prior to this study. We chose to study 63d because it is necessary to block C-6 β-enolization (homoenolization) (50) which scrambles C-6 and C-1 of camphenilone 16 and prevents determination of the extent of bridgehead H-D exchange. We reasoned that our study would demonstrate indirectly the extent to which bridgehead exchange competes with exchange via homoenolization in 16, the first substrate used in a quantitative study of homoenolization (40).

In summary, this thesis documents the synthesis of 63a, 63b, 63c and 63d, and it describes a study of the K^+ t-BuO^- catalyzed H-D exchange of 63d and 63a as well as 64, the rearrangement product of 63a. Studies on the chemistry of dithione 63b and monothione 63c in K^+ t-BuO^-/t-BuOH solution at 175°C were initiated.



64

CHAPTER 2

RESULTS

2.1 Synthesis of Substrates

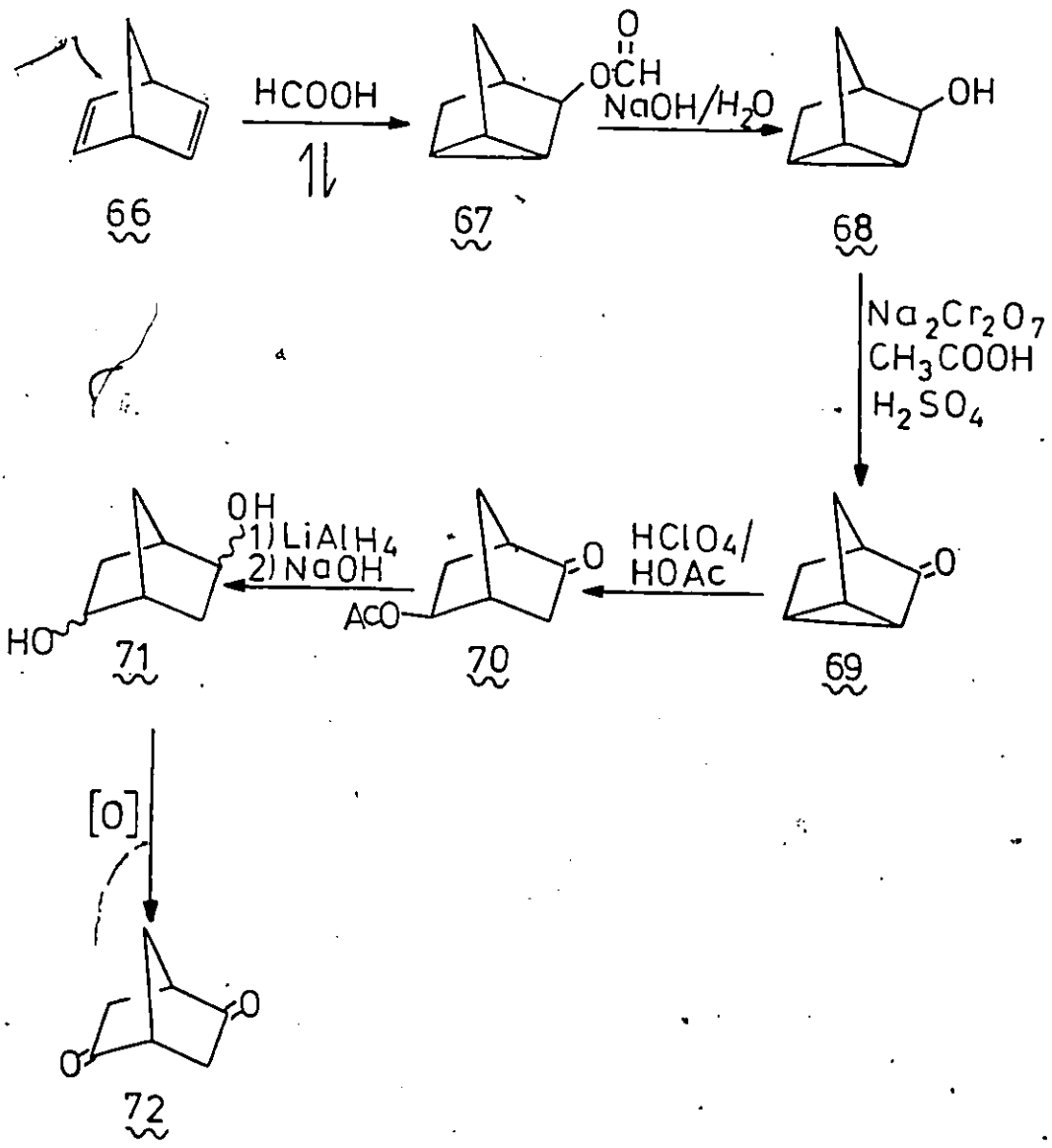
In order to determine the relative reactivities of a series of bicyclic carbonyl compounds and their thio-analogues under homoenolization conditions, substrates 63a - 63d were prepared.

2.1.1 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione (63a)

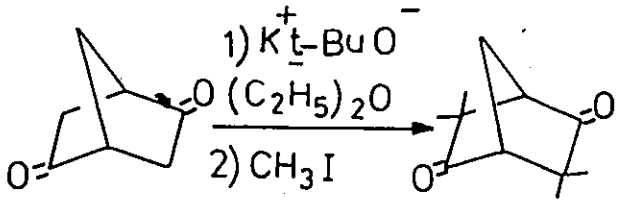
Dione 63a was prepared by tetramethylation of norbornane-2,5-dione 72, which was synthesized by the known route shown in scheme 13 (88,89). The oxidation of diol 71 to diketone 72 was carried out using a variety of oxidation procedures, such as those described by Fieser, Sarett, Cornforth, Thiele and Jones. There was some difficulty in recovering the diketone from the inorganic salts which were produced in the oxidations. However, it was found that the best yield was obtained by using a Jones (90-92) or modified Jones oxidation (93) on up to 10 grams of the diol. Purification of the dione was best achieved by sublimation.

The tetramethylation of norbornane-2,5-dione occurs very readily compared to the methylation of other norbornanones and deserves some comment. That methylation of 72 proceeds rapidly and that significant amounts of other methylated species could not be detected may be a consequence of the increased acidity of the hydrogens alpha to the carbonyl group, a point established earlier (43).

Preparation of Norbornane-2,5-dione

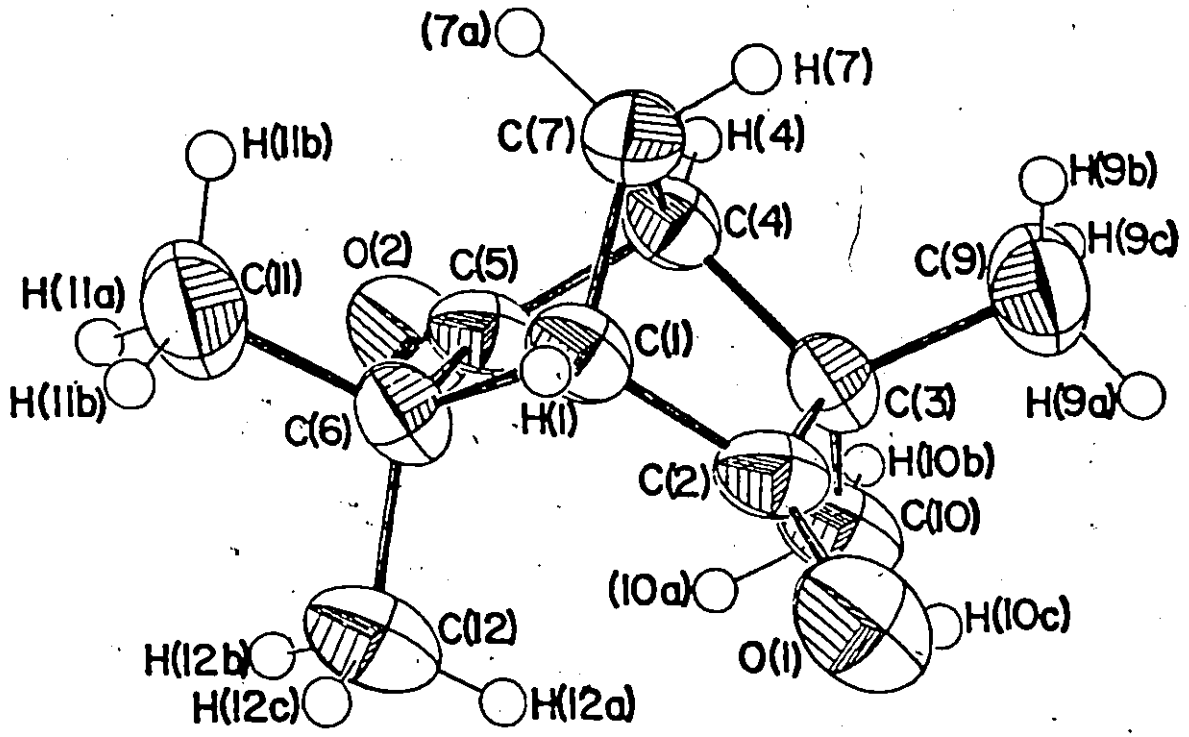


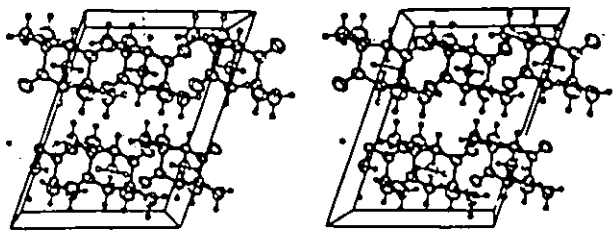
SCHEME 13



72 63a

In order to obtain more information about the structure of dione 63a, an x-ray crystal structure determination was carried out by Lock and coworkers (94). They established that 63a is monoclinic C2/c and has four formula units in the unit cell. The computer-drawn structure is shown in Figure I-A. Bond lengths and angles within the structure are normal, and selected interatomic distances (Å) and angles (degrees) are given in Tables IV and V. The opening up of the C(1)-C(2)-C(3) angle relative to bicyclo [2.2.1]heptane is caused by the carbonyl group and the consequent decrease in the C(2)-C(3)-C(4) angle brings C-2 nearer to the hydrogen atom attached to C-7. In general, in 63a all angles are less than those expected for an unconstrained system and compare reasonably well with those observed in other bicyclo[2.2.1]heptanes, although there are some differences which are discussed below. The crystal structure determination shows there is no unusual twist in this molecule, at least in the solid phase. Nevertheless the angles at the carbonyl group (C(1)-C(2)-C(3);107.7(4)°), are about 3° larger





(b)

Figure I-A. a) The Molecular Structure of 3,3,6,6-Tetramethylbicyclo-[2.2.1]heptane-2,5-dione.

b) The Contents of the Unit Cell for 3,3,6,6-Tetramethyl-bicyclo[2.2.1]heptane-2,5-dione.

Table IV. Selected Interatomic Distances in 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione(63a)

Interatomic Distance	A°	Interatomic Distance	A°
C(1)-C(2)	1.508(5)	C(3)-C(10)	1.524(7)
C(1)-C(7)	1.539(6)	C(3)-C(4)	1.550(6)
C(3)-C(9)	1.536(6)	C(2)-O(1)	1.206(6)
C(2)-C(3)	1.529(6)		

Table V. Selected Angles in 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione (63a)

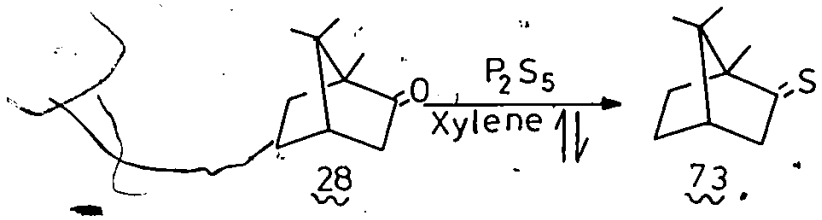
Angle	Degrees	Angle	Degrees
C(6)-C(1)-C(2)	107.0(3)	C(1)-C(2)-O(1)	127.1(4)
C(6)-C(1)-C(7)	101.0(3)	C(2)-C(3)-C(10)	112.1(4)
C(1)-C(7)-C(4)	94.8(4)	C(9)-C(3)-C(10)	109.1(4)
C(2)-C(3)-C(9)	109.7(4)	C(2)-C(3)-C(4)	100.3(3)
C(4)-C(3)-C(10)	115.1(4)	O(1)-C(2)-C(3)	125.2(4)
C(1)-C(2)-C(3)	107.7(4)	C(4)-C(3)-C(9)	110.3(4)
C(2)-C(1)-C(7)	100.0(3)		

than the average value of 103.4(7)° found in bicyclo[2.2.1]heptanes and there is a concomitant decrease of about 3° in the C(2)-C(3)-C(4) angle (99.3°). These values agree well with the average found for bicyclo[2.2.1] heptan-2-ones (95-100) (C(1)-C(2)-C(3), 106.7(7)°;C(2)-C(3)-C(4), 101.1(7)°). The effect of this distortion is to move C-2 closer to C-7 and C-3 further from C-7. There is no twisting at C-7 to bring H-7 near to C-2 or O-1.

The ^{1}H and ^{13}C NMR data for diones 63a and 72 as well as for dithione 63b, monoketone 63d and thioketone 63c, which are given in Tables VI and VII, are consistent with the proposed structures.

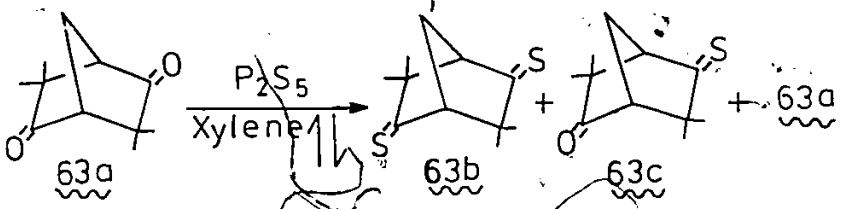
2.1.2 Synthesis of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dithione (63b), and 3,3,6,6-Tetramethyl-5-oxo-bicyclo[2.2.1]heptan-2-thione (63c)

Model studies were carried out with camphor and the best results were obtained when the ketone was refluxed in xylene which had been previously saturated with P_2S_5 at its reflux temperature.



28 73

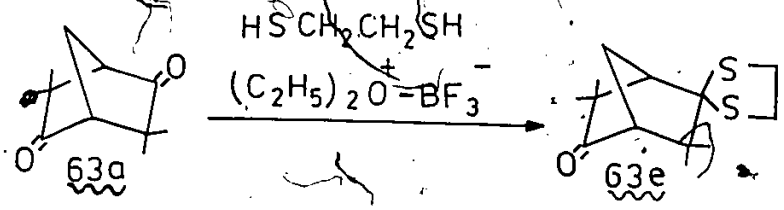
When 3,3,6,6-tetramethylbicyclo[2.2.1]heptane-2,5-dione (63a) was refluxed in xylene saturated with P_2S_5 for 12 - 150 h, a mixture of 63b, 63c and starting material was obtained with the average product composition being 43%, 35%, and 22%, respectively. The compounds were separated using a combination of column chromatography and preparative gas liquid partition chromatography (g.l.p.c.)

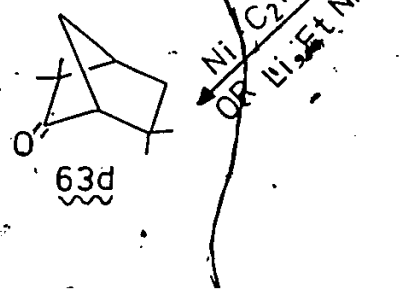


The ^1H and ^{13}C NMR data for 63b and 63c are summarized in Tables VI and VII and are consistent with the proposed structures.

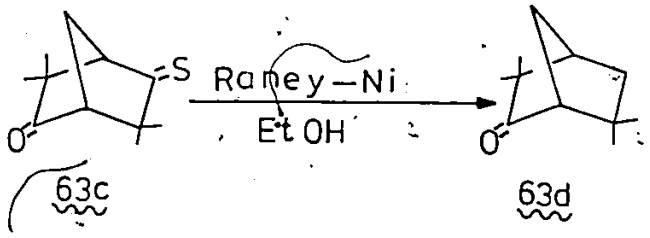
2.1.3 3,3,6,6-Tetramethylbicyclo[2.2.1]heptan-2-one (63d)

Initially an attempt was made to convert 63a into 63d by preparing the dithioketal 63e, with the intent of desulfurizing it with lithium in ethylamine (101,102), or with Raney-Nickel W-2 in ethanol. Unfortunately it was not possible to prepare dithioketal 63e from 63a efficiently.





However, monoketone 63d was prepared by desulfurizing 3,3,6,6-tetramethyl-5-oxo-bicyclo[2.2.1]heptan-2-thione (63c) using Raney-Nickel W-2 in super-dry ethanol. The ^{1}H and ^{13}C NMR data for 63d are given in Tables VI, VII, and VIII are consistent with the proposed structure.



63c 63d

Assignment of protons in ketone 63d

Signal assignments for the protons in ketone 63d were based on the use of high field (250 and 400 MHz) ^{1}H NMR spectral data. In addition to information from study of the signal multiplicities, double resonance experiments, comparison of the observed coupling constants with those reported in the literature for related model systems and the use of lanthanide shift reagents were employed.

The signals at δ 1.42, 1.63, 1.85, 1.96, 2.01 and 2.13 were assigned to exo-H-5, endo-H-5, anti-H-7, syn-H-7, H-1 and H-4 (bridgehead protons) respectively (Figure I-B).

On the basis of the relative values of the chemical shifts, the two bridgehead proton resonances would be expected to appear furthest down-

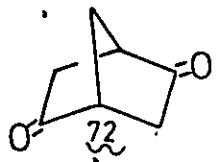
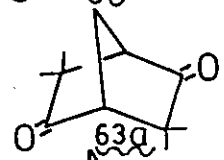
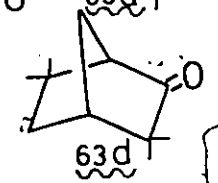
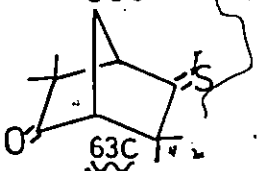
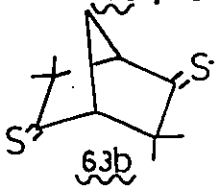
field. The signals from the methylene protons on C-7 and C-5 would be anticipated to occur in the upfield region. The resonance of the C-5 methylene protons would be expected to appear furthest upfield, since these protons are far removed from the carbonyl group.

The lowest downfield signal at δ 2.13 was assigned to the bridgehead methine proton H-4 based on the higher multiplicity (due to coupling with a greater number of neighbouring protons) observed. The second bridgehead proton H-1 has a lesser number of neighbouring protons and hence multiplicity of its signal would be less. The signal at δ 2.01 was therefore assigned to this proton.

In order to assign the signals for exo-H-5 and endo-H-5 a double resonance experiment was carried out. Irradiation of the signal at δ 2.13 (frequency of signal for H-4 proton) caused the doublet of doublets at δ 1.42 to collapse to a doublet with a large coupling constant (Figure I-B(b). The other doublet of doublets at δ 1.63 underwent no apparent change. Thus H-4 is coupled to only one of the protons on C-5. A study of a molecular model showed that the dihedral angle between the proton H-4 and exo-H-5 is small ($\sim 40^{\circ}$) while the angle between H-4 and endo-H-5 is very close to 90°. The endo-H-5 proton has small coupling to H-4. Consequently the signal at δ 1.42 was assigned to exo-H-5, and the signal at δ 1.63 was assigned to endo-H-5. The persistence of the multiplicity pattern for this latter proton in this double resonance experiment showed that this proton was coupled to some other proton besides exo-H-5. Further examination of the spectrum, Figure I-B(b) (on the irradiation of H-4) made

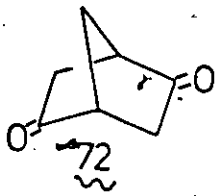
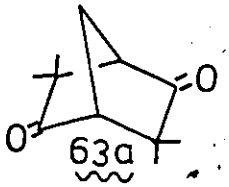
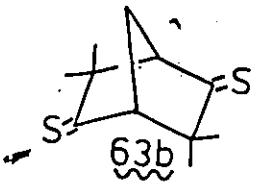
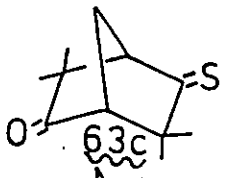
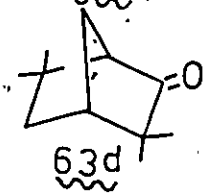
the assignment of the rest of the signals possible. The signal at δ 1.85 collapsed to a doublet with a large coupling constant. The signal at δ 1.96 underwent only marginal changes in its multiplicity. Thus the endo-H-5 proton must be coupled to the proton resonance which occurred at δ 1.96. A further investigation of the model revealed that the endo-H-5 proton has a "W" type arrangement with the syn-H-7 proton, and as a result these two protons are expected to have a "W" coupling between them. This type of coupling across single bonds has been observed in other norbornyl systems (103). On this basis the remaining two signals at δ 1.85 and 1.96 could be unambiguously assigned to protons anti-H-7 and syn-H-7 respectively. Further confirmation for these assignments was obtained when the signal at δ 1.96 (syn-H-7) was irradiated and the rest of the spectrum examined. The doublet of doublets at 1.63 (endo-H-5) collapsed to a doublet. These results are summarized in Table VIII, and double resonance experiments are given in Figure I-B.

Table VI . ^{13}C Chemical Shifts* of Bicyclic Ketones and Their Thione Analogues (ppm)

Substrate	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}
 72	47.40	213.70	36.40	47.40	213.70	36.40	33.80				
 63a	60.12	217.80	45.93	60.12	217.80	45.93	31.01	23.50	22.33	23.50	22.33
 63d	62.42	222.04	46.49	47.20	34.33	36.80	38.75	30.80	27.44	24.45	20.81
 63c	73.40	213.30	55.75	61.14	218.15	46.49	33.15	29.42	26.17	24.06	21.99
 63b	74.43	213.94	56.28	74.43	213.94	56.28	35.23	29.76	25.80	29.76	25.80

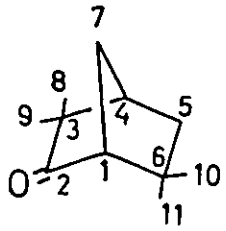
*in ppm from TMS in $CDCl_3$

Table VII . ^{1}H NMR Chemical Shifts* of Bicyclic Ketones and Their Thione Analogues (ppm)

Substrate	$C^{1}H$	$C^{4}H$	$C^{5}H_2$	$C^{3,6}H_2$	$C^{7}H_2$	$C^{8}H_3$	$C^{9}H_3$	$C^{10}H_3$	$C^{11}H_3$
 72	3.0	3.0	-	2.3†	2.3†				
 63a	2.60	2.60	-			2.20	1.15	1.00	1.15	1.00
 63b	3.42	3.42	-	-		2.30	1.27	1.06	1.27	1.06
 63c	2.7	3.32	-			2.23	1.21	1.06	1.15	0.94
 63d	2.01	2.13	H_x 1.42 H_n 1.63	-		H_a 1.85 H_s 1.96	1.04	1.00	1.11	0.97

* In ppm from TMS in $CDCl_3$.

† Unresolved multiplet from 2.0 - 2.6 ppm.



63d

Table VIII. ^1H Chemical shifts and Coupling Constants of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2-one

Proton(s)	Chemical shift (ppm)	Coupling Constant (Hz)
endo CH_3 (C-11)	0.97 s	-
endo CH_3 (C-9)	1.00 s	-
exo CH_3 (C-8)	1.04 s	-
exo CH_3(C-10)	1.11 s	-
H-5-exo	1.42 dd	$J_{5x,5n}$=12.8, $J_{5x,4}$=4.4
H-5-endo	1.63 dd	$J_{5n,5x}$=12.8, $J_{5n,7s}$ = 2.6, $J_{5n,4}$ = ∿0.3
H-7-anti	1.85 ddd	$J_{7a,7s}$=10.8, $J_{7a,1}$=0.8, $J_{7a,4}$= 1.8
H-7-syn	1.96 dm	$J_{7s,7a}$=10.8, $J_{7s,1}$=1.3, $J_{7s,4}$= 0.7 $J_{7s,5n}$ = 2.6
H-4	2.13 m	$J_{4,5x}$=4.4, $J_{4,7s}$=0.7, $J_{4,7a}$=1.8 $J_{4,5n}$ = ∿ 0.3
H-1	2.01 dd	$J_{1,7s}$ = 1.3, $J_{1,7a}$ = 0.8

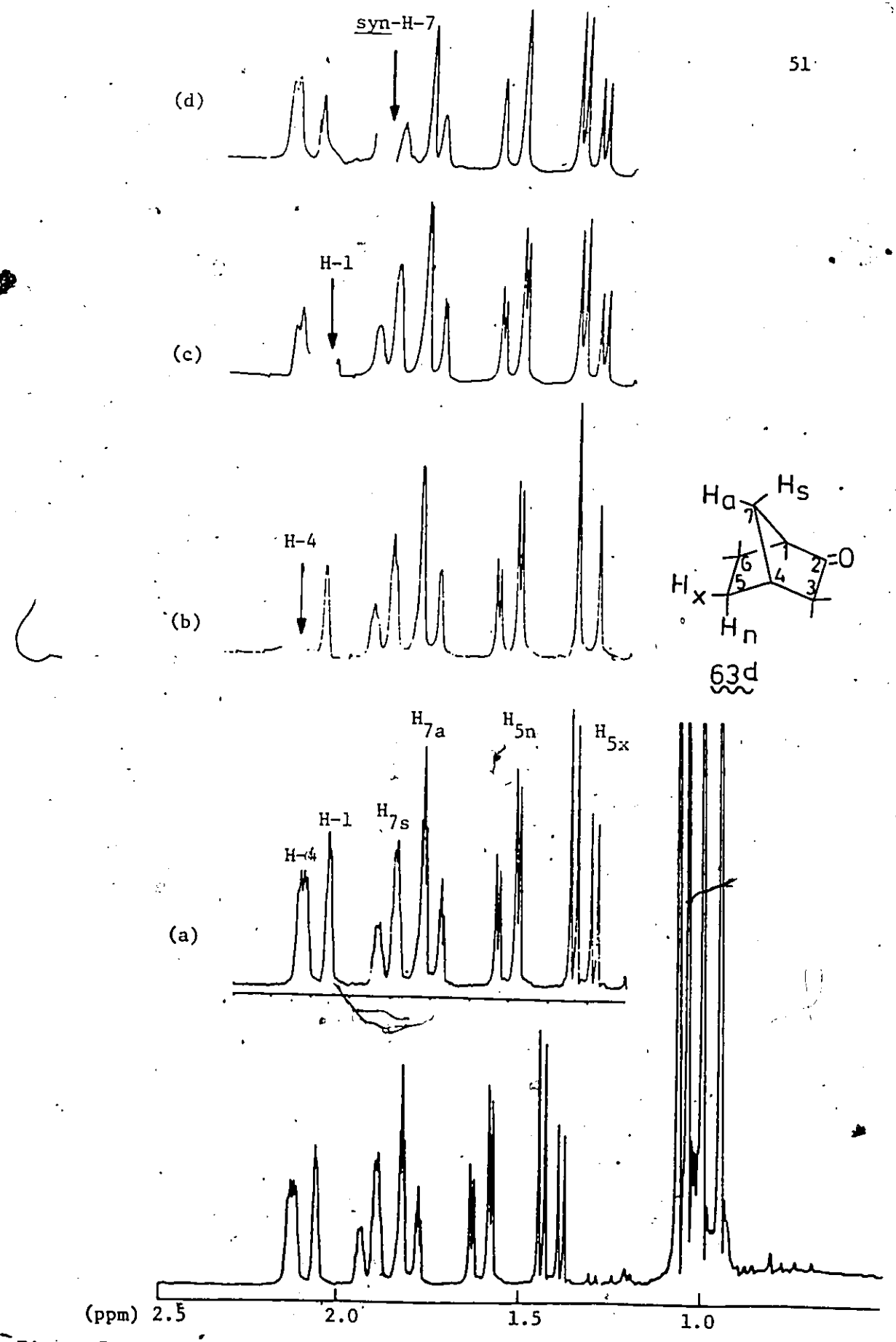


Figure I-B. Illustration of Double Resonance Experiment for Ketone 63d; a) Normal ^1H NMR Spectra (250 MHz), Irradiation at Resonance Frequency of H-4 (b), H-1 (c), syn-H-7 (d).

2.1.4 Preparation and Bromination of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione (64)

Diketone 64, obtained as a major rearrangement product in homoenolization of 63a, was brominated in acetic acid to give 6,6-dibromo-1,3,3-trimethylbicyclo[2.2.2]octane-2,5-dione 65. The ^{1}H and ^{13}C NMR data for 64 and 65 are summarized in Tables IX and XIV.

