



APPROACHES TOWARDS THE SYNTHESIS OF BICYCLOBUTANES WITH
ANGULAR OXYGEN FUNCTIONS

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(i)

SUMMARY

Acetylation of the anions formed from the reaction of 3-bromo-2,2-dimethylpropan-1-al and 3-bromo-2,2-dimethylpropiophenone with lithium gave 2,2-dimethylcyclopropyl acetate and 2,2-dimethyl-1-phenylcyclopropyl acetate. The structure of the intermediate anions is discussed in terms of their nuclear magnetic resonance spectra.

An attempt to synthesise substituted bicyclobutanes with angular oxygen functions by an analogous reaction of alkyl substituted 3-bromocyclobutan-1-ones with lithium was unsuccessful. A second route to these substituted bicyclobutanes involving the reaction of the ethylene ketals of two substituted 3-bromocyclobutan-1-ones with alkali metals was investigated. The reaction of 7-bromo-6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane with lithium gave an anion which, on acetylation, yielded a diene. An examination of the nuclear magnetic resonance spectra of this anion and certain products derived from it suggests that some O-substituted bicyclobutanes have been prepared but are unstable under the conditions used.

Attempts to prepare the dimethyl ketals of two 3-bromocyclobutan-1-ones are described.

(ii)

STATEMENT.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University, and to the best of my knowledge and belief contains no material previously published or written by another person, except where due reference is made in the text.

R.W. SINCLAIR

(iii)

ACKNOWLEDGEMENTS

I wish to thank most sincerely Dr. D.P.G. Hamon for his guidance and enthusiasm during supervision of this work.

I am also grateful to my wife and my colleagues who have made these last few years so pleasant.

This research was carried out during the tenure of a Commonwealth Postgraduate Award, which I am pleased to acknowledge.

(iv)

PUBLICATION.

Part of the work described in this thesis has been published in the following preliminary communication:

"The Acetylation of Homo-enolate Anions: A New Synthesis of Cyclopropyl Acetates",

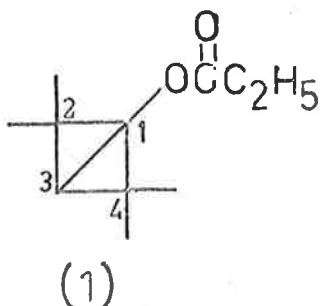
D.P.G. Hamon and R.W. Sinclair, Chemical Communications, 1968, 890.

INTRODUCTION



-1-

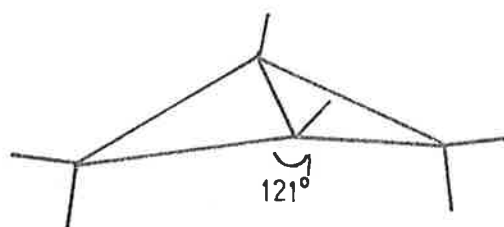
In 1964 Day and Whiting¹ proposed that 2,2,4,4-tetramethyl-bicyclo[1.1.0]butane-1-propionate (1) was a possible structure for the sex-attractant of the American cockroach Periplaneta americana, which had been isolated in minute quantities by two groups.^{2,3} Although this structure was later discounted on the basis of spectral



evidence,^{4,5} it seemed that its synthesis would be of interest. The structure (1) represents a new class of compounds - bicyclobutanes with angular* oxygen functions, none of which were known at the time.

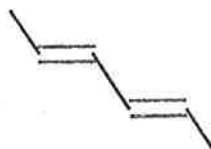
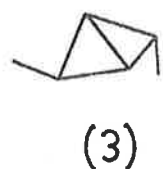
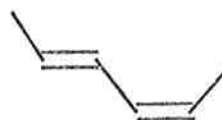
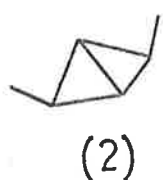
Bicyclobutanes may be considered as being made up of two equilateral triangular rings having one common edge.⁷ A study of microwave data has indicated that the angle between the rings is 121° .⁸ They are highly strained, reactive compounds. The strain energy of bicyclobutane has been estimated at 63.9 kcal/mole, the highest of the series of bicyclo[n.m.o]alkanes.⁹ This value is close

* Angular substituents are taken to be those at the 1- and 3-carbons.⁶



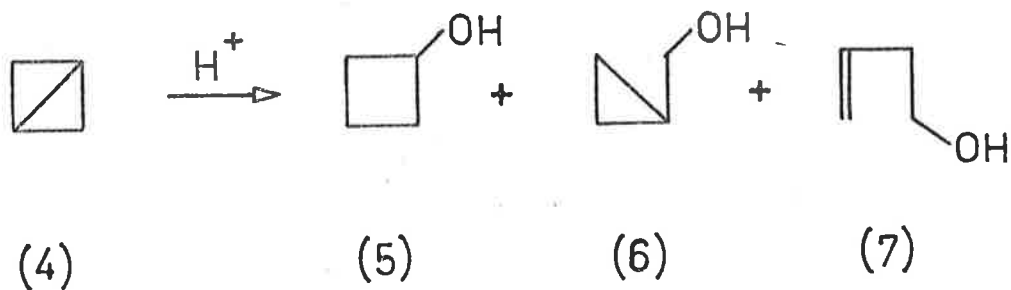
to that for the value of the C-C bond dissociation energy (82.6 kcal/mole).¹⁰ Molecular orbital calculations⁷ indicate that the bridgehead bond has a certain amount of π -character. This is supported by the dipole moment of 0.67D⁸ which is large for a saturated hydrocarbon and by the ultraviolet spectrum¹¹ of methyl bicyclobutane-1-carboxylate which has a band at about 210 m μ with $\epsilon_{\text{max}} = 7000$ indicating conjugation of the bridgehead bond with the carbonyl of the ester. Many of the reactions of bicyclobutanes can be rationalised in terms of the increased electron density in the bridgehead bond.

One of the more widely studied reactions of bicyclobutanes is their thermal rearrangement to butadiene derivatives. Wiberg⁹ has argued that the bridgehead bond is preserved in this reaction because 1,3-disubstituted bicyclobutanes always give 2,3-disubstituted butadienes. Closs and Pfeffer¹² have shown that the dienes derived from the bicyclobutanes (2) and (3) can only be formed by a concerted mechanism. The Woodward-Hoffmann rules have been successfully applied to these reactions. Thus in the opening of (2) the formation of the diene with the stereochemistry shown is explained in terms of a

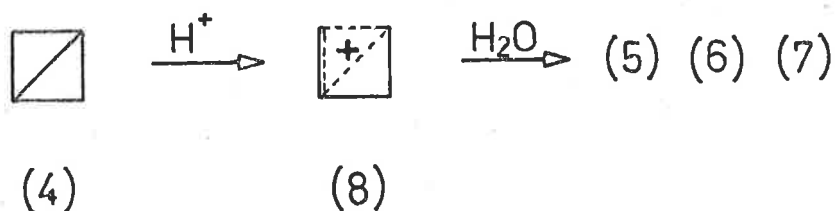


$[\sigma_s^2 + \sigma_a^2]$ process.¹³

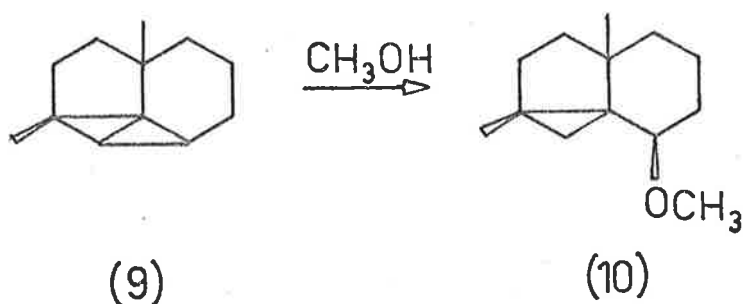
Another reaction which shows the increased electron density of the bridgehead bond is the extremely ready hydration of bicyclobutanes by dilute acid. Wiberg⁹ has calculated that bicyclobutane is 10^{10} times as reactive as cyclopropane in this reaction. Bicyclobutane (4) forms cyclobutanol (5), cyclopropylcarbinol (6), and a trace of allyl carbinol (7) when treated with dilute acid.¹⁴ The



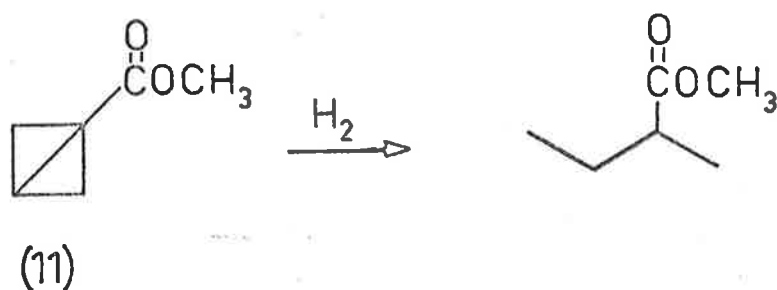
product ratio is similar to that found for reactions which are thought to involve the "bicyclobutonium" ion (8).¹⁵ Initial protonation of the bridgehead bond might be expected to produce this ion which could then react with the solvent to form the products shown above. Recently



it has been suggested¹⁴ that the mechanism involves attack by a proton on a peripheral bond in the plane of the ring involved; the products being derived from the cyclopropylcarbinyl cation formed. Methanol also adds to bicyclobutanes giving products which indicate the intermediacy of an ion possibly similar to (8).¹⁶ The more strained the bicyclobutane is the faster is the rate of addition of methanol. The very strained bicyclobutane (9) rearranges even in the presence of .01M sodium methoxide to give the ether (10).¹⁷

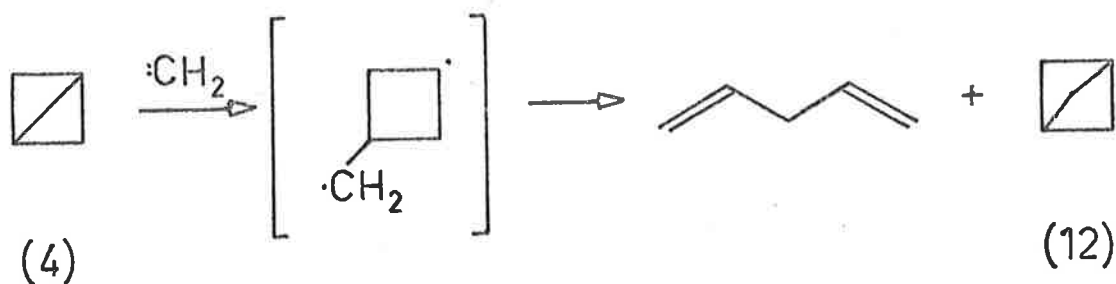


Many reactions of the strained ring system involve the addition of electrophilic reagents to the bridgehead bond. Iodine adds to bicyclobutane giving cis-1,3-diiodocyclobutane¹¹ and methyl bicyclobutane-1-carboxylate polymerises again through the reaction of the bridgehead bond.¹¹ On hydrogenation this ester (11) readily takes up two moles of hydrogen.¹¹ The product, methyl 2-methylbutyrate, results



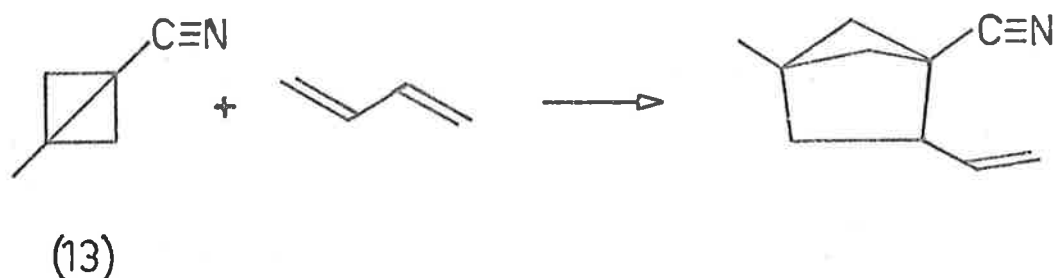
from cleavage of the bridgehead and a peripheral bond. Many other bicyclobutanes behave similarly.

The addition of methylene to bicyclobutane gives 1,4-pentadiene and a trace of bicyclo[1.1.0]pentane (12). A two-step



mechanism involving a diradical intermediate has been postulated.¹¹

The bridgehead bond is also susceptible to [2+2] cycloadditions of the type shown for 3-methylbicyclobutane-1-nitrile (13). This reaction



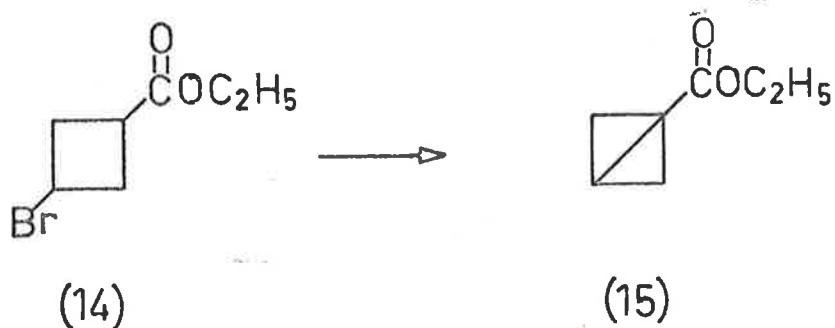
also appears to involve a diradical intermediate.¹⁸

Data on all these reactions are still limited however, and generalisations are difficult. For example the reaction of chlorine with bicyclobutane gives 2-chlorocyclopropylmethyl chloride in contrast to the reaction with iodine and 3-methylbicyclobutane-1-carboxylate (11) does not undergo the cycloaddition reactions shown by the nitrile (13).⁹

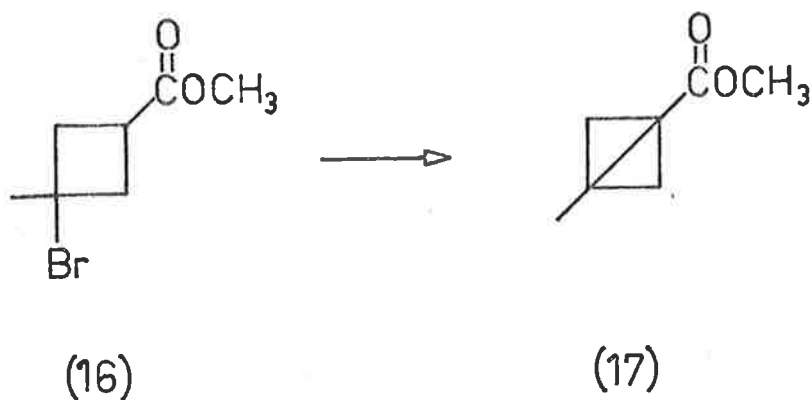
Although the bicyclobutane ring is so reactive, reactions can still be carried out in its presence provided acidic conditions and high temperatures are avoided. Thus the nitrile (13) can be converted to an amine by lithium aluminium hydride or to an amide by basic hydrogen peroxide without affecting the ring.¹⁹ The bridgehead hydrogens can also be removed with a base such as butyl-lithium. Their acidity has been related to the considerable (40%) s-character

of the C-H bond as indicated by the C^{13} -H spin-spin coupling constant.²⁰

A variety of methods have been reported for the synthesis of the bicyclobutane ring. The first authentic bicyclobutane, ethyl bicyclobutane-1-carboxylate (15) was prepared²¹ by the base-catalysed elimination of bromide from ethyl 3-bromocyclobutanecarboxylate (14).

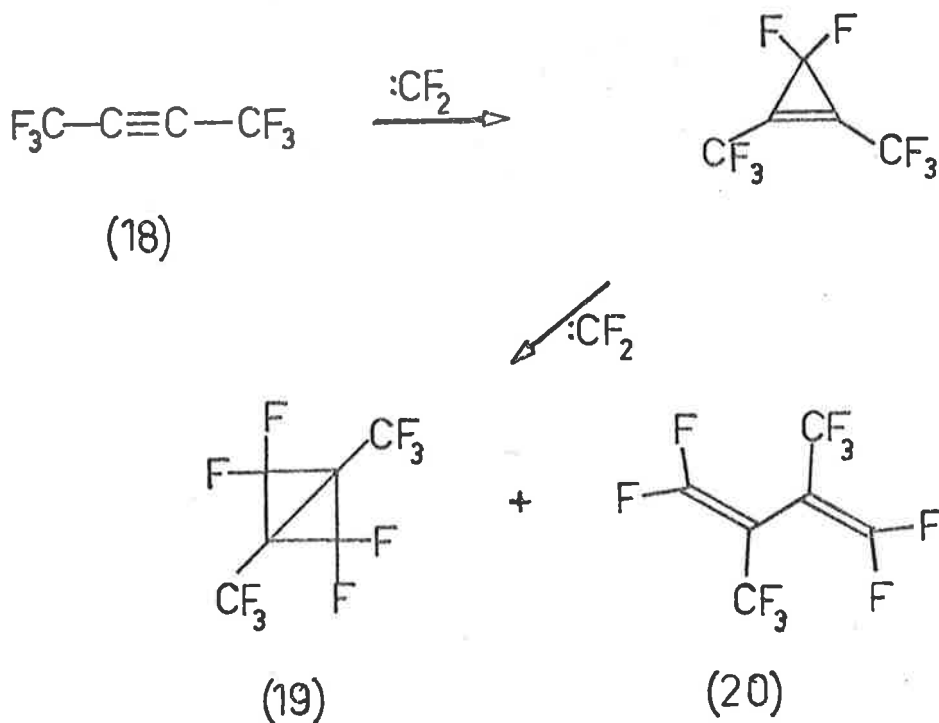


Later reactions using sodium hydride as base and the methyl ester have given yields of 77% for this reaction.¹¹ The tertiary bromide (16) gives a 90% yield of the bicyclobutane (17) under these conditions.¹¹

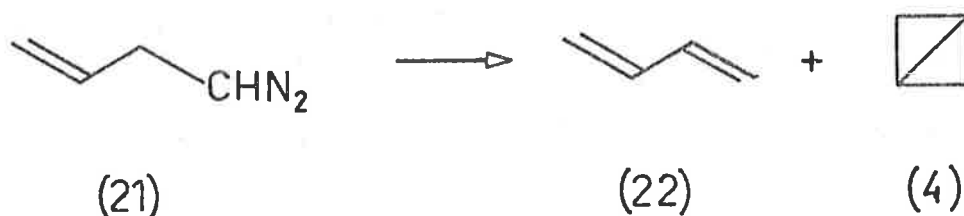


When a nitrile group is in the place of the ester group in (16) this type of reaction also proceeds in high yield.¹⁹

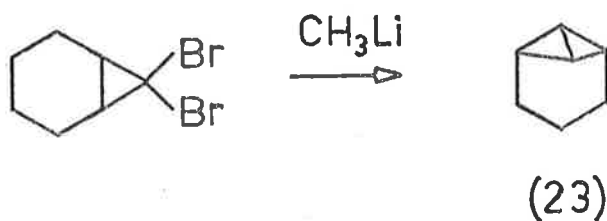
Intermolecular or intramolecular addition of a carbene intermediate to an unsaturated bond has been used widely for the synthesis of bicyclobutanes. The reaction of difluorocarbene with hexafluorobut-2-yne (18) proceeds in a stepwise manner to produce the bicyclobutane (19). Some of the diene (20) derived from the pyrolysis of (19)



is also formed.²² The first report²³ of bicyclobutane (4) itself showed that it could be prepared by the photolysis of allyldiazomethane (21). Butadiene (22), which is the main product, results

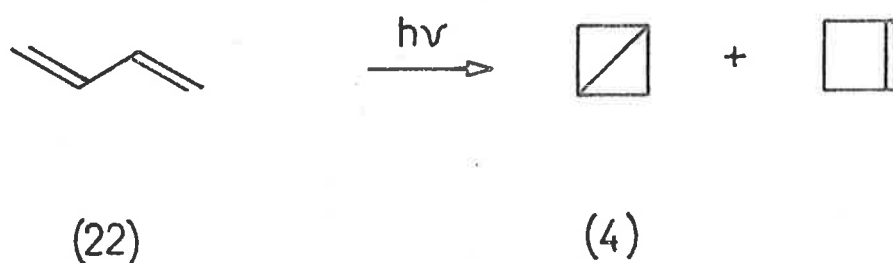


mainly from 1,2-hydrogen migration in the carbene intermediate rather than from bicyclobutane (4). The insertion of a carbene into a C-H bond has also been used for the synthesis of bicyclobutane derivatives as shown for the preparation of the bicyclobutane (23).²⁴

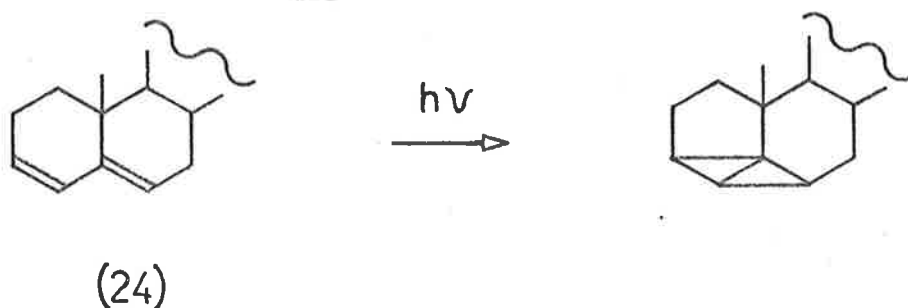


The reaction of cyclopropanecarboxaldehyde tosylhydrazone with base²⁵ and the deamination of cyclobutylamine with nitrous acid²⁶ both lead to bicyclobutane (4) but a simple carbonium ion is apparently not an intermediate. The mechanism has been discussed by Wiberg.⁹

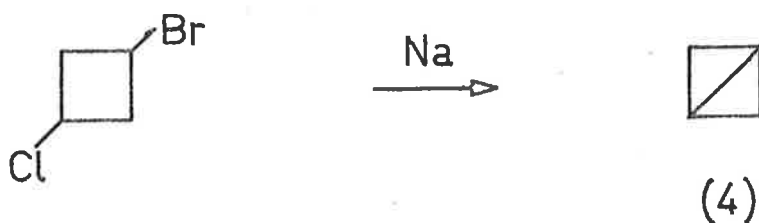
Bicyclobutane (4) is a product of the photolysis of butadiene (22). The major product from this reaction is cyclobutene. Cuprous chloride improves the yield of (4) apparently due to the formation of



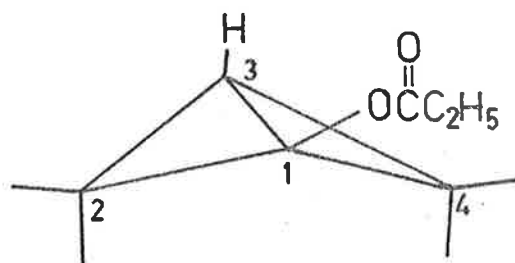
a complex with the diene which has a favourable conformation for the cyclisation to occur.²⁷ When the conformation of the double bonds is fixed in a favourable position as in the steroid (24) the copper salt is not needed.²⁸



Probably the best method for preparing bicyclobutane (4) is the intramolecular Würtz-type reaction shown below.²⁹ The electrochemical reductions of several similar dihalogenocyclobutanes³⁰ and of a dicarboxylic acid³¹ have been reported.



In proposing a scheme for the synthesis of the sex-attractant of the American cockroach (1) two specific problems had to be taken into account. These were the introduction of methyl groups at the

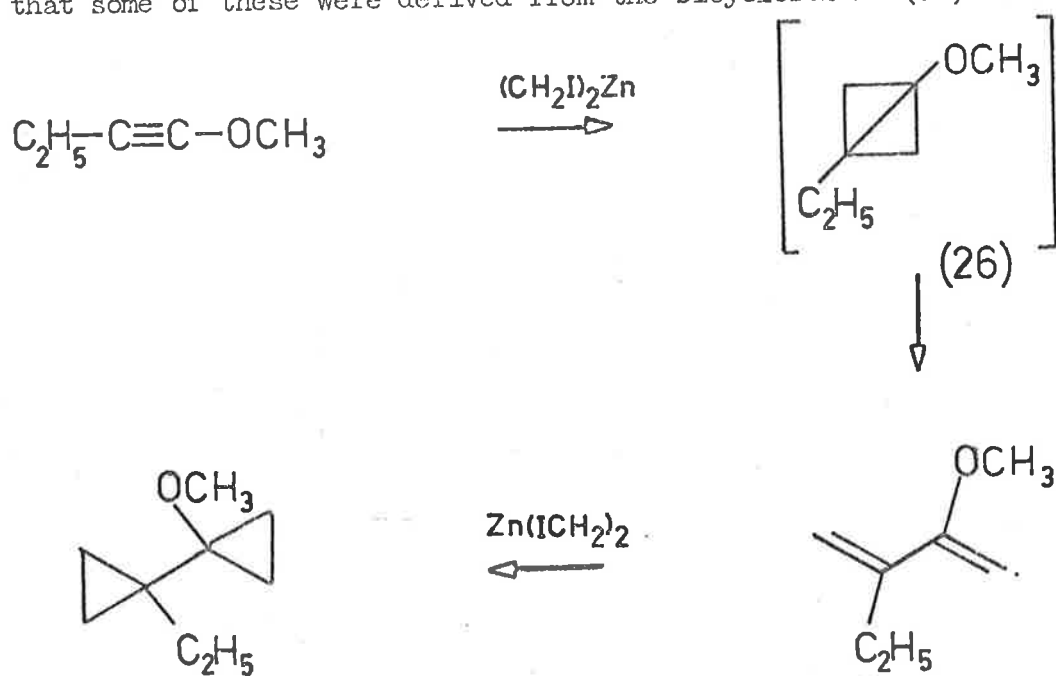


(1)

2- and 4-positions and the oxygen function at the bridgehead. An examination of models reveals that the two endo substituents bear a pseudo 1,3-diaxial relationship to each other if the geometry reported⁸ for bicyclobutane is considered. The greater steric bulk of methyl groups compared to hydrogens might be expected to cause an increase in the strain energy of the molecule due to non-bonded interactions. The activation energy for the pyrolysis of bicyclobutane has been estimated to be 4.1 kcal/mole³² so that the interactions would have to be considerable to cause the molecule to be unstable. Recently several 2,2,4,4-tetramethylbicyclobutanes have been reported from these laboratories^{6,33,34} and others^{30,35,36} showing that this non-bonded interaction is not critical to the stability of the molecule.

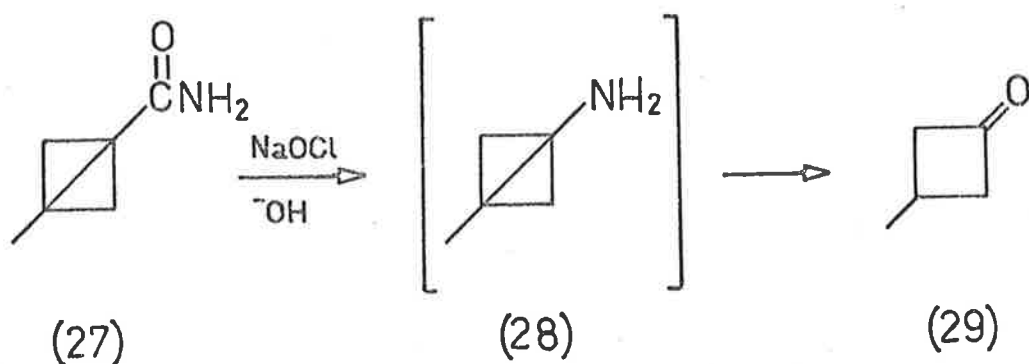
No bicyclobutanes with angular heteroatom functions have been isolated although some pertinent experiments have been reported.

Jautelat and Schwarz³⁷ allowed 1-methoxybut-1-yne (25) to react with iodomethylzinc and obtained a mixture of products. They concluded that some of these were derived from the bicyclobutane (26) with an

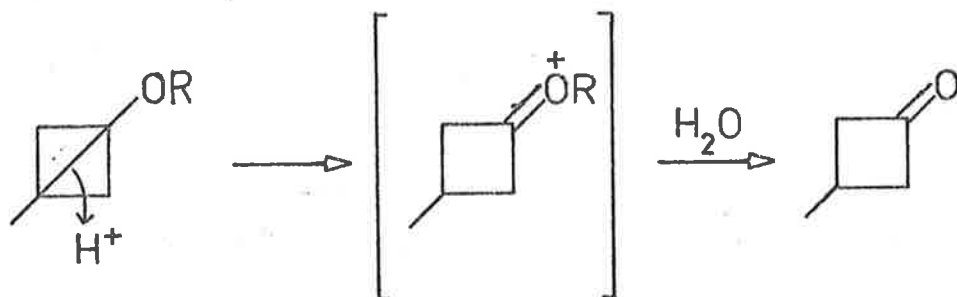


angular oxygen function, which was unstable under the conditions of the reaction.

Blanchard and Cairncross¹⁹ tried to convert 3-methylbicyclobutanecarboxamide (27) to the amine (28) by a Hofmann reaction but

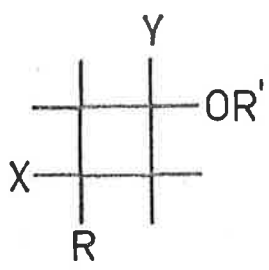


instead obtained 3-methylcyclobutanone (29). They postulated that the aminobicyclobutane (28) hydrolysed in a reaction analogous to the hydrolysis of an enamine. A bicyclobutane with an angular oxygen function might behave like an enol ether. The oxygen function might be expected to enhance the rate of addition of water to the bridgehead bond due to the participation of the lone pair of electrons on the oxygen. Enol ethers are only hydrolysed in the presence of acid.



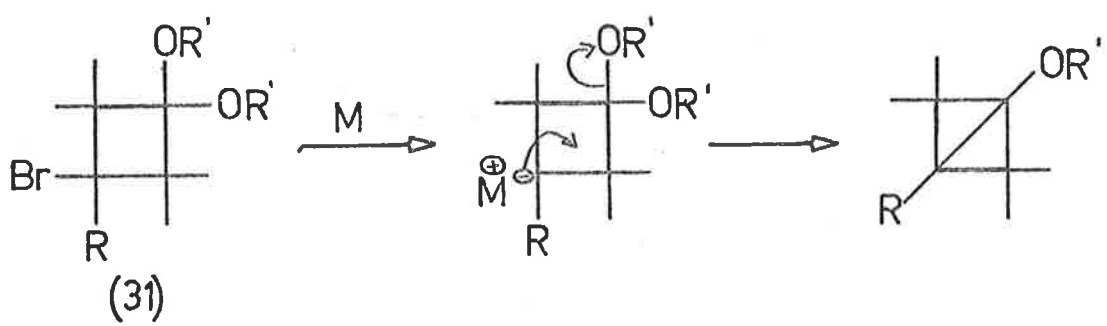
Strained bicyclobutanes have been shown to react with methanol even in the presence of base.¹⁷ A bicyclobutane with an angular oxygen function might therefore be hydrolysed in the presence of acid or base.

A synthetic approach which seemed promising for the preparation of bicyclobutanes with angular oxygen functions involved obtaining a tetramethylcyclobutane (30) with a group X such that an anion could be generated and a group Y which could be expelled intramolecularly by the anion leaving an oxygen function -OR'. It was proposed that the anion would be generated by the reaction of an alkyl bromide with a metal such as lithium or magnesium. The leaving group Y which could



(30)

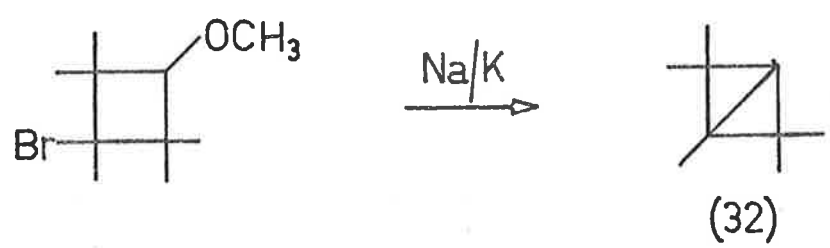
most easily be prepared was another oxygen function. Thus a bromo-ketal similar to (31) was required. This reaction would require the



(31)

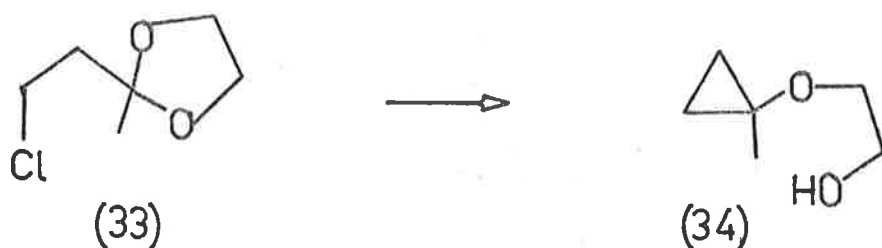
displacement of an alkoxide ion which is a poor leaving group.³⁸

Bicyclobutanes had not been synthesised by the elimination of a poor leaving group such as an alkoxide ion when this project was commenced but a report from these laboratories³⁴ has since shown that such a synthesis is possible. Pentamethylbicyclobutane (32) was prepared by the reaction shown.

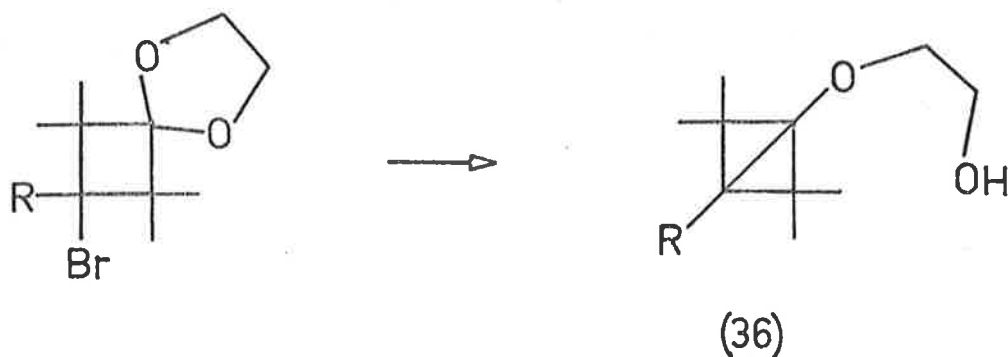


(32)

The reaction of halogenoketals with a metal has been reported. Feugeas³⁹ has prepared cyclopropyl ethers by allowing β -chloroketals to react with magnesium in tetrahydrofuran (T.H.F.) as solvent. The ketal (33) gives a 63% yield of the cyclopropyl ether (34). The

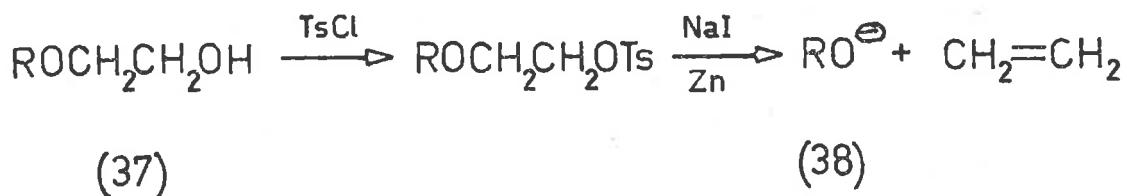


mechanism of this reaction presumably involves the formation of an alkylmagnesium complex which attacks the electron deficient β -carbon. This reaction has been applied to the synthesis of cyclobutyl and cyclopentyl ethers and also enol ethers. It seemed reasonable to anticipate that it might be applicable to the synthesis of bicyclobutyl ethers (Scheme 1). Johnson⁴⁰ has shown that molecules such as



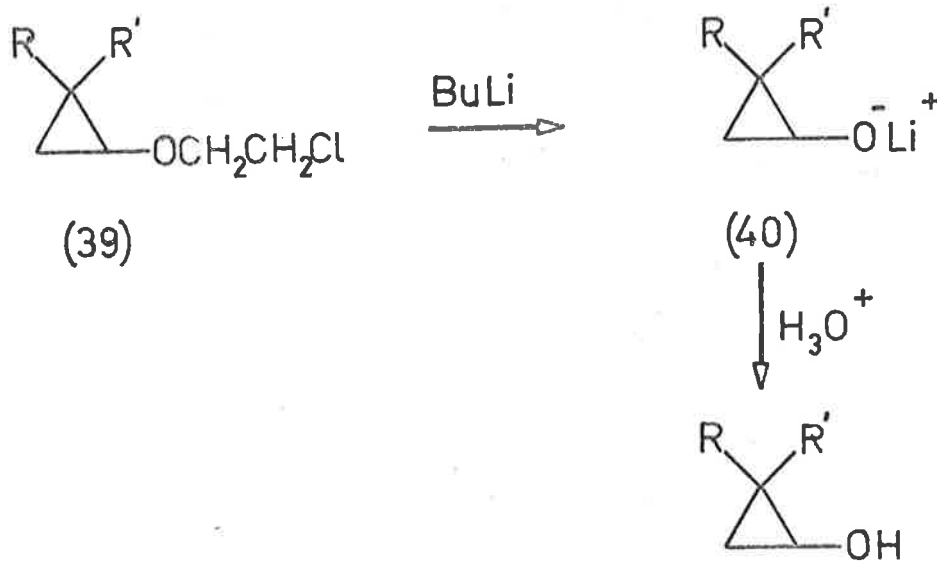
Scheme 1.

(37) can be converted to an alkoxide (38) by the reactions shown in Scheme 2. Other workers⁴¹ have reported that β -chloroethyl cyclopropyl



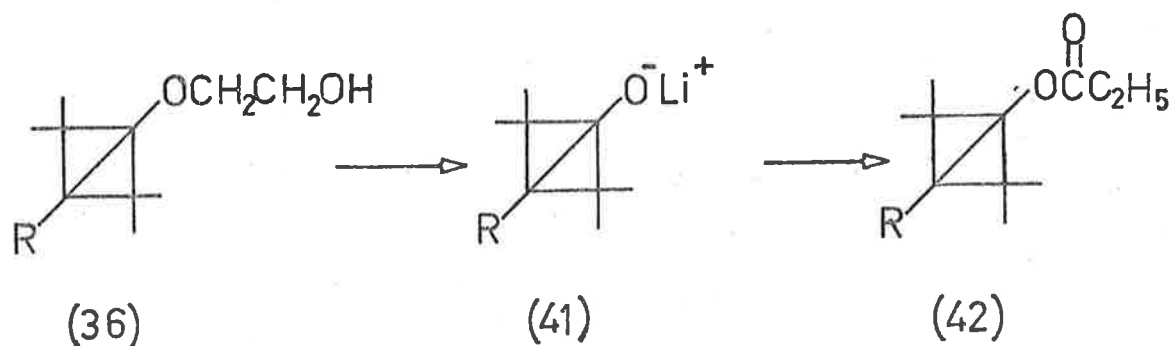
Scheme 2.

ethers (39) can be converted to cyclopropoxides (40) (Scheme 3). It

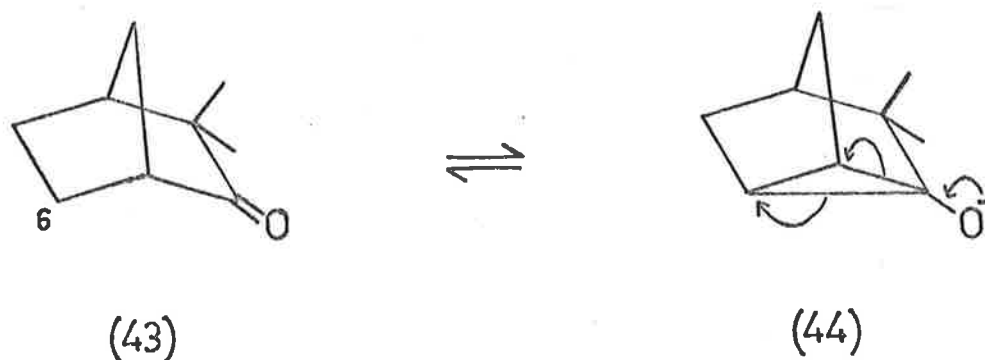


Scheme 3.

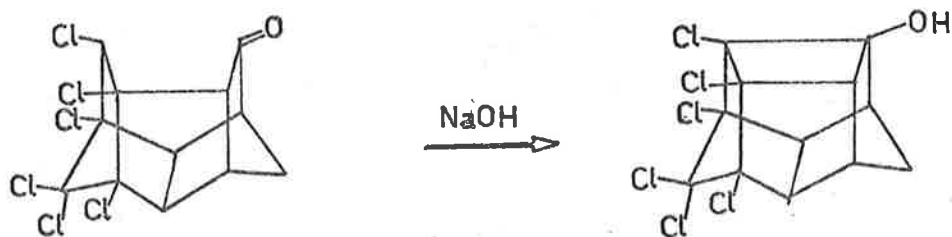
was anticipated that none of these reactions involved conditions which might decompose the bicyclobutane ring and thus, in principle, it should be possible to convert a bicyclobutane such as (36) to an alkoxide (41). Treatment of (41) in situ with propionic anhydride might lead to the structure suggested for the sex-attractant (42, R=H).