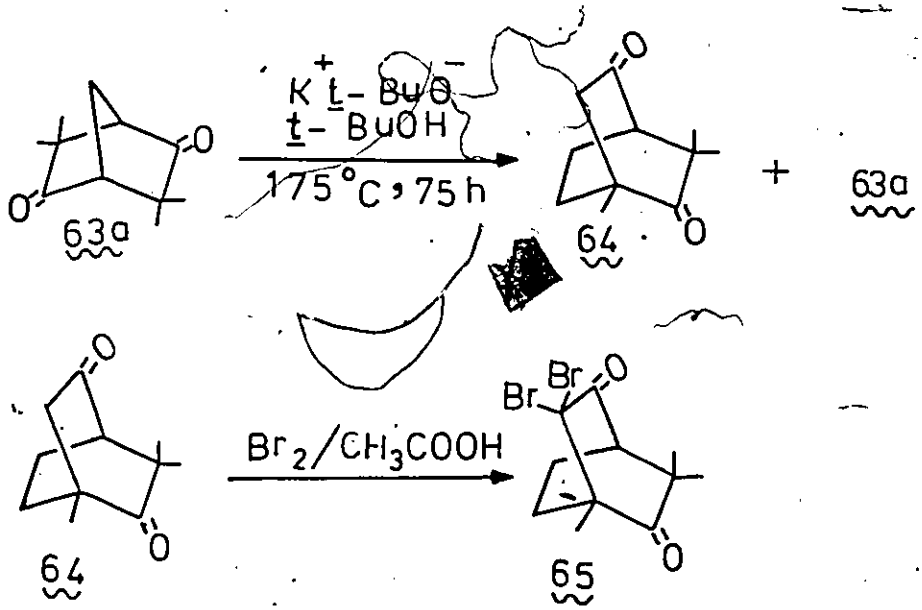


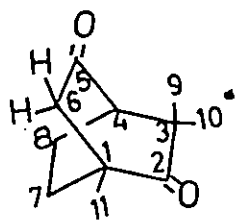
Table IX. ^{1}H NMR Chemical Shifts of 1,3,3-Trimethylbicyclo[2.2.1]octane-2,5-dione (64) and 6,6-Dibromo-1,3,3-trimethylbicyclo[2.2.2]octane-2,5-dione (65) (ppm)[a,b]

Substrate	C^4H	C^6H-s	C^6H-a	C^7H-x	C^7H-n	C^8H-x	C^8H-m	C^9H_3	$C^{10}H_3$	$C^{11}H_3$
64	2.24 m	2.22 bd	2.28 bd	1.77 m	1.77 m	1.88 m	2.15 m	1.04 s	1.17 s	1.02 s
65	2.64 dd	-	-	2.21 m	1.77 m	2.10 m	2.03 m	1.26 s[c]	1.21 s[c]	1.40 s

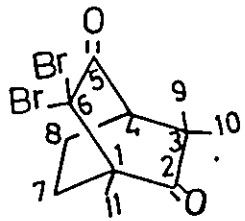
a bd = broad doublet, d = doublet, m = multiplet, s = singlet

b in ppm from TMS in $CDCl_3$

c These assignments may be reversed



64



65

2.2 Homoenolization

2.2.1 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione (63a)

The results of a number of homoenolizations of 63a at 175°C, which establish that 63a rearranges, are shown in Table X. The degree of exchange and the deuterium distribution in 63a, for reactions which were carried out in deuterated media, are tabulated in Tables XI and XII. The deuterium contents of the rearrangement products isolated from two runs (entries 24 and 15 from Table X) are given in Table XIII. Since the maximum conversion of 63a to the rearrangement product was only 65 - 70%, the behaviour of isomeric dione 64 under homoenolization conditions was studied. When the rearrangement product was treated under homoenolization conditions, analysis of the reaction mixture showed that 63a was not formed. The total deuterium incorporation and the relative amounts of deuterated species were obtained by mass spectrometry. Deuterium NMR was used to determine the distribution of deuterium within the molecule. Because the ^{2}H NMR signals overlapped, the spectra were fitted and the curve was resolved using the Nicolet curve analysis program on a Nicolet 1180 computer. An example is shown in Figure II. Further evidence was provided by the comparison of the ^{13}C NMR spectra of 63a and deuterated 63a, obtained under identical concentrations and spectroscopic conditions. The ^{13}C NMR spectrum of deuterated 63a showed reduced signal intensity for C-1, C-4 and C-7 as well as the exo and endo methyls - Figure III. The reduced signal intensities arise from the long relaxation time of a carbon atom bonded to a deuterium relative to a carbon bonded to a proton (104). The spectra in Figure III show precisely this effect. In

Table X. K^{+} t-BuO^{-} Catalyzed Isomerization of 3,3,6,6-Tetramethylbicyclo [2.2.1]heptane-2,5-dione in t-Butyl Alcohol at 175±3°C

Entry	[Ketone] (M)	[K^{+} t-BuO^{-}] (M)	Reaction time (h)	% Conversion to 64	Medium
1	0.32	0.86	64.0	31.3	H
2	0.33	0.82	64.0	31.7	D
3	0.37	1.04	75.0	40.0	H
4	0.39	1.17	75.0	50.0	D
5	0.31	0.88	87.3	30.5	H
6	0.31	0.78	87.3	17.2	D
7	0.39	1.28	52.7	51.0	H
8	0.37	1.10	56.0	24.0	H
9	0.40	1.27	75.0	40.6	H
10	0.37	1.42	75.0	63.4	H
11	0.37	1.37	75.0	61.0	H
12	0.38	1.16	75.0	50.0	H
13	0.40	1.48	72.0	62.0	H
14	0.40	1.45	72.0	56.5	H
15	0.34	1.01	94.0	60.1	D
16	0.38	1.15	102.0	62.9	H
17	0.40	1.03	78.5	34.5	H
18	0.45	1.03	78.5	33.1	H
19	0.40	1.16	98.0	44.0	H
20	0.38	1.16	98.0	43.9	H

(continued next page)

Table X (continued)

Entry	[Ketone] (M)	[K^+ t-BuO^-] (M)	Reaction time (h)	% Conversion to 64	Medium
21	0.39	1.28	72.0	38.0	H
22	0.39	1.25	87.0	44.1	H
23	0.38	1.25	87.0	46.0	H
24	0.59	1.44	30.0	35.0	D
25	0.47	1.37	92.0	62.4	H
26	0.31	1.44	92.0	63.0	H
27	0.39	1.30	76.0	44.0	H
28	0.39	1.30	73.0	52.7	H
29	0.39	1.49	96.0	74.0	H
30	0.33	1.40	96.0	63.1	H

Table XI. H/D Exchange of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione in K^+ t-BuO^-/t-BuOD at 175±3°C

Entry	[Ketone] (M)	[K^+ t-BuO^-] (M)	Reaction time (h)	^2H Content by Mass Spectrometry[a] 1D	2D	3D	4D	5D	6D	7D	Excess[c] D/Molecule
1	0.38	0.84	45.0	0.111	0.660	1.070	0.607	0.132	0.029	-	2.60
2	0.33	0.82	64.0	0.123	0.696	1.046	0.550	0.096	0.016	-	2.53
3	0.39	1.16	75.0	0.048	0.460	1.070	1.000	0.354	0.085	0.022	3.04
4	0.31	0.78	87.3	0.119	0.727	1.023	0.487	0.092	0.025	-	2.47
5[b]	0.19	0.94	94.0	0.022	0.214	0.783	1.22	0.535	0.612	0.146	3.53

a - Atom H±0.001

b - Temperature was 185°C.

c - Determined mass spectrometrically at low voltage (10-15 e.v.).

Table XII. H/D Exchange of 3,3,6,6,Tetramethylbicyclo[2.2.1]heptane-2,5-dione in K^+ t-BuO^-/t-BuOD at 175±3°C

Entry	[Ketone] (M)	[K^+ t-BuO^-] (M)	Reaction Time (h)	Excess[a] D/molecule	Deuterium Distribution			
					C-1,C-4[b]	C-7[b]	Exo-methyl[b]	Endo-methyl[b]
1	0.38	0.84	45.0	2.60	1.37	1.07	0.09	0.07
2	0.33	0.82	64.0	2.53	1.44	0.94	0.10	0.05
3	0.39	1.16	75.0	3.04	1.40	1.38	0.14	0.11
4	0.31	0.78	87.3	2.47	1.41	0.91	0.10	0.05

a - Determined mass spectrometrically at low voltage (10-15 e.v.)

b - Determined by ^2H NMR spectroscopy by computer fitting the spectra.

c - Determined by ^2H NMR (13.4 MHz) spectra obtained on CCl_4 solution ~ 0.1 M in ketone.

Table XIII. Deuterium Content of Rearrangement Product (64) Obtained from Rearrangement of 63 in K^+ t-BuO⁻/t-BuOD at 175 ± 3°C

[ketone, 63a] (M)	[K^+ t-BuO⁻] (M)	Reaction Time (h)	^{2}H Content By Mass Spectrometry [d]												Excess D/Molecule [c]
			1D	2D	3D	4D	5D	6D	7D	8D	9D	10D	11D	12D	
0.59[a]	1.44	30	0.015	0.103	0.237	0.421	0.797	1.225	1.358	1.001	0.477	0.089	0.013	-	5.74
0.34[b]	1.01	94	0.001	0.006	0.034	0.189	0.546	1.179	1.766	1.735	1.064	0.373	0.040	0.111	6.94

a - entry 24 from Table X

b - entry 15 from Table X

c - Determined mass spectrometrically at low voltage (10-15 e.v.)

d - Atom ^{2}H±0.001.

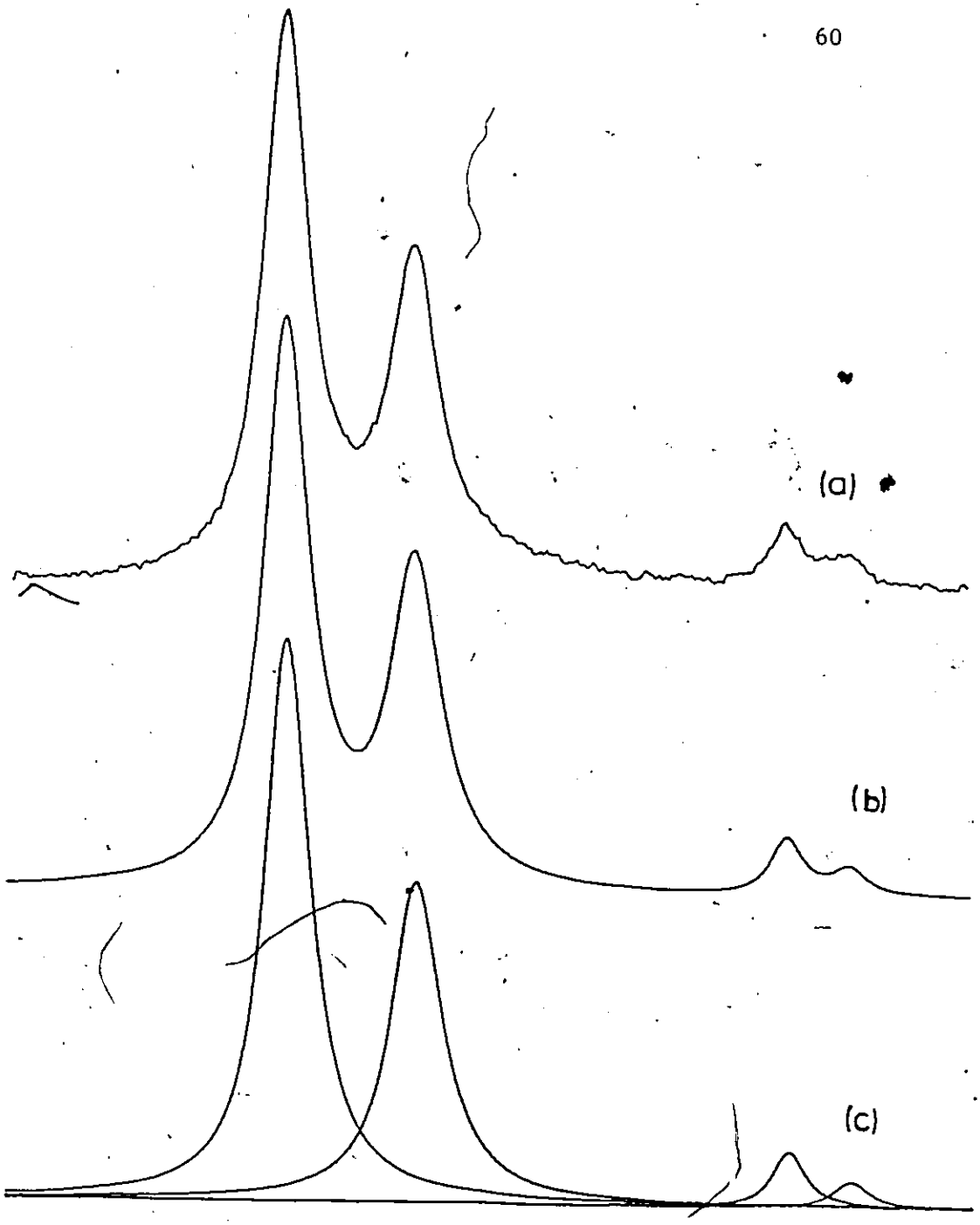


Figure II. ^{2}H NMR Spectra of 3,3,6,6-Tetramethylbicyclo[2.2.1]-heptane-2,5-dione

a) observed spectrum, b) computer fitted
c) curve resolved.

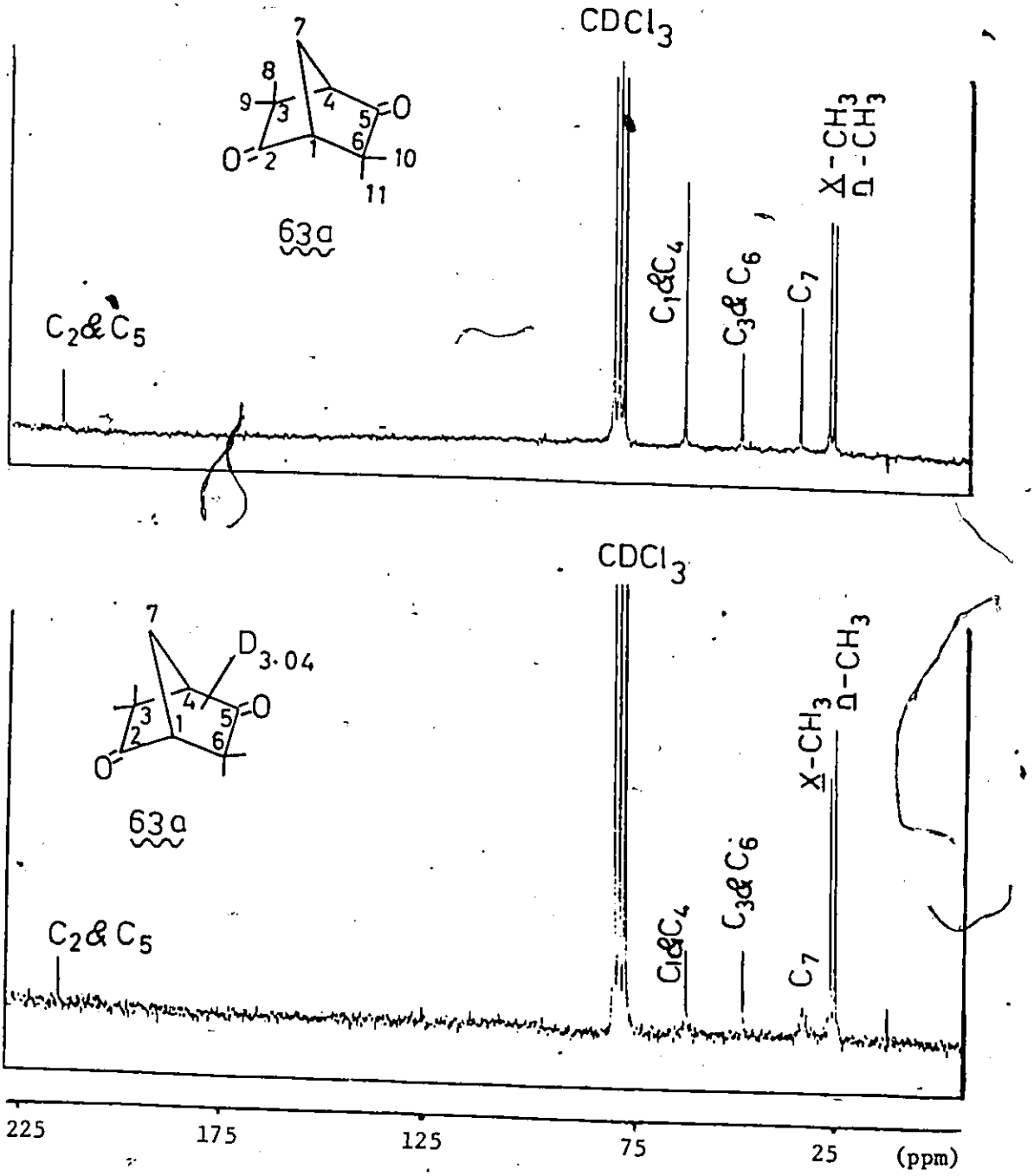


Figure III. ^{13}C NMR Spectra of Deuterated and Non-deuterated 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione.

addition, deuterium coupling was observed at C-7; $^{13}C - ^{2}H \sim 20$ Hz. The deuterium isotope shift was too small to be measured accurately.

2.2.2 Structure Determination of Rearrangement product 64

The rearrangement product obtained from homoenolization of 63a had a melting point of 48 - 49°C and was shown by mass spectrometry to be an isomer of 63a. Its ^{13}C NMR spectrum showed eleven distinct signals whereas the spectrum of the symmetrical starting diketone had six signals. The ^{13}C NMR chemical shifts along with assignments are given in Table XIV. Off resonance ^{13}C NMR studies were used to make the assignments.

The ^{1}H NMR spectrum shown in Figure IV clearly indicates the presence of three methyl groups, at δ 1.17, 1.04 and 1.02 ($CDCl_3$ solution). Integration of the spectrum revealed the presence of sixteen protons. Elemental analysis was in accord with the molecular formula $C_{11}H_{16}O_2$. The assignments of the different proton signals for 64 were based on the high field ^{1}H NMR (250 MHz) spectrum and decoupling experiments. Furthermore, comparison of this spectrum with the high field ^{1}H NMR spectrum of dibrominated derivative 65 was used to confirm these assignments. The infrared spectrum exhibited the presence of carbonyl groups stretching frequencies at 1725 and 1740 cm^{-1} as shown in Figure V.

The isomeric diketone reacted with bromine to form a dibromide of m.p. 120 - 121°C, the mass spectrum of which, at low ionization voltage (14 e.v.) showed parent ion peaks at m/e 336, 338, and 340 (ratio $\sim$ 1:2:1) with the correct relative intensities for a species which contains two bromine

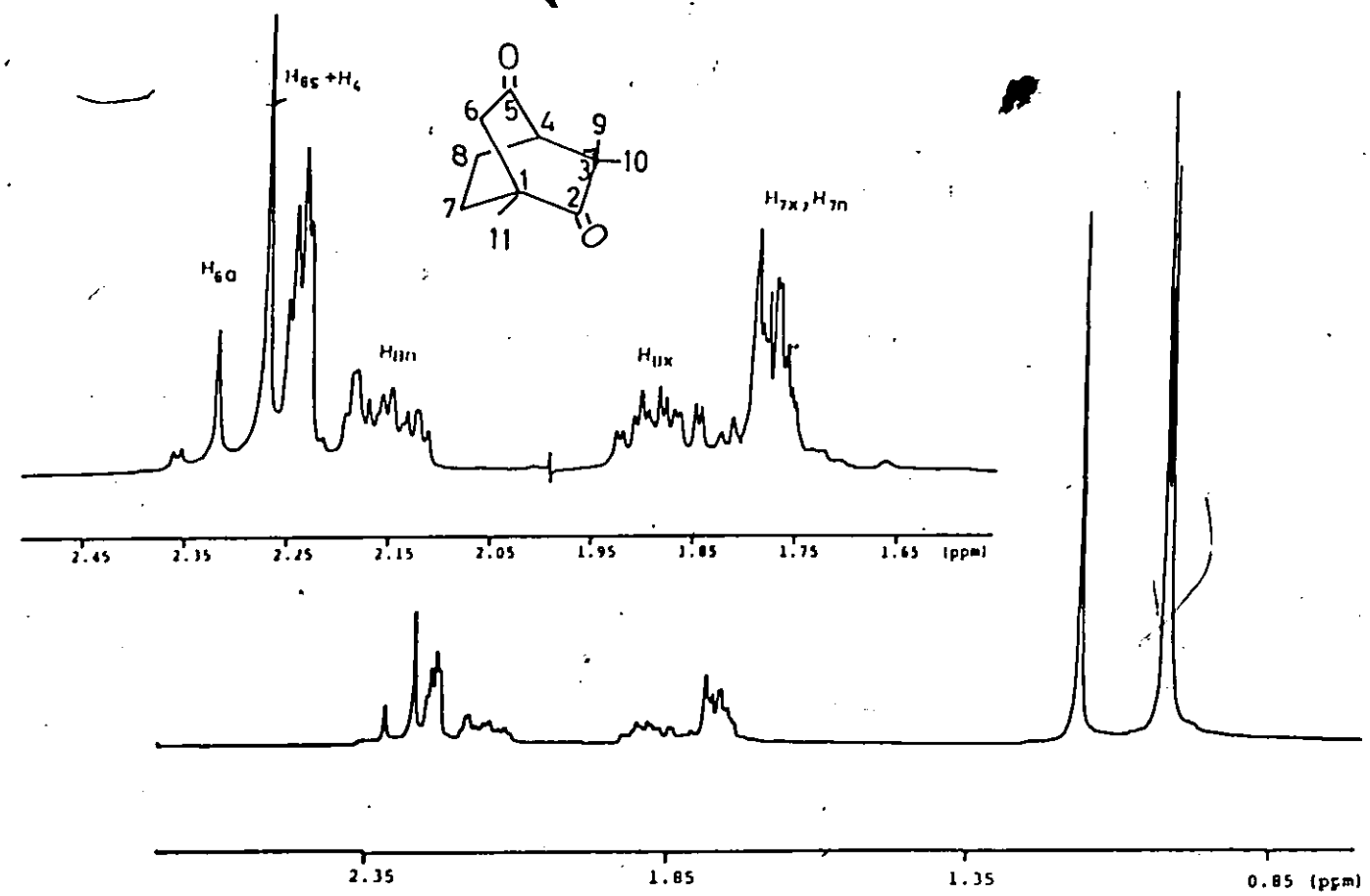


Figure IV. 250 MHz ^{1}H NMR Spectra of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione.

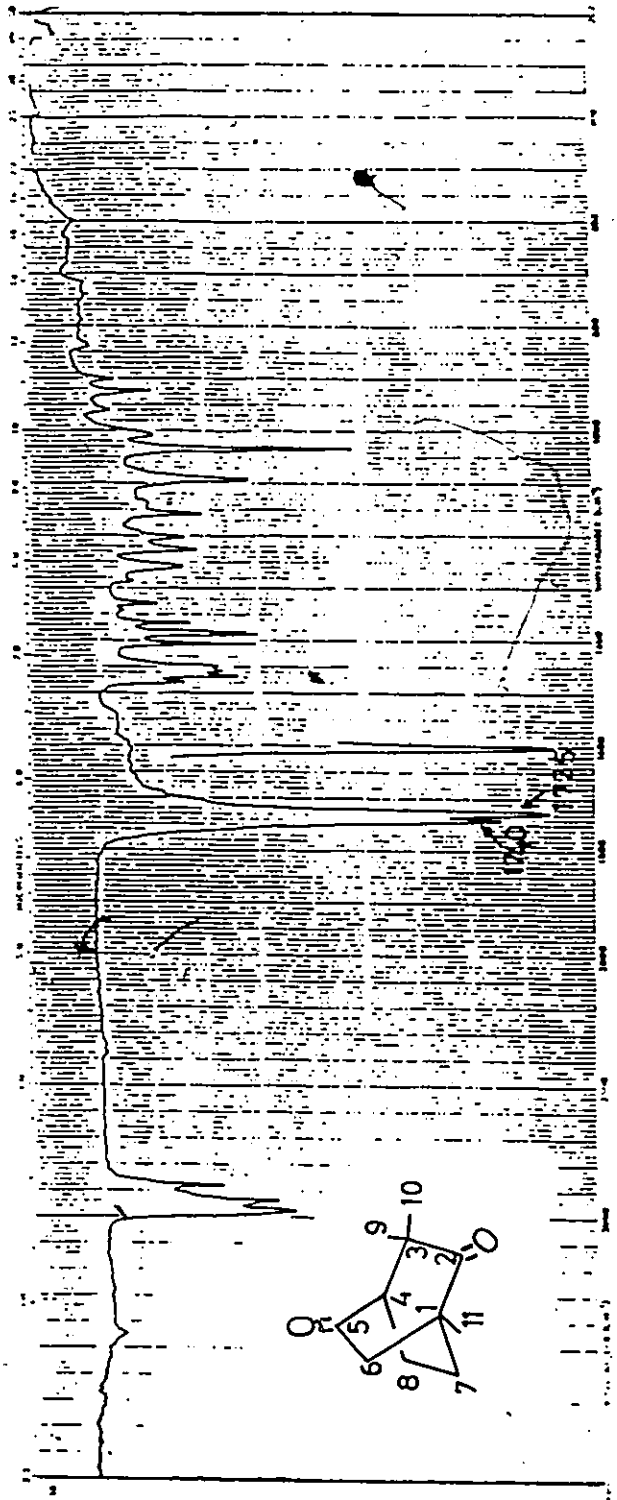
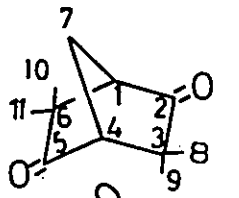
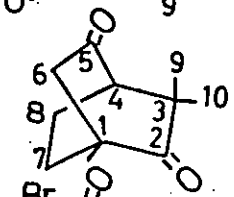
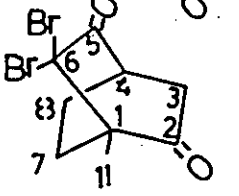


Figure V. IR Spectrum of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione in CCl_4.

Table XIV. ^{13}C Chemical Shifts of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione, 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione and 6,6-Dibromo-1,3,3-trimethylbicyclo[2.2.1]octane-2,5-dione (ppm)[a]







Substrate	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
63a	60.1	217.8	45.9	60.1	217.8	45.9	31.0	23.5	22.3	23.5	22.3
64	44.5	217.6	46.2	56.4	211.8	46.1	29.8	18.8	24.9	22.9	19.4
65	59.7	210.4	45.4	54.2	199.5	67.9	28.6	17.6	25.7[b]	23.9[b]	18.1

a In ppm from TMS in $CDCl_3$.

b These assignments may be reversed.

atoms. In addition, peaks at m/e 257 and 259 of equal intensities corresponded to the loss of a bromine atom and peaks at m/e 229 and 231 corresponded to the loss of CO from the ions of m/e 257 and 259, respectively, which is a very common fragmentation pattern for cyclic carbonyl compounds (105). The ^{13}C NMR data for dibromide 65 are given in Table XIV, and its ^{1}H NMR spectrum is shown in Figure VI. Hydrogen-deuterium exchange studies utilizing 60% dioxane-40% bicarbonate buffer, pD = 10.84 (106), at 30±0.1°C established that there were two readily exchangeable protons alpha to a carbonyl group. An x-ray crystal structure determination was carried out on the dibromide of the rearrangement product by Lock and coworkers (94). It was established that the dibromide was 6,6-dibromo-1,3,3-trimethylbicyclo-[2.2.2]octane-2,5-dione 65 , and therefore that the rearrangement product was the corresponding 1,3,3-trimethylbicyclo[2.2.2]octane-2,5-dione 64 . The computer drawn structure of 65 is shown in Figure VII. The crystals of 65 were orthorhombic of the space group P_{cab}, with cell dimensions a = 11.2, b = 18.82, c = 11.69 Å and had eight formula ~~units in~~ the unit cell. The structure was solved by the heavy atom method. Bond lengths and angles within the structure were normal and comparable to values found in acetone (107,108). Selected interatomic distances (Å) and angles (degrees) are given in Tables XV and XVI.

The structure of 65 (94) is very much like that of 2-p-bromobenzoyl-1,5,5-trimethylbicyclo[2.2.2]octane-6,8-dione (109). A detailed comparison of corresponding bond lengths and angles showed few differences. The crystal packing of 65 is shown in Figure VIII. There was no indications of any strong intermolecular interactions, as judged by the bond

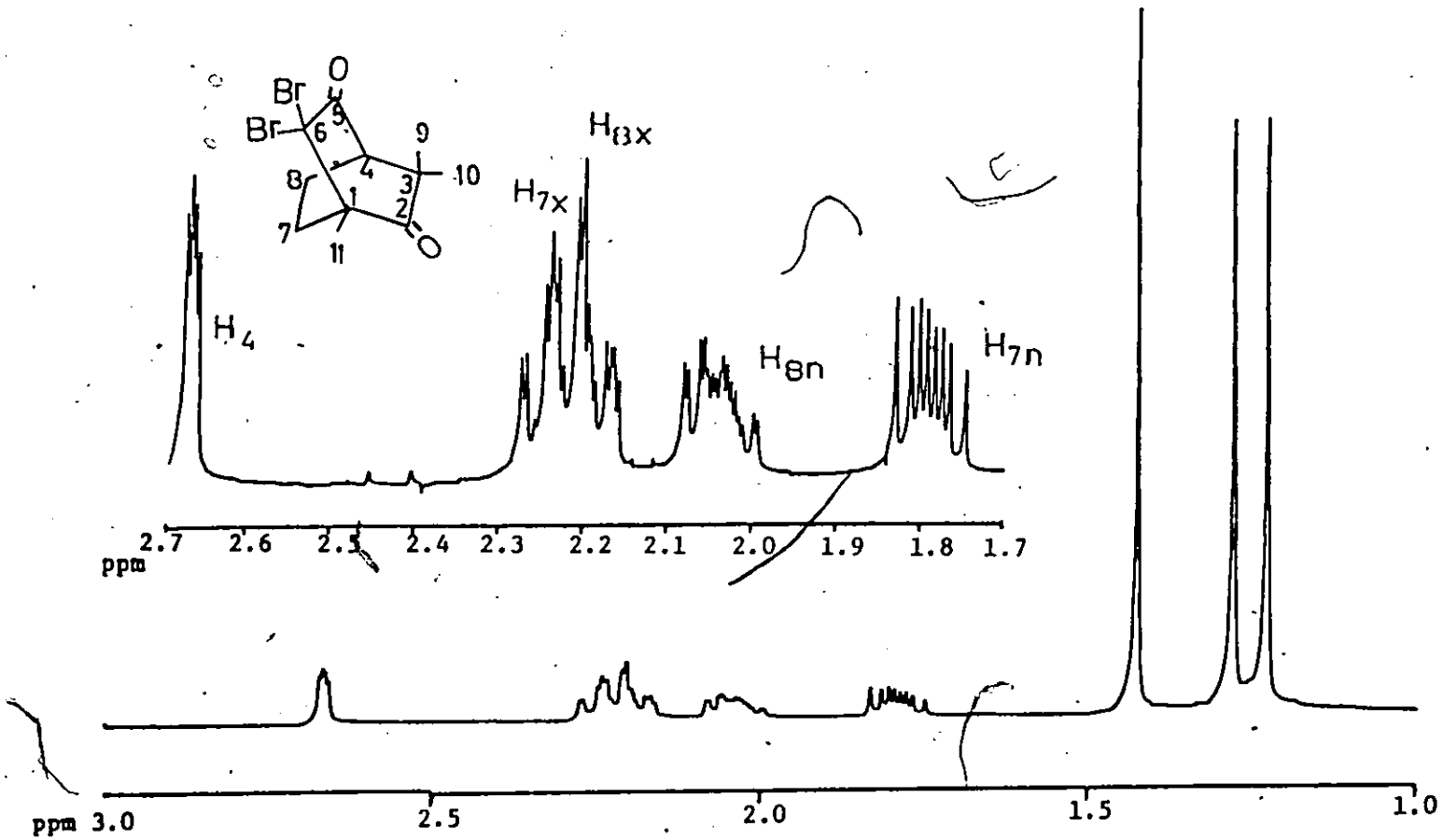


Fig. VI ^{1}H NMR Spectra of 6,6-Dibromo-1,3,3-trimethylbicyclo[2.2.2]octane-2,5-dione.