The anion (41) may be classified as a homoenolate ion.⁴² Nickon⁴³ has shown that optically active camphenilone (43) is racemised by strong base at elevated temperatures. The mechanism postulated involves abstraction of a proton from the 6-position forming an

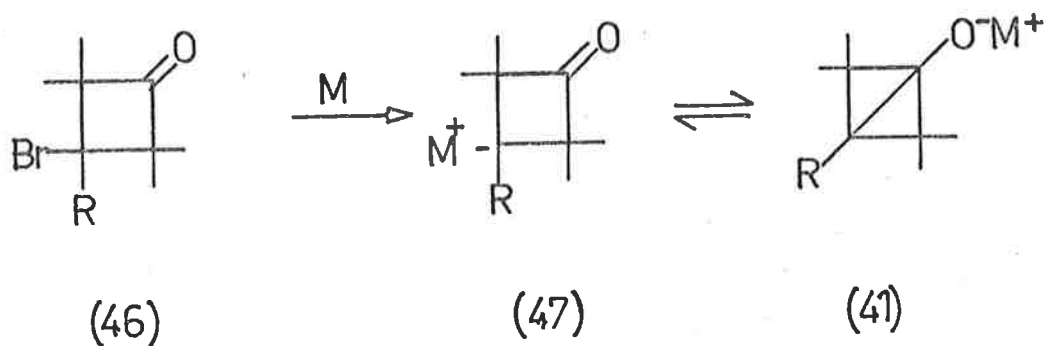


anion which interacts with the β -carbonyl group forming the symmetrical ion (44). This ion can rearrange in two ways leading to racemic starting material. Another reaction which shows the interaction of an anion with a carbonyl group is the cyclisation of the bird-cage compound (45).⁴⁴ This reaction indicates that the geometrical relationship between the carbon bearing the acidic hydrogen and the carbonyl group



(45)

is a key factor in these reactions.⁴³ Support for this hypothesis is given by the work of Gassman and Zalar⁴⁵ who found that certain norbornanones do not undergo homoenolisation. A three-membered ring might be expected to form fairly readily by this type of reaction in an acyclic molecule or in a 1,3-reaction across a cyclobutane ring because of the favourable probability factor.⁴⁶ It was proposed that if a molecule such as (46) could be prepared then by allowing it to react

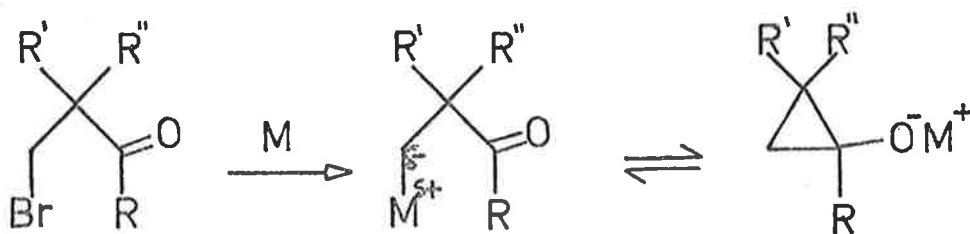


Scheme 4.

with a metal such as lithium, the anion (47) might be formed (Scheme 4). This ion might be in equilibrium with the cyclic anion (41) which had been proposed as an intermediate in the first approach to the sex-

attractant (1). It seemed reasonable to assume that acylation of an equilibrium mixture of the anions (47) and (41) might be favoured on oxygen⁴⁷ particularly as approach to the anion (47) might be hindered due to the vicinal methyl groups.

It had been shown that lithium propoxides (40) could be protonated on oxygen producing cyclopropanols.⁴¹ As a model for the synthesis of bicyclobutanes with angular oxygen functions it was decided to synthesise β -bromocarbonyl compounds and see if cyclopropyl derivatives could be obtained by allowing them to react with a metal and acetylating the anion produced (Scheme 5). The difference in



Scheme 5.

strain energy between a bicyclobutane and a cyclobutane is about 40 kcal/mole while that between a cyclopropane and a propane is about 27 kcal/mole.⁴⁸ There might be expected to be less loss of entropy in forming a bicyclobutane from a cyclobutane than in forming a cyclopropane from a propane. Thus, on a semiquantitative basis, if it is possible to

synthesise cyclopropyl derivatives by the reaction shown in Scheme 5 it might be possible to prepare bicyclobutanes by the reaction of a 3-bromocyclobutanone (46) with a metal (Scheme 4).

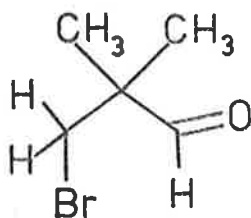
It is the purpose of this thesis to describe the work carried out in relation to the approach to cyclopropyl derivatives outlined in Scheme 5 and then in relation to the two basic approaches to bicyclobutanes with angular oxygen functions outlined in Schemes 1 and 4.

RESULTS AND DISCUSSION

THE REACTION OF LITHIUM WITH CERTAIN β -BROMOCARBONYL COMPOUNDS.

1.1 3-Bromo-2,2-dimethylpropan-1-al.

The title compound (48) was chosen as the most suitable for reaction with lithium. It possesses gem-dimethyl groups which prevent

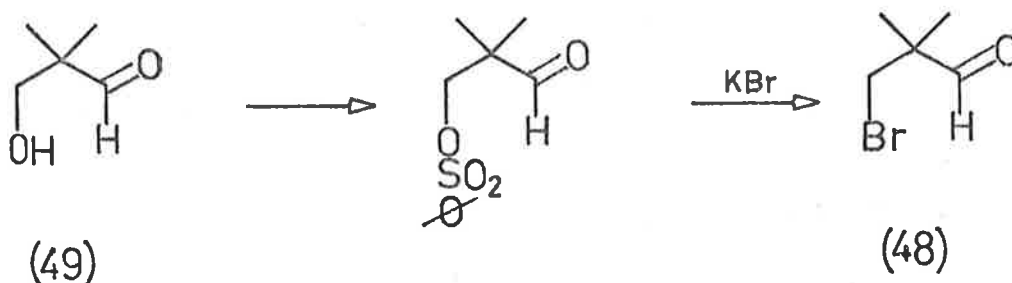


(48)

enolisation of the carbonyl group and thus the otherwise facile loss of hydrogen bromide.⁴⁹ The aldehydic carbonyl group is more susceptible to nucleophilic attack than a ketone carbonyl group and is likely to form a greater amount of cyclic addition compound in an equilibrium reaction.⁵⁰

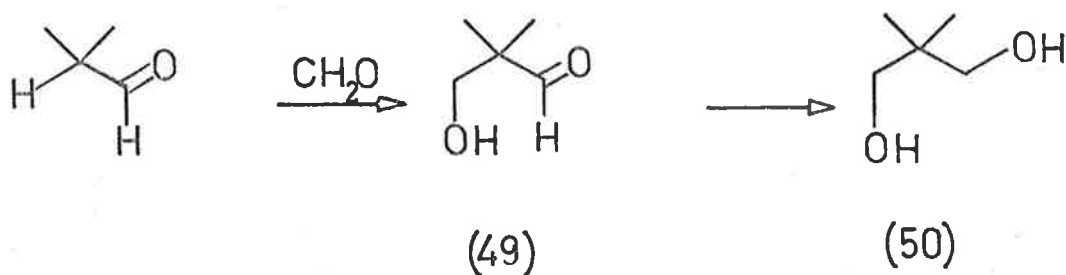
At the start of this work only one report of this compound was found in a literature survey. Russian workers⁵¹ had prepared it in poor yield by treatment of the benzenesulfonate derivative of 3-hydroxy-2,2-dimethylpropan-1-al (49) with aqueous potassium bromide. The liquid trimerised readily preventing its complete characterisation.

Nerdel⁵² reported the preparation of a series of β -iodoaldehydes by a similar method and on the basis of this work it was decided to prepare the aldehyde (48) from the hydroxyaldehyde (49) by tosylation



and replacement of the tosyl group with a bromide in a dipolar aprotic solvent.⁵³

The hydroxyaldehyde (49) is an interesting compound which presented some difficulties in its preparation. Wessely⁵⁴ first prepared it in 1900 by an aldol condensation between formalin and isobutyraldehyde as shown in the scheme below. Stiller⁵⁵ could not repeat this

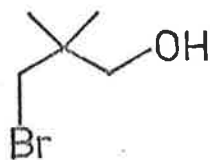


work but prepared (49) in "good yield" by a modified procedure using potassium carbonate as base. Späth⁵⁶ later repeated Wessely's original method and reported that the hydroxyaldehyde (49) existed as a dimer (m.p. 89°) which could be converted to the monomer (m.p. 24°) by distillation. The monomer was found to dimerise in about two hours at room temperature.

Difficulty was experienced in obtaining reproducible results from Stiller's method. On occasions the hydroxyaldehyde (49) was obtained in yields of up to 70%, while on others no reaction occurred. This difficulty was probably due to the mixture of reactants being heterogeneous. On several occasions 2,2-dimethylpropan-1,3-diol (50) was obtained, presumably as the result of a Cannizzaro reaction between the hydroxyaldehyde (49) and formaldehyde. This is the normal method of preparation of this diol.⁵⁷

While this work was in progress a report appeared of a patented method for the preparation, in 99% yield, of the hydroxyaldehyde (49) using a basic ion-exchange resin in the carbonate form.⁵⁸ Attempts to adapt this method to a laboratory preparation were unsuccessful. The highest yield of the hydroxyaldehyde (49) realised was only 25% of the theoretical yield.

At this stage it was decided to try an alternative approach to the bromoaldehyde (48). The approach adopted involved oxidation of the known 3-bromo-2,2-dimethylpropanol (51).⁵⁹ The prevention of



(51)



(52)

further oxidation of the aldehyde was seen as a difficulty in this approach.⁶⁰ Oxidation of the alcohol (51) by the methods of Jones⁶¹ and Sarett⁶² gave oils whose infrared spectra showed broad absorptions in the region near 1700 cm^{-1} . The reaction of dimethyl sulfoxide and acetic anhydride⁶³ with the alcohol (51) gave an oil whose infrared spectrum showed no sign of the absorptions expected for the aldehydic C-H stretching ($\text{c. } 2720\text{ cm}^{-1}$).⁶⁴ Meinwald⁶⁵ has reported similar difficulty in the oxidation of the neopentyl alcohol (52).

The aldehyde (48) was finally obtained in 50% yield by the use of the oxidation procedure of Barton.⁶⁶ This method involves the treatment of the chloroformate ester of an alcohol with dimethyl sulfoxide to give an intermediate which eliminates carbon dioxide. The reaction of the intermediate formed with a base such as triethylamine gives the aldehyde. The mechanism, as suggested by Barton, is outlined in the following scheme.

The adaption of this highly exothermic reaction to a preparative scale was only successful when the temperature was strictly maintained at about 5°C during the addition of dimethyl sulfoxide. The product was obtained as an oil (b.p. $62\text{-}68^{\circ}/23\text{ mm}$). Its structure was confirmed by its infrared spectrum which showed absorptions at 1740 and 1250 cm^{-1} (carbonyl group), 2820 and 2720 cm^{-1} (aldehyde C-H), and 660 cm^{-1} (C-Br) and by its nuclear magnetic resonance (n.m.r.) spectrum which is recorded in Table 1.

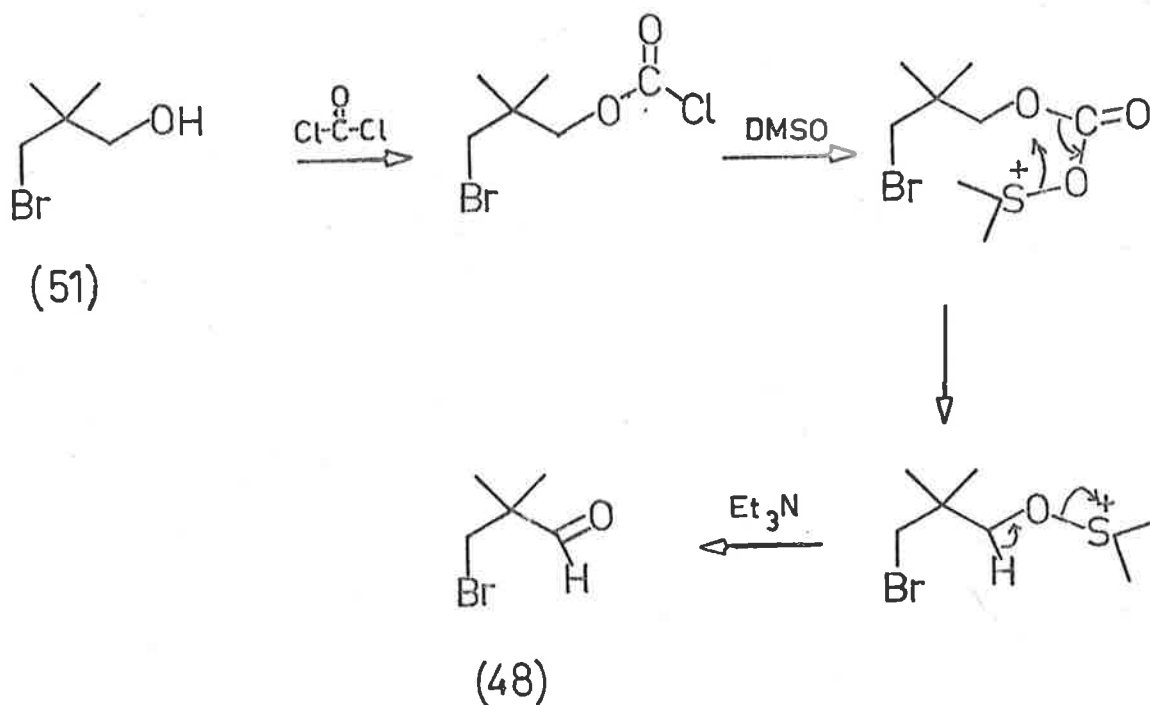
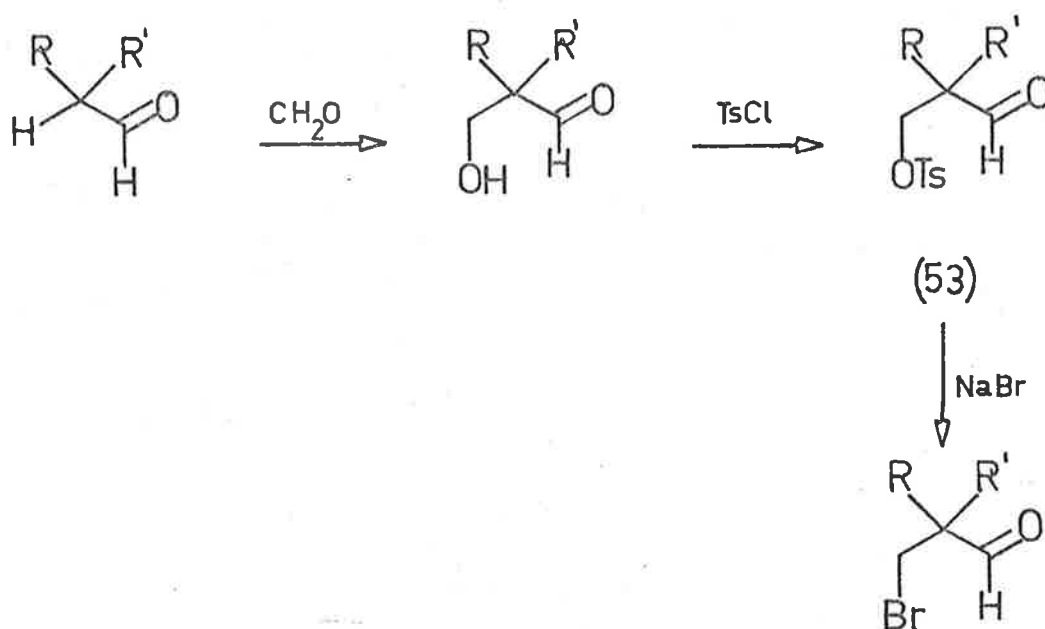


Table 1.

N.m.r. spectrum (CCl_4) of 3-bromo-2,2-dimethylpropan-1-al.

δ (p.p.m.)	Appearance	Proton Count	Assignment
1.18	singlet	6	gem-Me ₂
3.37	singlet	2	-CH ₂ Br
9.40	singlet	1	-CHO

Recently Nerdel and co-workers⁶⁷ have given details of the preparation of the tosylaldehyde (53, R = R' = Me) required as a precursor of the bromoaldehyde (48) in the first route. It has been

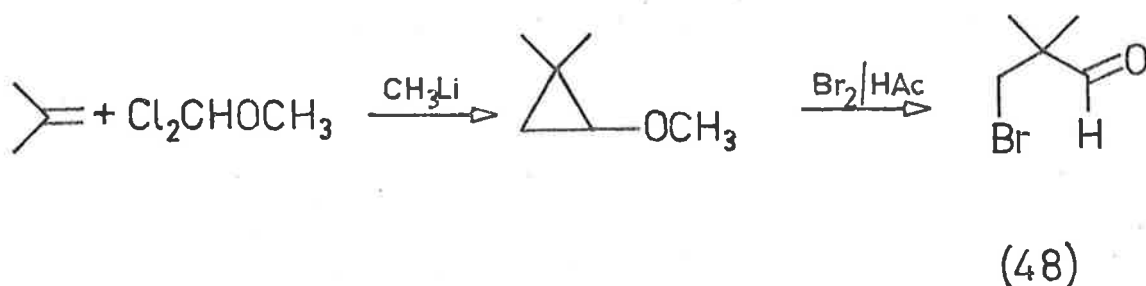


Scheme 6.

possible to convert this tosylaldehyde to the bromoaldehyde (48) in a 69% yield by means of sodium bromide in dimethyl sulfoxide. As a number of tosylaldehydes have been prepared by the route outlined in Scheme 6,⁶⁷ it seems likely that a number of bromoaldehydes may now also be accessible by the reaction of sodium bromide with the appropriate tosylaldehydes. However the large scale chromatography required for the purification of the tosylaldehydes tends to make the method uneconomic.

After this work was completed a further reference to the preparation of the bromoaldehyde (48) was noted.⁶⁸ No details of

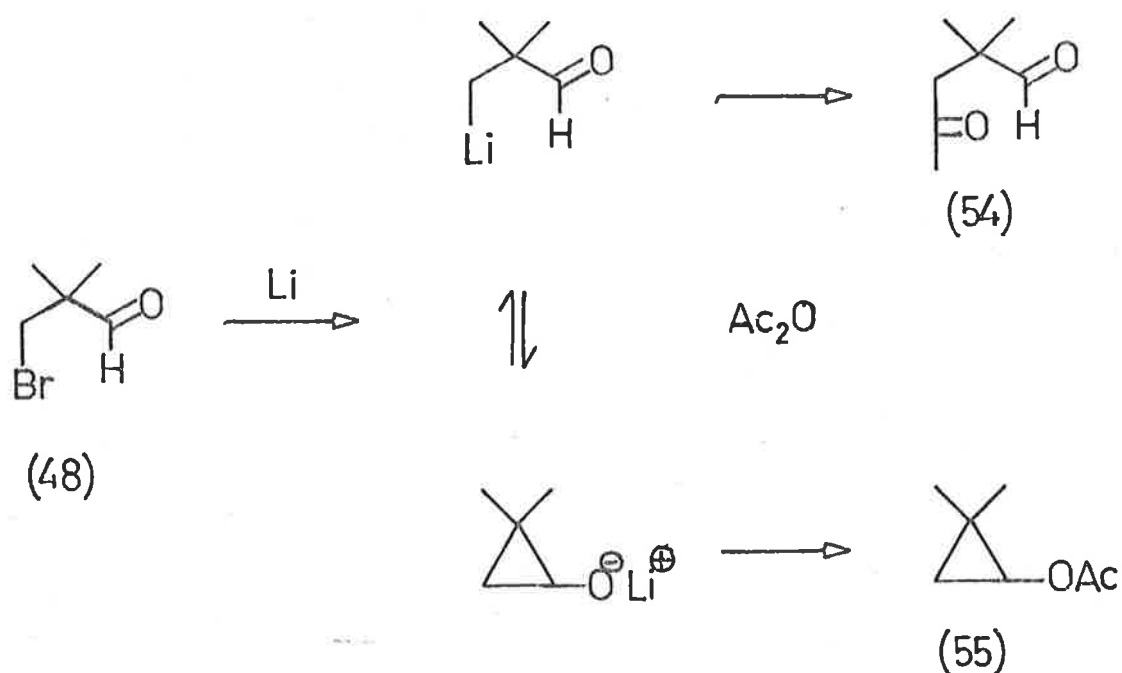
the preparation were given, but communication with the authors revealed that this is probably the best method for obtaining this compound. It involves addition of bromine, in acetic acid, to a cyclopropyl ether as outlined in Scheme 7.



Scheme 7.

The reaction of 3-Bromo-2,2-dimethylpropan-1-al with lithium.

It was envisaged that two products were possible from the acetylation of the anion derived from the reaction of the bromoaldehyde (48) with lithium; the acetylaldehyde (54) from acetylation on carbon and/or the cyclopropyl acetate (55) from acetylation on oxygen (Scheme 8). It was thought that the amount of intermolecular product which might also be formed could be reduced by carrying out the reaction in dilute solution. Slow addition of the bromoaldehyde, in ether, to a stirred suspension of finely cut lithium, in ether under nitrogen, at 10° during six hours and subsequent addition of the filtered solution to an excess of acetic anhydride gave, after work-up and distillation



Scheme 8.

(100°/26 mm) one volatile product in a 40-60% yield. Its infrared spectrum showed peaks attributable to the $-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$ group (1740 and 1230 cm^{-1}) and its n.m.r. spectrum (Table 2) was in accord with that expected for the cyclopropyl acetate (55).

The ring protons form an ABX system ($J_{\text{AX}} + J_{\text{BX}} = 10.5\text{ Hz}$). Due to the nature of the spectrum an accurate calculation of the three spin-spin coupling constants was not possible. The assignment of the structure was confirmed by an independent synthesis. The acylcyclopropane (56)⁶⁹ underwent a Baeyer-Villiger oxidation to yield the cyclopropyl acetate (55).

Table 2.

N.m.r. spectrum (CCl_4) of 2,2-dimethylcyclopropyl acetate.

δ (p.p.m.)	Appearance	Proton Count	Assignment
1.03	singlet	3	ring Me
1.05	singlet	3	ring Me
1.97	singlet	3	-O-COCH ₃
3.68	4 peaks (X)	1	>CHOCO-
0.34-0.72	6 peaks (A,B)	2	ring CH ₂

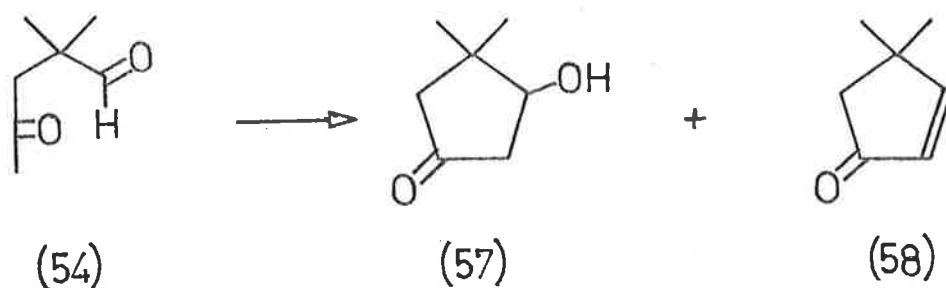


(56)



(55)

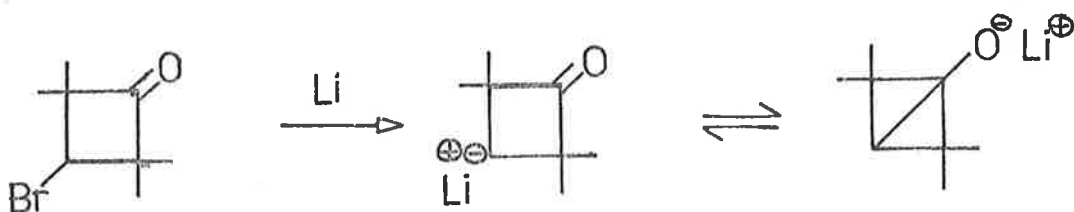
The remainder of the material from the lithium reaction was an intractable mixture of high boiling compounds. No peaks due to the C-acylated product (54) were detected in the n.m.r. spectrum of the product. The possibility that (54) cyclised as outlined below could not be ignored.⁷⁰ However, no peaks expected for the cyclic ketones (57) and (58) were observed in the n.m.r. spectrum of the product. After this work had been completed it was noted that 2,2-dimethylcyclopropanol had been prepared in 84% yield by the protonation of the anion



formed by this method.⁶⁸ The high yield suggests that the amount of intermolecular product formed, if any, is small.

1.2 3-Bromo-2,2-dimethylpropiophenone.

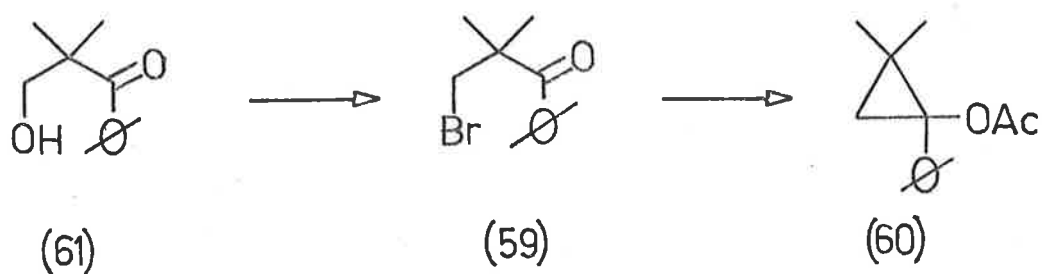
One of the proposed routes to the bicyclobutane skeleton involved the attack of an anionic species on a ketone carbonyl group (Scheme 4).



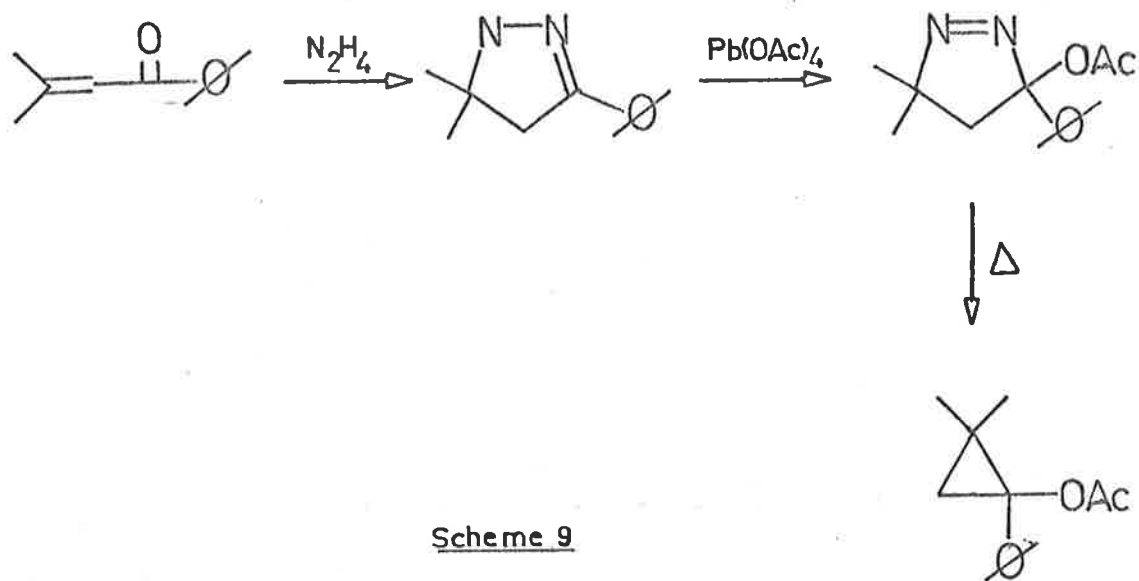
Scheme 4.

The preceding reaction was therefore extended to a β -bromoketone. The title compound (59) was chosen because it was anticipated that it could be readily synthesised. Further, the cyclopropyl acetate (60)

which would be expected to be produced from it was a known compound.⁷¹
The bromoketone (59) was prepared from the corresponding hydroxyketone (61)⁷² by the use of hydrogen bromide in ether.⁵¹



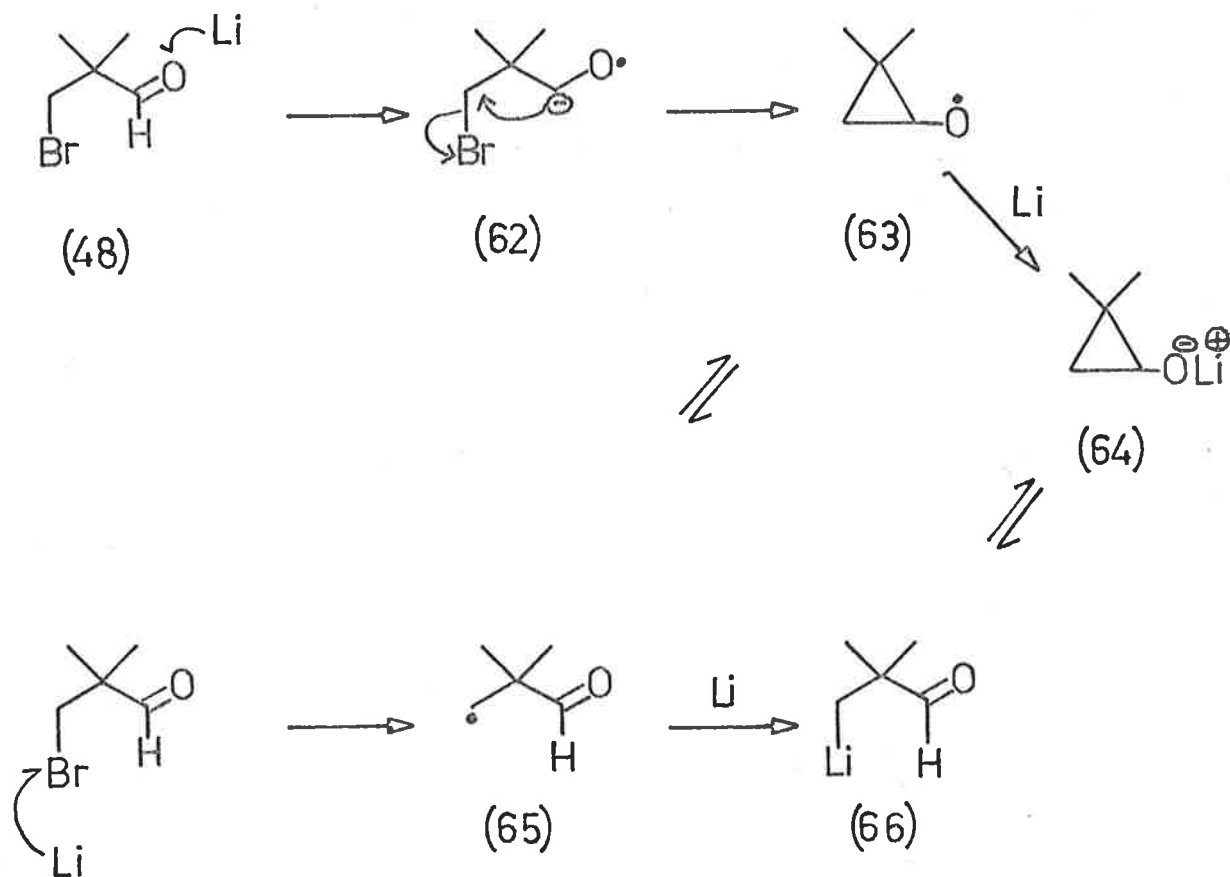
Treatment of the bromoketone (59) with lithium followed by the addition of acetic anhydride as described previously produced 2,2-dimethyl-1-phenylcyclopropyl acetate (60) in 40% yield. The structure of (60) was confirmed by comparison with an authentic sample which was synthesised by the literature procedure⁷¹ (Scheme 9).



Scheme 9

1.3 The mechanism of the cyclisation reaction.

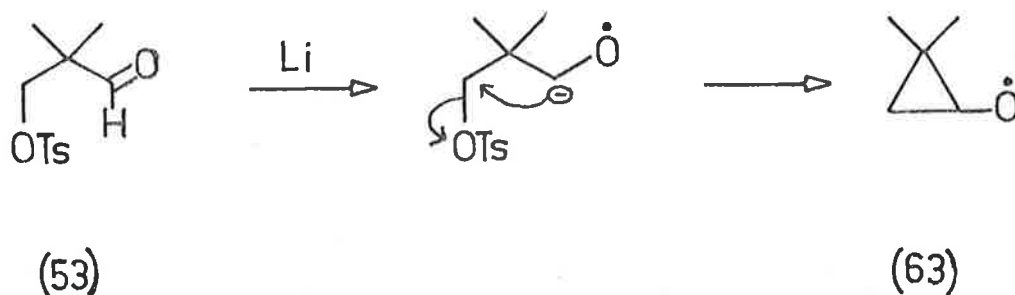
Several mechanisms are possible for this reaction. The lithium might be expected to reduce either the bromine or the carbonyl group. Available data on half-wave potentials⁷³ do not allow a distinction to be made. Reduction of the carbonyl group would give a radical anion (62) (Scheme 10) which could displace the bromine to form the cyclopropoxy radical (63). This could be reduced to the alkoxide (64).



Scheme 10.

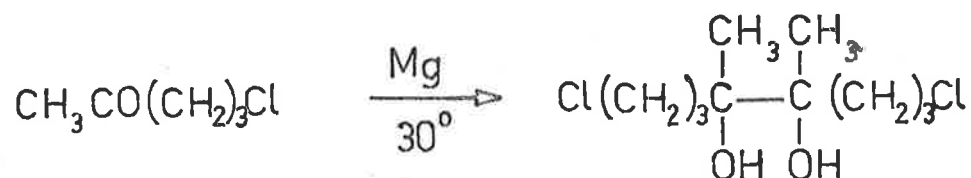
Reduction of the alkyl bromide with lithium could lead to the radical (65)^{74a,b} which could cyclise to (63)⁷⁵ or be reduced to the alkyl-lithium (66) which could cyclise to (64). Studies of the properties of radicals similar to (63) have shown that they readily ring open and form dimeric aldehydes.^{76,77} Because of the high yields of cyclised material obtained, the cyclopropoxy radical (63), if formed, must be very rapidly reduced to the alkoxide (64). It may account for some of the high boiling material obtained.

The reaction of the tosylaldehyde (53) with lithium under the conditions used for the bromoaldehyde (48) produced no reaction contrary to what might be expected if reduction of the carbonyl group was involved.^{78a,b}



Recently Leroux⁷⁹ has investigated the action of magnesium on certain γ - and δ -halogenated ketones. Good yields of cyclobutanols and cyclopentanols were obtained when tetrahydrofuran (T.H.F.) was used as the solvent. Ether was less satisfactory because of insolubility of the magnesium alkoxides. Dihalopinacols were always produced and became the major products when chloroketones or higher temperatures

were used (Scheme 11). Reduction of the carbonyl group rather than the alkyl halide is thus a possible path for these reactions.





Scheme 11.

Leroux found that the reaction was more complex when lithium was used as the metal. The products obtained were dependent on the temperature and the basicity of the solvent. The results for the reaction of lithium with 1-bromopentan-4-one are given in Table 3 and illustrate the complex nature of the reaction.

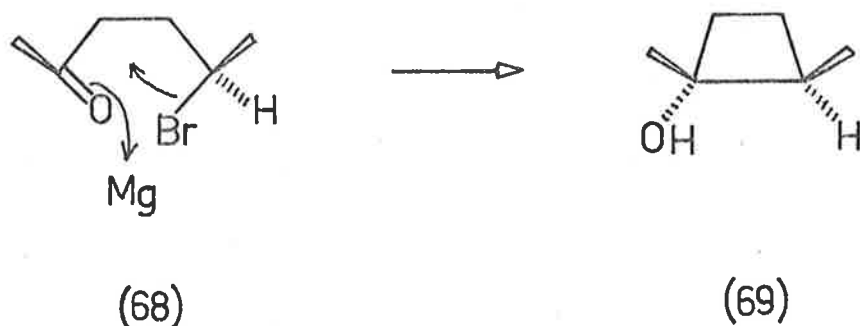
Table 3.

The reaction of lithium with 1-bromopentan-4-one.

Solvent	Temperature	Product	Yield
T.H.F. + H.M.P.T.*	ambient		major product
ether	-10 → +10°C		30%
ether	-10°C	$\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2\text{CH}_2\text{CH}_3$	25%

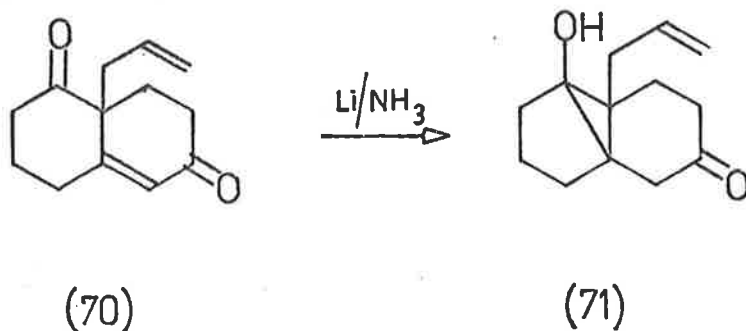
* hexamethylphosphoramide.

From a study of the stereochemistry of the products Leroux concluded that the reaction occurs on the surface of the metal. Thus, the γ -bromoketone (68) produces cis-1,2-dimethylcyclobutanol (69).

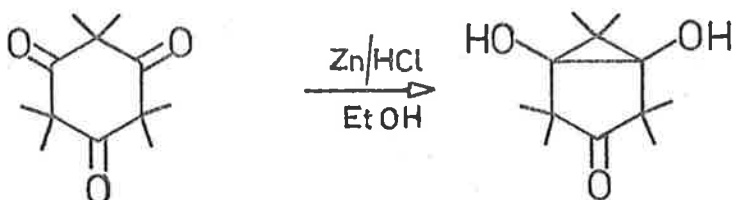


Very recently Corey and co-workers⁸⁰ have synthesised cyclopentanol and cyclohexanol derivatives by the reaction of δ - and ϵ -haloketones with certain anionic transition metal complexes. A similar dependence on temperature and solvent for this reaction was noted.

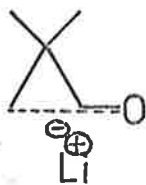
Several other papers have appeared^{81,82,83} which describe the intramolecular attack of an anionic species on a β -carbonyl group forming a cyclopropanol derivative or intermediate. Thus, the ketone (70) forms the tricyclic compound (71) on treatment with lithium in liquid ammonia.⁸¹ Related cyclisations of the type shown below⁸⁴ also



illustrate that the formation of strained three-membered ring oxygen derivatives is a favoured reaction.



The question arises as to the nature of the intermediate lithium anion. It may exist as an equilibrium mixture of the two anions (66) and (64) or as a delocalised anion (67), subsequent acylation being kinetically controlled on oxygen in each case.



(67)

In order to investigate the nature of the anion involved in the formation of the cyclopropyl acetates the n.m.r. spectra of the appropriate solutions were investigated. The anions were generated using dimethoxyethane (D.M.E.) as solvent. Spinning side bands and C^{13} -H satellite peaks are not a problem above $\delta 1.7$ and below $\delta 5.0$ with this solvent. Absorptions were taken relative to the two

dimethoxyethane absorptions which were assigned the values $\delta 3.25$ and $\delta 3.42$. Benzene, which would have allowed a more useful region of the spectrum to be observed, could not be used as a solvent because lithium did not react appreciably with the bromoaldehyde (48) in it. This may have been due to the precipitation of insoluble lithium salts on the surface of the metal. The results of this investigation are tabulated below (Tables 4-6). Accurate integration of the absorptions was difficult, probably due to the effect of having suspended solids in the samples.

Table 4.

N.m.r. spectrum (D.M.F.) of the anion produced from the reaction of 3-bromo-2,2-dimethylpropan-1-al with lithium.

δ (p.p.m.)	Appearance	Proton Count	Assignment
1.07	singlet	3	MeB
0.83	singlet	3	MeA
0.80	shoulder	-	impurity
-0.27 - + 0.13	broad multiplet	2	Ha, Hb

Table 2. N.m.r. spectrum (CCl_4) of 2,2-dimethylcyclopropyl acetate.