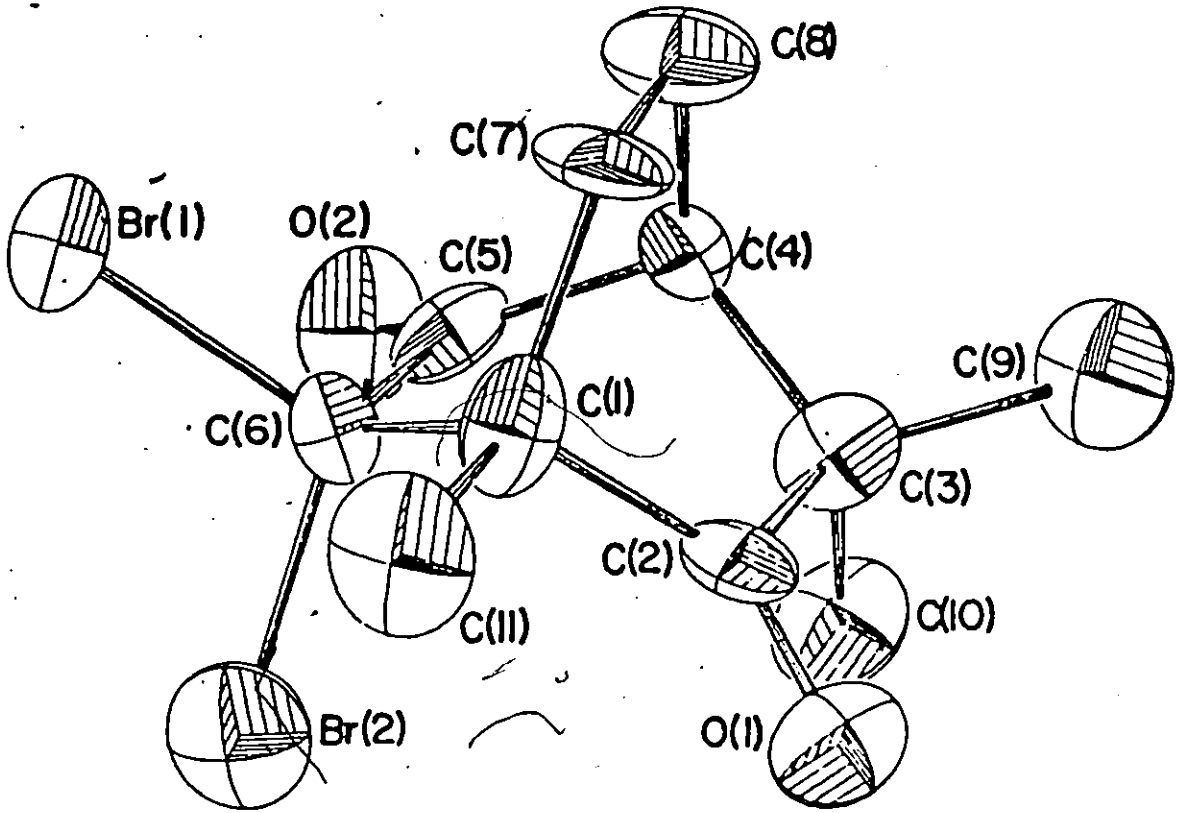


Figure VII The Molecular Structure of 6,6-Dibromo-1,3,3-trimethylbicyclo[2.2.2] octane-2,5-dione.

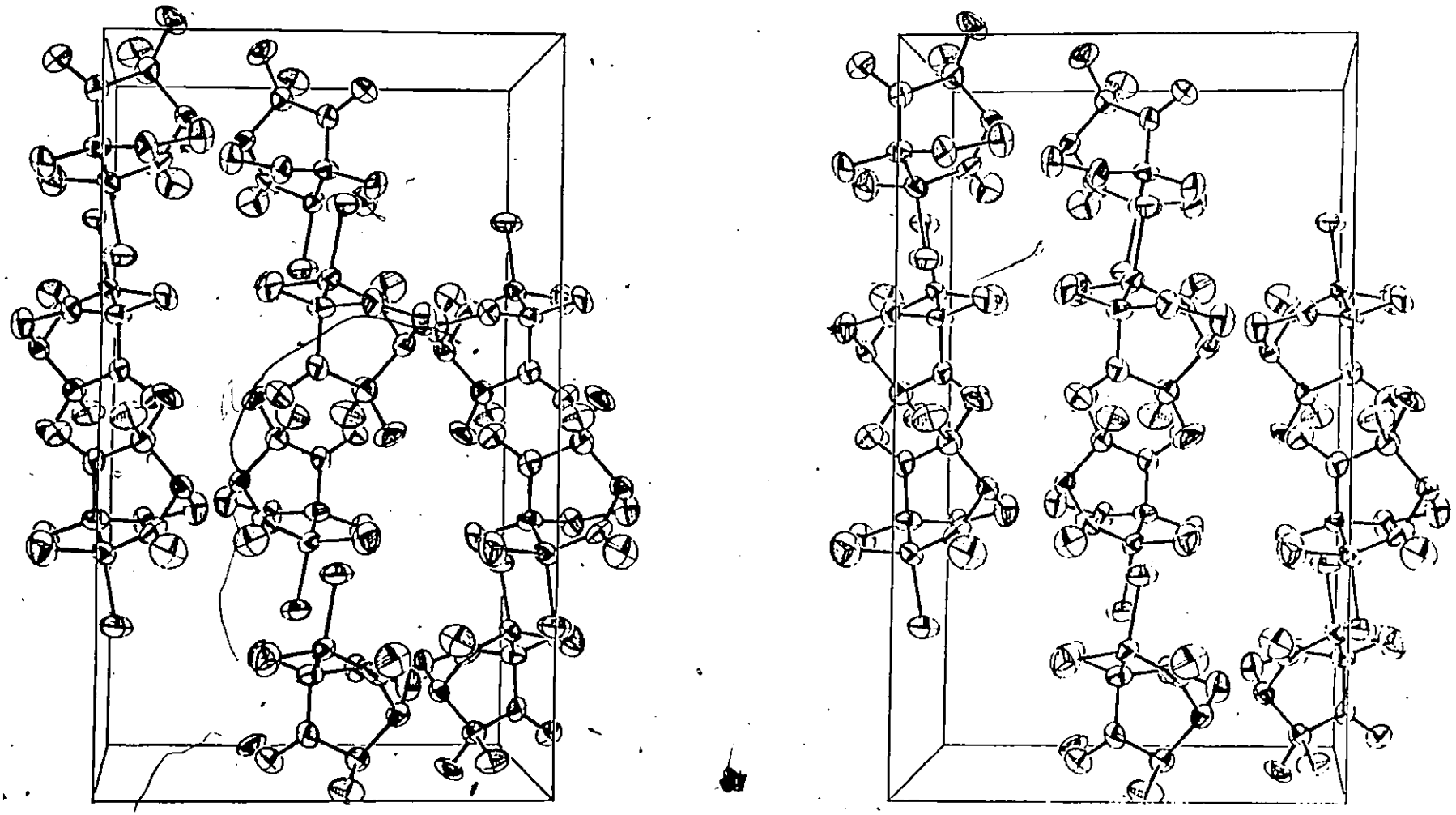


Figure VIII. The Contents of the Unit Cell for 6,6-Dibromo-1,3,3-trimethylbicyclo[2.2.2] octane-2,5-dione

Table XV. Selected Interatomic Distances for 6,6-Dibromide-1,3,3-trimethylbicyclo[2.2.2]octane-2,5-dione (65)

Interatomic Distance	Å	Interatomic Distance	Å
C(1)-C(2)	1.55(2)	C(7)-C(8)	1.56(2)
C(4)-C(5)	1.52(2)	C(3)-C(10)	1.55(2)
C(1)-C(7)	1.54(2)	C(1)-C(11)	1.57(2)
C(3)-C(9)	1.58(2)	C(3)-C(4)	1.54(2)
C(5)-O(2)	1.20(2)	C(6)-C(1)	1.57(2)
C(2)-C(3)	1.53(2)	C(8)-C(4)	1.58(2)
C(5)-C(6)	1.55(2)	C(2)-O(1)	1.23(1)
		C(6)-Br(1)	1.94(1)

Table XVI Selected Angles in 6,6-Dibromo-1,3,3-trimethylbicyclo[2.2.2] octane-2,5-dione (65)

Angle	Degree	Angle	Degree	Angle	Degree
C(6)-C(1)-C(2)	105.0(8)	C(1)-C(2)-C(3)	116(1)	C(2)-C(3)-C(4)	107.9(9)
C(3)-C(4)-C(5)	108.1(9)	C(4)-C(5)-C(6)	113.2(9)	C(5)-C(6)-C(1)	110.4(9)
C(6)-C(1)-C(7)	109.2(9)	C(2)-C(1)-C(7)	103.8(9)	C(5)-C(4)-C(8)	105.9(9)
C(3)-C(4)-C(8)	110.2(9)	C(1)-C(7)-C(8)	112.8(9)	C(4)-C(8)-C(7)	109.3(9)
C(2)-C(3)-C(9)	107.6(9)	C(1)-C(2)-O(1)	121(1)	O(1)-C(2)-C(3)	123(1)
C(4)-C(3)-C(10)	110.8(9)	C(2)-C(3)-C(10)	107.7(9)	C(4)-C(3)-C(9)	111.5(9)
C(2)-C(1)-C(11)	112.6(9)	C(9)-C(3)-C(10)	107.6(9)	C(7)-C(1)-C(11)	112.4(9)
C(6)-C(5)-O(2)	122(1)	C(6)-C(1)-C(11)	113.2(9)	C(4)-C(5)-O(2)	125(1)
C(1)-C(6)-Br(1)	111.1(7)	C(5)-C(6)-Br(1)	107.8(7)	C(5)-C(6)-Br(2)	107.2(7)
C(1)-C(6)-Br(2)	111.7(7)	Br(1)-C(6)-Br(2)	108.5(5)		

lengths and bond angles; the packing forces are van der Waals interactions. The molecule, which can be approximated by a sphere, forms a roughly hexagonal close-packed structure with the layers parallel to the bc plane with a and b layers laying roughly at $x = 0$, $x = \frac{1}{2}$.

2.2.3 Homoenolization of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptan-2-one (63d)

Unlike 63a, substantially longer reaction times (400 - 500 h) were required to incorporate significant amounts of deuterium into 63d. The results of a series of homoenolization studies are listed in Table XVII. Analyses by g.ℓ.p.c. showed that the reaction mixture contained only small amounts (1 - 1.5%) of two other compounds of longer retention time. Due to the small quantities of the minor components, it was not possible to collect enough for positive identification. Average recovery of deuterated 63d was in the 80% range and samples were assayed for deuterium by mass spectrometry. Deuterium NMR was used to establish the locations of the deuterium atoms. Representative ^{2}H, ^{1}H and ^{13}C NMR spectra of non-deuterated and deuterated 63d are given in Figures IX to XI, and establish that exchange occurred predominantly at C-1 and at one of the methyl groups. To obtain a more quantitative assessment of the deuterium distribution a lanthanide shift study using $Eu(fod)_3$ and high field ^{1}H and ^{2}H NMR was undertaken. The 400 MHz ^{1}H and 61.4 MHz ^{2}H NMR spectra of deuterated 63d in the presence of $Eu(fod)_3$ shown in Figure XII provide evidence that deuterium was located at C-1, syn at C-7, and in the endo-6 and exo-3-methyl groups. The 38.4 MHz ^{2}H NMR spectrum of deuterated 63d, taken in the absence of shift reagent and compared to the deuterated 250 MHz ^{1}H spectrum shown in Figure XIII, confirmed the analysis.

Table XVII. H/D Exchange of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptan-2-one in K^{+} t-BuO^{-}/t-BuOD at 175±3°C

Entry	[Ketone] (M)	[K^{+} t-BuO^{-}] (M)	Reaction time (h)	^{2}H Constant by Mass spectrometry[b] 1D	2D	3D	4D	Excess D/Molecule[a]
1	0.170	1.206	80.5	0.127	0.015	-	-	0.140
2	0.225	1.010	210.0	0.289	0.091	0.022	-	0.402
3	0.226	1.240	403.0	0.356	0.163	0.036	(0.056)	0.560
4	0.257	1.240	500.0	0.333	0.114	0.048	0.010	0.505

a - Determined mass spectrometrically at low voltage (10-15 e.v.).

b - Atom %H±0.001.

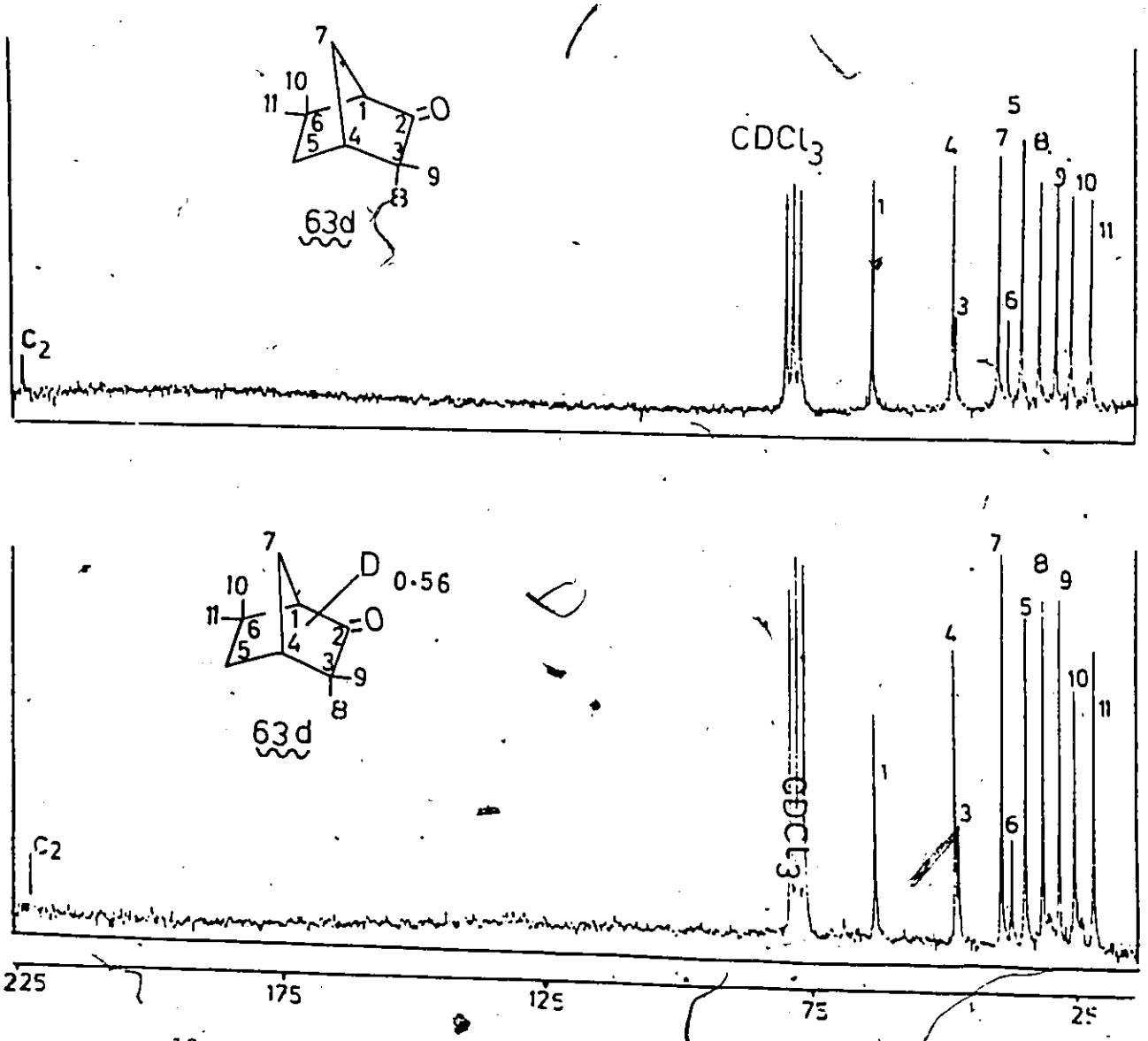


Figure IX. ^{13}C NMR Spectra of Deuterated and Non-deuterated 3,3,6,6-Tetramethyl-bicyclo [2.2.1]heptan-2-one.

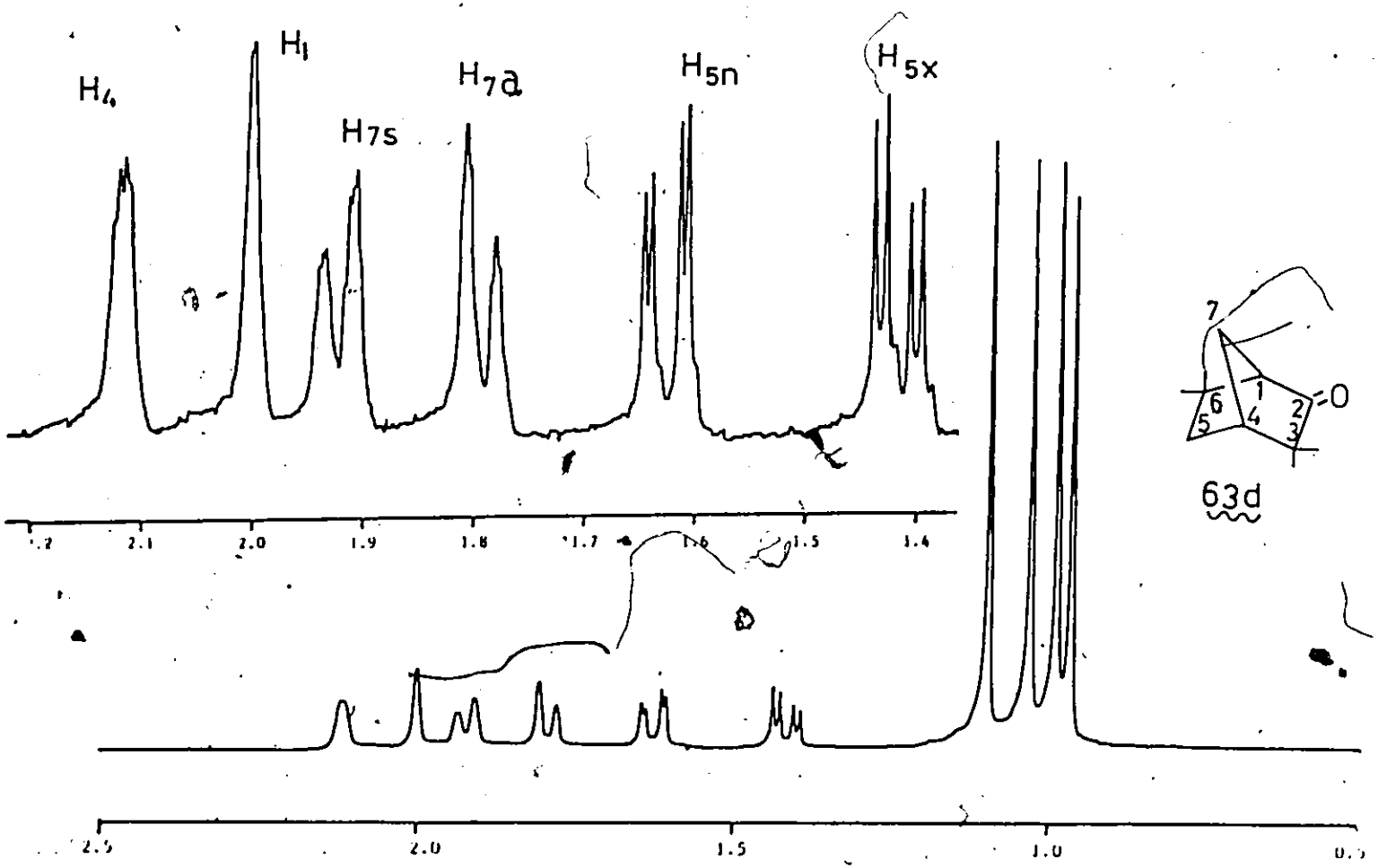


Figure X. 400 MHz ^{1}H NMR Spectra of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptan-2-one.

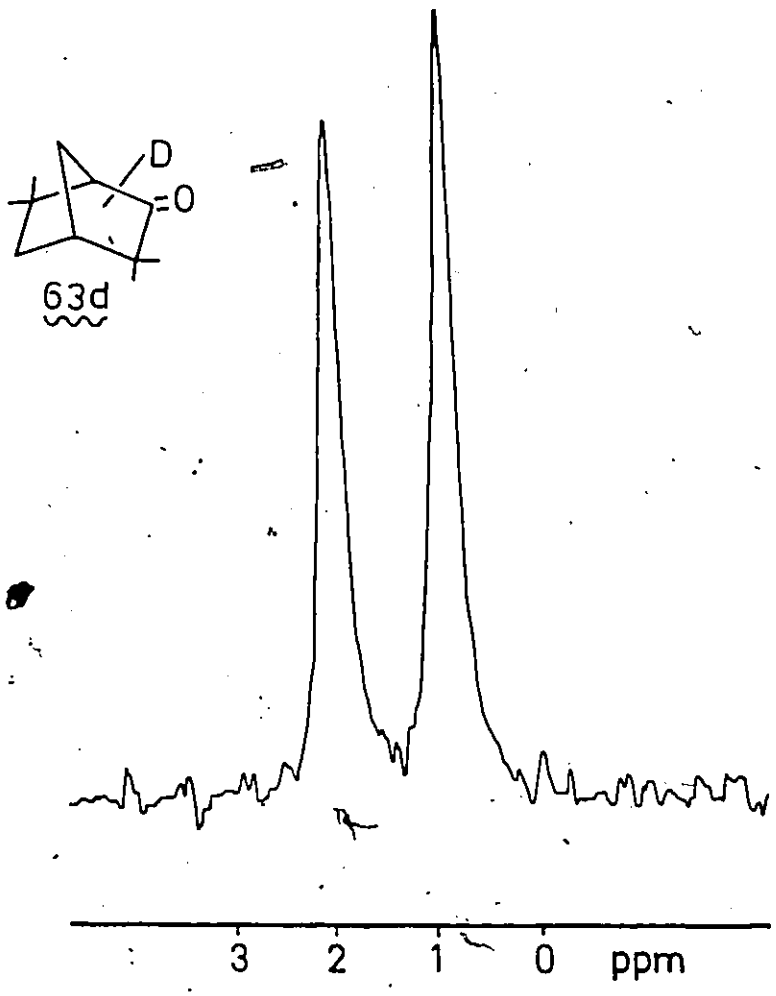


Figure XI. ^{2}H NMR Spectrum of Deuterated 3,3,6,6-Tetramethyl-bicyclo[2.2.1]heptan-2-one (63d)

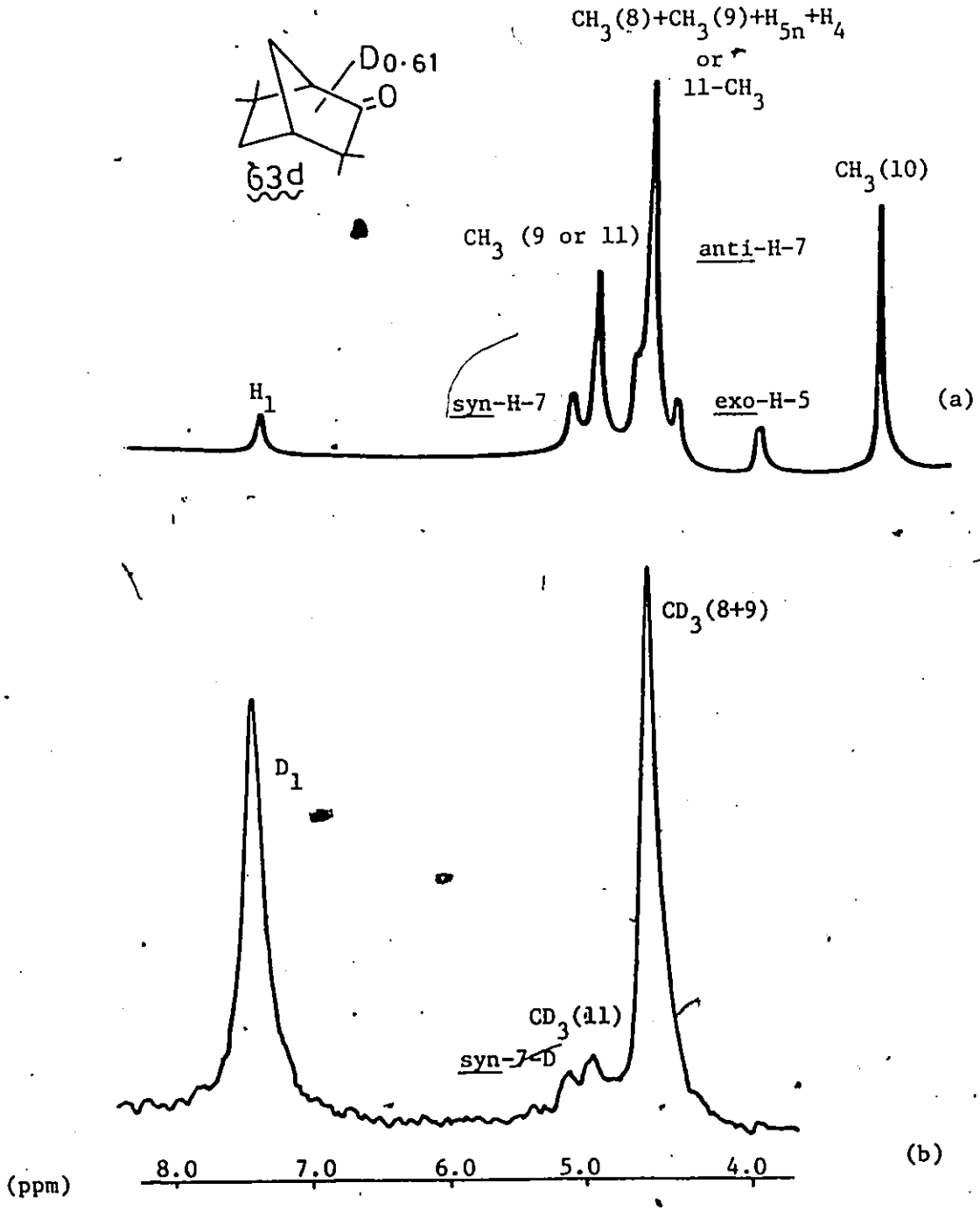
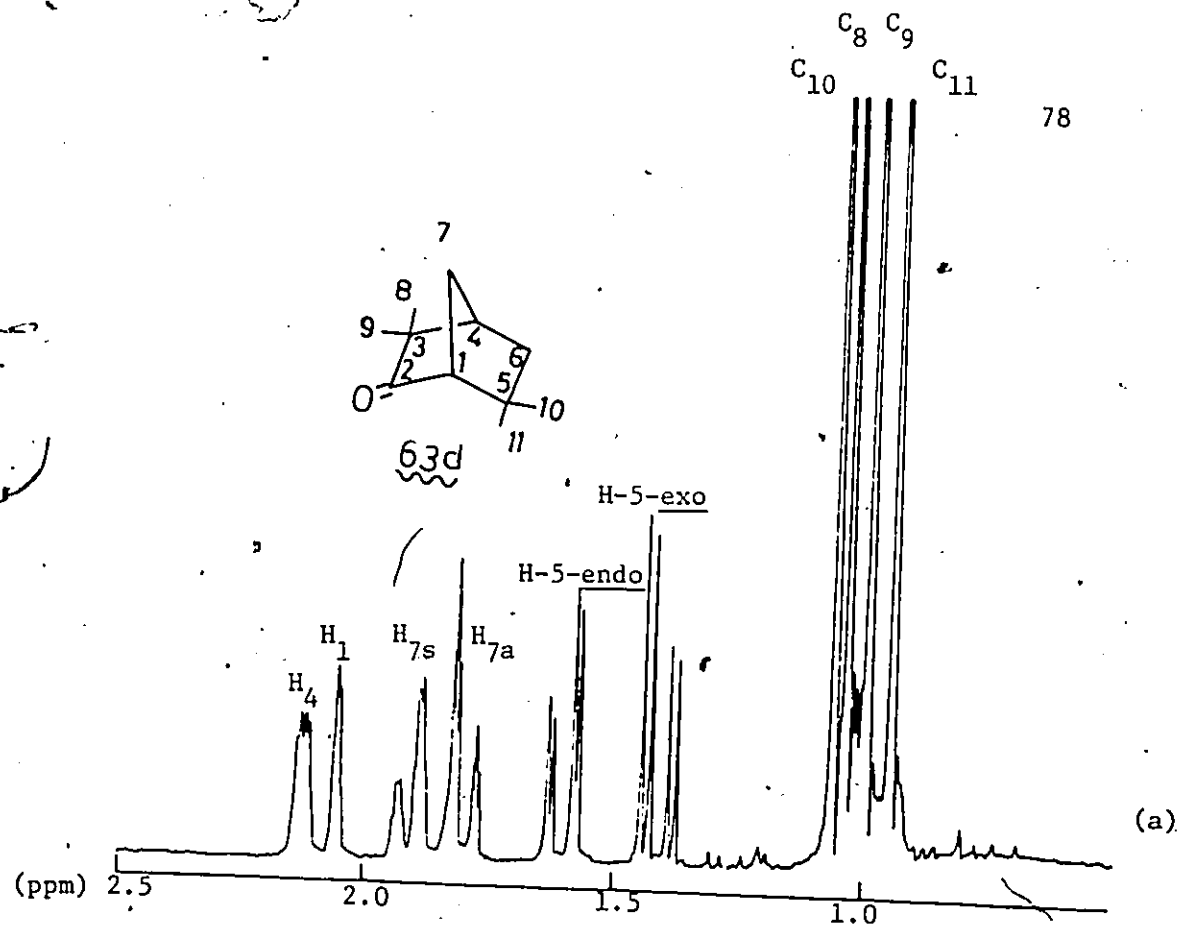


Figure XII. a) 400 MHz ^{1}H NMR Spectrum of Deuterated Dione 63d in Presence of $Eu(fod)_3$ (large excess)

b) 61.4 MHz ^{2}H NMR Spectrum of the Same Sample.