1.03	singlet	3	ring Me
1.05	singlet	3	ring Me
1.97	singlet	3	-OCOMe
3.68	4 peaks (X)	1	>CHOCO-
0.34 - 0.72	6 peaks (A,B)	2	ring CH_2

Table 5.

N.m.r. spectrum (D.M.E.) of the anion produced from the reaction of 3-bromo-2,2-dimethylpropiophenone with lithium.

δ (p.p.m.)	Appearance	Proton Count	Assignment
7.15-7.67	multiplet	5	aromatic C-H
1.27	broad singlet	3	MeB
0.63	broad singlet	3	MeA
0.17	broad multiplet	2	Ha, Hb

Table 6.

N.m.r. spectrum (CCl_4) of 2,2-dimethyl-1-phenylcyclopropyl acetate.

δ (p.p.m.)	Appearance	Proton Count	Assignment
7.10-7.47	multiplet	5	aromatic C-H
1.90	singlet	3	$-\text{OCOCH}_3$
1.30	singlet	3	ring Me
0.80	singlet	3	ring Me
1.10*	multiplet	2	ring CH_2

* see ref. 71 for a discussion of this absorption.

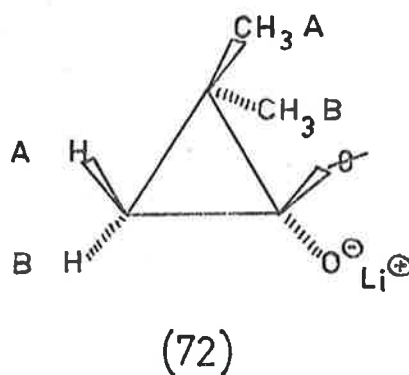
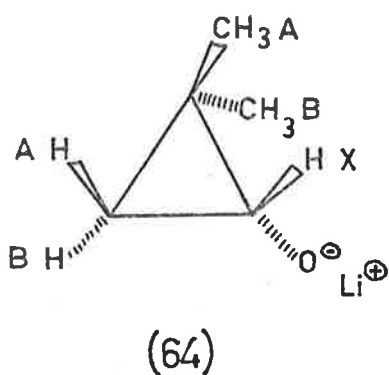
No absorption due to an aldehydic proton could be detected in the spectrum of the anion detailed in Table 4. Addition of deuterium

oxide to the n.m.r. sample of this anion caused the spectrum to alter. The new spectrum was similar to that reported for 2,2-dimethylcyclopropanol⁶⁸ in having peaks in the region $\delta 0.1-0.4$. Addition of acetic anhydride to an n.m.r. tube containing the anion also caused the spectrum to alter. The new spectrum, in the regions not obscured by the absorptions of the solvent, was similar to that of 2,2-dimethylcyclopropyl acetate (Table 2). That the compound was in fact this acetate was confirmed by its isolation and the comparison of its spectral data with that of an authentic sample. The peak in the spectrum of the anion (Table 4) at $\delta 0.8$ did not alter on the addition of deuterium oxide or acetic anhydride and was presumably due to an impurity.

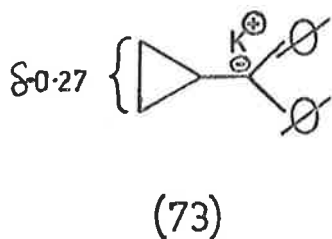
Addition of acetic anhydride to the n.m.r. tube containing the anion produced from the bromoketone (59) caused the spectrum detailed in Table 5 to alter. It was shown that the new spectrum was due to 2,2-dimethyl-1-phenylcyclopropyl acetate by a comparison of its spectral data with that of an authentic sample (Table 6).

The lack of an absorption due to an aldehydic proton in the spectrum of the anion produced from 3-bromo-2,2-dimethylpropan-1-al and the relative simplicity of both spectra suggests that the anions exist predominantly in the cyclic forms (64) and (72).

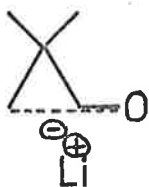
The absorptions due to the ring protons are shifted upfield from their positions in the acetates suggesting that the lithium-oxygen bond is polar in nature, some of the negative charge on the



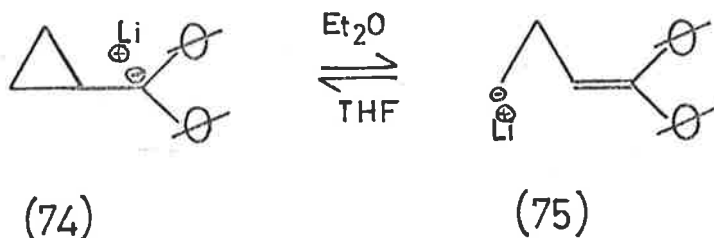
oxygen being delocalised over the ring. A similar upfield shift has been noted for the cyclopropylcarbinyl anion (73).⁸⁵ It is interesting



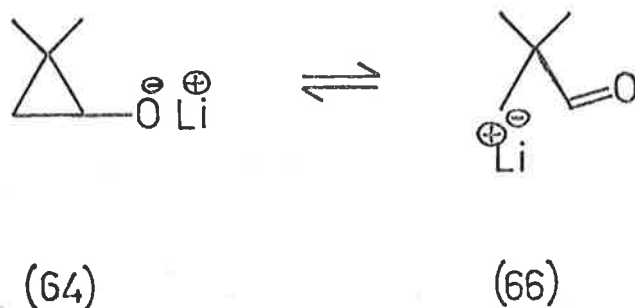
to speculate whether a delocalised anion such as (67) might account for this upfield shift. Several studies of cyclopropylcarbinyl anions,



which are analogous to the cyclopropoxide ion under consideration here, relate to this point. Lansbury and co-workers⁸⁶ concluded that cyclopropylcarbinyl lithium has little, if any, "non-classical" character in agreement with molecular orbital studies on this ion by Howden and Roberts.⁸⁷ Roberts and Maercker⁸⁵ showed that an equilibrium exists between the anions (74) and (75). The position of the

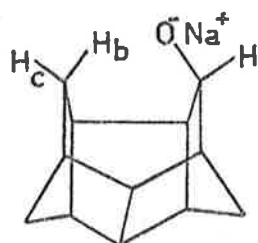


equilibrium depends on the solvent. Addition of T.H.F. to an ether solution of the anion (75) results in the formation of (74). The cyclopropylcarbinyl anion (74) is stabilised by delocalisation of the negative charge on carbon over the aromatic rings. In the case of the cyclopropoxide (64) the electronegativity of oxygen may be great



enough to stabilise the negative charge and prevent ring opening. The role of the solvent and the cation in this case is probably an important factor also. The lithium-oxygen bond is relatively covalent⁸⁸ and this may be a factor contributing to the stability of the more highly strained cyclic anion (64).

The substituents on a cyclopropane ring have a fixed stereochemical relationship to each other but the assignment of the stereochemistry of the methyl groups relative to the lithium alkoxide in (64) and (72) is difficult. Most substituents cause vicinal cis-alkyl groups or protons on a cyclopropane ring to resonate at higher fields than those which are trans.⁸⁹ However, acetyl and carboxyl groups are exceptions. For the anion (72) it is expected that the methyl group A, trans to the alkoxide, will be about 0.5 p.p.m. upfield from its cis counterpart B due to the shielding of the phenyl group.⁹⁰ In the spectrum of this anion the chemical shift difference between A and B is 0.64 p.p.m. suggesting that the >O-Li group may cause some deshielding of the methyl group B which is cis to it. On this basis the lowfield peak ($\delta 1.07$) in the spectrum of (64) is assigned to the methyl group B. It has been reported⁹¹ that the proton H_b in the compound (76) is deshielded by the alkoxide group by more than 1 p.p.m. compared to the proton H_c . This effect has been attributed to the repulsion of the electrons in the $C-H_b$ bond away from the hydrogen H_b



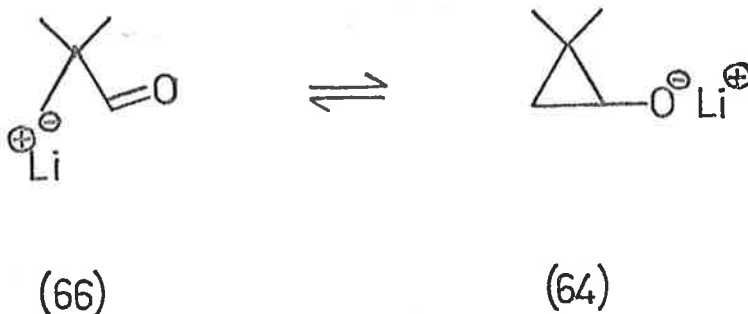
(76)

by the negative charge on the oxygen. On this basis it might be expected that the methyl group B cis to the alkoxide group would resonate at a lower field than its trans counterpart. The role of the solvent in complexing with the cation is also likely to be an important factor in determining the relative chemical shifts of the methyl groups.⁹²

APPROACHES TO THE SYNTHESIS OF CERTAIN BICYCLOBUTANES.

2.1 3-Bromo-2,2,3,4,4-pentamethylcyclobutanone.

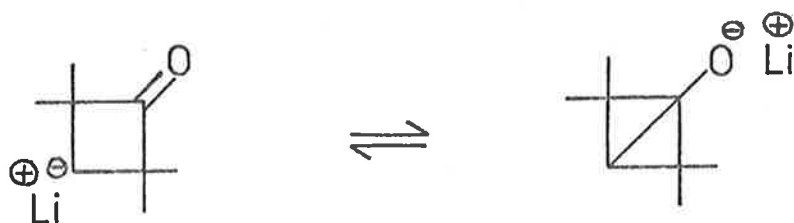
The successful synthesis of cyclopropyl acetates by the reaction of lithium with β -bromocarbonyl compounds meant that the extension of this reaction to the cyclobutane system as discussed in the Introduction was now feasible. The fact that the cyclic anion (64) appears to predominate in the equilibrium shown in Scheme 12 means that the calculated



Scheme 12.

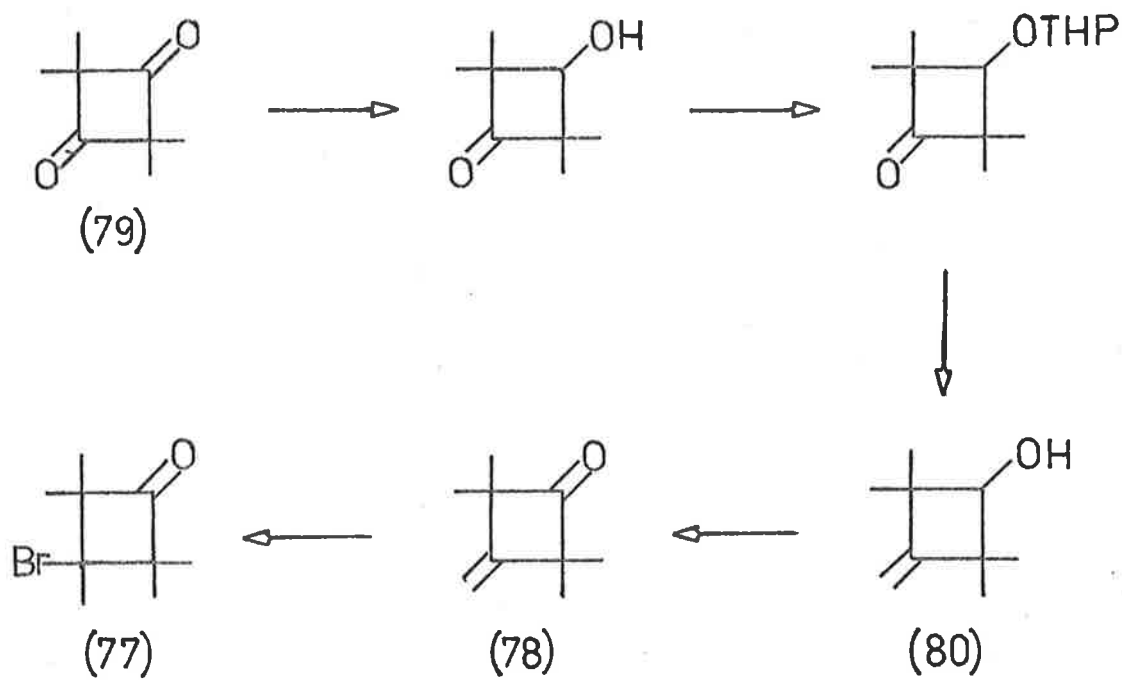
difference in energy between the two ions can be increased by about 4 kcal/mole⁹³ to over 30 kcal/mole. The calculated difference in energy between the two ions shown in Scheme 13 is about 40 kcal/mole. Thus, on a semiquantitative basis, it seems worth trying to prepare a bicyclobutane with an angular oxygen function by this method.

The title compound (77) was chosen because of its ready availability. 3-Methylene-2,2,4,4-tetramethylcyclobutanone (78)



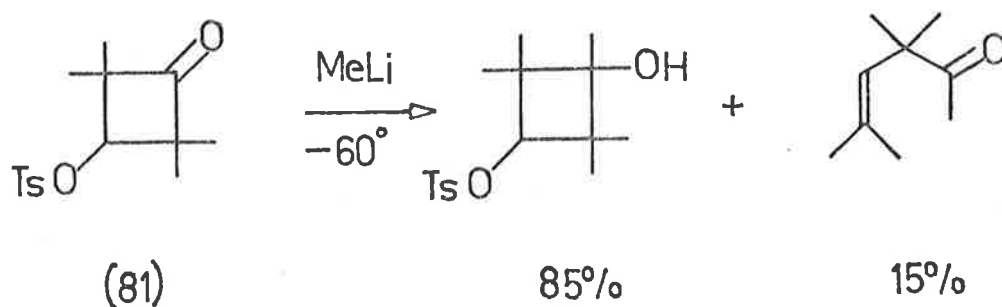
Scheme 13.

had been prepared in these laboratories by the route shown in Scheme 14.⁶ It was envisaged that the addition of hydrogen bromide to (78)



would give the bromoketone (77) which would serve as a suitable compound for reaction with lithium.

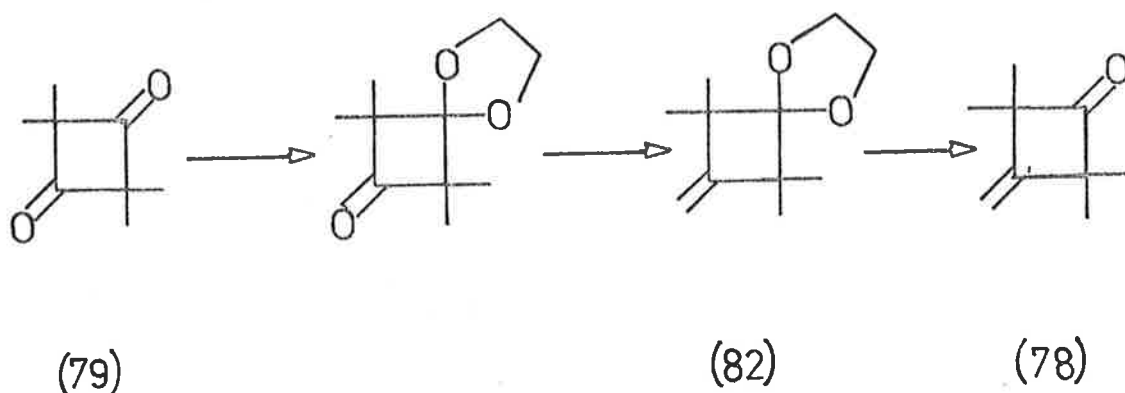
The reduction of the cyclobutadione (79) to the alcohol was necessary because of the facile ring opening of this dione when treated with nucleophiles in general and Wittig reagents in particular.⁹⁴ An attempted Wittig reaction at -60°C still lead to ring-opened product indicating that the activation energy for this reaction is very low. It has recently been reported⁹⁵ that the ketonetosylate (81) does not ring-open to a large extent when treated with methyl-lithium at this temperature despite the fact that the *p*-toluenesulfonate anion is a good leaving group.³⁸



The methyleneketone (78) was obtained from the corresponding alcohol (80) by oxidation using chromic acid in ether or acetone.⁶ The yield of the ketone was only 51% of the theoretical yield. The main by-product was believed, from spectral data, to be a lactone from

oxidation of the cyclobutane ring.^{96,97} Attempts to improve the yield of this step were unsuccessful. Ruthenium tetroxide, which was used successfully in oxidising another cyclobutanol,⁹⁸ did not react with the alcohol (80). Attempted oxidation with dimethyl sulfoxide and acetic anhydride⁶³ was also unsuccessful. Other workers have also experienced difficulty in oxidising cyclobutanols.⁶⁰

Alternative methods for the preparation of the methyleneketone (78) were sought. The ketal derivative of (78) had been reported⁹⁹ but lack of experimental details made repetition of this work difficult until communication with the authors provided the necessary details.¹⁰⁰ The route followed is outlined in Scheme 15. An improved yield was

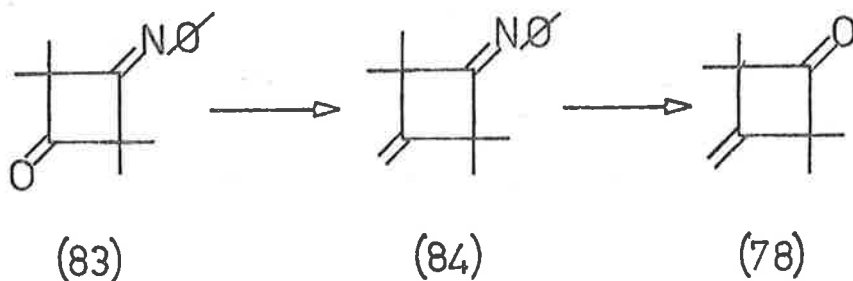


Scheme 15.

obtained for the Wittig reaction when potassium tertiary-butoxide in ether, rather than sodium hydride in dimethyl sulfoxide,¹⁰⁰ was employed as base. Hydrolysis of the ketal (82) with aqueous methanolic hydrochloric acid gave the methyleneketone (78) in 85% yield. An advantage

of this method was that the methyleneketal (82) proved useful for the synthesis of certain key compounds in later studies.

Another approach to the methyleneketone (78) proved to be the best route. The known¹⁰¹ mono-imine (83) of the dione (79) was converted to the methyleneimine (84) by means of a Wittig reaction. The imino group was removed by use of 50% aqueous acetic acid giving the required methyleneketone (78) in greater than 90% yield for the two steps.



Addition of hydrogen bromide to this methyleneketone produced the bromoketone (m.p. 65-66°) in 63% yield. The structure was supported by the infrared spectrum which showed a carbonyl absorption (1775 cm^{-1}) and loss of the methylene group absorption (900 cm^{-1}), and by the n.m.r. spectrum (Table 7).

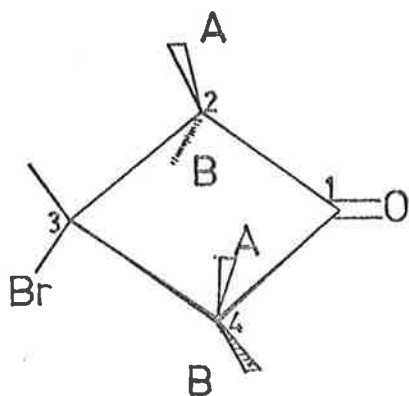
The appearance of two peaks for the four methyl groups attached to the 2- and 4-positions of the cyclobutane ring is considered to be due to the C-3 substituents. Those methyl groups which are cis to the bromine would be expected to be in a different chemical environment

Table 7.

N.m.r. spectrum (CCl_4) of 3-bromo-2,2,3,4,4-pentamethylcyclobutanone.

δ (p.p.m.)	Appearance	Proton Count*	Assignment
1.13	singlet	6	ring Me_2^A
1.43	singlet	6	ring Me_2^B
1.90	singlet	3	C-3 Me

* Based on molecular weight. The integration gives the ratio 2:2:1.



from those which are cis to the C-3 methyl group. Thus a peak would be expected for the two methyl groups cis to the bromine and another for their trans counterparts. The peak at $\delta 1.13$ is tentatively assigned to the two methyl groups cis to the C-3 methyl group due to the expected greater shielding of a C-C bond compared to the $>\text{C-Br}$ group.

The reaction of the bromoketone (77), with lithium in ether yielded a mixture of products, one of which was isolated by preparative vapour phase chromatography (v.p.c.). The compound was an orange solid (m.p. 66-68°) whose infrared spectrum (CHCl₃) contained a strong peak at 1700 cm⁻¹. This data coupled with the n.m.r. spectrum (Table 8) suggested that the compound was the α-diketone (85). The mass spectrum

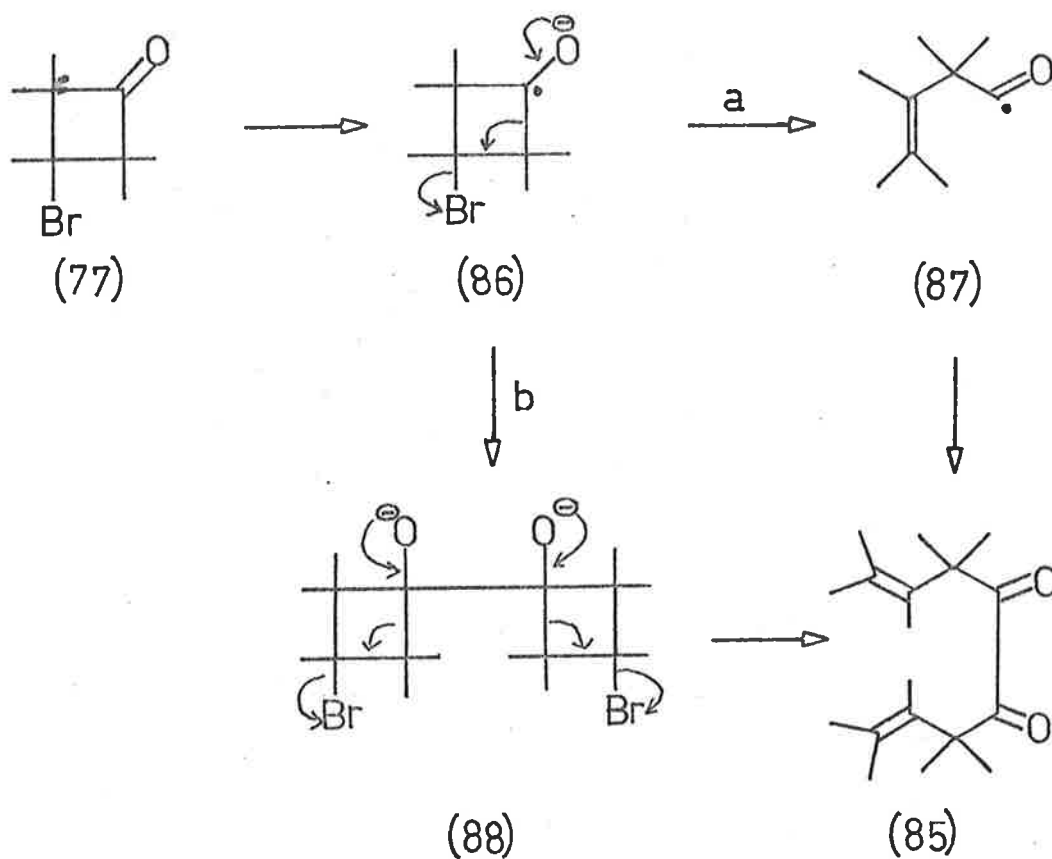
Table 8.

N.m.r. spectrum (CCl₄, CDCl₃) of octamethyldeca-2,8-diene-5,6-dione (85).

δ (p.p.m.)	Appearance	Proton Count	Assignment
1.27	singlet	12	<u>gem-Me</u> ₄
1.43	singlet	6	} Me ₈ on double bond
1.65	singlet	6	
1.83	singlet	6	

showed a parent ion at m/e 278 which is the molecular weight for this compound.

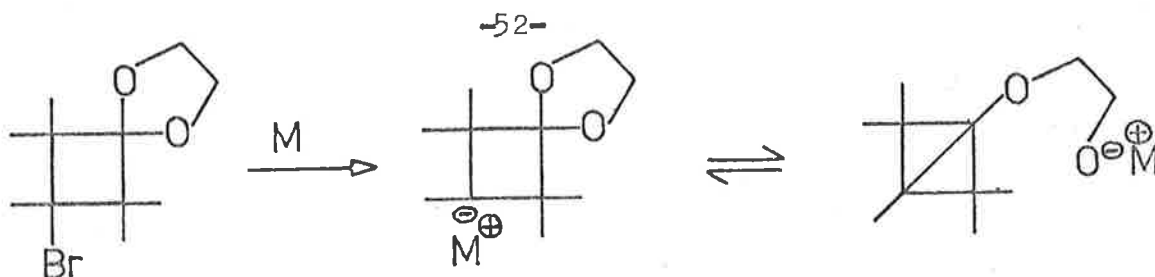
Possible mechanisms for the formation of this diketone are shown in Scheme 16. Reduction of the carbonyl group would lead to the radical anion (86) which could react in two ways. Ring opening with loss of bromide ion (path a) could produce the acyl radical (87) which might be expected to be stable.¹⁰³ Dimerisation of this radical



Scheme 16.

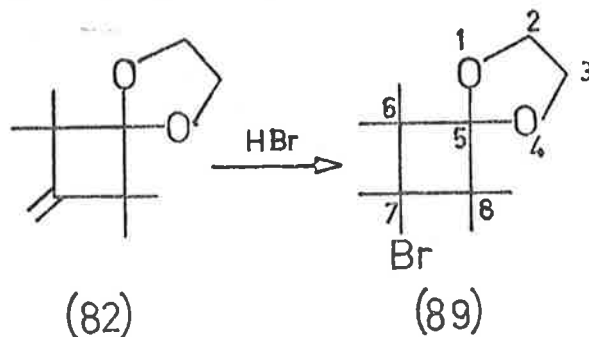
could lead to the α -diketone (85). It is possible that the radical anion (86) could dimerise forming (88) in a reaction similar to that for the formation of pinacol. Ring opening of this species could lead to (85).

Because of the difficulty with this reaction it was decided to try the alternative approach to the bicyclobutane ring. This involved the reaction of a bromoketal with a metal. It avoided the complication of having the reducible carbonyl group present in the molecule.



2.2 7-Bromo-6,6,7,8,8-pentamethyl-1,4-dioxaspiro[4.3]octane (89).

It seemed possible that a suitable compound with which to study the reaction of a bromoketal with a metal might be produced from the addition of hydrogen bromide to the methyleneketal (82) as shown below.



However, this molecule possesses the acid labile ketal group. Anhydrous hydrogen bromide has a dielectric constant of 6.29 at $-80^{\circ}\text{C}^{104}$ and it would be expected to be a poor ionising solvent and a weak acid. It was considered that the reaction was worth trying provided suitable precautions were taken to exclude water. In the event, the methyleneketal (82) was dissolved in liquid hydrogen bromide which was evaporated under a stream of dry nitrogen. Liquid ammonia, distilled from potassium, was added to remove the last traces of hydrogen bromide. This procedure produced the desired bromoketal (89) as a solid (m.p. $118-120^{\circ}$) in a 70%

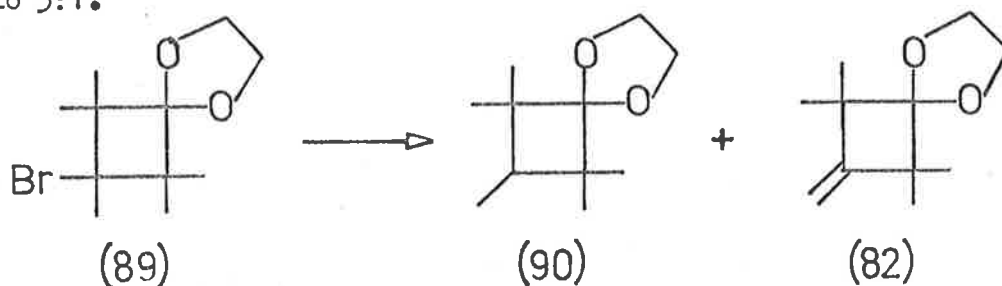
Only a trace of the ketone (77) was present and this was removed by column chromatography. The n.m.r. spectrum of the bromoketal (89) is detailed in Table 9.

Table 9.

N.m.r. spectrum (CCl_4) of the bromoketal (89).

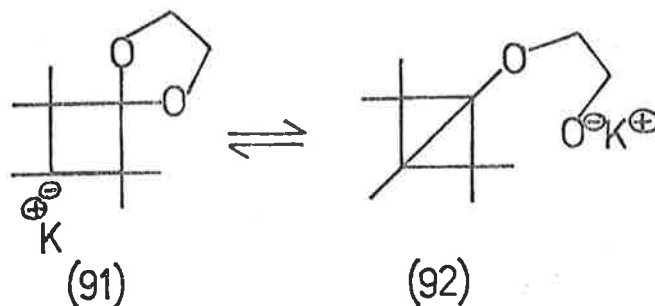
δ (p.p.m.)	Appearance	Proton Count	Assignment
0.92, 1.28	2 singlets	6,6	ring Me_4
1.75	singlet	3	C-7 methyl
3.75	singlet	4	ketal protons

Sodium-potassium alloy was used as the metal for reaction with the ketal (89) following the successful synthesis of pentamethylbicyclobutane by the elimination of an alkoxide ion using this alloy.³⁴ Benzene was used as solvent and an aqueous work-up was employed. The n.m.r. spectrum of the product appeared to be that of the superimposition of the absorptions of the two compounds (90) and (82) in the ratio 3:1.



The methylketal (90) was synthesised by catalytic hydrogenation of the methyleneketal (82).⁹⁹ The composition of the mixture was confirmed by the v.p.c. behaviour of the mixture as compared with standard compounds.

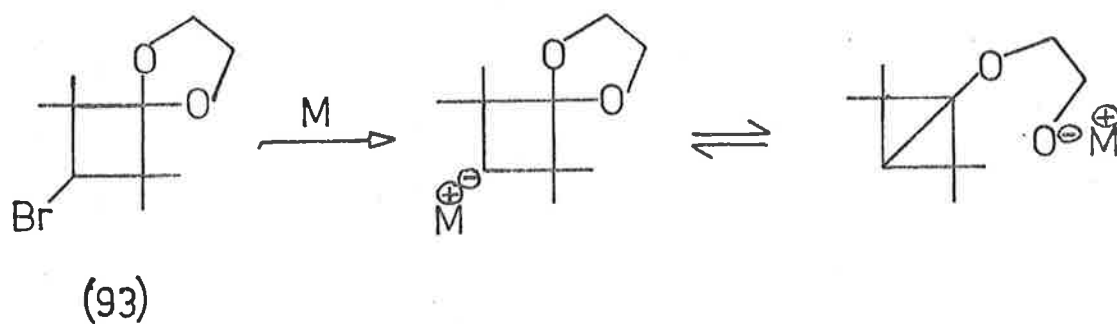
The formation of the methyleneketal (82) can be explained in terms of an intramolecular hydride elimination by the alkyl-potassium¹⁰⁵ or an intermolecular elimination of hydrogen bromide from (89) by the alkyl-potassium. The possibility that an equilibrium exists between the ions (91) and (92) cannot be excluded. The excess of the methylketal (90) may be due to the abstraction of a proton from the solvent



during the reaction or from the water upon aqueous work-up. The presence of the two compounds (90) and (82) was observed in the n.m.r. of the benzene solution before work-up, suggesting that the proton came from the solvent.

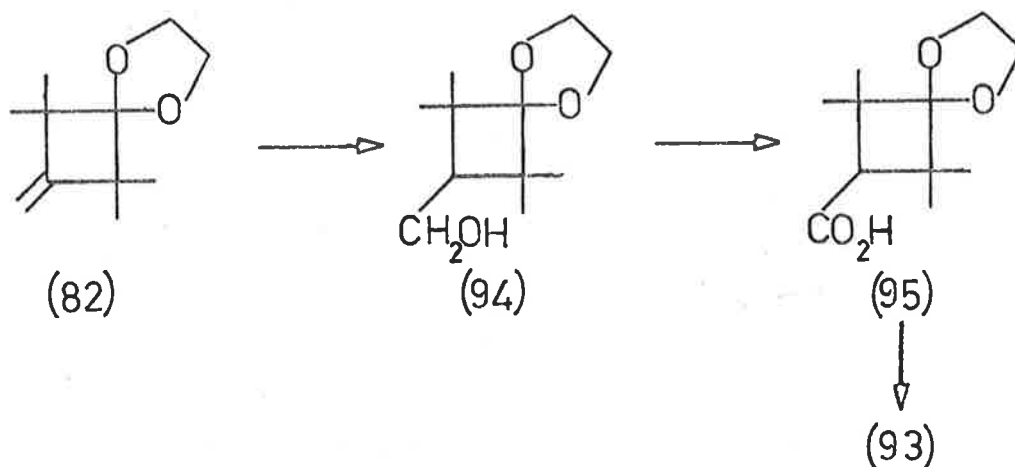
To exclude the possibility of complications arising from the tertiary bromide (89) it was decided to prepare the secondary bromide (93) corresponding to it. The use of a secondary bromide had the

additional advantage that the bicyclobutane, if formed, would have the same basic skeleton as that proposed for the sex-attractant of the American cockroach.



2.3 7-Bromo-6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane (93).

The title compound (93) was synthesised from the methyleneketal (82) by the sequence outlined in Scheme 17. Hydroboration of the



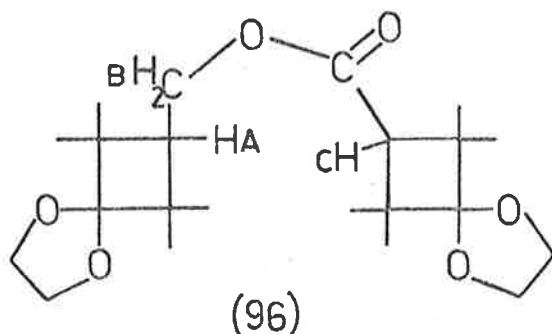
Scheme 17.

olefin (82) followed by oxidative work-up gave the alcohol (94) (m.p. 79-80°) in 93% yield. This alcohol was oxidised by "Jones⁶¹ reagent" and the acid (95) (m.p. 128-129°) was obtained in 67% yield. A neutral compound (m.p. 88-92°) was also isolated from this reaction. On the basis of its n.m.r. spectrum (Table 10) and absorptions in the infrared spectrum at 1720 and 1230 cm⁻¹ it was assigned the structure (96). It probably was formed by attack of the alcohol (94) on the intermediate aldehyde and subsequent oxidation of the hemiacetal formed.⁶⁰

Table 10.

N.m.r. spectrum (CDCl₃, CCl₄) of ester (96).

δ (p.p.m.)	Appearance	Proton Count	Assignment
1.06	singlet	12	} ring Me ₈
1.10	singlet	6	
1.21	singlet	6	
1.71	triplet (J=8 Hz)	1	H _A
2.30	singlet	1	H _C
3.81, 3.83	slightly split peak	8	ketal protons
4.06	doublet (J=8 Hz)	2	H _B



The acid (95) was converted to the bromide (93) (m.p. 64-65°) in 60% yield by means of the Critchfield-Firth¹⁰⁶ modification of the Hunsdiecker reaction. Water was removed azeotropically from the reaction by use of carbon tetrachloride in a modified Dean and Stark apparatus.¹⁰⁷ Pure samples of the bromoketal were obtained only after column chromatography. The n.m.r. spectrum of this compound, which confirms the structure, is detailed in Table 11.

Table 11.

N.m.r. spectrum of bromoketal (93).

δ (p.p.m.)	Appearance	Proton Count	Assignment
1.03, 1.11	singlets	6,6	ring Me ₄
3.74	singlet	1	C-7 H.
3.81	singlet	4	ketal protons

The bromoketal (93) was allowed to react with sodium-potassium alloy in benzene and the mixture was subjected to an aqueous work-up.

The major product was the ketal (97) the n.m.r. spectrum of which is detailed in Table 12. The structural assignment was confirmed by an

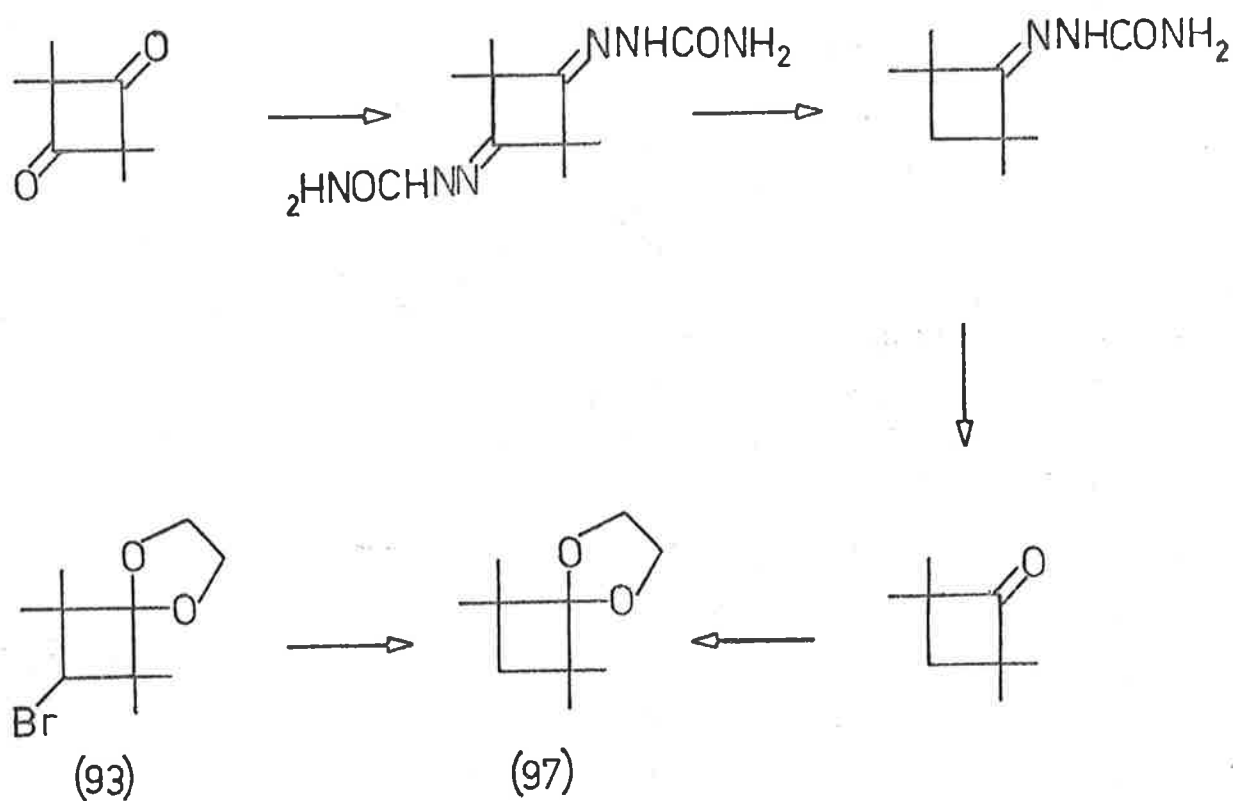
Table 12.

N.m.r. spectrum of 6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane (97).