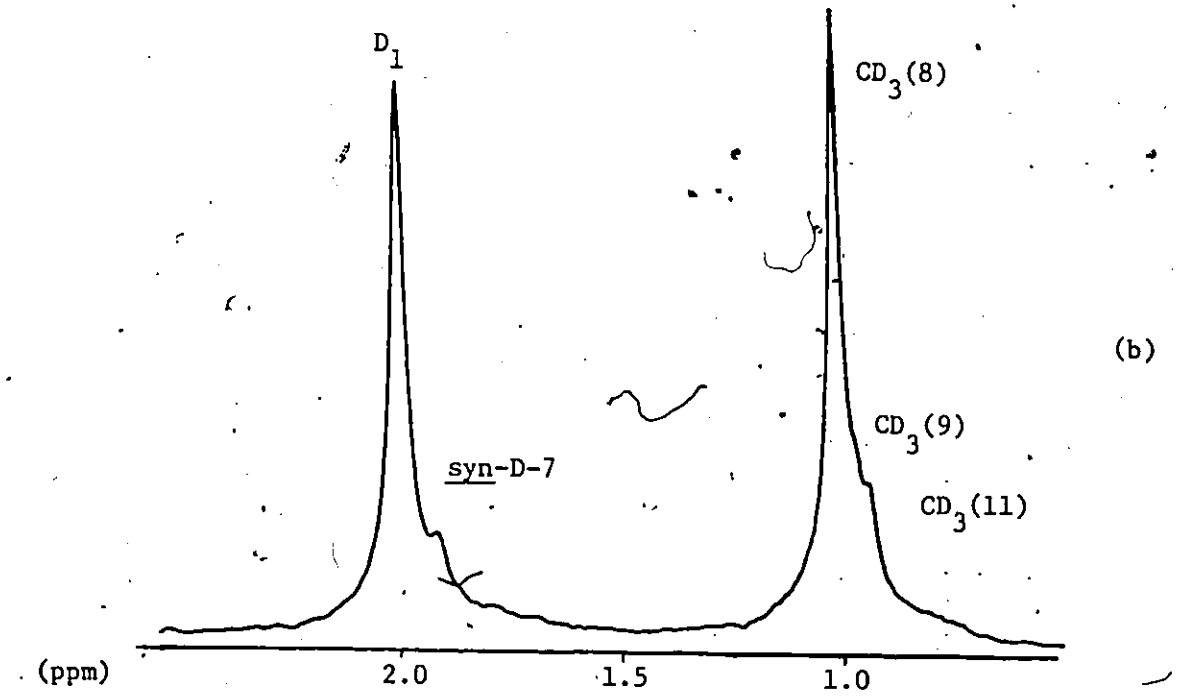


Figure XIII. a) 250 MHz ^{1}H NMR Spectrum of Deuterated Dione 63d

b) 38.4 MHz ^{2}H NMR Spectrum of the Same Sample in the Absence of Shift Reagent.

2.2.4 Homoenolization of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione (64)

The results of a series of homoenolizations of dione 64 are given in Table XVIII. Analyses by g.ℓ.p.c. of the recovered material did not show any significant rearrangement products (< 1%). Material recovery was usually in the range of 80 - 85%. As expected, exchange of hydrogens α to the carbonyl group was fast. Interestingly, the hydrogens of one of the methyl groups underwent very rapid exchange as was established by ^{1}H, ^{2}H and ^{13}C NMR studies. Exchange occurred at other sites when longer reaction periods were used - some deuterium was incorporated in one other methyl group and the C-7 and C-8 methylene groups. The extent and sites of exchange in 64 were determined using a combination of ^{1}H, ^{2}H and ^{13}C NMR spectroscopy and mass spectrometry. For clear identification and assignment of the different signals in the ^{1}H and ^{2}H spectra of 64, a $Eu(fod)_3$ shift study was carried out. At a ratio of 2:1 substrate to $Eu(fod)_3$, the methyl region was well resolved, whereas at a ratio of 1:3, the signals from the methylene and the bridgehead protons were well resolved. Figure XIV gives representative spectra of deuterated and non-deuterated dione 64, with and without shift reagent. In addition, Figure XV shows the ^{13}C NMR spectra of deuterated dione 64 in comparison with the protium sample. In the ^{13}C NMR spectrum of dione 64 obtained in CCl_4 or $CDCl_3$ solution the signals due to C-3 and C-6 overlapped. In order to resolve these signals the spectrum was obtained in C_6D_6, Figure XVI. A 250 MHz ^{1}H NMR spectrum of 64 along with the assignments of the different signals is given in Figure IV.

To obtain an approximate measure of the rate of exchange at the C-4 bridgehead, the deuterium α to the carbonyl group was removed using dioxane/1N NaOH. Figure XVII shows the ^{2}H NMR spectra of dione 64 before and after treatment with base, which were obtained in the presence of a shift reagent. Table XIX lists the results of several experiments. To obtain an accurate measure of the rate of H-D exchange of the hydrogens of the methyl group of 64, homoenolization was carried out at lower temperature and the results are summarized in Table XX. The ^{2}H NMR analysis for a sample of compound 64 which was obtained from treatment under milder homoenolization reaction conditions displayed only two major signals. Figure XVIII shows the ^{2}H NMR spectra of deuterated 64 after 5, 25, and 75 hours at 100°C. The signal at $\delta \sim 2.30$ (1.5 - 1.6 deuterium atoms) is due to the deuterons alpha to the carbonyl group which were incorporated rapidly into 64 on equilibration with the deuterium pool. The rates of exchange of the diastereotopic hydrogen at C-6 of dione 64 were measured in a mixture of 60% dioxane and 40% bicarbonate buffer and are summarized in section 2.3.

The proton NMR signal at $\delta \sim 1.02$ arose from the deuterated C-1 bridgehead methyl group. The assignment of the ^{13}C NMR signals, especially the C-1 bridgehead methyl carbon, was consistent with the chemical shift data of related structures, Figure XIX.

As is shown in Figure XV, a reduction in the intensity of the signal assigned to the C-1 bridgehead methyl carbon was observed for the deuterated sample relative to non-deuterated 64. Both spectra were recorded under the same spectroscopic conditions (concentration and solvent). Ad-

Table XVIII H/D Exchange of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione in K^+ t-BuO$^-$/t-BuOD at 175±3°C

Entry	[Ketone] (M)	[K^+ tBuO$^-$]	Reaction time (h)	^{2}H Content by Mass Spectrometry[a]											Excess D/Molecule[b]
				1D	2D	3D	4D	5D	6D	7D	8D	9D	10D	11D	
1	0.150	1.000	2	0.004	0.045	0.370	1.444	2.252	0.084	0.012					4.21
2	0.156	1.250	5	0.007	0.040	0.257	1.097	2.237	0.786	0.148	0.081	0.029			4.68
3	0.166	1.000	5	0.003	0.025	0.206	1.064	2.472	0.713	0.166	0.072	0.0245			4.70
4	0.148	1.320	9	0.010	0.084	0.501	1.400	1.560	0.575	0.117	0.044				4.29
5	0.127	1.250	36	0.002	0.009	0.061	0.341	1.111	1.802	1.481	1.712	0.358	0.165	0.041	6.08
6	0.158	1.000	37	0.002	0.008	0.009	0.477	1.462	1.861	1.080	0.458	0.183	0.050	0.014	5.61
7	0.166	1.000	50	0.002	0.027	0.194	0.795	1.650	1.590	0.720	0.109	0.060	0.012	-	5.16
8	0.150	1.140	55	0.005	0.020	1.104	0.432	1.107	1.715	1.433	0.693	0.220	0.075	0.073	5.86

a - Atom ^{2}H±0.001.

b - Determined mass spectrometrically at low voltage (10-15 e.v.).

Table XIX. D/H Exchange of Deuterated 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione

1 In 1M NaOH/Dioxane (40:60)[a]

Entry	^{2}H Content by Mass Spectrometry[c]											Excess D/Molecule[d]	D loss[d]
	1D	2D	3D	4D	5D	6D	7D	8D	9D	10D	11D		
1	0.005	0.020	0.104	0.432	1.107	1.715	1.433	0.693	0.720	0.075	0.073	5.86	1.40
1X[b]	0.016	0.073	0.447	1.213	1.465	0.787	0.249	0.145	0.067	-	-	4.46	
2	0.015	0.103	0.237	0.421	0.797	1.225	1.358	1.001	0.477	0.090	0.013	5.74	1.31
2X[b]	0.028	0.176	0.497	0.879	1.125	1.016	0.530	0.149	0.033	-	-	4.33	
3	0.002	0.027	0.194	0.795	1.650	1.590	0.920	0.109	0.060	0.012	-	5.16	1.67
3X[b]	0.032	0.217	1.022	1.300	0.549	0.372	-	-	-	-	-	3.49	

a - Exchange was carried out at 30±0.1°C for 25-30 h.

b - Refers to the sample after exchange.

c - Atom ^{2}H±0.001.

d - Determined mass spectrometrically at low voltage (10-15 e.v).

Table XX. H/D Exchange of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione in K^+ t-BuO^-/t-BuOD at 100-160°C

Entry	[Ketone] (M)	[K^+ t-BuO^-]	Reaction time (h)	Temperature	^2H Constant by Mass Spectrometry							Excess D/molecule [a]
					1D	2D	3D	4D	5D	6D	7D	
1	0.126	~1.050	5	100	0.332	1.039	0.020	0.137	0.150	-	-	1.68
2	0.108	1.030	25	100	0.222	1.070	0.050	0.195	0.468	0.003	-	2.01
3	0.114	1.082	75	100	0.146	0.873	0.124	0.503	1.129	0.001	-	2.78
4	0.123	1.050	4	150	0.019	0.075	0.411	1.487	2.093	-	-	4.10
5	0.126	0.986	4	160	0.013	0.206	1.280	1.430	0.451	0.022	0.010	3.42

a - Determined mass spectrometrically at low voltage (10-15 e.v.).

b - Atom $^2H \pm 0.001$.

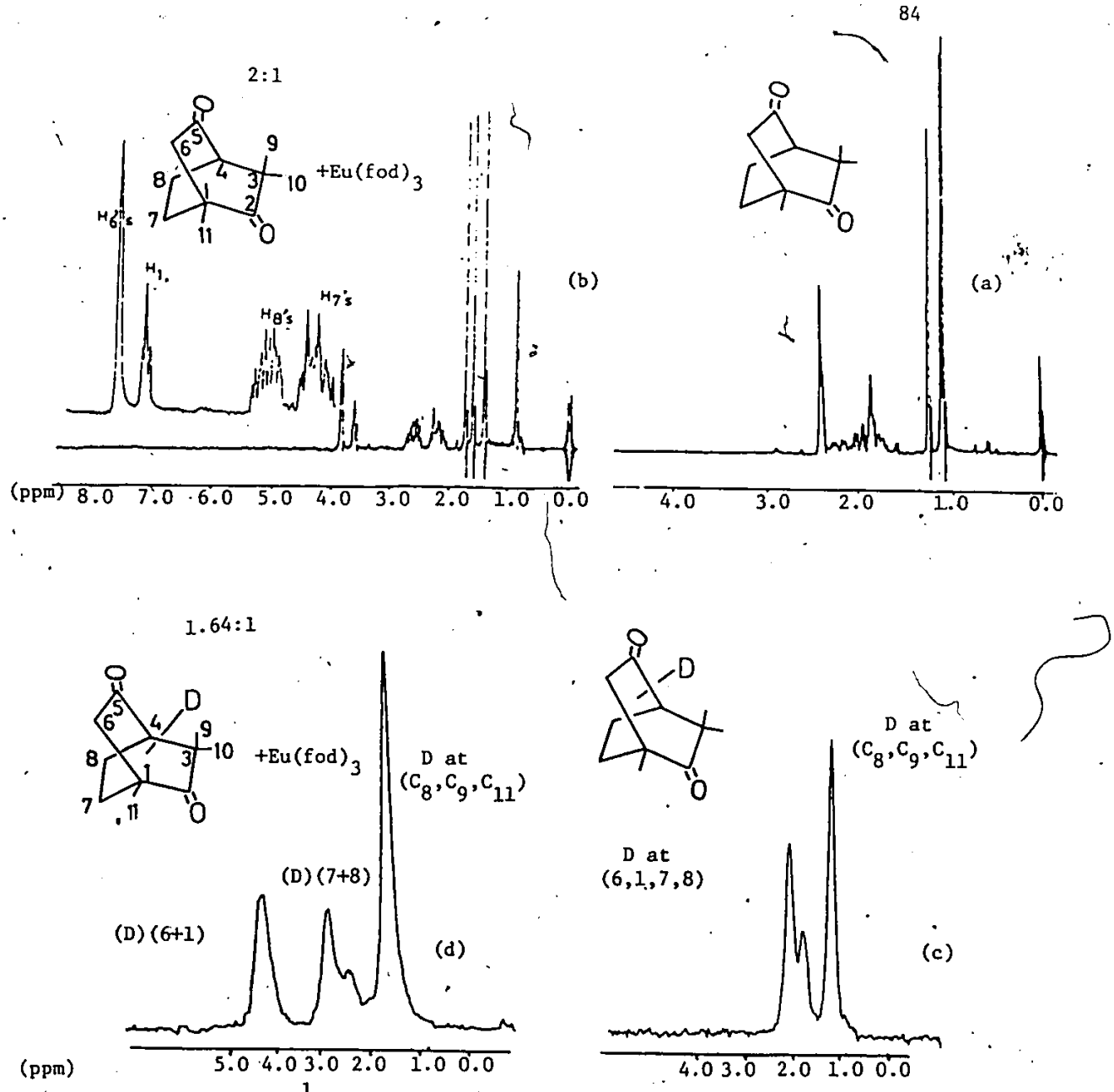


Figure XIV. 90 MHz ^{1}H NMR Spectrum of Dione 64 (a); Spectrum of the Same Sample in Presence of $Eu(fod)_3$. (2:1 Ratio) (b); 38.4 MHz ^{2}H NMR Spectrum of Deuterated Dione 64 (c) and Spectrum of the Same Sample in Presence of $Eu(fod)_3$ (Ratio of 1.64;1) (d).

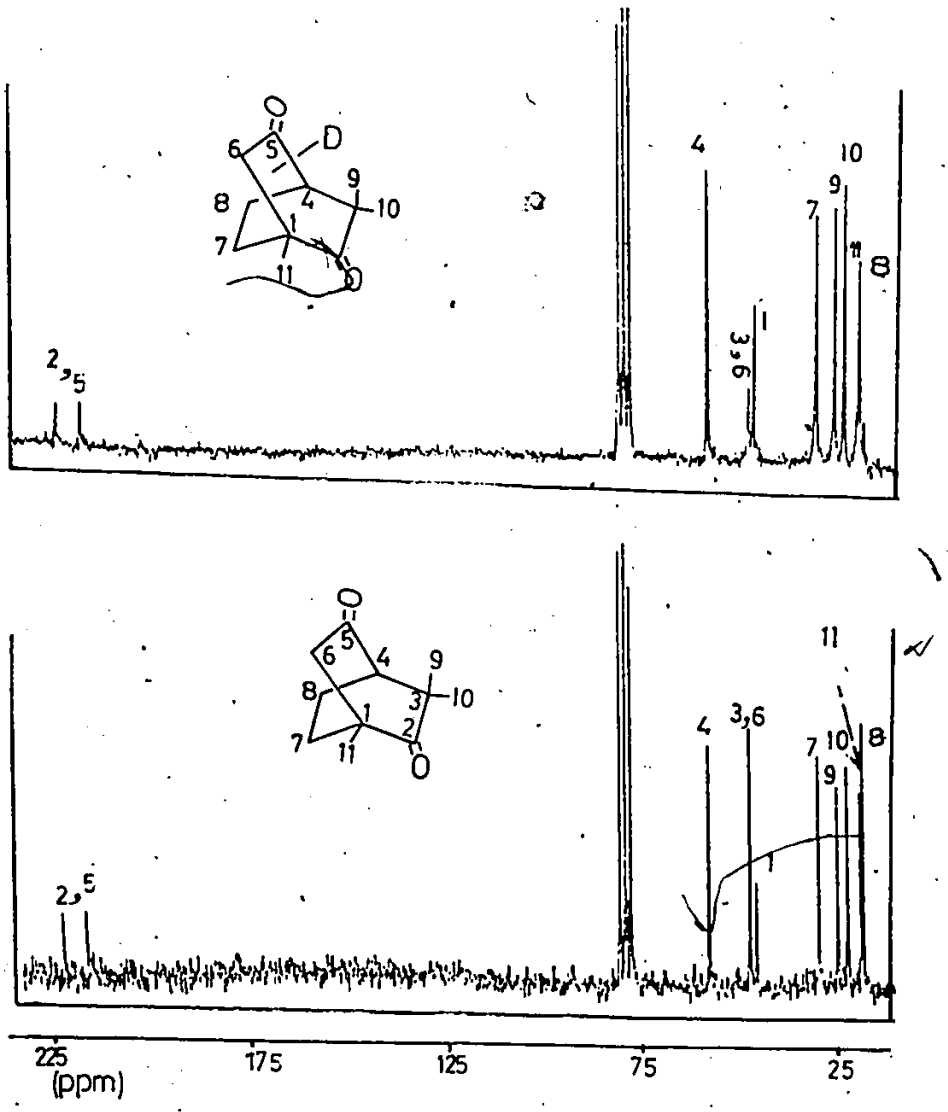


Figure XV. Broad Band Decoupled ^{13}C NMR Spectra of Deuterated and Non-deuterated 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione

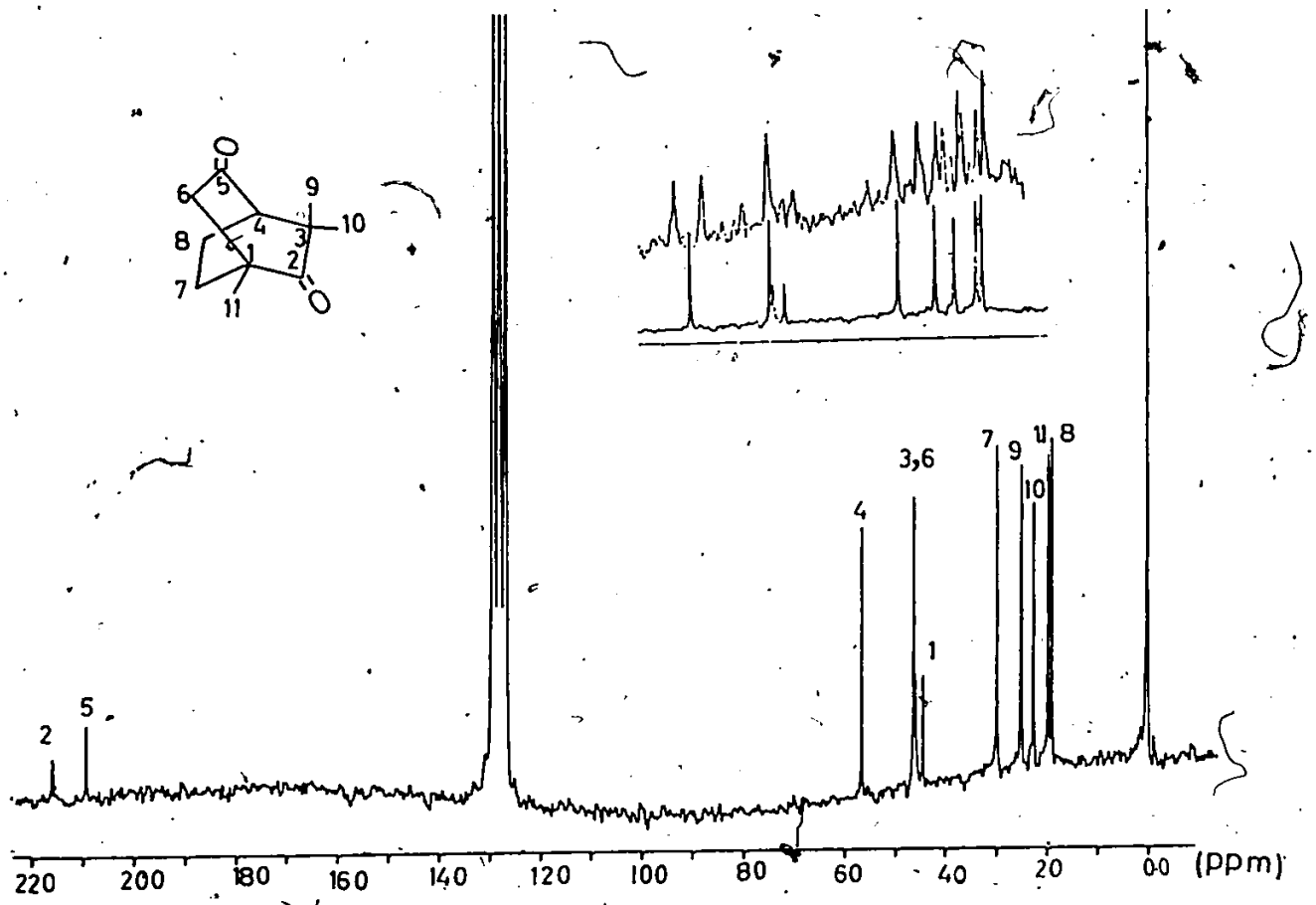


Figure XVI. Broad Band Decoupled and Off Resonance Decoupled ^{13}C NMR Spectra of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione in C_6D_6.

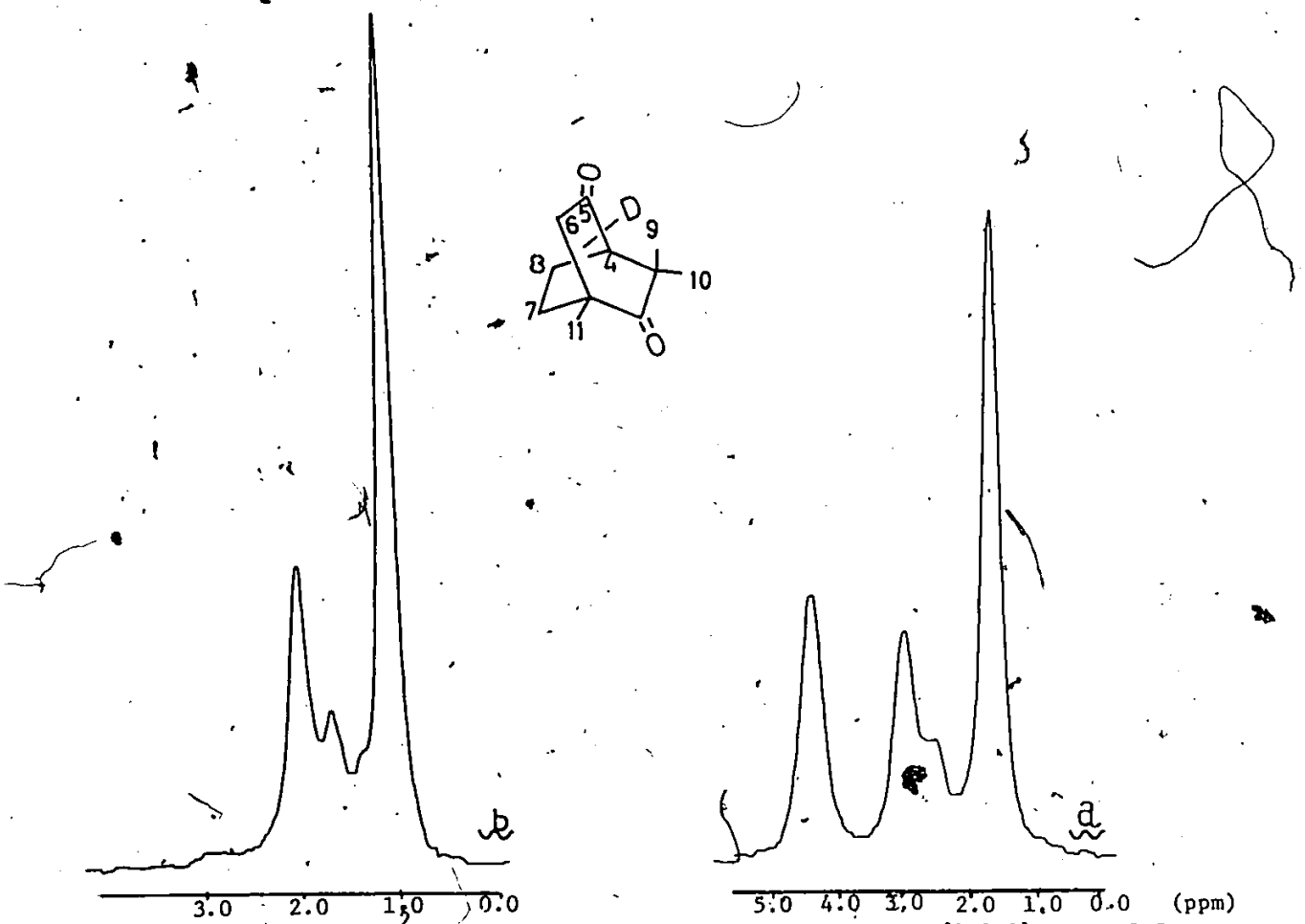


Figure XVII. 38.4 MHz ^{2}H NMR Spectra of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione (64) in the Presence of Eu(fod)$_3$, Ratio of 1.64:1
a) Sample Isolated from the Deuteration Experiment (55 h),
b) The Same Sample After Back Exchange of the Deuterons at C_6.

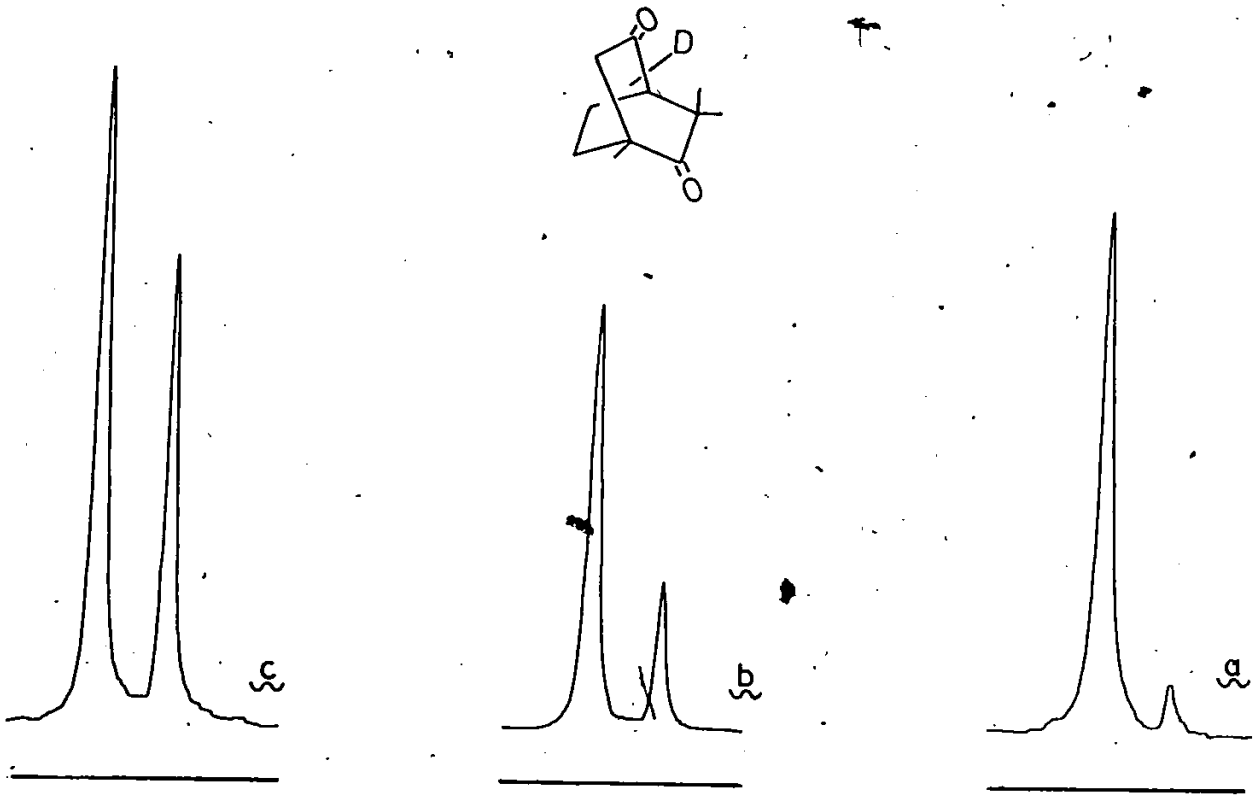


Figure XVIII. ^{2}H NMR Spectra of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione After Treatment with K^{+} t-BuO/t-BuOD at 100°C
a) 5 h b) 25 h c) 75 h.

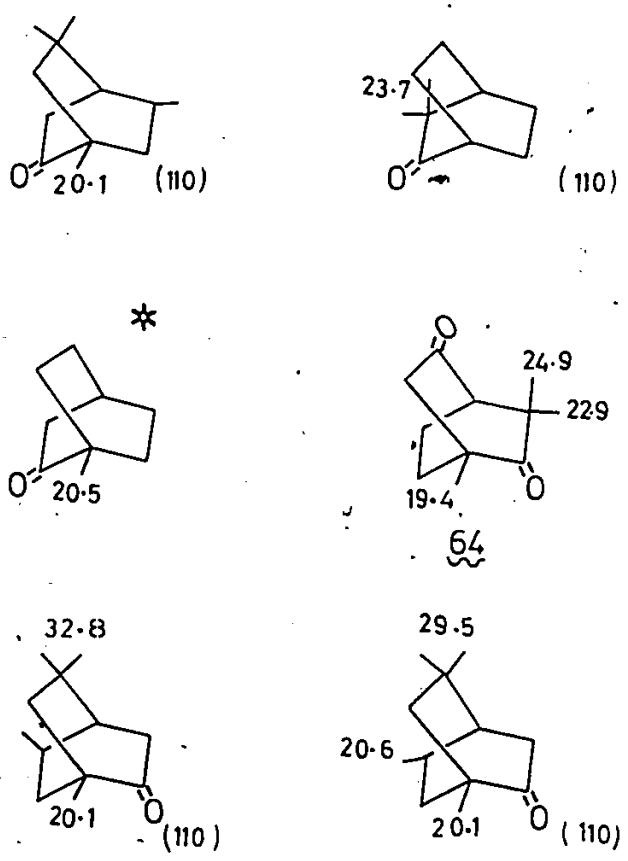
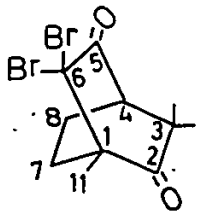


Figure XIX. Model Compounds Used to Confirm the ^{13}C NMR Assignment for the Bridgehead Methyl in 1,3,3-Trimethyl-bicyclo[2.2.2]octane-2,5-dione (64)

* We thank Professor C. Djerassi for providing a sample of 1-methyl-bicyclo[2.2.2]octan-2-one.

ditional evidence that the hydrogens of the bridgehead methyl group undergo facile exchange was acquired by examination of the ^{13}C NMR spectra of 65 and highly deuterated 65. The bromines at C-6 caused, by a γ-effect (110a),



65

a small but observable shielding of the bridgehead methyl carbon (∿ 1.4 ppm). The other methyl carbons, which are in an ε position, were deshielded slightly (0.8 - 1.0 ppm). These effects are illustrated by the spectra in Figure XX. As expected, deshielding was observed for protons of the bridgehead methyl group in the ^{1}H NMR spectra of 65. The ^{13}C NMR spectrum of a sample of highly deuterated 65 (≃ 5.5 - 6 D/molecule) prepared from a sample of 64 which was isolated from the rearrangement of 63a in deuterated medium, is included in Figure XXI. The signal assigned to the bridgehead methyl carbon is reduced in intensity as are the signals due to C-7 and C-8. Most importantly, the intensity of the ^{13}C signal due to C-1, which bears the highly

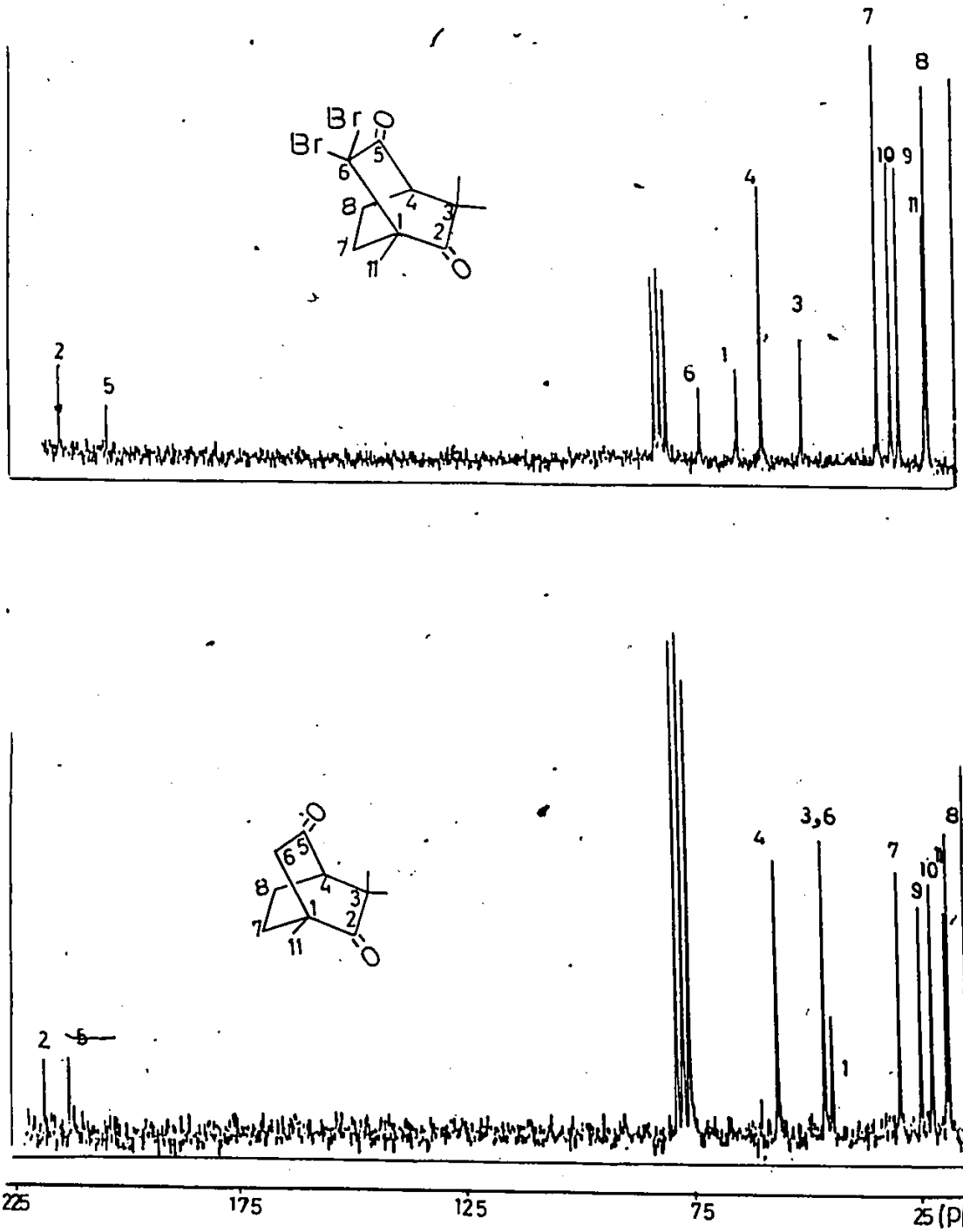


Figure XX. Broad Band Decoupled ^{13}C NMR Spectra of 6,6-Dibromo-1,3,3-trimethylbicyclo[2.2.1]octane-2,5-dione and 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione.

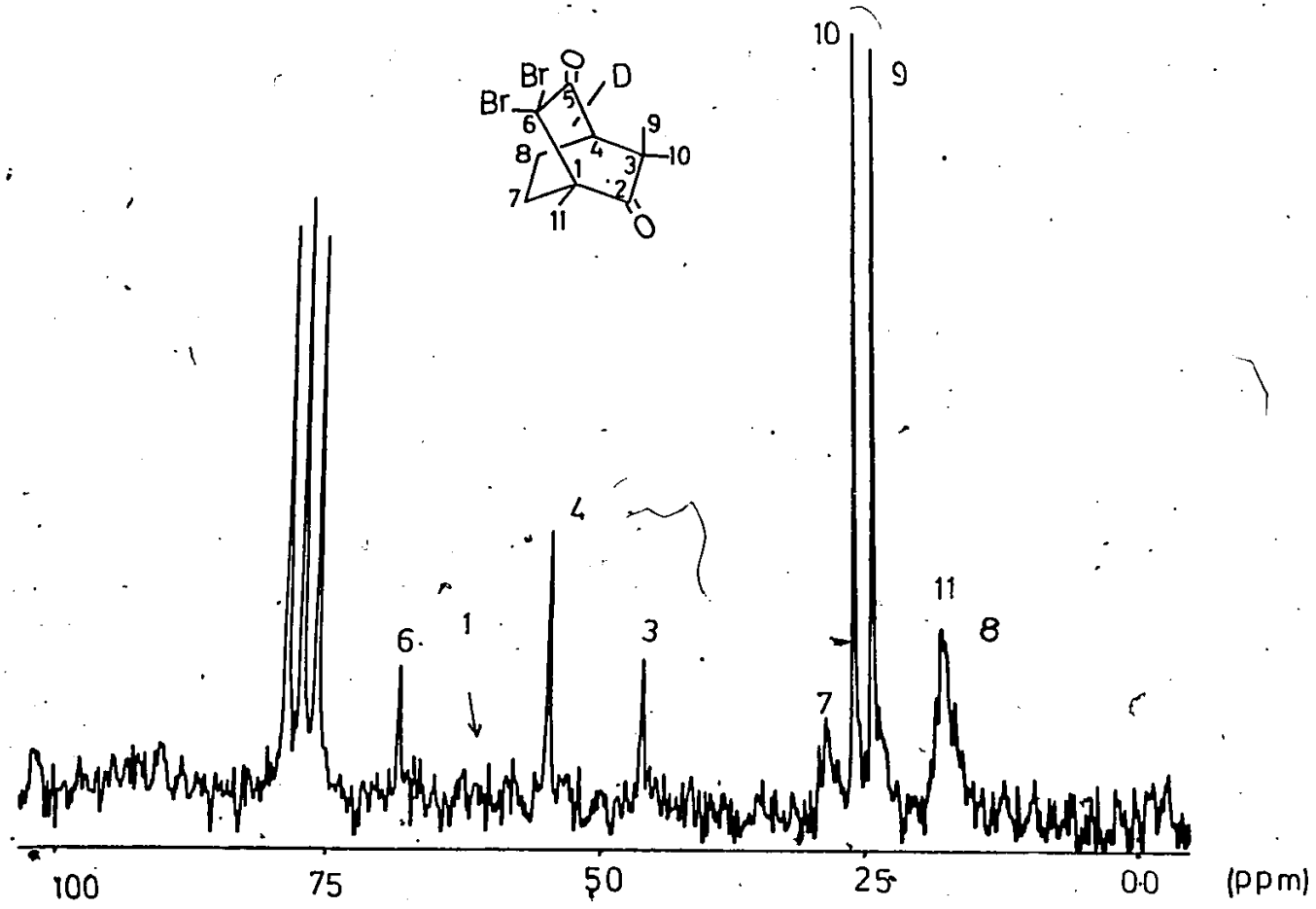


Figure XXI. Broad Band Decoupled ^{13}C NMR Spectrum of Highly Deuterated (5.5 - 6 Excess D/molecule) of 6,6-Dibrimo-1,3,3-trimethylbicyclo[2.2.2]octane-2,5-dione (65)

deuterated methyl, is reduced to base line noise because there are no neighbouring protons to relax C-1. The quarternary bridgehead carbon, which is usually of low intensity under normal spectrometer conditions, was almost non-observable. Further supporting evidence for deuterium incorporation at the bridgehead methyl was obtained by determining the Nuclear Overhauser effects (NOE) of the non-exchanged methyl groups on H-4. Samples of 64 which were highly deuterated at C-6 and at one of the methyl groups were used in this experiment. The samples were irradiated selectively at each of the two remaining methyl groups (δ = 1.04 and δ = 1.17), and the bridgehead proton H-4 was monitored for NOE enhancement. Multiple integrations were taken and the experiment was repeated at least twice for each sample. The bridgehead proton showed NOE enhancements of 9.2±3.5% and 7.9±2.6% on irradiation of the signals at δ = 1.04 and 1.17 respectively.

An unusual isotopic distribution pattern was observed for deuterated 64 recovered after treatment with K^+ t-BuO$^-$/t-BuOD under milder conditions (lower temperature and shorter reaction time). The molecular ion cluster for two of these experiments is given in Figure XXII. The correction for M+1 and M+2 contribution of d_1 and d_2 to d_3 and d_4 established that the d_3:d_4:d_5 ratio was similar to the d_0:d_1:d_2 ratio.

2.2.5 Homoenolization of 3,3,6,6-Tetramethyl-5-oxo-bicyclo[2.2.1]heptane-2-thione (63c) and 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dithione (63b)

Preliminary studies on the homoenolization of 63b and 63c have been carried out. Analysis by g.l.p.c. showed in both cases the emergence of new compounds with longer retention times than the starting materials. The

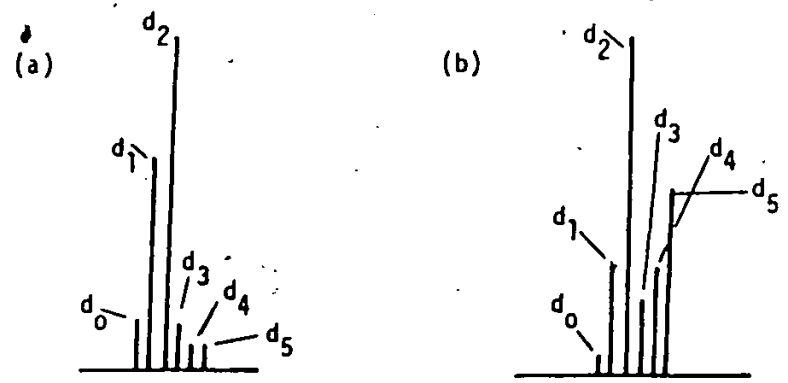


Figure XXII. Molecular Ion of 64 Which Had Been Deuterated in K^{+} t-BuO^{-}/t-BuOD at 100°C.

a) After 5 h.

b) After 75 h.

new compounds were isolated and mass spectrometry showed that the molecular weights were the same as those of the starting material in both cases. Thus the new compounds could have arisen from a rearrangement similar to that observed for dione 63a. However, compounds 63b and 63c appeared to be much more reactive than dione 63a, based on the shorter times used in the preliminary experiments.

2.2.6 Homoenolization of Fenchone (29)

The results of homoenolization of 63d indicated that exchange of the syn-7-hydrogen of fenchone 29 should be expected as well, even though Lambert (60) and Stothers and coworkers (61) apparently did not observe exchange at this site. As a consequence of repeating the homoenolization of 29 to calibrate our reactions, it was found that prolonged treatment of fenchone (175°C, 680 h and K^+ t-BuO^- ≃ 1.0 M) resulted in exchange of syn-7-H. In accord with Stothers' findings the hydrogens at C_6 (exo and endo) and at the methyl groups exchanged. The ^1H and ^2H NMR spectra of fenchone 29, and partially deuterated 29, are shown in Figure XXIII. Assignments of the ^1H resonances of 29 were accomplished with the aid of decoupling experiments. It was clear that significant exchange had occurred at syn-7-H after prolonged treatment with base. Unlike the case for 63d it was not possible to establish directly the extent of exchange at anti-7-H because the anti-7-H peak overlapped the peak due to exo-6-H.

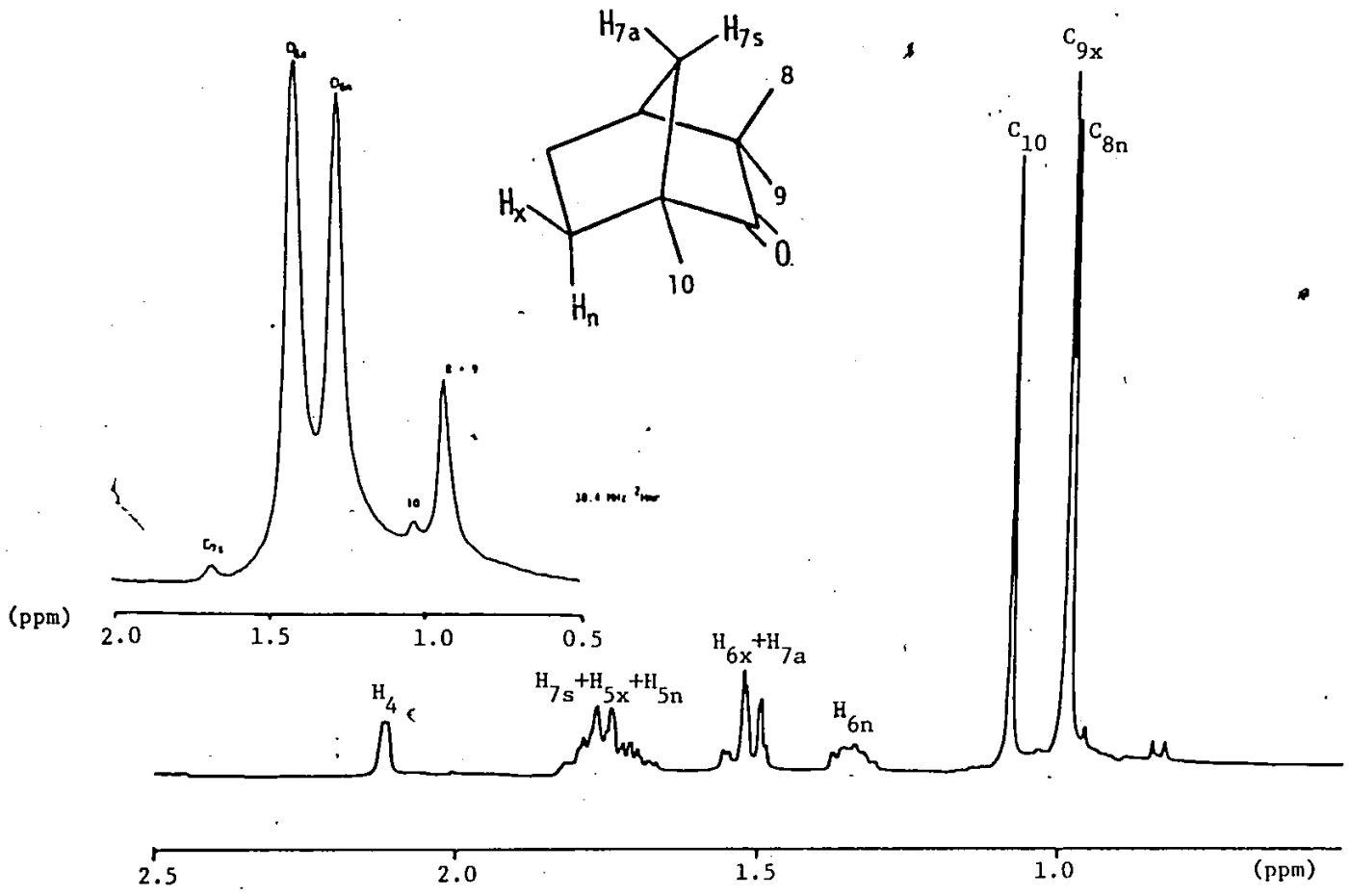


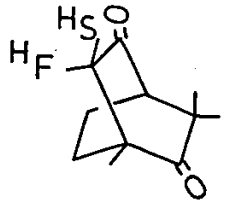
Figure XXIII. 250 MHz ^{1}H and 38.4 MHz ^{2}H NMR (insert) Spectra of Fenchone (29)

2.3 Kinetic Studies

2.3.1 Rate Constants of H-D Exchange at C-6 of 1,3,3-Trimethylbicyclo-[2.2.2]octane-2,5-dione (64).

The rates of exchange of the C-6 protons in dione 64 were determined at 30±0.1°C in a solution composed of 60% dioxane and 40% $NaDCO_3$/NaOD (pD 10.84*) which had been equilibrated in a constant temperature bath. The aliquots were quenched with a K_2HPO_4† buffer and extracted with ether. The rates of H-D exchange of the diastereotopic protons at C-6 were obtained by mass spectrometry. Since the preferred stereochemistry of exchange has not been determined, the protons are referred to as H_F and H_S. A tentative assignment of H_F and H_S was based on the assumption that the homoconjugative effect of the C-2 carbonyl group enhanced the rate of exchange of the anti-proton (H_F).

Kinetic studies were carried out under pseudo-first-order



64

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* Buffer of pD = 10.84 (pD = PH+0.4) composed of 50 ml of bicarbonate (0.05 M) and 16.0 ml NaOD (0.1 M).

† Buffer of pH = 6.5 composed of 50 ml of KH_2PO_4 (0.1 M) and 13.9 ml of NaOH (0.1 M).

conditions and the first-order rate constants were converted to second-order rate constants. The second-order rate constant for exchange of H_F was 2.6±0.24 M^{-1} s^{-1} (an average of four determinations), and the rate constant for exchange of H_S was 0.36±0.17 M^{-1} s^{-1} (an average of six determinations). That is k_F was approximately 7 times greater than k_S.

2.3.2 Rate Constants of β and γ-enolization of 63a, 63d and 64

The approximate rate constants for H-D exchange at different positions were obtained from one point kinetic analyses. Since the ketone and base concentrations ranged from 0.2 to 0.35 M and 0.8 to 1.4 M, respectively, and the basicity of the strongly basic solutions was difficult to reproduce accurately, the precision of the rate constants in a series of exchanges was about ±10%.

Therefore, experiments which were similar in initial concentration and were comparable to those carried out by Stothers were chosen for analyses so that the rate data could be compared.

2.3.3 Exchange Rate Constants of 63a

The rate constants for dione 63a were obtained from an experiment in which the extent of rearrangement was 27% and thus the rate constants reported are minimum values. When 63a (0.38 M) was heated in 0.84 M K^+ t-BuO^-/t-BuOD for 45 h, it incorporated 2.61 deuterium atoms and was a composite of 2.1% d_0, 11.1% d_1, 33.0% d_2, 35.5% d_3, 15.2% d_4, 2.7% d_5 and 0.5% d_6 species. The deuterium distribution -- 1.37 D at C-1 (4), 1.07 D at C-7, 0.10 D at the exo-methyl groups (C-8 and C-10) and 0.07 D at the endo-methyl groups (C-9 and C-11) -- was determined by computer curve fitting

a 13.8 MHz ^2H NMR spectrum. Hence, exchange was 68.5%, 50.4%, 1.7% and 1.2% complete at C-1(4), C-7, the exo-methyl and endo-methyl groups, respectively. From these data, using the integrated first-order rate expression with $A_0 = 100\%$, the rate constants at 175°C for H-D exchange at C-1(4), C-7, exo-methyl

$$\ln \frac{A_t}{A_0} = -kt$$

and endo-methyl groups and rearrangement were approximately 7.0×10^{-6} s^{-1}, 4.5×10^{-6} s^{-1}, 1.0×10^{-7} s^{-1}, 8.0×10^{-8} s^{-1} and 2.0×10^{-6} s^{-1}, respectively. In order to compare these rate data, which were obtained at 175°C, with the literature data obtained at 185°C it was assumed that the rate doubles for a 10°C increase in temperature. Consequently the rate constants at 185°C would be approximately 1.4×10^{-5} s^{-1}, 9.0×10^{-6} s^{-1}, 2.0×10^{-7} s^{-1}, 1.6×10^{-7} s^{-1} and 4.0×10^{-6} s^{-1} for exchange at C-1(4), C-7, the exo-methyl and the endo-methyl groups and for rearrangement, respectively, as summarized in Table XXI.

Table XXI Approximated First-order Rate Constants* for H-D Exchange at Various Sites of Dione 63a

$k_{at\ 175°C}$	k at 185°C	Site
7.0×10^{-6} s^{-1}	1.4×10^{-5} s^{-1}	H-1 (4)
4.5×10^{-6} s^{-1}	9.0×10^{-6} s^{-1}	H-7 (s)
1.0×10^{-7} s^{-1}	2.0×10^{-7} s^{-1}	exo-methyl protons
8.0×10^{-8} s^{-1}	1.6×10^{-7} s^{-1}	endo-methyl protons
2.0×10^{-6} s^{-1}	4.0×10^{-6} s^{-1}	rearrangement

*Throughout this thesis, the rate constants for H-D exchange are referred to as first-order rate constants to be consistent with the previous literature reports. It should be realized, however, that these exchange reactions have actually been carried out under pseudo-first order conditions using excess base.

2.3.4 Exchange Rate Constants for 64

Diketone 64 was prepared by rearranging 63a in K^+ t-BuO^-/t-BuOH and its exchange was studied over a range of temperatures. When dione 64 (0.15 M) was treated at 175°C in 1.14 M K^+ t-BuO^-/t-BuOD, it incorporated 5.86 excess atoms of deuterium and was a composite of 0.4% d_0, 0.5% d_1, 1.0% d_2, 3.5% d_3, 10.8% d_4, 22.1% d_5, 28.6% d_6, 20.5% d_7, 8.7% d_8, 2.5% d_9, 0.8 % d_{10} and 0.7% d_{11} species. That the deuterium was located at the bridgehead methyl group (2.65 D), at C-6 and C-4 (1.63 D) and C-7 and C-8 (1.58 D) was established by curve fitting the $Eu(fod)_3$ shifted ^2H NMR spectrum obtained at a dione 64: $Eu(fod)_3$ weight ratio of 1.64:1. It was desired to determine the amount of exchange at C-4. However, it was not possible to measure the extent of deuteration at C-4 directly, since the signals due to syn-6-D, anti-6-D (relative to the carbonyl at C-2 position) and C-4 were overlapped. The deuteriums at the C-6 position were back exchanged for protiums, by treating 64 - $d_{5.86}$ with an aqueous solution of 1N NaOH/dioxane (40:60) at 25±0.1°C. The ^2H NMR spectrum of the resulting 64 - $d_{4.46}$ (64 - $d_{4.46}$:$Eu(fod)_3$ = 1.64:1, Figure XXIV) showed only a small peak at δ 4.6 (0.06 D) which corresponded to D-4 and the first-order rate constant was ∿ 3.0×10^{-7} s^{-1} at 175°C ($k_{185°C} \sim 6.0\ 10^{-7}\ s^{-1}$). The ^2H NMR of 64 - $d_{5.86}$ (64 - $d_{5.86}$: $Eu(fod)_3$ weight ratio 1.64:1) showed four major signals at δ 4.3, 2.9, 2.5 and 1.6 in addition to a small shoulder at ∿ δ 1.9 on the peak at δ 1.6. While the signal at δ 4.6 was due to deuterons at C-6 and C-4 and the signals at δ 2.9 and 2.5 were due to the deuterons at C-7 and C-8, the peak at δ 1.6 corresponded to the deuterated bridgehead methyl. The

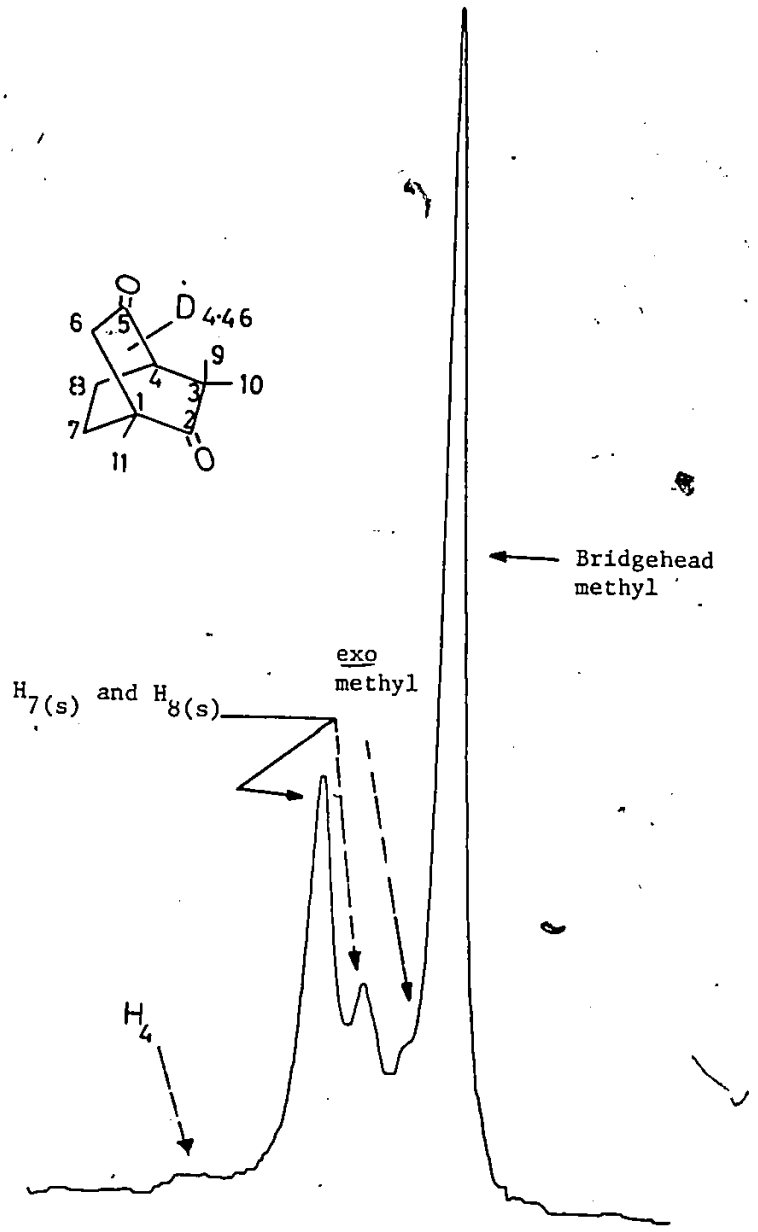

Figure XXIV. 38.4 MHz ^{2}H NMR Spectrum of Deuterated 1,3,3-Trimethylbicyclo[2.2.1]octane-2,5-dione (64) After Back Exchange of Deuterons at C-6; in Presence of $Eu(fod)_3$, 1.64:1 Ratio

shoulder at δ 1.9 was due to the deuterium in one of the other methyls, most likely the exo-3-CH_3. Assuming that $k_{8n} \sim k_{7x}$ and that the peak at δ 2.9 was due to D-8_n and D-7_x, the apparent rate constant for deprotonation exo to the carbonyl group was 4.5×10^{-6} s^{-1} at 175°C ($k_{185°C} \sim 9.0\times10^{-6}$ s^{-1}). On the assumption that the signal at δ 2.5 was due to D-7 and D-8 and $k_{8x} \sim k_{7n}$, the apparent rate constant for abstraction endo to the carbonyl group of 64 was 1.0×10^{-6} s^{-1} at 175° ($k_{185°C} \sim 2.0\times10^{-6}$ s^{-1}). A separate analysis of 64 (0.17 M) for 50 h in 1.0 M K^+ t-BuO^-/t-BuOD was carried out using high field ^1H (400 MHz) and ^2H (61.4 MHz) NMR in the absence of Eu(fod)$_3$ (Figure XXV). The high field ^2H NMR of 64-$d_{5.16}$ showed a doublet centred at δ 2.2 due to syn-6-D and anti-6-D that overlapped a broad signal at δ 2.15 (endo-8-D). There were also broad peaks at δ 1.85 (exo-8-D) and 1.75 (endo-7-D and exo-7-D) and a singlet at δ 1.14 (bridgehead methyl) with a visible shoulder on the low field side. A very weak signal was also discernible at δ 1.20. The deuterium distribution was obtained from the peak areas of these ^2H NMR signals by a cut and weigh technique. The peak area at δ 2.2 corresponded to 2.04 D and, since 1.60 D were washed out from 64-$D_{5.16}$ (NaOH/dioxane), it was established that there were approximately 0.44 D located at the endo-8 position. From the areas of the peaks at δ 1.85 and 1.75, it was determined that 0.26 deuterium atoms were incorporated at the exo-8 position and 0.28 deuterium atoms were located at the exo-7 and endo-7 positions combined. On the assumption that k_{endo}-7-H $\sim k_{exo}$-7-H and the exo-3-methyl exchanged faster than the endo-3-methyl, the first-order rate constants at 175°C and 185°C for H-D exchange at the various