δ (p.p.m.)		Appearance	Proton Count	Assignment
(CCl ₄)	(PhH)			
1.01	1.21	singlet	12	ring Me ₄
1.25	1.30	singlet	2	C-7 H's
3.73	3.42	singlet	4	ketal protons

independent synthesis of the compound by the method shown in Scheme 18.¹⁰⁸

Again the question arises as to whether a proton is abstracted from the solvent by a potassium-alkyl during the reaction or upon the aqueous work-up. An examination of the n.m.r. spectrum of the benzene solution before work-up showed the presence of (97) in substantial quantities. Since reasonable precautions were taken to exclude moisture this suggests that the alkyl-potassium formed abstracts a proton from the solvent. Interestingly, the spectrum of the ketal (97) showed a remarkable dependence on the solvent used as shown in Table 12. This solvent shift is probably due to the association of benzene molecules with the polar ketal group.¹⁰⁹



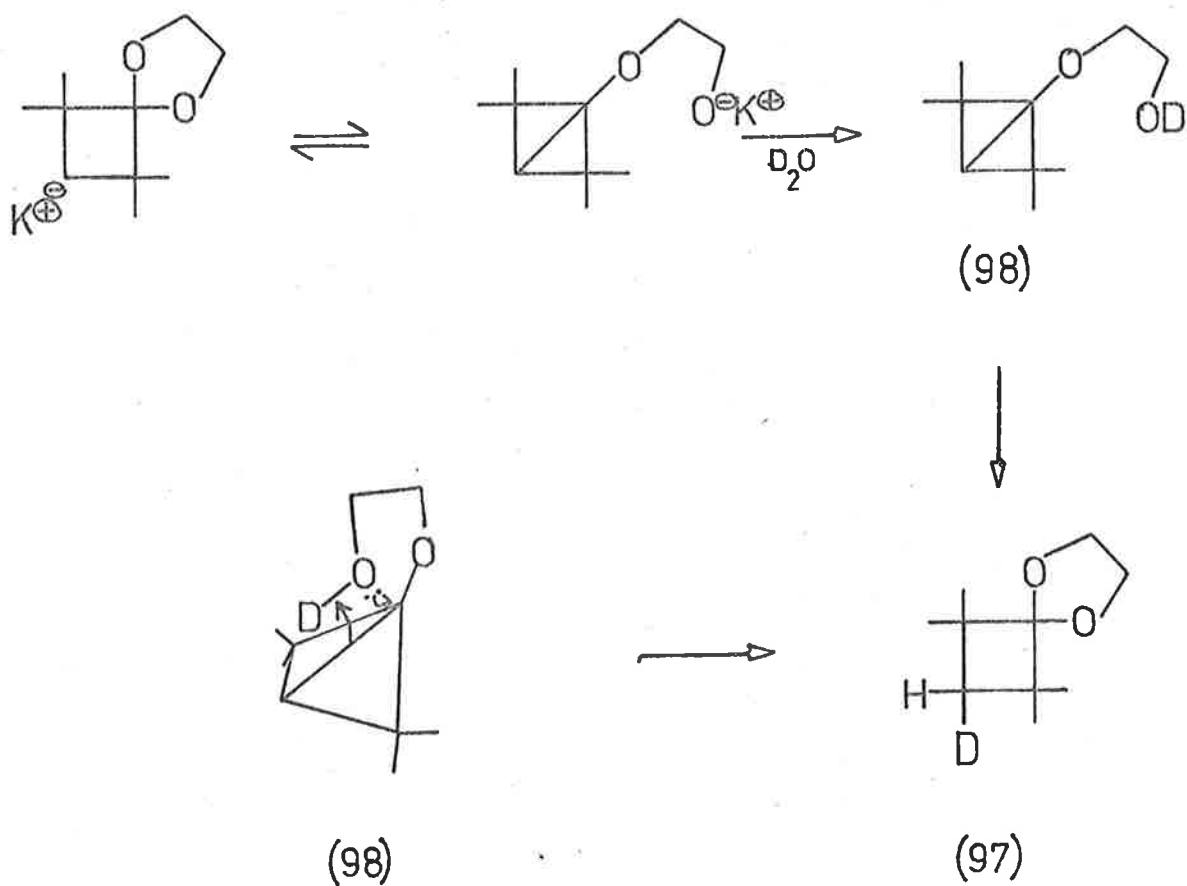
Scheme 18.

It has been estimated¹¹⁰ that benzene is 10^8 times more acidic than cyclohexane. The use of the latter solvent, however, still led to the formation of the ketal (97) after aqueous work-up. When deuterium oxide was used instead of water for the protonation of the anion it was found that deuterium was incorporated in the ketal (97) at the 7-position. The infrared spectrum of the product showed a peak at 2200 cm^{-1} corresponding to the C-D stretching frequency. In the

n.m.r. spectrum the integral of the absorption at $\delta 1.25$ corresponded to 1.3 protons indicating that in about 70% of the molecules one atom of deuterium had been incorporated. It was not possible to determine the exact amount of deuterium present from the mass spectrum because of the weakness of the parent ion peak.

At first sight it would appear that the potassium-alkyl had survived for several hours even though these compounds are known to be extremely reactive.¹⁰⁵ If the bicyclobutane had been formed by reaction of the anion across the ring then addition of deuterium oxide might have produced the bicyclobutyl alcohol (98). Daubin and Willy^{e 28} have shown that strained bicyclobutanes are not stable to alcohols and it has been argued that a bicyclobutane with an angular oxygen function might also be unstable to alcohols (vide supra). An examination of models has revealed that this alcohol (98) could take up a position ideal for adding across the central bond forming the ketal (97) (Scheme 19).

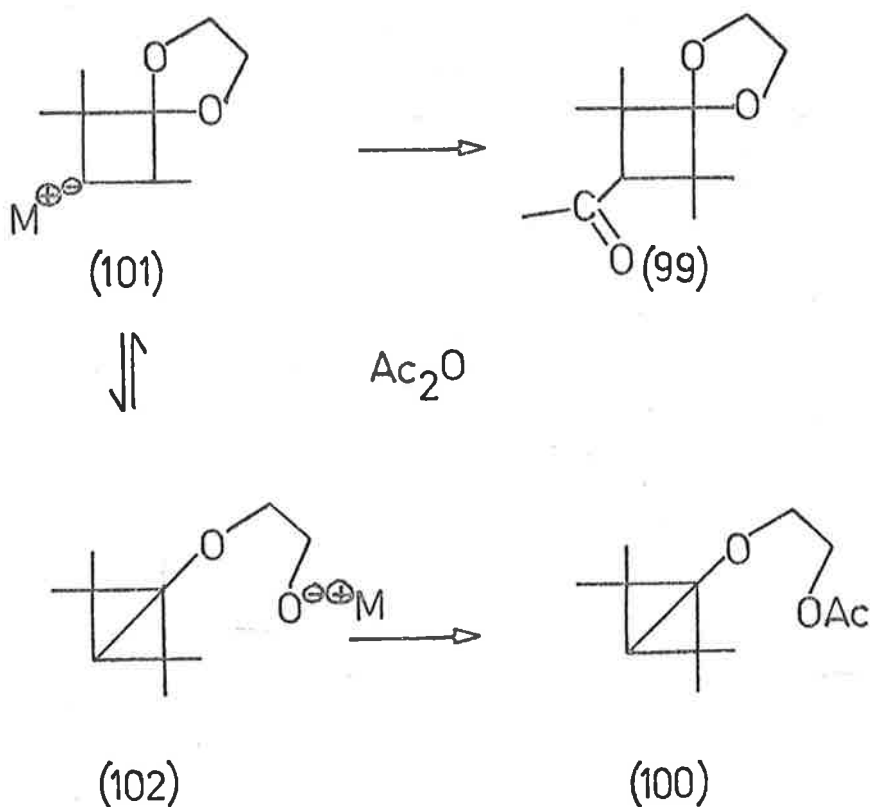
The two alternatives could be distinguished, in principle, by reaction of the anion with acetic anhydride. Depending on the nature of the anion, acetylation could occur on carbon or on oxygen (Scheme 20). Acetylation on carbon would give the acetylketal (99) while acetylation on oxygen might be expected to give the bicyclobutyl acetate (100). Because of the strain of the bicyclobutane ring the anion (101) might predominate in an equilibrium mixture of the two ions (101) and (102). However, acetylation on oxygen might be expected to be



Scheme 19.

favoured.⁴⁷

Sodium-potassium alloy was unsuitable for this reaction because of the difficulty of removing it before the addition of acetic anhydride. Lithium amalgam had been used successfully in the synthesis of bicyclo[1.1.0]pentane.¹⁰⁷ In a preliminary study lithium amalgam



Scheme 20.

was found to give a solid (m.p. $113-114^{\circ}$) upon reaction with the bromo-ketal (93). The mass spectrum of the solid contained a series of peaks characteristic of the isotopes of mercury and a spot test¹¹¹ confirmed its presence. The n.m.r. spectrum (Table 13) allowed assignment of the structure (103) to the solid. The methyl groups and α -protons (Ha) would be expected to be broadened due to coupling with the mercury atom.¹¹² The reaction of sodium amalgam with alkyl halides has been

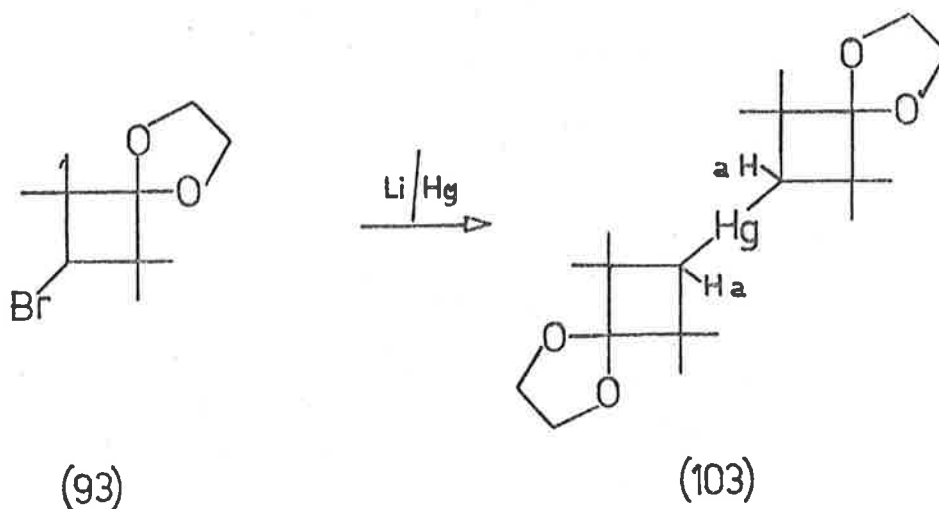


Table 13.

N.m.r. spectrum (CCl_4) of the mercury compound (103).

δ (p.p.m.)	Appearance	Proton Count	Assignment
1.02, 1.12	broad singlets	12,12	ring Me_8
1.31	broad singlet	2	Ha
3.77	singlet	8	ketal protons

reported to give dialkylmercury compounds.¹¹³

Lithium in the form of a dispersion in mineral oil or as freshly drawn wire was found to be suitable for reducing the bromoketal (93). On addition of acetic anhydride to a filtered solution of the anion an exothermic reaction took place and a white precipitate formed. An oil, which was purified by preparative v.p.c., was isolated from the reaction mixture. Its infrared spectrum (CCl_4) contained absorptions

at 1740 and 1230 cm^{-1} indicative of an $-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$ group and at 1660 cm^{-1} characteristic of an enol double bond. This data, coupled with the n.m.r. spectrum which is detailed in Table 14, suggested that the compound was the diene (104). The protons of the ethylenedioxy group

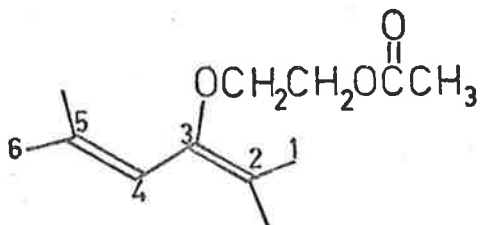
Table 14.

N.m.r. spectrum (CCl_4) of the diene (104).

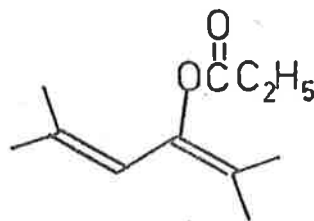
δ (p.p.m.)	Appearance	Proton Count	Assignment
1.53	singlet	3	} Me_4 on double bond
1.67	broad singlet	6	
1.82	broad singlet	3	
2.0	singlet	3	$-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$
3.63, 4.10	two triplets ($J=5$ Hz)	2,2	$-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$
5.52	broad peak	1	C-4 H

formed two triplets corresponding to an A_2X_2 system although some further splitting was apparent indicating that a first order interpretation was not possible.

A diene (105) similar to (104) has been reported.¹¹⁴ The n.m.r. spectrum (CCl_4) of this diene was reported to show three peaks at δ 1.5-1.75 due to the methyls on the double bonds and a multiplet at δ 5.55 due to the proton on the double bond as well as peaks due to the ethyl group.

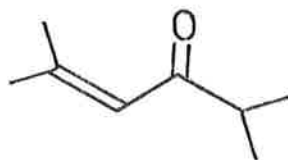


(104)



(105)

The analytical figures for the diene (104) were a little low. This problem has also been reported for (105) and may be due to the ready hydrolysis of these compounds. The structure of the diene (104) was confirmed by its hydrolysis to the known ketone (106).¹¹⁵ The

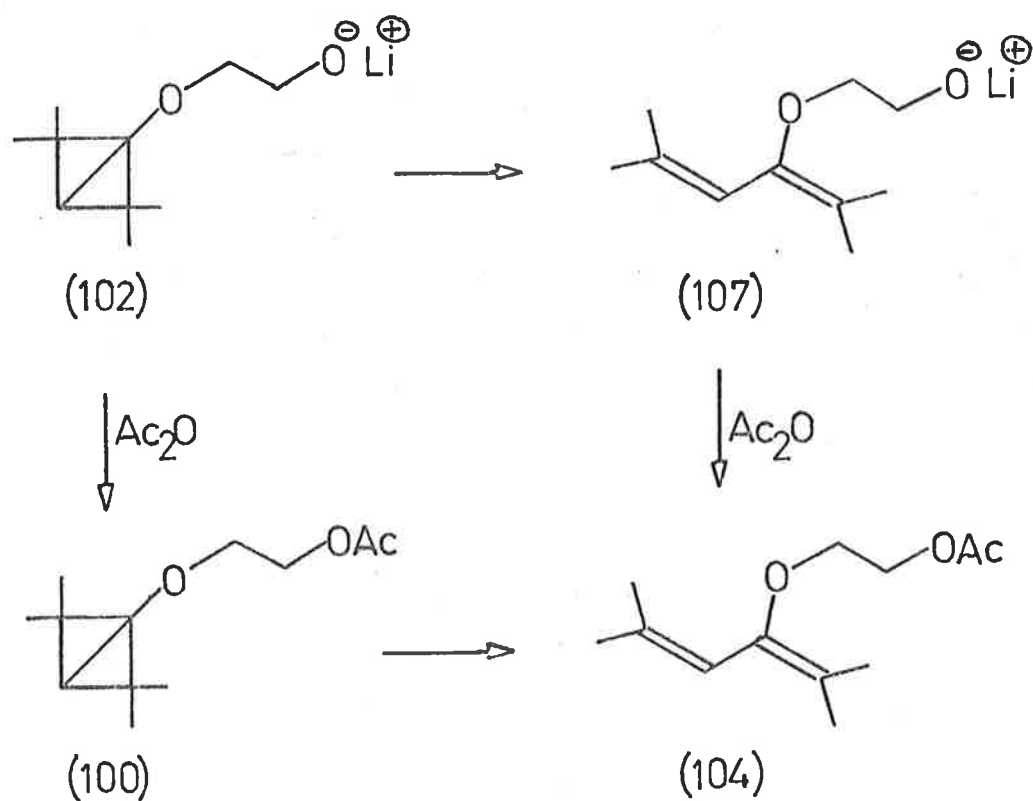


(106)

n.m.r. spectrum of this ketone agreed with that reported and the 2,4-dinitrophenylhydrazone derivative melted at the same temperature as that in the literature.¹¹⁶

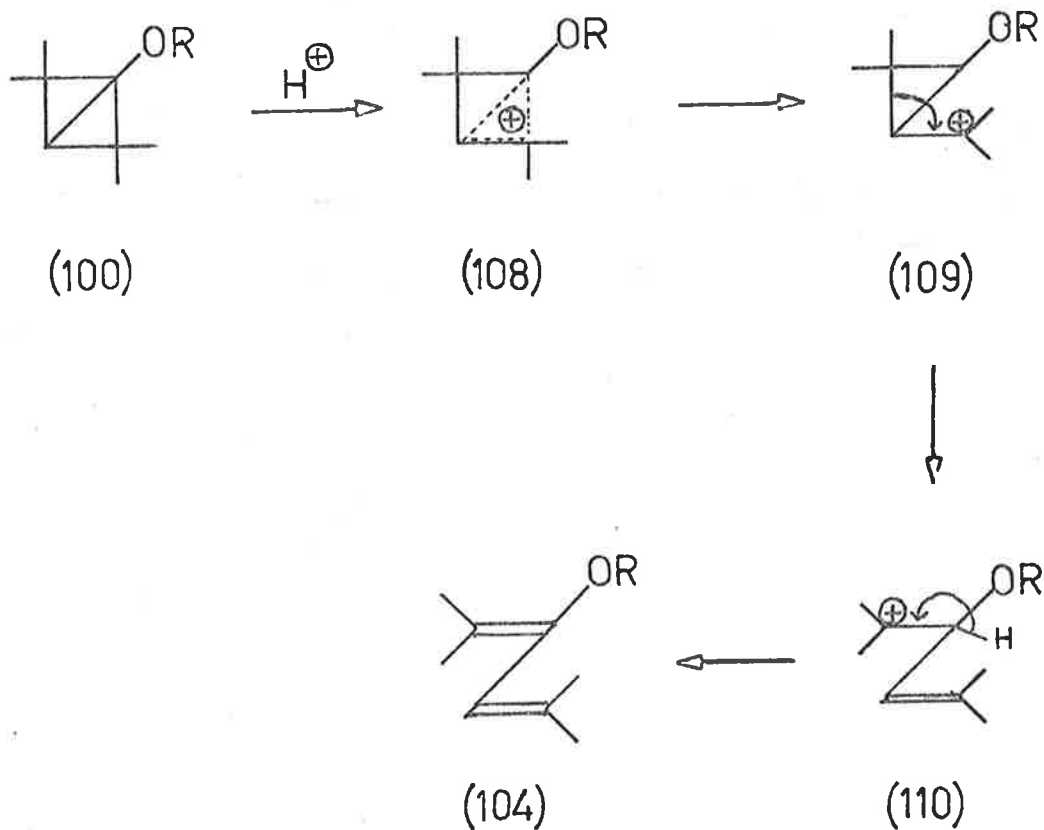
The formation of the diene (104) represents strong evidence for the intermediacy of the bicyclobutane (100) or at least the anion (102).

A similar diene was formed in an earlier attempted synthesis of a bicyclobutane with an angular oxygen function.³⁷ Dienes may be formed from bicyclobutanes by thermal or acid-catalysed rearrangement. Pyrolysis of the alkoxide (102) or the acetate (100) could lead to the diene as outlined in Scheme 21. This type of ring opening reaction, which is



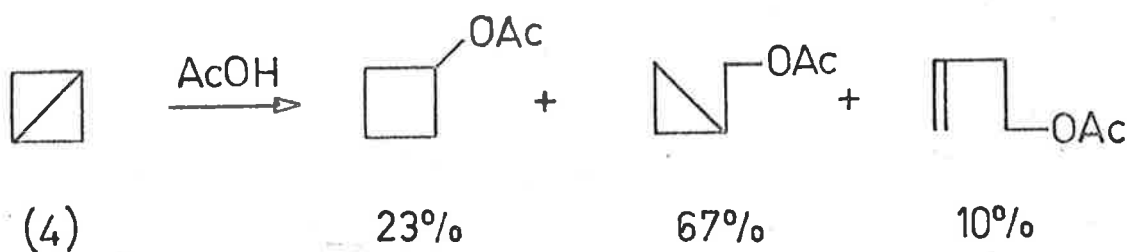
Scheme 21.

believed to be concerted, is typical of that undergone by most bicyclobutanes (vide supra). A working hypothesis which accounts for the formation of the diene from the bicyclobutane by a protonolysis reaction is outlined in Scheme 22. The first step involves the formation



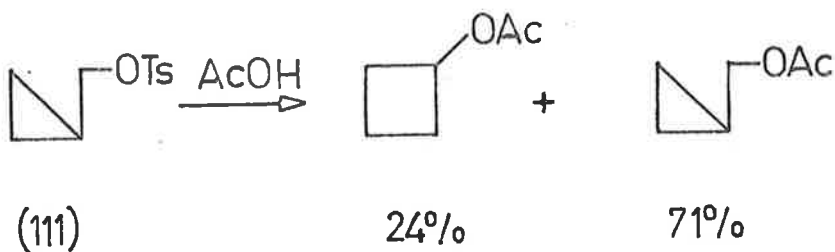
Scheme 22.

of the "bicyclobutonium" ion¹⁵ (108) by addition of a proton to the bicyclobutane (100). This ion has been used to account for the close similarity in products derived from the reaction of bicyclobutanes with acid and certain solvolyses reactions.¹¹⁷ Thus, bicyclobutane (4) on treatment with acetic acid gives the products shown in Scheme 23,¹⁴



Scheme 23.