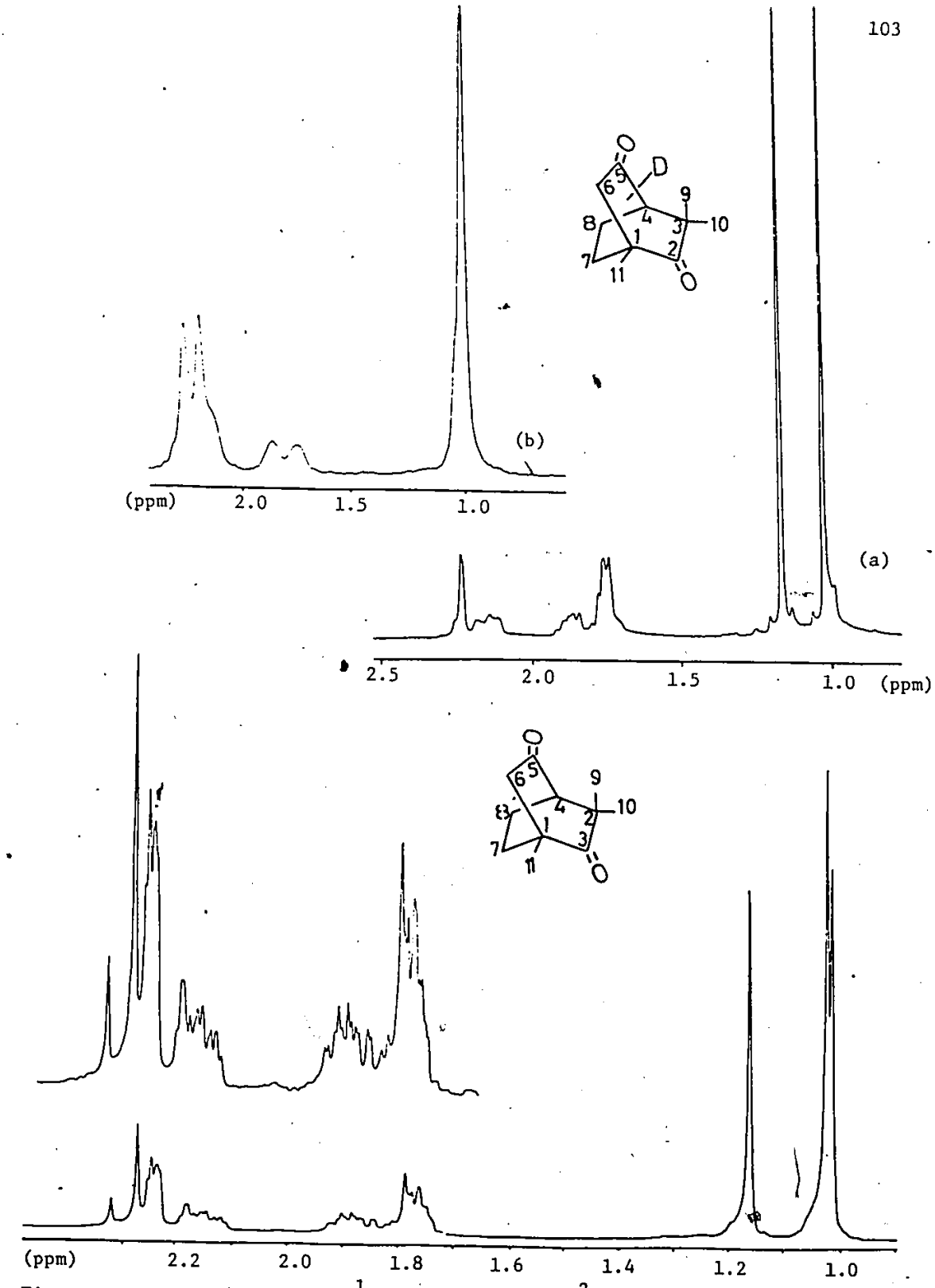

Figure XXV. Top, (a) 400 MHz ^{1}H and (B) 61.4 MHz ^{2}H NMR Spectrum of Deuterated Dione 64, Bottom, 400 MHz ^{1}H NMR Spectra of Dione 64

sites were calculated (Table XXII).

Table XXII Approximate First-Order Rate Constants for H-D Exchange at Various Sites of Dione 64

$K_{at\ 175^{\circ}C}$	$K_{at\ 185^{\circ}C}$	Site
$3.0\times10^{-6}\ s^{-1}$	$6.0\times10^{-6}\ s^{-1}$	endo-8-H
$1.5\times10^{-6}\ s^{-1}$	$3.0\times10^{-6}\ s^{-1}$	exo-8-H
$8.5\times10^{-7}\ s^{-1}$	$1.5\times10^{-6}\ s^{-1}$	endo-7-H*
$8.5\times10^{-7}\ s^{-1}$	$1.5\times10^{-6}\ s^{-1}$	exo-7-H*
$3.0\times10^{-7}\ s^{-1}$	$6.0\times10^{-7}\ s^{-1}$	exo-3-methyl protons

* An average rate

To obtain the rate constant for bridgehead methyl exchange, reactions were carried out at 100°C (111). For example, when 64 (0.11 M) was treated with K^{+} t-BuO^{-}/t-BuOD (1.03 M) for 25 h it incorporated 2.01 deuterium atoms. Deuterium analysis by ^{2}H NMR established that deuterium was located at C-6 (1.50 D) and at the bridgehead methyl (0.51 D). The first-order rate constant for the methyl bridgehead exchange was $\sim 2.0\times10^{-6}\ s^{-1}$ at 100°C and $\sim 8\times10^{-4}\ s^{-1}$ at 185°C.

2.3.5 Exchange Rate Constants for 63d

The first-order rate constants for exchange of 63d were determined by heating it in 1.24 M K^+ t-BuO^-/t-BuOD at 175°C for 500 h. Ketone 63d incorporated 0.56 excess atoms of deuterium. High field (61.4 MHz) ^2H NMR coupled with $Eu(fod)_3$ experiments revealed that this deuterium was distributed at different positions: 0.258 D at the C-8 and C-9 methyl groups, 0.253 D at C-1, 0.016 D at syn C-7 and 0.013 D in the C-11 methyl group. From these data the first-order rate constants for exchange at 175°C and 185°C were evaluated and are summarized in Table XXIII.

Table XXIII Approximate First-order Rate Constants for H-D Exchange at Various sites of 63d

k at 175°C	k at 185°C	Site
1.6×10^{-7} s^{-1}	3.2×10^{-7} s^{-1}	H-1 (bridgehead)
7.0×10^{-9} s^{-1}	1.4×10^{-8} s^{-1}	Syn H-7
5.0×10^{-8} s^{-1}	1.0×10^{-7} s^{-1}	C-8 and C-9 methyl protons
3.0×10^{-9} s^{-1}	6.0×10^{-9} s^{-1}	C-11 methyl protons

CHAPTER 3

DISCUSSION

3.1 Homoenolization of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione (63a) and 3,3,6,6-Tetramethylbicyclo[2.2.1]heptan-2-one (63d).

Several definite deductions can be drawn from the data in Table X. These data summarize the conversion of dione 63a to isomer 64. From entries 1 and 2 along with 15 and 16, it is clear that the extent of isomerization in deuterated and non-deuterated media is the same, within experimental error. Hence, isotope effects are negligible. In addition, by comparing entries 9, 10 and 11 with 28 and 29 it is evident that the rate of isomerization, as expected, increases as the base concentration is increased. For any set of conditions, as the reaction time is increased, the percentage conversion increases. There is, however, a limit to the degree of isomerization. A possible explanation is that 64 undergoes slow decomposition and/or conversion to other products, such as an isomer with a [3.2.1] type skeleton, which was formed in small amounts in several reactions. The base concentration is one of the important factors controlling the isomerization. However, there is a limit ($\sim$ 1.4 - 1.5 M) to the solubility of K^{+} t-BuO^{-} in t-BuOH(D). In addition, entries 17 and 18, 19 and 20, as well as 22 and 23 show that the homoenolization is easily reproducible. Another possible explanation for the incomplete conversion of 63a to 64 could be the reduction of the effectiveness of K^{+} t-BuO^{-} with time. This may be caused by reaction with the glass

surface or aggregation (112). In any event, this phenomenon is not well understood. By introducing fresh K^+ t-Bu$\bar{O}$ after an average initial reaction time, it may have been possible to increase the conversion of 63a to 64.

As described in the results section, the deuterium incorporation at various sites of 63a and 63d were used to obtain approximate first-order rate constants, which are shown in Figure XXVI.

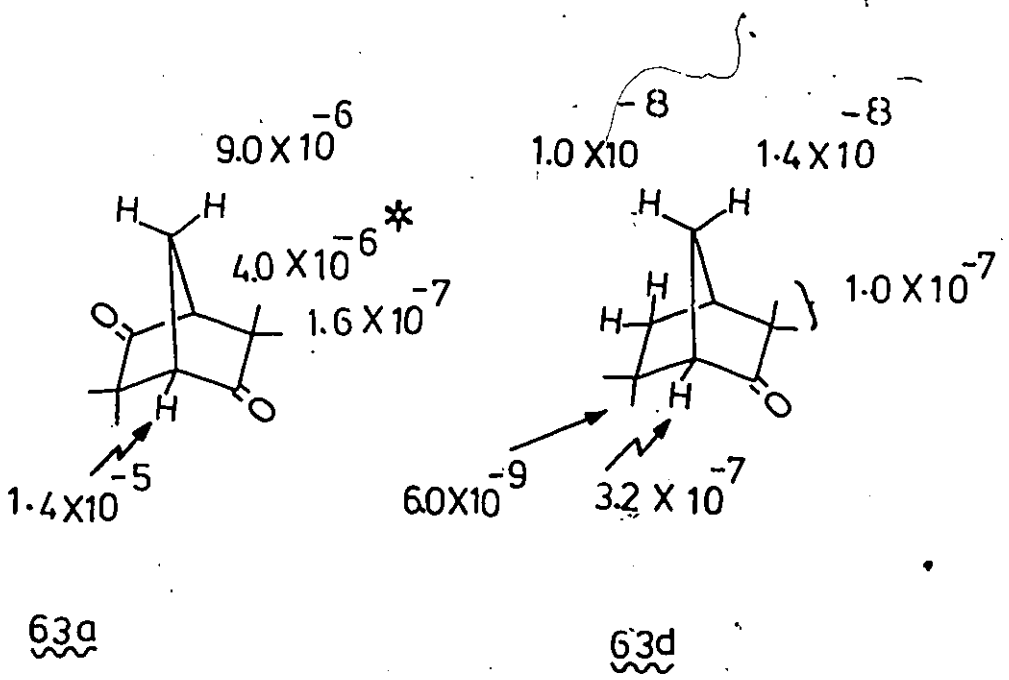

Figure XXVI. Rate Constants of H-D Exchange for 63a and 63d at 185°C in K^+ t-Bu$\bar{O}$/t-BuOD

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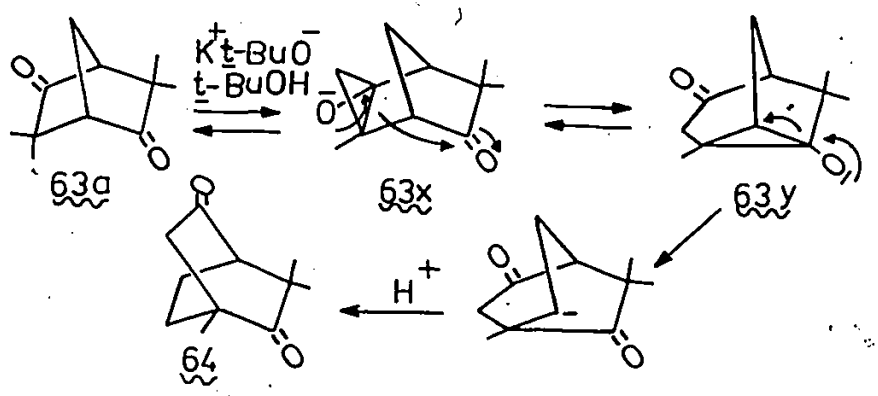
* This rate constant of 4.0×10^{-6} s^{-1} is a combination of the observed rate constant of deuterium incorporation in the exo-methyl and the rate constant of rearrangement of 63a to 64 (2.0×10^{-7} s^{-1} + 3.8×10^{-6} s^{-1} = 4.0×10^{-6} s^{-1}).

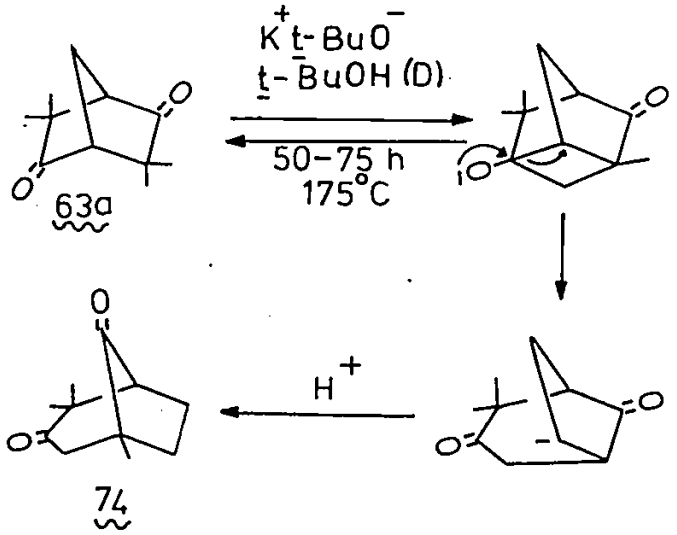
3.2 Rearrangement of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione, (63a)

Since the discovery of homoenolization in the early sixties, a number of homoenolization experiments of polycyclic monoketones have been reported (vide supra) but, prior to this work, polycyclic polyketones had not been studied. 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione 63a undergoes a novel rearrangement to 1,3,3-trimethylbicyclo[2.2.2]octane-2,5-dione 64. Our proposed mechanism for the rearrangement is given in Scheme 14. Homoenolization (β-enolization) of an exo-methyl group yields exo-homoenolate 63x, which in turn undergoes an unusual β-homoenolate switch to β-enolate 63y. Homoketonization of 63y produces the more thermodynamically stable bicyclo-[2.2.2]octane-2,5-dione 64. The rate constant for rearrangement (3.8×10^{-6} s^{-1}) compares favourably with the rate constant for exo-methyl exchange of fenchone (2.0×10^{-7} s^{-1}). That deprotonation of the exo-methyl of 63a occurs more readily than deprotonation of the exo-methyl of fenchone 29 indicates that the second carbonyl group exhibits an inductive and/or field effect.



SCHEME 14

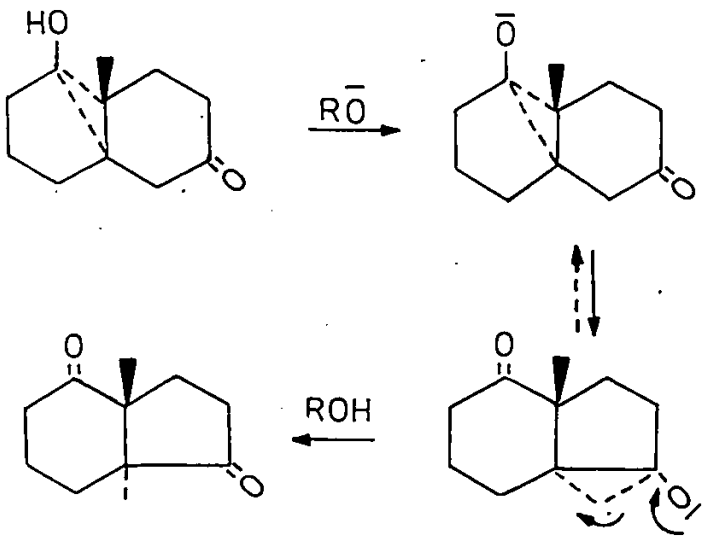
There is at least one other possible isomeric diketone 74 which satisfies all of the ^{1}H and ^{13}C NMR spectroscopic data. This can be obtained from the simple one step γ-homoenolization shown in Scheme 15. In fact, it was proposed initially that dione 74 was the rearrangement product (87).



SCHEME 15

However, the x-ray crystal structure determination of the dibromide of the rearrangement product established positively that the isomer was dione 64, and therefore Scheme 14 is an acceptable route for the rearrangement. Only one other example of a β-enolate switch has been reported. Reusch and coworkers (113,114) have shown that 6-methyl-5-hydroxytricyclo-[4.4.0.0]decan-9-one (Scheme 16) and some of its derivatives rearrange in base via a β-enolate switch. Our work, however, has provided the first

example of rearrangement via a β-homoenolate switch where the β-enolate is generated from a ketone in strong base.



SCHEME 16

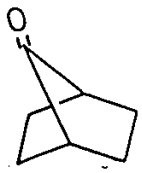
This work documents one of the first examples of a ring expansion in a bicyclic system by homoenolization of a ketone. Examples of chain expansion through a β-enolate involving methyl sites for acyclic ketones have been reported earlier (69); di-t-butyl ketone has been found to isomerize slowly to two other isomeric ketones as shown in Table II. In the acyclic system it has been assumed that the bulkiness of the methyl groups causes an increase in the C-C-C bond angle of the carbonyl. The major driving force for the opening of the three membered ring intermediate (β-enolate) to the

rearranged product has been attributed by Stothers and coworkers (69) to the formation of a more stable product in which the C-C-C bond angle of the carbonyl is not as strained. Furthermore, it was stated that ring expansion does not occur via β-enolates generated from methyl sites in bicyclic systems because skeletal constraints prevent significant release of angle strain. The driving force in our case undoubtedly is the formation of a stable β-enolate. Furthermore, ketonization of β-enolate 63y yields dione 64, because the extra carbon atom in 64 removes most of the strain within the bicyclic system. Thus, most C-C-C angles are closer to the tetrahedral angles than in 63a as is indicated by the data obtained from the x-ray crystal structure determination of the dibromide of 64.

The base-catalysed conversion of a methyl group to a methylene on going from [2.2.1] dione 63a to [2.2.2] dione 64, may be a useful general synthetic method where an increase in ring size is desired.

3.3 Bridgehead H-D Exchange of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione (63a), and 3,3,6,6-Tetramethylbicyclo[2.2.1]heptan-2-one (63d)

The formation and reactions of bridgehead enolates in bicyclic or polycyclic ketones have been studied actively. An enolate can be formed at the bridgehead when the ring is fairly large ($n \geq 6$), depending on the type of system and its stereochemistry (115). While Gassman and Zalar (44) observed bridgehead exchange of 7-norbornanone 6 and nortricyclanone 7, prior to our report of the bridgehead exchange of dione 63a (87), there were



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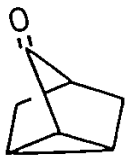

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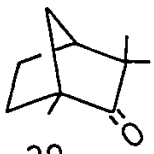
no reports of bridgehead exchange alpha to the carbonyl group of bicyclo-[2.2.1]heptan-2-ones. Only inductive (and/or electrostatic) stabilization of the anions generated from 6 and 7 is possible . From the data of Gassman and Zalar, we estimate the first-order rate constant for exchange at the bridgehead of 6 and 7 at 185°C to be 3.8×10^{-7} s^{-1} and 7.0×10^{-6} s^{-1}, respectively. That the rate constants for bridgehead exchange of 63d and 63a at 185°C are approximately 3.2×10^{-7} s^{-1} and 1.4×10^{-5} s^{-1} respectively establishes that the introduction of the carbonyl group at C-5 increases the rate of the bridgehead H-D exchange by a factor of about 40 - 45. This might provide a good measure of the inductive (electrostatic) stabilization of an anion β- and anti- to a carbonyl group where homoconjugative stabilization is not possible. This observation is in accord with the work of Werstiuk and coworkers (116) on the exchange reaction of dione 72, where it was estimated that the β-carbonyl inductively enhances the rate of α-enolization by a factor of 75. The exchange at the bridgehead of 63d allows an estimate to be made of the rate of bridgehead exchange of camphenilone 16, first studied by Nickon (50). Beta homoenolization at C-6 yields a symmetrical

intermediate, thus scrambling C-6 and C-1 and preventing direct determination of the extent of bridgehead H-D exchange. Since the rate constants for exchange at C-6 of camphenilone 16 are not available, the first-order rate constants for exchange of <u>exo</u> and <u>endo</u> hydrogen at C-6 of fenchone 29 (7×10^{-6} s^{-1} and 2.0×10^{-6} s^{-1}, respectively) obtained by Stothers (61) are used. This



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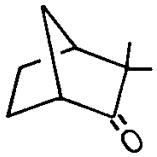


16

analysis assumes that the bridgehead methyl does not significantly affect the rate of exchange at C-6. In addition, if the rate of bridgehead exchange in 63d is a reasonable measure of the rate of exchange at C-1 of camphenilone 16 (assuming that the steric effect of the two methyl groups at C-6 of 63d has a minimal effect on the rate of the exchange at C-1), then, based on this analysis, exchange at C-6 of camphenilone occurs approximately 25 - 30 times as fast as exchange at C-1. This is in agreement with Nickon's (50) observation that the rate of racemization of camphenilone is approximately equal to the rate of incorporation of deuterium.

3.4 Exchange of 3,3,6,6-Tetramethylbicyclo[2.2.2]heptane-2,5-dione 63a and 3,3,6,6-Tetramethylbicyclo[2.2.1]heptan-5-one 63d at C-7.

Deuterium analysis of recovered 63a showed that deuterium was incorporated at C-7 as well as at the bridgehead positions and in the methyl groups. This was the first example of exchange at C-7 of a bicyclo[2.2.2]-heptan-2-one. In earlier studies of β-enolization, exchange at C-7 of bicyclo[2.2.1]heptyl ketones, such as camphenilone 16 and fenchone 29 was not observed, and it was suggested that this was a consequence of the strain in the homoenolate anion and/or the improper geometry of the alignments of the C-H bonds at C-7 with the π system of the carbonyl group at C-2. According to an earlier report (61), no exchange was observed at C-7 of fenchone when it was heated for 300 h at 185°C in 1 M K^+ t-BuO^-/t-BuOD. Nickon and coworkers (51) prepared 7,7-dideuterated camphenilone and treated it under homoenolization conditions. Analysis of recovered material by mass spectrometry detected no loss of deuterium*. However, as documented in the results section, we have studied fenchone and found that there is slow exchange at the syn-7 position, in accord with the observation for monoketone 63d. However as the data in Table X shows, dione 63d is stable in the strongly basic media and undergoes unusually facile exchange at C-7 (as well as C-1 and C-4). Our findings revealed β-enolization at C-7 of 63d occurs and it is interesting to note that syn-7-exchange is at least 10 times faster than anti-7-exchange. The rate of exchange for syn-7 is 1.4×10^{-8} s^{-1} and in

*"Labelled ketone was heated with K^+ t-BuO^-/t-BuOH at 185°C for 98 h. After this period of time, no deuterium loss was detected. Recovered ketone was recycled at 185°C for an additional 200 h at a higher concentration of base. That no deuterium was washed out indicates C-7 is not a homoenolizable site." (51)

dione 63a the exchange rate is 9.0×10^{-6} s^{-1}, 800 - 900 times faster.

According to calculations by Schlegel (30, 117), at any given dihedral angle "β" of adjoining carbons - Figure XXVII - β-enolate stability is at a maximum when the β-carbon is sp^3 hybridized and at a minimum when sp^2 hybridized. In addition, substantial stabilization is present whether the anion is pointed towards or away from the carbonyl

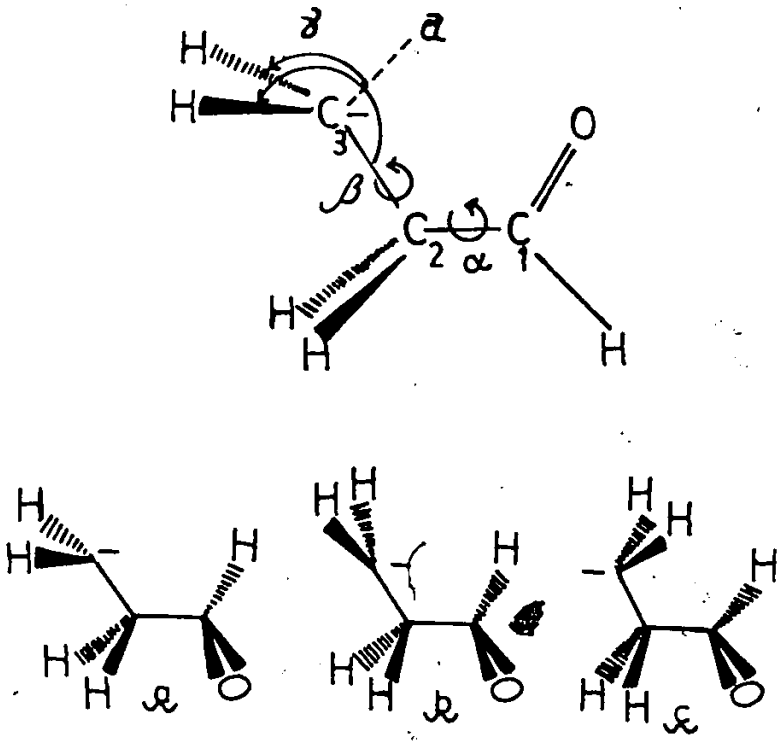


Figure XXVII. Illustrates the Three Conformers Obtained From β-γ Inversion Surface of $\overline{CH}_2CH_2CHO$ ($\alpha = 120^\circ$), a and c are more stable than b[2] (117).

as shown in Figure XXVIII. However, no comment was made on whether the stabi-

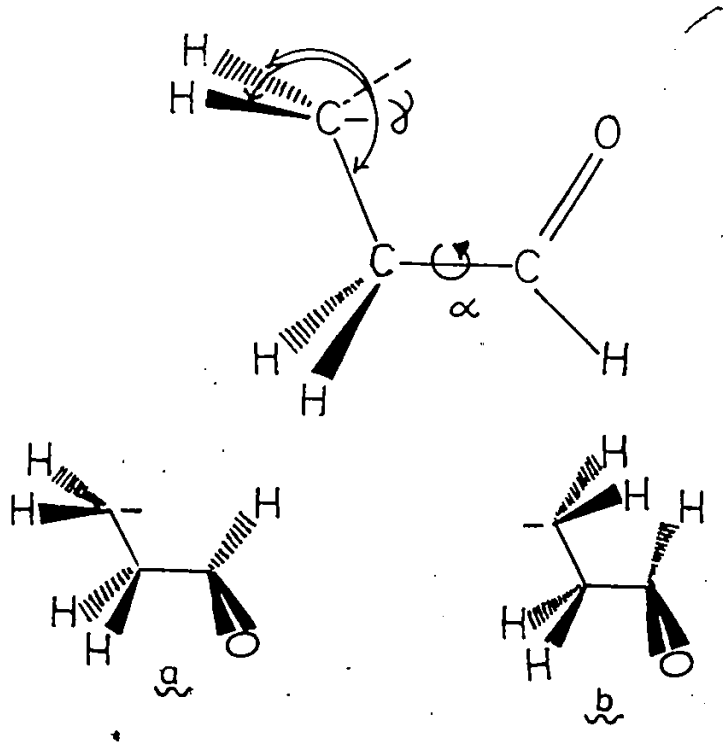
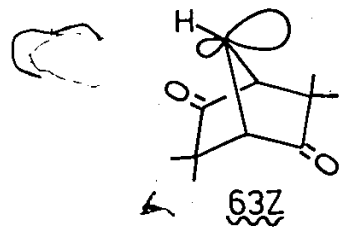


Figure XXVIII. Illustrates the Two Stable Conformers of $\bar{C}H_2CH_2CHO$
a) $\alpha = 120°$, $\beta = 0°$, $\gamma = 115°$
b) $\alpha = 120°$, $\beta = 180°$, $\gamma = 115°$ (117)

lization resulted from homoconjugative or electrostatic interaction. Due to the angle strain at C-7 the anion is predicted to be pyramidal - 63z -

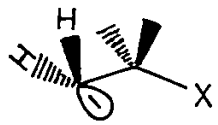


with a significant barrier to inversion. Consequently it is "syn" to one carbonyl group and "anti" to the other and, in principle, would be stabilized by both carbonyl groups according to Schlegel's calculation. It is clear from the data in Figure XXIX that the interaction of a carbonyl group at C-5 enhances the rate of exchange of the syn-7-H approximately by a factor of 10^3 and the anti-7-H by a factor of at least 10^4, assuming that k_{syn}-7-H of 63d is at least 10 times k_{anti}-7-H (vide supra). On this basis, introduction of a carbonyl group at C-2 of hydrocarbon 75 results in a rate enhancement of at least 10^4 for the K^+ t-Bu$\bar{O}$ catalyzed H-D exchange at C-7. Introduction of two carbonyl groups enhances the rate by at least 10^8. Since the x-ray crystal structure determination showed

75

that the bond lengths and angles of 63a are normal, that the syn-7-H exchanges faster than anti-7-H is interesting because the exo-6-H's of fenchone 29 and camphenilone 16 which are anti to the carbonyl groups exchange faster than the endo-H's which are syn. Perhaps, the backlobe of the developing sp^3-like orbital at C-7 does not interact effectively with the π-system. Perhaps syn overlap is more efficient and the syn-anion is elec-

trostatically stabilized by the carbonyl group dipole to a greater degree than the anti-anion. It is interesting to note that Noest and Nibbering (118), using ion cyclotron resonance (ICR), have found that 2-methyl-2-nitrosopropane 77b, and 2,2-dimethyl-propanal 77a undergo facile H-D β-exchange in the presence of $O\bar{D}/D_2O$ in the gas phase. Using simple electrostatic theory and the conformation of 77, they calculated that the dipolar



77

77a, X = HCO

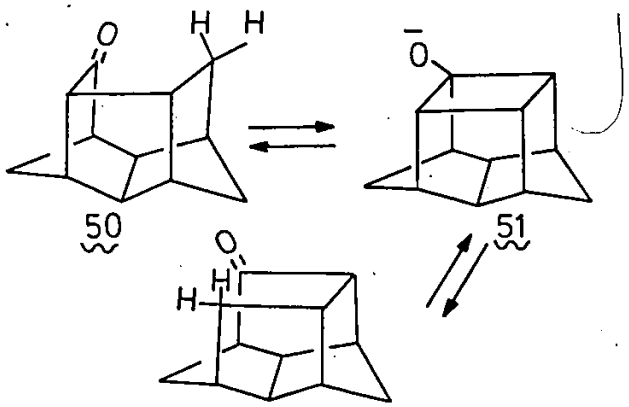
77b, X = NO

stabilization of the anion by the carbonyl group is in the order of 84 kJ/mol, which could account for a major portion of the stabilization of the anion.

3.5 γ-Enolization of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptan-2-one, (63d)

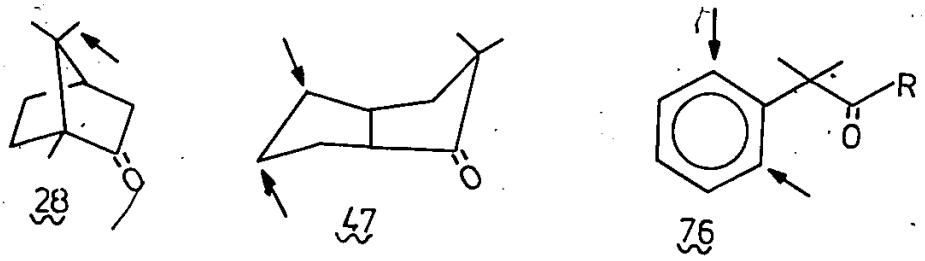
As described in the results section, 63d undergoes slow γ-enolization of the endo-methyl at C-6 (C-11 methyl) and the first-order rate constant was estimated to be 6.0×10^{-9} s^{-1} at 185°C. There are only four other examples of γ-enolization. The first example was reported for the half-cage ketone 50 (73 - 75) which, under homoenolization conditions, isome-

rized to 52 quantitatively. The rate of γ-enolization (3.8×10^{-5} s^{-1}) at 185°C can be estimated from the rate of isomerization (7.58×10^{-5} s^{-1}) at 195.5°C.



50 51 52

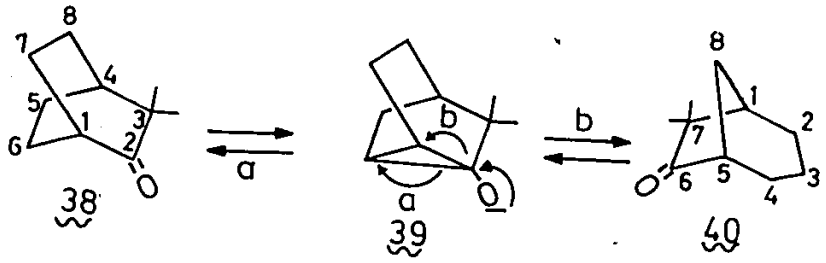
The other compounds which undergo γ-enolization are 28 (119), 47 (68) and 76 (120).



28 47 76

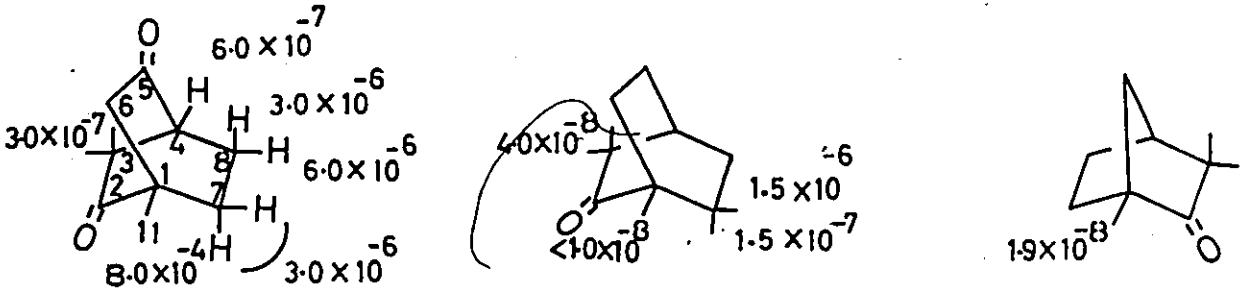
3.6 Homoenolization of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione (64)

The only other study of a carbonyl containing bicyclo[2.2.2]octane was conducted by Stothers and coworkers (64,65). They showed that when 3,3-dimethylbicyclo[2.2.2]octan-2-one, 38, was treated under strongly basic conditions it slowly isomerized to 7,7-dimethylbicyclo[3.2.1]octan-6-one 40, and incorporated deuterium.



38 39 40

As is described in chapter 2, when 63a was treated under homoenolization conditions, it rearranged to the isomeric form 64. In addition, one of the methyl groups of 64 underwent facile H-D exchange. Consequently, homoenolization of 64 was carried out at a range of temperatures, from 100 to 175°C. The rate constants for exchange of 64a as well as ketone 38 and 29 studied by Stothers are given in Figure XXIX.



64 38 29

Figure XXIX. Rate Constants of H-D Exchange for 64, 38 and 29 at 185°C in K^{+} t-BuO^{-}/t-BuOD.

It is clear that the rate constants for exo and endo-exchange at C-8 are slightly larger than the rate constants for ketone 38. The increase most likely results from an inductive and/or field effect of the γ-carbonyl group at C-2. The preference for the hydrogen anti (endo-8-H) to the π-system is in accord with Stothers' findings for ketone 38. No comment can be made on the exo/endo preference at C-7 because their resonances overlap in the ^{2}H NMR, and it is assumed that the rate constants are equal in the analysis. The exo-3-methyl (C-9) exchange is slightly faster than the methyls of 38 and this is in keeping with the effect of the γ-carbonyl group on exchange. Bridgehead exchange of 64 is approximately 60 times faster than exchange of 38 and this rate enhancement is comparable to the rate increase observed in [2.2.1]dione 63a over monoketone 63d, where a carbonyl group is also β to the site of exchange.

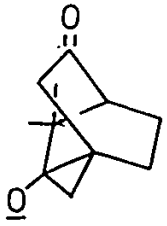
It is interesting to note that exchange of 64 at sites β to the carbonyl group establishes that β-enolization occurs in [2.2.2]-systems where α-enolization is possible - the first documented example for a [2.2.2]-system.

As was presented in the results section, various methods were used to establish which methyl group was exchanging rapidly. All the studies established that it is the bridgehead methyl which undergoes the remarkably facile H-D exchange. An NOE study involving irradiation at the two remaining methyl groups of a deuterated sample of 64 (deuterium was mostly located at methylene C-6 and at one of the methyl groups) showed enhancements of the bridgehead proton signal of 9.2±3.5% and 7.9±2.9%, respectively. Although the magnitudes were smaller than predicted (121), the enhancement in bridge-

head proton signal from irradiation of the two methyls at 1.02 and 1.17 is in accord with our assignment of the methyl groups. The observation of these NOEs confirms that the deuterated methyl is at the bridgehead. Otherwise, an enhancement should have not been observed on irradiation of both non-deuterated methyl groups. This conclusion can be confirmed on the basis of the distance from the bridgehead methyl to the bridgehead proton, 5.7 Å, (the interatomic distances were determined using Dreiding stereomodels) which is clearly too far away for any NOE to be observed. On the other hand, due to the close proximity of the gem dimethyls to the bridgehead proton (2.5 - 2.6 Å), an observable NOE is expected (CH_3-H NOE $\alpha \frac{1}{r^6}$). Other confirming evidence was obtained from a ^{13}C NMR study of the dibromide derivative of 64. Bromines at C-6 had a small shielding effect on the ^{13}C NMR signal of the bridgehead methyl whereas it had a deshielding effect on the ^{1}H NMR signal, as expected. Further evidence to support the assignments was obtained from the ^{13}C spectrum of the highly deuterated sample of dibromide. The intensity of the ^{13}C signal due to C-1 is reduced to base line noise, because there are no neighbouring protons to relax C-1. The quarternary bridgehead carbon which is usually of low intensity under the conditions that the spectra were obtained is almost non-observable. Also, from the model, bicyclo[2.2.2] octanone which was methylated at various sites was used to confirm our assignment of the ^{13}C NMR signals, specifically the methyl groups.

The x-ray crystal structure of the dibrominated derivative of 64 does not show any unusual features or deviations from similar compounds for which the crystal structure determination has been carried out (109).

That the first-order rate constant for bridgehead methyl exchange is $\sim 2\times10^{-6}$ s^{-1} at 100°C and $\sim 8\times10^{-4}$ at 185°C establishes that exchange of the bridgehead methyl is ~ 42,000 times faster than exchange of the bridgehead methyl of fenchone 29 at 185°C - Figure XXIX. This fact suggests, even though the rate of exchange of a bridgehead methyl of a bicyclo[2.2.2]octan-2-one has not yet been established, that the C-11 methyl of 64 does not exchange via formation of the β-enolate 64x, but proceeds via



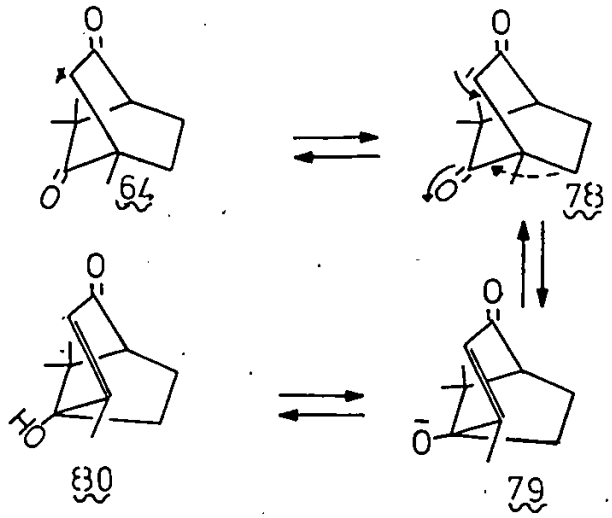
64x

a different route. That this is the case is supported by the observation that deuterium is incorporated into 64 in an unusual sequence. If exchange of 64 occurs via β-enolate 64x, then the methyl hydrogens will be replaced sequentially with

$$d_0 \xrightarrow{k_1} d_1 \xrightarrow{k_2} d_2 \xrightarrow{k_3} d_3 \xrightarrow{k_4} d_4 \xrightarrow{k_5} d_5 \quad \text{and } k_1 > k_2 >> k_3 \sim k_4 \sim k_5 .$$

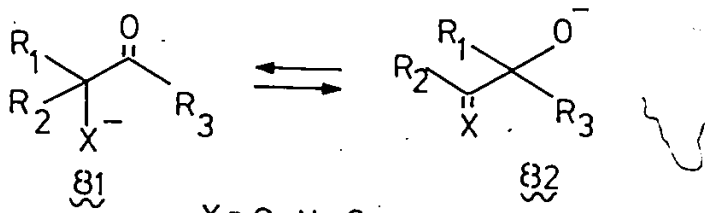
Such a scheme would lead to a build-up and then a gradual decrease of d_3 and

d_4 species as conversion to 64 - d_5 takes place. However, mass spectral analysis of 64 - $d_{2.78}$ (100°C, 75 h) showed that the deuterated dione was a composite of 2.4% d_0, 14.7% d_1, 43.7% d_2, 4.1% d_3, 12.5% d_4, 22.5% d_5 and < 1% d_6 species and suggested that exchange via the β-enolate is not the major exchange pathway. Thus, exchange of 64 must occur via an isomer which is in equilibrium with 64 and the rate determining step is conversion of 64 to its isomer rather than exchange. It is proposed that exchange of the bridgehead methyl proceeds via a mechanism which involves a carbon analogue of an acycloin rearrangement, Scheme 17. A general scheme of an acycloin



SCHEME 17

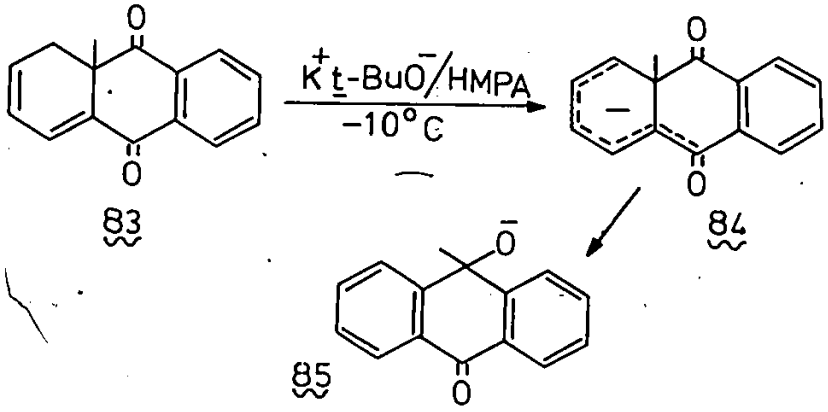
rearrangement is shown in Scheme 18 (rearrangement of 81 to 82).



X = C, N, O

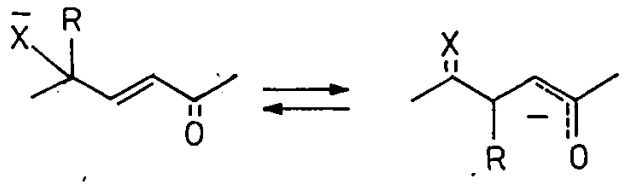
SCHEME 18

There are a large number of examples where X = O (112,123), one example where X = N (124) and, as far as the author is aware, only one other example when X = C. Miller and Bhattacharya (125) showed that 83 rearranges to 85 in K^{+} t-BuO^{-} (HMPT) even at -10°C.



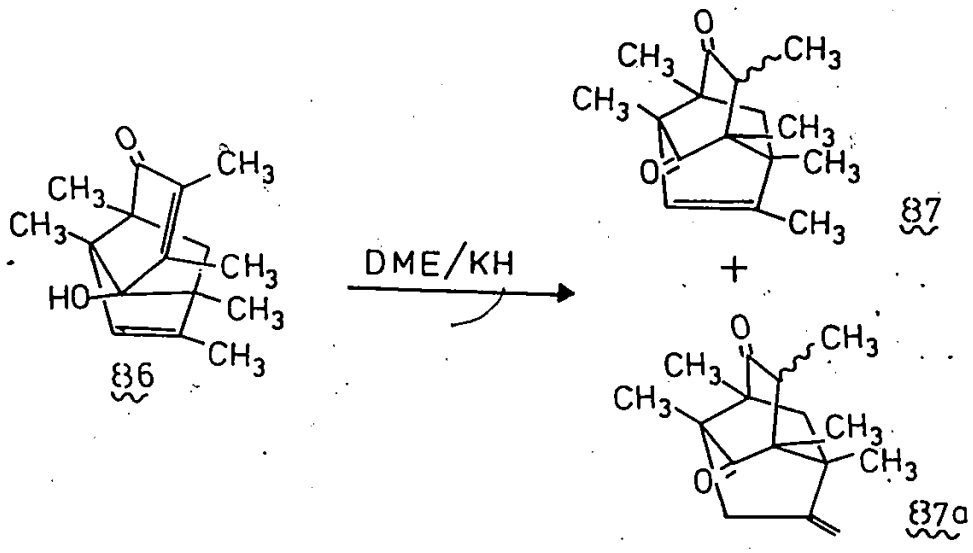
That rearrangement of the enolate of dienedione 83 occurs at -10° while the α-enolate 78 rearranges at a significant rate at 100°C is due to the formation of an aromatic ring in the former. Of course, in 80, the methyl group is attached to an enone and it undergoes rapid H-D exchange. That 64 is not isolated indicates that the dione 64 is more stable than hydroxy-enone 80

which rearranges rapidly to 78 via 79. It is interesting to note that the conversion of 79 into 78 involves a vinylogous acycloin rearrangement, the general representation of which is given in Scheme 19.

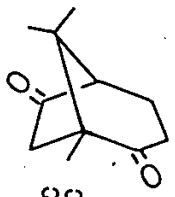


SCHEME 19

Only a few cases of this rearrangement have been observed (126). Of particular significance is the rearrangement of 86 into 87 reported by Scheffer and coworkers (127,128). These results provide support for the hypothesis

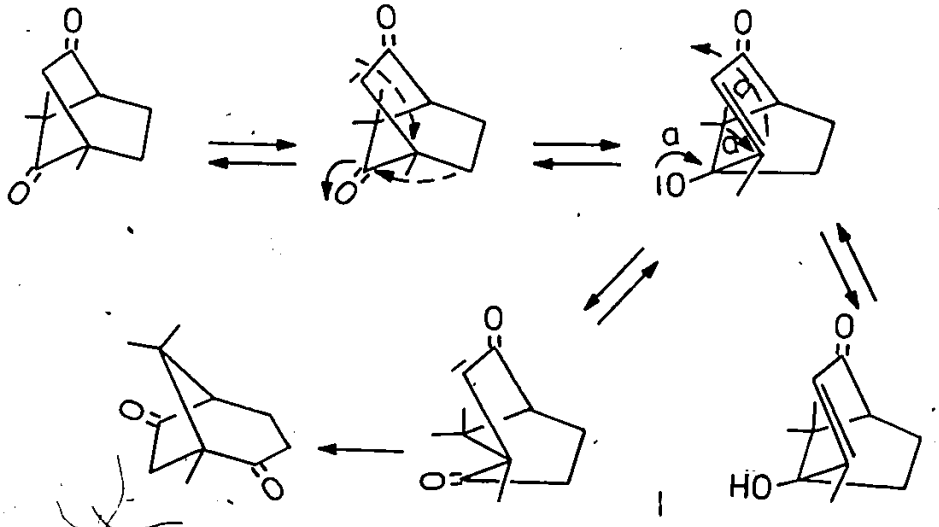


that 80 is an intermediate in the exchange reaction. Furthermore, a small amount of an isomer of 64 was isolated from several reactions and its 400 MHz ^{1}H NMR spectrum was consistent with the spectrum expected for [3.2.1]-dione 88. The[3.2.1]-dione, of course, could possibly be formed by a vinylo-



88

gous rearrangement which involves a shift of the other C-C bond attached to the carbon bearing the oxygen, Scheme 20.



SCHEME 20

3.7 Exchange at C-6

The second-order rates of H-D exchange for the protons of the C-6 methylene group alpha to the carbonyl group were measured. It was found that the first proton exchanged about 7 - 8 times faster than the second one. The rate of H-D exchange of the alpha protons in the monocarbonyl[2.2.2] system 35 has been studied at three different temperatures by Tidwell and coworkers (129). It was found that in bicyclo[2.2.2]octan-2-one, the corrected rate constant of exchange for each proton at 25°C was $\sim 3.03\times10^{-2}$ M^{-1} s^{-1}. At 30°C the rate constant would be approximately 4.50×10^{-2} M^{-1} s^{-1}. However in the dione 64 these two protons are stereochemically different and their rates of exchange were found to be different (as mentioned in the results section). For convenience, we have arbitrarily referred to these rate constants as k_S and k_F. The ratio of the rate constant k_F to the rate constant for H-D exchange in monoketone 35 is approximately 60:1. It is proposed that in the diketone 64 the proton undergoing slower H-D exchange has a "syn" orientation relative to the carbonyl at the C-2 position. The homoconjugative effect is expected to cause an enhanced rate of exchange for H_F (anti-6-H). The syn-6-hydrogen can be expected to undergo exchange at a relatively slower rate due to diminished homoconjugative stabilization. However, to arrive at a definite conclusion, further investigation needs to be carried out to establish the stereochemistry of H_S and H_F with certainty.

EXPERIMENTAL

CHAPTER 4

EXPERIMENTAL

4.1 Materials and Instruments

4.1.1 Instruments

Nuclear magnetic resonance (NMR) spectra were recorded on the Varian T-60, HA-100, Bruker WH-90F, EM-390, HR-220 and Bruker WM-250 instruments. Tetramethylsilane (TMS) was the internal standard and samples were dissolved in either deuterated chloroform or carbon tetrachloride (certified A.C.S. spectra analyzed) sold by Fisher Scientific Company. Nuclear magnetic resonance (NMR) spectra, which were run at 220-MHz, were recorded by Dr. Art Grey at the University of Toronto. ^{13}C nuclear magnetic resonance spectra were recorded by Mr. Brian G. Sayer on a Varian Associates HA-100 spectrometer. Deuterium magnetic resonance (DMR) spectra were recorded in carbon tetrachloride solutions by Mr. Brian Sayer of McMaster University using an XL-100 spectrometer with ^{19}F perfluorobenzene as the internal lock signal.

Chemical shifts are reported in parts per million, downfield from internal tetramethylsilane (δ 0.0). In NMR abbreviations are as follows:

s = singlet, d = doublet, dd = doublet of doublets, m = multiplet, t = triplet and dt = doublet of triplets, etc.

The spectra will be denoted as follows: NMR ($CDCl_3$/TMS, Em-390); this represents a spectrum recorded on the EM-390 using $CDCl_3$ as solvent and tetramethylsilane as the internal standard. This will be followed by the main

chemical shifts which will be reported as "δ" values (ppm downfield from TMS). Mass spectra were recorded on Hitachi Perkin Elmer model RMU-6A and Consolidated Electrodynamics Corporation (CEC-21-110B) V.G. Micromass 7070F mass spectrometers. Deuterium assay analyses were performed at low ionizing voltage, 13 or 14 e.v., on the above mass spectrometers and are expressed as atoms of deuterium per molecule in excess of natural abundance deuterium.

Two analytical gas chromatographic instruments were used; a Varian Aerograph series 200 (Model 204B) dual column instrument equipped with dual flame ionization detectors and a Tracor-560 instrument (also dual channel) with ionization detectors. In both instruments the carrier gas was helium. Preparative scale gas-liquid partition chromatography was performed with a Varian Associates Aerograph Model 200 (A-700) with manual sample collection or with a Varian Aerograph Model A-90-P gas chromatograph. Helium was used as the carrier gas. The percentage conversion and/or the product ratios in all gas-liquid partition chromatograms were obtained with an Aerograph Model 485 Electronic Digital Integrator. Preparative columns were packed with either carbowax 20 M or SE-40 on 60-100 mesh chromosorb W, whereas analytical columns were packed with a finer support, 80-100 mesh chromosorb W. Analysis by gas-liquid partition chromatography will be denoted as follows:

g.ℓ.p.c (10% Carbowax, 10' × ¼", 200°) .

This denotes 10% Carbowax 20 M (on chromosorb W) liquid phase; the column was 10 feet long and ¼ inch in diameter and the analysis was carried out at 200°C. The flow rate of helium was normally 20-30 mℓ/min. for analytical

columns whereas for preparative work the flow rate was 50-60 mℓ/min. Infrared spectra were recorded on a Perkin-Elmer infrared spectrophotometer 283. All absorptions are in reciprocal centimeters and calibrated with a polystyrene film. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tennessee, 37921. All organic solutions were dried either with anhydrous magnesium sulphate or with sodium sulphate. Melting points were measured using a Kofler Hot Stage melting apparatus with a calibrated thermometer, and are reported uncorrected. Boiling points also are not corrected and refer to the pressure indicated in parentheses; for example b.p. 55-58°C (15 mm) denotes the boiling point range to be 55-58°, at a pressure of 15 mm of mercury.

4.1.2 Materials and Solvents

Materials

All materials for the synthesis of the compounds under investigation (3,3,6,6-tetramethylbicyclo[2.2.1]heptane-2,5-dione and analogous compounds) were obtained from the following major chemical companies:

1. Bicyclo[2.2.1]2,5-heptadiene was obtained from Frinton Laboratories, P.O. Box 301, Grant Ave., S. Vineland, N.J. 08360.
2. Iodomethane and t-butyl alcohol were obtained from J.T. Baker Chemical Co., Phillipsburg, N.J. 08865.
3. Deuterium oxide 99.7 atom. % D was obtained from Merck Sharp and Dohme of Canada Limited, Montreal, Canada or from Stohler Isotope Chemicals, 92 Beckwith Place, Rutherford, N.J. 07070, P.O. Box 399, AZ, U.S.A.

4. t-butyl alcohol (OD) was obtained from Aldrich Chemical Company, Inc. in five gram quantities which were used at once or in 25 gram quantities which were stored under nitrogen and kept in a desiccator containing $CaCl_2$.

5. Resolve-AlEu(foD) 99+% or Resolve-Al[Eu(Thd)$_2$,tris(2,2,6,6-tetramethyl-3,5-heptanedionato)Europium] in gold label were obtained in one gram quantities from Aldrich Chemical Company, Inc., 940 W. Saint Paul Ave., Milwaukee, Wisconsin 53233.

Solvents

Solvents which were used mainly in spectroscopic work, were as follows:

$CDCl_3$ chloroform-d, min. isotopic purity, 99.8 atom. % D was obtained in 100 gram quantities from Merck Sharp and Dohme Canada Limited, Montreal, Canada, or from Stohler Isotope Chemicals, 49 Jones Road, Waltham, MA 02154, U.S.A.

CCl_4 The carbon tetrachloride used was either NMR Grade CCl_4 obtained from Norell Chemical Co., Inc., Landing, N.J. 07850 or Certified A.C.S. spectranalyzed CCl_4 obtained from Fisher Scientific Co., Chemical Manufacturing Division, Fair Lawn, N.J. 07410.

4.2 Synthesis

4.2.1 Preparation of Bicyclic Carbonyl Compound Thio Carbonyl Compounds 3,3,6,6-tetramethylbicyclo[2.2.1]heptane-2,5-dione,(63a)

Compound 63a was prepared by permethylation of norbornane-2,5-dione, 72, which in turn was synthesized by the known procedure (89) using bicyclo[2.2.1]heptane-2,5-dione as precursor, Scheme 13.

4.2.2 Nortricyclyl Formate [Tricyclo[2.2.1.$0^{2,6}$]heptyl-3-formate], (67)

Bicyclo[2.2.1]heptane-2,5-dione (198.0 g, 2.06 mol) was refluxed for 3 h with formic acid (90%, 130.0 g, 2.54 mol). The reaction mixture was cooled, diluted with an equal amount of water and extracted with ether (4×100 mℓ). The combined ether extracts were washed with water (100 mℓ) and then with saturated aqueous sodium chloride solution (100 mℓ). The ether layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed by distillation. The major product of the reaction, nortricyclyl formate, was vacuum distilled, between 55-60°C (4.7-6.0 mm). The yield of formate was 42% (118.8 g, 0.86 mol). It was identified by comparison of its g.ℓ.p.c. retention time with that of an authentic sample.

4.2.3 Nortricyclyl Alcohol, (68)

Nortricyclyl formate (166.0 g, 1.2 mol) was hydrolyzed by refluxing with 20% (W/W) aqueous sodium hydroxide solution (450 mℓ) using an oil bath, for a period of 3.0 h. Progress of the reaction was followed by g.ℓ.p.c. When the hydrolysis was complete, the reaction mixture was cooled to room temperature and extracted with ether (3×100 mℓ). The combined ether layers were washed with water (100 mℓ) and with saturated aqueous sodium chloride solution (100 mℓ). The ether extracts were dried ($MgSO_4$), and filtered before the ether was removed by distillation. The alcohol was purified by recrystallization from n-pentane; yield was 88% (117 g, 1.06 mol) with m.p. of 105-106°C (lit.' 108-109); I.R.(CCl_4): 3320 cm^{-1}(OH). The g.ℓ.p.c. analysis was identical to that of an authentic sample in all aspects.

4.2.4 Nortricyclanone (Tricyclo[2.2.1.$0^{2,6}$]heptan-3-one), (69)

Chromium trioxide (70.g, 0.7 mol) was dissolved in 100 mℓ of water. The solution was cooled in an ice bath and concentrated sulfuric acid (61 mℓ, 112 g, 1.10 mol) was added slowly, followed by the addition of water (200 mℓ), with stirring, while maintaining the temperature between 0 and 5°C. Nortricyclyl alcohol (55.0 g, 0.5 mol) was dissolved in acetone (300 mℓ, Analytical Reagent grade) or ether which was previously treated with oxidizing reagent and placed in a 3-necked round bottom flask, fitted with a condenser, a pressure-equalizing dropping funnel and a thermometer. The flask was immersed in an ice bath and the temperature of the solution was reduced to between 0-5°C. The pre-cooled oxidizing reagent (190 mℓ of stock solution) was added to the stirred solution at such a rate as to maintain the temperature of the reaction at ambient temperature (20-24°C), and the stirring was continued for 4 h after the oxidizing reagent was added. When the oxidation was 98% complete, excess oxidizing reagent was destroyed by addition of small portions of sodium bisulfite. The top layer was decanted and the dense, green bottom layer was extracted with petroleum ether (30-60°C, 3×80 mℓ). The combined organic layers were washed with saturated aqueous sodium chloride (2×30 mℓ), sodium bicarbonate (2×30 mℓ), and saturated aqueous sodium chloride (25 mℓ). The organic layer was dried ($MgSO_4$) and filtered before the solvent was removed by distillation. The residue was distilled under reduced pressure (b.p. 81°C (30 mm)), yielding 82% (44.1 g, 0.408 mol) nortricyclanone. ^1H NMR ($CDCl_3$/TMS, T-60) of nortricyclanone showed a complex spectrum at δ = 1.0-2.2 ppm.

4.2.5 5-Acetoxybicyclo[2.2.1]heptan-2-one(88,89),(70)

Nortricyclanone (38.7 g, 0.358 mol) was dissolved in glacial acetic acid (118 mℓ) containing 70% perchloric acid (5.6 mℓ) and the solution was heated on the steam bath for 5 h. The dark red-brown solution was cooled to room temperature and poured into ice-cooled sodium hydroxide solution (10%, 200 mℓ) which was then neutralized using solid sodium bicarbonate. The solution was extracted with ether (6×100 mℓ) and the combined ether layers were washed with saturated aqueous sodium bicarbonate, dried over Na_2SO_4 and filtered. The solvent was removed on a rotary evaporator and the ketoacetate was isolated by vacuum distillation (b.p. 96-98° (1.30 mm)) (lit (89) b.p. 88-90; (1-2 mm)) to give an 84% (50.6 g, 0.4 mol) yield of pure compound. The fraction which was collected at 96-98°C was analyzed by g.ℓ.p.c. and the retention time was identical to that of an authentic sample. I.R. (neat): 1750 cm^{-1} (C=O); 1250 cm^{-1} (acetate).

4.2.6 Norbornane-2,5-diol,(71)

A solution of 5-ketonorbornyl acetate (25.0 g, 149 mmol) in ether (170 mℓ, distilled from lithium aluminium hydride) was added dropwise over a period of 2 h to a slurry of lithium aluminium hydride (21.5 g) in ether (600 mℓ). The reaction mixture was refluxed for 12 h then the solution was cooled in ice and 10% aqueous sodium hydroxide (35 mℓ) was added dropwise followed by cautious addition of water (45 mℓ). The inorganic salts were removed by filtration and washed with ether. The ether layers were combined, dried over Na_2SO_4 and concentrated using a rotary evaporator. Upon cooling, the diol was obtained as a white solid which was recrystallized from ether

to yield 83% (15.8 g, 123 mmol). Analysis by g.ℓ.p.c. (10% carbowax, 10'×¼", 185°C) showed only one major compound (r.t. 10 min) which was consistent with the reference sample (130), I.R. ($CHCl_3$) 3575 and 3400 cm^{-1} (OH) and no carbonyl absorption around 1750 cm^{-1}.

4.2.7 Norbornane-2,5-dione, (72)

Norbornane-2,5-diol (10.g, 78 mmol) was dissolved in acetone (60-70 mℓ). The solution was placed in a round bottomed flask fitted with a mechanical stirrer and a pressure equalizing dropping funnel, which was immersed in ice. Freshly prepared oxidizing reagent** (60 mℓ), which was previously cooled was added dropwise over a period of 1½ h and the reaction mixture was kept cold for 20-24 h with continuous stirring. The progress of the reaction was monitored by gcℓ.p.c. and, when most of the diol had been converted to dione (∿ 24 h), excess oxidizing reagent was destroyed by addition of $NaHSO_3$ and the reaction mixture was extracted with ether (7×60 mℓ). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride and sodium bicarbonate (40-50 mℓ). It was then dried over Na_2SO_4, filtered, and the excess solvent was removed by fractional distillation to yield crude diketone (8.8 g, 69.8 mmol). The crude material was sublimed yielding 76% (7.5 g, 59.5 mol) of diketone, m.p. 140-142°C (lit (89) m.p. 141.5-143°C).

^1H NMR ($CDCl_3$/TMS, EM-390) δ = 2.0-2.6 (m,6H); δ = 3.0 (1 broad signal, 2H) bridgehead protons.

^{13}C NMR ($CDCl_3$/TMS, WH-90) $C_1 = C_4 = 47.4$; $C_3 = C_6 = 36.4$; $C_2 = C_5 = 21.37$;

** Oxidizing reagent was prepared as described previously.

C_7 = 33.8 ppm.

M.S. analysis showed a peak at M/e = 126; M^+ in accord with molecular weight.

IR (CCl_4) 1769, 1738 cm^{-1} (C = O)

u.v. (1.6 mg/mℓ in hexane) λ_{max} = 250 n.m. (131)

4.2.8 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione, (63a)

Norbornane-2,5-dione (5.28 g, 42.5 mmol) was placed in a round bottomed flask and dry ether (800 mℓ) and potassium t-butoxide (30.4 g, 270 mmol) were added. The solution became pale yellow and eventually darkened. After the solution was stirred for ½ h, methyl iodide (60 mℓ) dissolved in an equal portion of ether was added. The solution was stirred for 2 h. The progress of reaction was monitored by g.ℓ.p.c. and after 3 h methylation was complete; the solution was filtered and the solvent was removed by distillation. The concentrated solution was cooled to obtain the desired white solid, which was recrystallized from ether. Dione 63a was obtained in 56% yield (4.2 g, 23 mmol) and exhibited a m.p. of 114-115°C. The M.S. showed a molecular ion of M/e = 180 (M^+) which is consisistent with the molecular weight of this compound. The structure of dione 63a was confirmed by carrying out an x-ray crystal structure determination (94).

^1H NMR ($CDCl_3$/TMS,EM-390); δ = 1.0 (s, 6H, $2CH_3$), δ = 1.15 (s, 6H,$2CH_3$), δ = 2.20 (t, 2H, two protons at C_7), δ = 2.6 (t, 2H, two bridgehead protons)

^{13}C NMR ($CDCl_3$/TMS,WH-90): δ = 217.8 ($C_2 = C_5$) carbonyl group; δ = 70.1 ($C_1 = C_4$) bridgehead carbons; δ = 45.9 ($C_3 = C_6$)CH; δ = 31.0 (C_7) methylene group and the four methyl groups are at

δ = 23.5 and 22.3 ppm.

	H	C
Anal. calcd.	8.95	73.23
Found	8.89	73.58

4.2.9 Bromination of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione, (64) (132-135)

1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione (0.076 g, 0.426 mmol) was dissolved in acetic acid (7.5 mℓ) and the solution was slightly cooled. A solution of bromine (0.852 mmol, 19 μℓ) in acetic acid (1 mℓ) was added to the diketone solution very slowly over a long period of time (20 - 24 h). The progress of the reaction was monitored every 5 - 6 h by g.ℓ.p.c. After 60 - 65 h the analysis indicated that the major product was dibromide, and that some monobromide was present. The reaction mixture was kept at 50°C for 4 h, cooled, neutralized using sodium bicarbonate and extracted with n-pentane (6×6 mℓ). The fractions were combined, dried ($MgSO_4$) and concentrated. The concentrated solution was cooled and the crude product which was collected was recrystallized twice from n-pentane to give the dibromide in 66% yield (0.0951 g, 0.2813 mmol). Its g.ℓ.p.c. analysis (O.V. 1, 7'×$\frac{1}{8}$", 180° r.t. 5 min) showed only one compound, purity 99.80%.

^{1}H NMR ($CDCl_3$, WM-250) δ = 1.21 (s,3H,CH_3); δ = 1.26 (s,3H,CH_3) δ = 1.40 (s,3H,CH_3); δ = 1.77 (m,1H,7n) δ = 2.03 (m,1H,8n); δ = 2.10 (m,1H,9x); δ = 2.21 (m,1H,7x); δ = 2.64 (dd,1H,bridgehead proton)

^{13}C NMR ($CDCl_3$/TMS,WH-90) δ = 210.4 (C=O); δ = 199.5 (C=O); δ = 67.9 (C_6); δ = 59.7 (C_1); δ = 54.2 (C); δ = 45.45 (C_3), δ = 28.61 (C_7); δ = 17.62 (C_8); and the three methyls are at δ = 25.68, 23.92 and 18.1 ppm.

M.S. showed the parent ion peaks at masses 336, 338, 340 which had the correct isotopic distribution, and correspond to the dibromide. The structure of dibromide 65 was confirmed by carrying out an x-ray crystal structure determination (94).

4.2.10 Synthesis of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dithione (63b) and 3,3,6,6-Tetramethyl-5-oxo-bicyclo[2.2.1]heptane-2-thione (63c)

A round bottomed flask containing 100 mℓ of xylene was fitted with a Soxhlet extractor, a reflux condenser and a drying tube. P_2S_5 (10.0 g, 45 mmol) was placed in the Soxhlet thimble and the xylene was refluxed for about 2 h to saturate the xylene with P_2S_5. Dione 63a (3.0 g, 16.66 mmol) was dissolved in the xylene solution and the reaction mixture was stirred and refluxed for 5½ h. During this period the progress of the reaction was monitored by g.ℓ.p.c. The reaction mixture was cooled and filtered to remove excess P_2S_5, most of the xylene was removed by vacuum distillation, and the

concentrate was extracted with 50:50 (V/V) of ether in petroleum ether (30-60°, 5×75 mℓ). The combined extracts were dried ($MgSO_4$), filtered, and concentrated by distillation. The components were separated by column chromatography on neutral alumina (activity 1 and mesh size 80-200). The elution was carried out using petroleum ether (30-60°) first and the polarity of the eluant was gradually increased by varying the proportions of ether. Overall, 110 fractions were collected (110×15 mℓ), checked by g.ℓ.p.c. and appropriate fractions were combined. The order of elution was 63b, 63c and 63a. The recovery was almost quantitative. The isolated products were in the ratio of 35% 63c, 43.0% 63b and the remainder was starting material.

^1H NMR for 63b ($CDCl_3$/TMS,EM-390) δ = 1.06 (s,6H, $2CH_3$).

δ = 1.27 (s, 6H, $2CH_3$), δ = 2.3 (s, 2H, CH_2 at position 7),

δ = 3.42 (s, 2H, two bridgehead protons (C_1H, C_4H)).

^{13}C NMR for 63b ($CDCl_3$,WP-80)*1 δ = 213.94 (C = S), $C_1 = C_4 = 74.43$

C_7 = 35.23, $C_3 = C_6 = 56.28$ and methyls are at 29.76 and 25.8 ppm

I.R. (CCl_4) for 63b 1060 cm^{-1}, 1167 cm^{-1} (C = S)

M.S. molecular ion M/e = 212 (M^+) which corresponds to the molecular weight of 63b.

^1H NMR for 63c($CDCl_3$/TMS, M-390) δ = 0.94 (s, 3H, CH_3);

δ = 1.06 (s, 3H, CH_3); δ = 1.15 (s, 3H, CH_3); δ = 1.21 (s, 3H, CH_3);

δ = 2.23 (s, 2H, $CH_2(C_7)$), δ = 2.7 (s, 1H, H_1 bridgehead proton),

δ = 3.23 (s, 1H, H_4 bridgehead proton).

^{13}C NMR for 63c ($CDCl_3$,WP-80)*1 δ = 218.15 (C = O); 213.30 (C = S); C_1 = 73.40 ; C_4 = 61.14; C_7 = 33.15; C_3 = 55.75; C_6 = 46.49 and four methyls at 21.99, 24.06, 26.17 and 29.41 ppm.

I.R. (CCl_4) for 63c 1073 cm^{-1}, 1178 cm^{-1} (C = S); 1754 cm^{-1} (C = O)

M.S. Molecular ion M/e = 196 (M^+), corresponding to the molecular weight of 63c.

4.2.11 Synthesis of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptan-2-one (63d)

3,3,6,6-Tetramethyl-5-oxo-bicyclo[2.2.1]heptan-2-thione (1.47 g, 7.5 mmol) was dissolved in super dry ethanol (25 mℓ) in a 100 mℓ round bottomed flask, fitted with a reflux condenser, and Raney-nickel (10-15 g) was added. The mixture was stirred and refluxed for 10 h and the progress of the reaction was monitored by g.ℓ.p.c. The reaction mixture was filtered through a sintered glass funnel containing celite and washed with ethanol (10 mℓ). The excess ethanol was removed by fractional distillation and 63d was isolated as an oil from the concentrated solution by preparative g.ℓ.p.c. (15% Carbowax, 10'×½", 195° r.t. 8.5 min). M.S. molecular ion at M/e = 166 (M^+) was in accord with the molecular weight of 63d.

^1H NMR (CCl_4/TMS, WM-250)

δ = 0.97 (s, 3H, CH_3); δ = 1.00 (s, 3H, CH_3); δ = 1.04 (s, 3H, CH_3)

δ = 1.11 (s, 3H, CH_3); δ = 1.42 (dd,1H,5-exo,$J_{5x,5n}$ = 12.8,$J_{5x,4}$ = 4.4 Hz)

δ = 1.65 (broadened dd, 1H, 5-endo, $J_{5n,5x}$ = 12.8, $J_{5n,7s}$ = 2.6,$J_{5n,4}$ = ~0.3 Hz)

δ = 1.85 (ddd,1H,7-anti, $J_{7a,7s}$ = 10.8, $J_{7a,1}$ = 0.8, $J_{7a,4}$ = 1.8 Hz)

*1 Chemical shifts are referenced to the internal standard $CDCl_3$ ($CDCl_3$ at 77.2 ppm downfield from T.M.S.). Chemical shifts are considered to be within ± 0.1 ppm.

δ = 1.96 (dm,1H,7-syn, $J_{7s,7a}$ = 10.8, $J_{7s,5n}$ = 2.6, $J_{7s,4}$ = 0.7, $J_{7s,1}$ = 1.3 Hz)

δ = 2.01 (dd,1H,$C_1\underline{H}$, $J_{1,7s}$ = 1.3, $J_{1,7a}$ = 0.8 Hz)

δ = 2.13 (m,1H,$C_4\underline{H}$, $J_{4,5x}$ = 4.4, $J_{4,5n}$ = ~0.3, $J_{4,7a}$ = 1.8, $J_{4,7s}$ = 0.7 Hz)

^{13}C NMR ($CDCl_3$ WH-90), δ = 222.04 (C_2) carbonyl group,

δ = 62.42 (C_4), δ = 47.20 (C_1), δ = 46.49 (C_3), δ = 36.80 (C_6)

δ = 38.75 (C_7), δ = 34.32 (C_5) four methyl groups were at

δ = 30.89, 27.44, 24.45 and 20.81 ppm.

Elemental analysis was as follows:

	C	H
Found	79.27	11.03
Calcd.	79.46	10.91

4.2.12 Preparation of Raney Nickel, W-2 (136)

In a 2 ℓ beaker fitted with an efficient stirrer was placed aqueous sodium hydroxide solution (76 g in 300 mℓ). The beaker was immersed in ice and cooled to 10°C. Nickel-aluminium alloy (60g)* (137) was added to the solution in small portions, at a rate such that the temperature did not rise above 20°C, over a period of 2½ h. The beaker was taken out of the cooling bath, the solution was warmed to room temperature, and the nickel was kept in suspension by stirring. When the evolution of hydrogen slowed, the beaker was placed on the steam bath for 10 h, after which evolution of hydrogen had again become slow. During heating the level of solution was kept constant by addition of small amounts of water and a watch glass was

*BDH Nickel-Aluminium 50% Ni, 50 % Al Product No. 29312

used to cover the beaker to condense the solvent. The nickel was allowed to settle and the solvent was decanted. This solid was washed with water and decanted again. This procedure was repeated using aqueous solution of sodium hydroxide (10 g in 100 mℓ). Then washing was repeated many times with water until the wash water was not alkaline. Eventually the solid was washed three times further with water, four times with 95% ethanol and finally with absolute ethanol. The product (22 g) was stored in dry ethanol under nitrogen in the refrigerator. The reactivity of the Raney-nickel was established by drying a small sample of it on filter paper and observing its ignition.

4.2.13 Preparation of "Super-Dry" Ethanol (138)

Super dry ethanol was prepared by the method of Lund and Bjerrum. Magnesium (5g), iodine (0.5 g) and absolute ethanol (70 mℓ) were placed in a 2 liter round bottomed flask fitted with a reflux condenser and a drying tube. The mixture was warmed until all the iodine disappeared and hydrogen evolution started. Heating was continued until most of the magnesium was converted to ethoxide, at which point dry absolute ethanol (900 mℓ) was added and refluxed for ½ h. The ethanol was distilled into a dry container.

4.3. Density Measurements

The density of 6,6-dibromo-1,3,3-trimethylbicyclo[2.2.2]octane-2,5-dione, 64 was measured using the flotation method. A solution of zinc bromide was used and a density of 1.76 g/cm^3 was obtained. The density of 3,3,6,6-tetramethylbicyclo[2.2.1]heptane-2,5-dione, 63a was measured, via

two methods, flotation in zinc bromide solution and displacement using water. The average value was $\bar{\rho}$ = 1.08±0.05 g/cm^3.

4.4 Column and Collection Efficiency

Since preparative g.ℓ.p.c. was used extensively for the separation of reaction mixtures, it was essential to know the column and collection efficiency.

A standard solution of pure material was made and a known amount was put through the column under the same conditions which were used for the purification of reaction mixtures. From the weight of recovered material, the column and collection efficiency was determined (assuming that loss of material during the collection is constant). For example, to determine the efficiency of a 15% Carbowax column (10'×¼") at 185°C (injector temperature, 220°C, detector temperature, 220°C; He flow rate, 55 mℓ / min), a number of injections were made totalling 17.1 mg, and 14.9 mg of material was collected. This gave an efficiency of 87 percent.

4.5 Homoenolization

The procedure is essentially as described by A. Nickon et.al. (40). All the glassware was carefully dried with a heat-gun or flamed to complete dryness before usage and placed in the glovebox under a nitrogen atmosphere. Prior to an experiment, two large evaporating dishes containing potassium hydroxide pellets and phosphorus pentoxide were placed in the glovebox under a slow flow of dry nitrogen. Tertiary-butyl alcohol (Fisher-Scientific Co. or J.T. Baker Chemical Co.) was dried by distillation from potassium and stored over activated molecular sieves (type 4A or 3A). Tertiary-butyl alcohol (OD)

(Aldrich Chemical Company, Inc.), mostly in 5 g quantities, was used without further drying. The larger containers were stored in a desiccator containing $CaCl_2$.

In a dry-box, the basic solution was freshly prepared for each reaction by dissolving potassium metal in t-butyl alcohol (t-BuOH or t-BuOD) and was added to a medium wall tube which contained the substrate to be homoenolized. The tube containing the ketone, potassium t-butoxide, and t-butyl alcohol (H or D) was degassed four or five times and then was sealed under vacuum. The sealed tube was then placed in a steel bomb containing water (to offset the pressure inside the tubes) and was usually heated at 150°C to 175°C. After heating for different periods of time, the tubes were frozen and then opened by the hot spotting method. The contents of the tubes were poured into a small amount of distilled water (H_2O or D_2O) which was saturated with sodium chloride and the neutral products were isolated by extraction with a mixture of ether/pet-ether (b.p. 30-60°C) or ether/n-pentane in a 1:1 (V/V) ratio. The organic extracts were combined, dried with anhydrous sodium or magnesium sulfate, filtered, and the solvent was distilled off through a one-foot column packed with glass helices. The total product composition was analyzed by gas chromatography on a 15% Carbowax column. ($10' \times \frac{1}{8}''$). The percentage conversion for the compound or ratio of products from homoenolization were calculated using areas produced by electronic integration (average of 6-10 injections). Usually the reaction mixture was separated by preparative g.l.p.c. using Carbowax or SE-30 columns.

Typical conditions using a 15% SE-30 column (5'×¼") were as follows:

Column temperature	160°C
Collector temperature	200°C
Detector temperature	210°C
Injector temperature	200°C
Flow rate	50 mℓ/min

In the following section, representative examples of the homoenolization of carbonyl and/or thione containing compounds will be discussed.

4.5.1 Homoenolization of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dione (63a)

Potassium t-butoxide solution was prepared by dissolving potassium (0.199 g, 5.09 mmol) in t-butanol (4mℓ) in a drybox flushed with dry nitrogen. The solution was added to a dry pyrex tube containing 63a (0.29 g, 1.6 mmol). The tube was degassed by five freeze-pump-thaw cycles and sealed under vacuum. The tube was placed in a steel bomb containing some water to offset the pressure, and heated at 175±3°C for 75 h. After cooling to room temperature, the reaction mixture was frozen in liquid nitrogen and the tube was opened. The reaction mixture was poured into 15 mℓ of a saturated NaCl solution and extracted using 1:1 (V:V) ether-petroleum ether (5×15 mℓ). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Using analytical g.ℓ.p.c. equipped with electronic integration, the degree of isomerization was determined. The reaction was separated by preparative g.ℓ.p.c. (15% carbowax 10'×¼"). The collection

efficiency for that specific column under the given conditions was 78 percent (as was explained previously). From a total of 5 mℓ of the concentrated organic layer, 1 mℓ was separated using 100 μℓ inections. Two components were collected and found to be starting diketone 63a (20.9 mg) and dione 64 (16.7 mg). When corrections were made for collection efficiency and for the fact that one fifth of the concentrate was separated, it was established that 83% of the material was recovered. Note: The data in Table X indicates that for the effective conversion of dione 63a to 64, a high concentration of K^{+} t-BuO^{-} is required. However concentrated base is difficult to transfer (because of salt formation in dropping pipets or in the mouth of the reaction tube). To overcome this, K^{+} t-BuO^{-} was prepared directly in the reaction tube. A slow stream of dry nitrogen was passed around the tube to prevent evaporation of t-BuOH.

4.5.2 Homoenolization of 3,3,6,6-Tetramethylbicyclo[2.2.1]heptan-2-one (63d)

As in the previous case, the sample was prepared in a drybox under a nitrogen atmosphere. A strong basic medium was prepared by dissolving potassium (0.17 g, 4.36 mmol) in 3.5 mℓ of t-butyl alcohol (OD), to give a base concentration of 1.24 M. This solution was transferred to a tube containing 63d (0.13 g, 0.79 mmol), yielding a concentration of 0.23 M. The solution was degassed and sealed under vacuum. This mixture was heated at 175±3°C in a steel bomb for 403 h. The reaction mixture was worked up as described in the general procedure for homoenolization (vide supra). The reaction mixture was concentrated, the remaining solvent was distilled off using a one foot column packed with glass-helices, and the last traces of

solvent were removed under vacuum to yield 116.6 mg (89%) of 63d. Before removal of all solvent, the extract was analyzed by analytical g.ℓ.p.c. (OV-1, 7'×¼", 200°C, r.t. 2 min) and showed that no other products (< 1%) other than starting dione were present. To be certain that there was no solvent present, this material was put through a preparative g.ℓ.p.c. (15% carbowax, 10'×¼", 200°C r.t. 8 min). This sample was assayed for deuterium by mass spectrometery and found to incorporate 0.56 excess deuterium atoms per molecule (Table XVII). In addition, ^{2}H, ^{1}H, and ^{13}C NMR spectra were also recorded.

4.5.3 Homoenolization of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione, (64)

The general homoenolization procedure was followed. Deuterated strongly basic media (3.5 mℓ of 1.25 M) was prepared and added to a tube containing compound 64 (80 mg., 0.40 mmol). The tube was sealed as before, and heated for 35 h at 175±3°C. After the work up and removal of solvent, dione 64 was recovered in 86.5% yield (69 mg, 0.38 mmol). The analytical g.ℓ.p.c. analysis indicated that only starting dione 64 was present. The recovered sample was assayed for deuterium via mass spectrometery and it was found that it contained 6.08 excess deuterium atoms per molecule. The composition of deuterium in this sample was 0.05% d_0, 0.15% d_1, 0.43% d_2, 2.04% d_3, 8.54% d_4, 22.22% d_5, 30.04% d_6, 21.16% d_7, 8.91% d_8, 3.97% d_9, 1.61% d_{10} and 0.37% d_{11}.% species. This sample was further analyzed by ^{1}H, ^{2}H, ^{13}C NMR and in addition for clearer assignment of different signals, a lanthanide shift ($Eu(fod)_3$) reagent was used.

4.5.4 Homoenolization of 3,3,6,6-Tetramethyl-5-oxo-bicyclo[2.2.1]heptane-2-thione (63c) and 3,3,6,6-Tetramethylbicyclo[2.2.1]heptane-2,5-dithione (63b)

Only a few preliminary homoenolization experiments for compounds 63b and 63c have been carried out. On the basis of previous knowledge of H-D exchange of thiocamphor, it was expected to observe faster rate of exchange in 63b and 63c relative to their carbonyl analogues, so homoenolization was carried out for shorter periods of time. Both 63b and 63c appear to be much more sensitive to moisture (with possible conversion of a thione to a carbonyl group) than the carbonyl compounds. An additional problem to solve concerns the work-up procedure. Due to the reactivity and instability of thiones and facile exchange of the alpha protons, the products isolated after work-up in aqueous solution could be different from those actually obtained from the reaction. Further it is well known (139,140) that thiones containing alpha protons undergo dimers, trimers or polymers. By analogy with the rearrangement product of the dione 63a, it was anticipated that a similar product would be produced from the thione which would contain α-methylene groups. Therefore a suitable work-up procedure was chosen to minimize polymerization and back-exchange. One possible work-up would involve the use of neutral conditions and low temperature. Neutral or basic conditions were used here and the deuterated starting material was separated and analyzed by mass spectrometry (other products were present but not identified as yet). An example for each case is given below:

63c

Compound 63c (0.39 g, 1.9 mmol) was treated with K^{+} t-BuO^{-} (1.3 M) in t-BuOD (3 mℓ) at 175±2-3°C for 5 h. The recovered starting material was

assayed for deuterium content and it was found that it contained 0.31 excess deuterium per molecule. This recovered substrate was a composite of 76.40% d_0, 17.80% d_1, 3.85% d_2 and 1.94% d_3 species.

63b

The dithione 63b (0.46 g, 2.18 mmol) was treated with K^+ t-BuO^- (0.9 M) in t-BuOD (3 mℓ) at 175±3°C for 5 h. The analysis of recovered starting material by mass spectrometry revealed that it contained 0.52 excess deuterium per molecule. This deuterium was a composite of 59.10% d_0, 32.85% d_1, 4.50% d_2, 2.44% d_3 and 0.84% d_4 species.

4.5.5 Homoenolization of Fenchone (29)

A sealed sample tube containing fenchone (29) (150 mg, ∿ 1 mmol) and K^+ tBuO^-/t-BuOD (0.8 M) was prepared as described in the general procedure. This sample tube was heated for a total of 680 h at 175±3°C. After the work-up and purification using preparative g.ℓ.p.c. (10% SE-30, 6'×¼"; 155°C), this sample was assayed for its deuterium content by mass spectrometry. It was found that the sample contains 1.70 excess deuterium per molecule. This deuterium was a composite of 16.03% d_0, 30.20% d_1, 42.44% d_2, 9.60% d_3, 1.53% d_4 and 0.21% d_5 species.

^2H NMR spectra showed a small amount of deuterium incorporated at syn-H-7, as well as exo-H-6, endo-H-6 and all the three methyl protons.

4.6 Kinetic Studies

4.6.1 Base-Catalyzed Deuterium-Protium Exchange from a Deuterated Sample of 1,3,3-Trimethylbicyclo[2.2.2]octane-2,5-dione.

A container with 1N sodium hydroxide solution (2mℓ) and dioxane (3 mℓ) was placed in a constant temperature bath (maintained at 25°C). Following an equilibration period, deuterated dione 64 (52 mg, 0.29 mmol) was added. After 23 h, the reaction was quenched with a buffer (5.5 mℓ) of pH ∿ 6.5* and the mixture was saturated with sodium chloride and extracted with ether. The combined ether layers were dried over $MgSO_4$, the ether was distilled off and the dione was isolated by preparative g.ℓ.p.c. on a 15% Carbowax 7'×¼" column at 175°C. The dione was assayed for deuterium mass spectrometrically and was found to contain 4.46 excess atoms of deuterium per molecule. Since the starting dione contained 5.86 excess deuteriums per molecule, 1.4 excess deuteriums per molecule were removed by back exchange.

4.6.2 Base-Catalyzed Protium-Deuterium Exchange in 1,3,3,Trimethylbicyclo[2.2.2]octane-2,5-dione

Freshly distilled dioxane (0.6 mℓ (141) and bicarbonate buffer (0.4 mℓ) (142,106) of pD ∿ 10.84** were transferred into a reaction container and equilibrated in a constant temperature bath (30±0.1°C) for 30 minutes. A small amount of dione 64 (4-8 mg) was accurately weighed and added to the solution with shaking. Aliquots were removed at various intervals (from 0.5 - 200 minutes) and quenched in 1.5 - 2.0 mℓ of a phosphate buffer of pH 6.5.

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*The pH 6.5 buffer was obtained from a mixture of 50 mℓ of KH_2PO_4 solution (0.1 M) and 13.9 mℓ of NaOH (0.1 M).

**The pD 10.84 buffer was obtained from a mixture of 50 mℓ of sodium bicarbonate (0.05 M) and 16.5 mℓ of NaOD (0.1 M).

The aqueous solution was immediately extracted 2 - 3 times with ether and the combined ether layers dried ($MgSO_4$) and concentrated. Depending on the half-life of the exchange rate, five to eight samples were taken in each run. The composition was assayed mass spectrometrically under identical conditions as the starting material, and at least eight to ten scans were recorded. After corrections for "natural abundance" were made, the averages of these corrected scans were recorded. These points, which represent the percentage deuterated compound or concentration and the corresponding times, were used to calculate the rate constant. The rates of exchange were measured under pseudo-first order conditions, using excess base. The data were fitted to a first-order rate expression by means of a least squares program*.

*These programs were obtained from Dr. Sujit Banerjee.

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