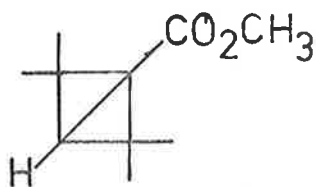
while cyclopropylcarbinyl tosylate (111) on treatment with acetic acid gives the products shown in Scheme 24.¹¹⁸ An ion similar to (108)



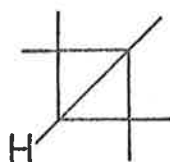
Scheme 24.

has been postulated as a possible intermediate in the solvolysis of certain 3-hydroxy-2,2,4,4-tetramethylcyclobutane tosylates.¹¹⁹ The formation of the cyclopropylcarbinyll cation (109) by rearrangement of this ion (108) or directly from the bicyclobutane (100)¹⁴ and its subsequent rearrangement to the diene (104) are the next steps in the Scheme. While the mode of decomposition of the cyclopropylcarbinyll cation (109) shown is unusual it can be argued that the stability of the tertiary carbonium ion (110) could favour this mode. The actual nature of the "bicyclobutonium" ion has been under attention recently¹⁵ and it is difficult to be sure which intermediate ions could be involved in the formation of the diene (104).

It was decided to examine the n.m.r. spectrum of the anion produced from the reaction of the bromoketal (93) with lithium to see if the bicyclobutane (102) could be detected. It was anticipated that two peaks would be seen for the ring methyl groups because of the difference in chemical environment of the endo methyls compared to the exo methyls. Two peaks at $\delta 1.25$ and $\delta 1.30$ are observed for the ring methyls in the n.m.r. spectrum of the bicyclobutane (112)³³ and at $\delta 1.01$ and $\delta 1.16$ for those of (32).³⁴ Although the assignment of a particular value to the exo or endo methyls is difficult Hamon³⁴ has concluded from a study of solvent shifts that the endo methyls in (32) probably absorb at a lower field ($\delta 1.16$). The position of the absorption of the angular proton of the ester (112) is $\delta 2.03$ while that of (32) is $\delta 0.64$. Williamson and co-workers¹²⁰ have related the chemical

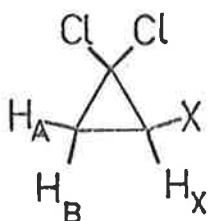


(112)

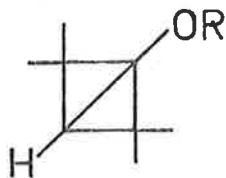


(32)

shift of the A, B, and X protons in the cyclopropane (113) to the electronegativity of the group X. The chemical shifts of the proton H_A for compounds where X is the carboxyl group and the methoxyl group



(113)



(114)

are shown in Table 15. Assuming that the value for the $\overset{\text{O}}{\parallel}{\text{-C-OMe}}$ group is similar to that for the carboxyl group one might expect that the

Table 15.

The chemical shift of H_A for compounds (113).

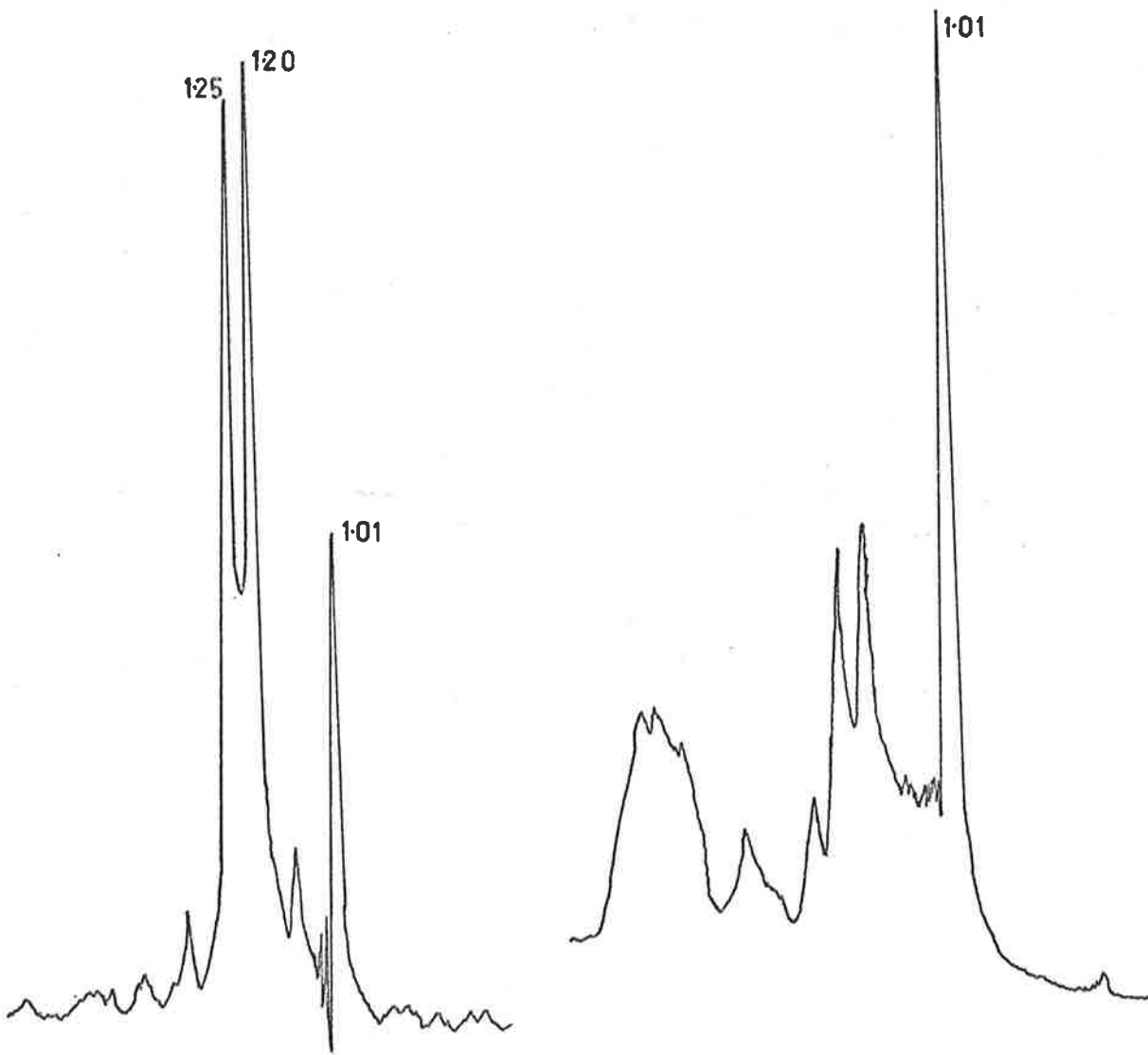
δH_A (p.p.m.)	Substituent X
2.02	$-\text{CO}_2\text{H}$
1.52	$-\text{OMe}$

chemical shift for the angular proton in an alkoxybicyclobutane (114) would be about 0.5 p.p.m. upfield from that for the bicyclobutyl ester (112).

The spectrum of the anion was recorded using dimethoxyethane (D.M.E.) as solvent and is shown in Diag. 1. The position of the peaks are relative to those of D.M.E. which are taken as being at $\delta 3.25$ and $\delta 3.42$. Three major absorptions at $\delta 1.01$, 1.20, and 1.25 were observed above $\delta 1.83$. The spectrum below $\delta 1.83$ was obscured by absorptions due to the solvent. Integration of the spectrum showed that the peaks at $\delta 1.20$ and 1.25 were in the ratio of 1:1. The spectrum (Diag. 1) altered slowly and after 18 hours its appearance was as shown in Diag. 2.

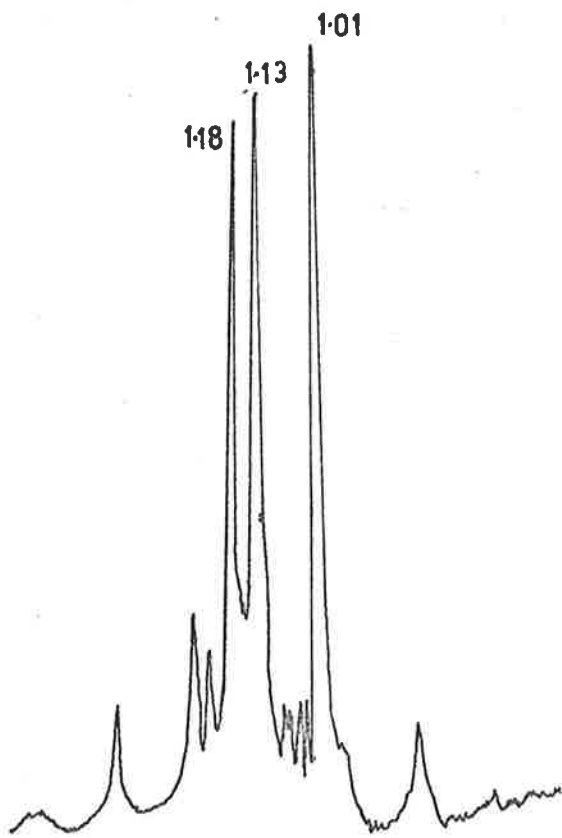
Addition of deuterium oxide to the n.m.r. tube containing the anion caused the spectrum shown in Diag. 1 to alter to that shown in Diag. 3. The three major absorptions shown occurred at $\delta 1.01$, 1.13, and 1.18. After 30 minutes this spectrum had altered to that shown in Diag. 4 in which the absorptions at $\delta 1.13$ and 1.18 had decreased in size relative to the peak at $\delta 1.01$.

The spectrum shown in Diag. 1 is rationalised as being due to the bicyclobutyl anion (102). The absorptions at $\delta 1.20$ and 1.25 are assigned to the ring methyls. Several small peaks are present but it is not possible to assign one of them to the angular proton. The absorptions due to the ethylenedioxy group are probably obscured by the solvent. The absorption at $\delta 1.01$ is believed to be due to the

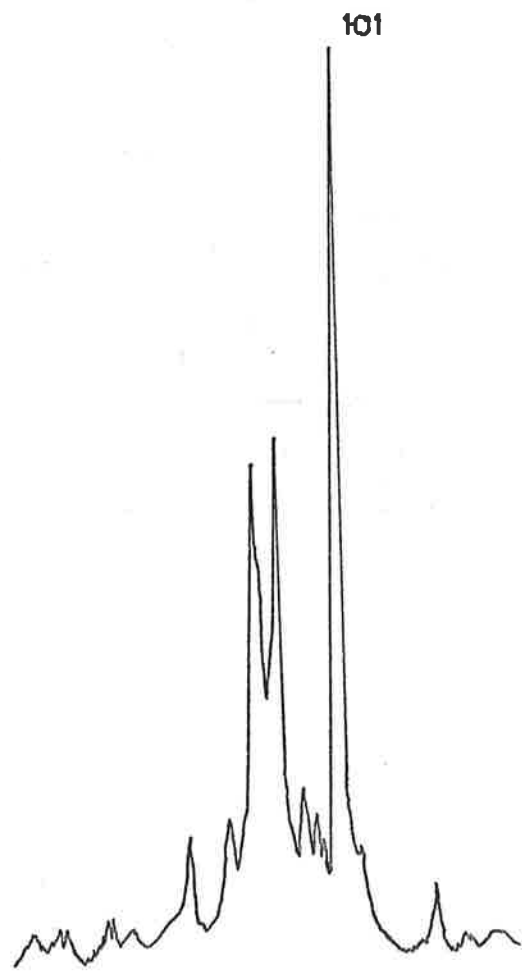


Diag.1

Diag.2

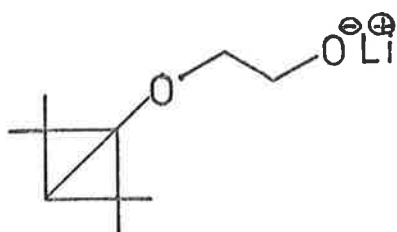


Diag. 3

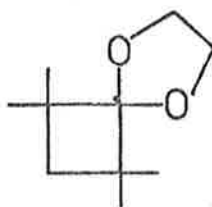


Diag. 4

methyl groups of 6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane (97). Support for this assignment is gained from the observation that this compound is formed when water is added to a solution of the freshly

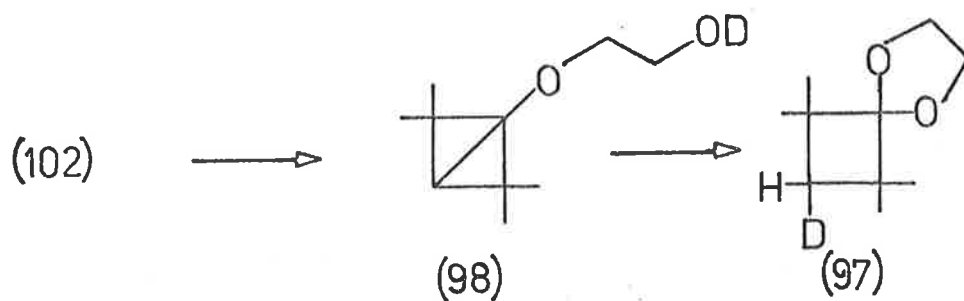


(102)



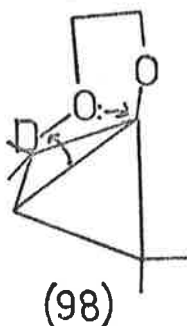
(97)

prepared anion. The size of this peak varies from sample to sample compared to the other two peaks. The ketal (97) is probably formed by abstraction of a proton from the solvent or from water introduced during the manipulation of the solution for the running of the spectrum. Further support for this assignment is gained from the results of the addition of deuterium oxide to the n.m.r. tube containing the anion. The absorptions in Diag. 3 at δ 1.13 and 1.18 are assigned to the ring methyls of the bicyclobutyl alcohol (98) obtained from the anion (102) by protonation* of the alkoxide ion. The alteration of the spectrum

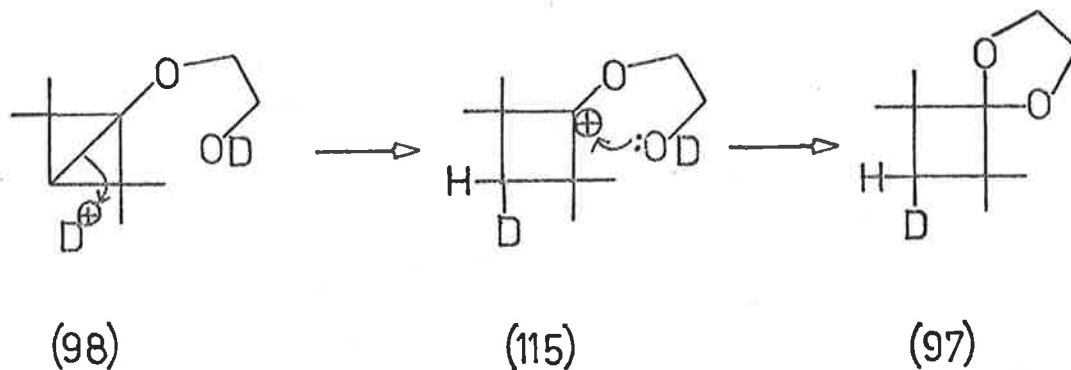


shown in Diag. 3 to that shown in Diag. 4 is believed to be due to the slow rearrangement of the alcohol (98) to the ketal (97). Work-up of the reaction mixture responsible for the spectrum shown in Diag. 3 produced a compound which was shown to be the ketal (97) by comparison of its spectral data with that of an authentic sample.

The rearrangement of the alcohol (98) to the ketal (97) could occur by the mechanism shown below which has been discussed (*vide supra*). Alternatively, the central bond of the bicyclobutane could



be protonated by deuterium oxide leading to the carbonium ion (115) (Scheme 25). The favourable spatial arrangement of the oxygen of the

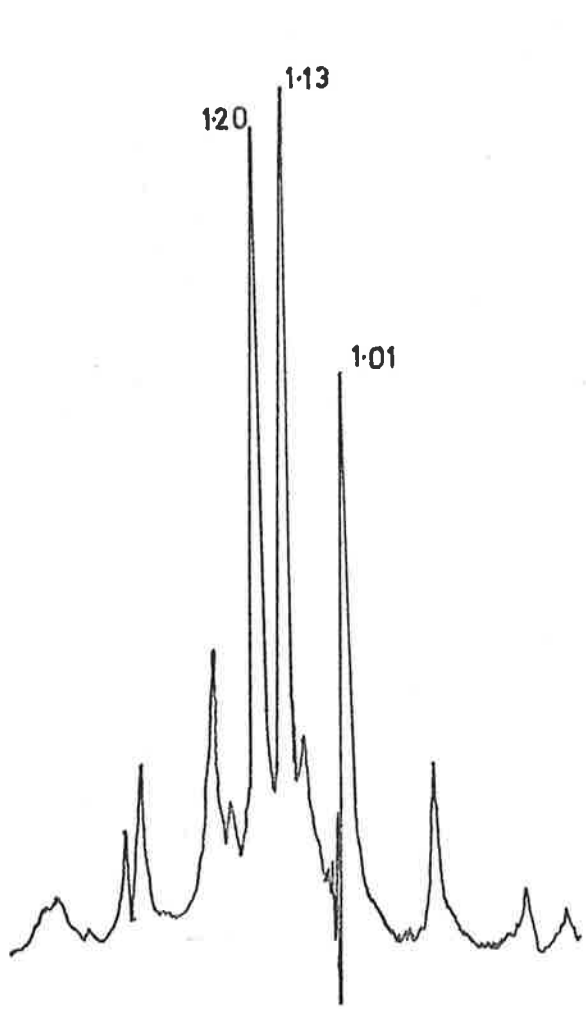


Scheme 25.

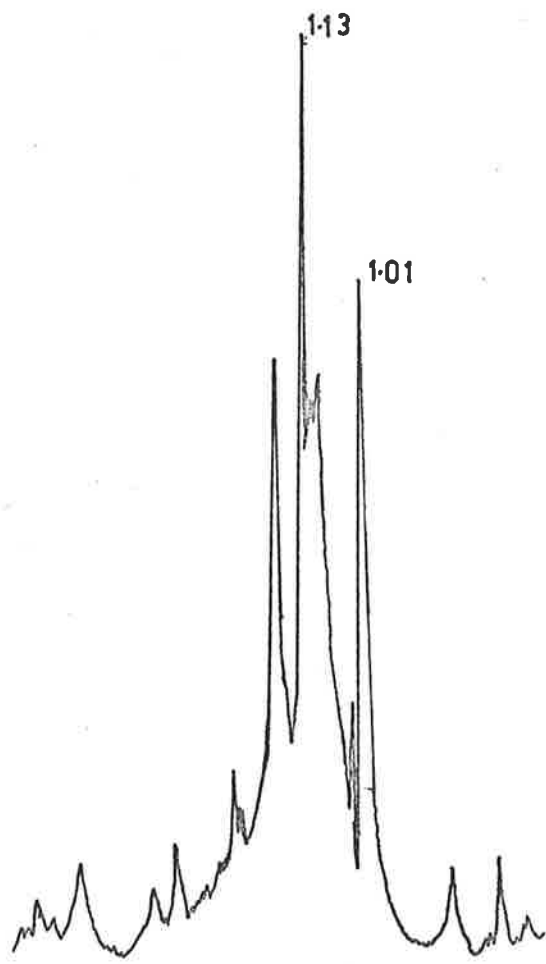
ethylenedioxy group could lead to the formation of the cyclic ketal rather than a hemiacetal formed by attack of a deuterium oxide molecule.

Addition of acetic anhydride to the n.m.r. tube containing the anion also caused the spectrum shown in Diag. 1 to alter. The new spectrum is shown in Diag. 5. Once again the absorption of $\delta 1.01$ was present together with two other main absorptions at $\delta 1.13$ and $\delta 1.20$ in the ratio of 1:1. This spectrum also altered with the passage of time. After 2 hours the spectrum of this solution was as shown in Diag. 6. A new absorption at $\delta 1.13$ was present. Addition of deuterium oxide to solution responsible for the spectrum shown in Diag. 5 resulted in the disappearance of the absorption at $\delta 1.20$. The major absorption present in this new spectrum was at $\delta 1.13$. Repetition of this experiment on a larger scale resulted in the formation of an oil whose n.m.r. spectrum showed the presence of three main compounds. These were identified by a comparison of the absorptions present with those of authentic compounds as the diene acetate (104), 6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane (97) and 2,2,4,4-tetramethylcyclobutanone (116). These compounds were present in the ratio of 1:1:2. The major compound, the cyclobutanone, showed an absorption due to the ring methyls at $\delta 1.13$ and an absorption due to the C-3 protons at $\delta 1.72$ in its n.m.r. spectrum. The behaviour of the mixture on a v.p.c. column supported the above assignment of structures.

These results can be rationalised by assuming that the absorptions

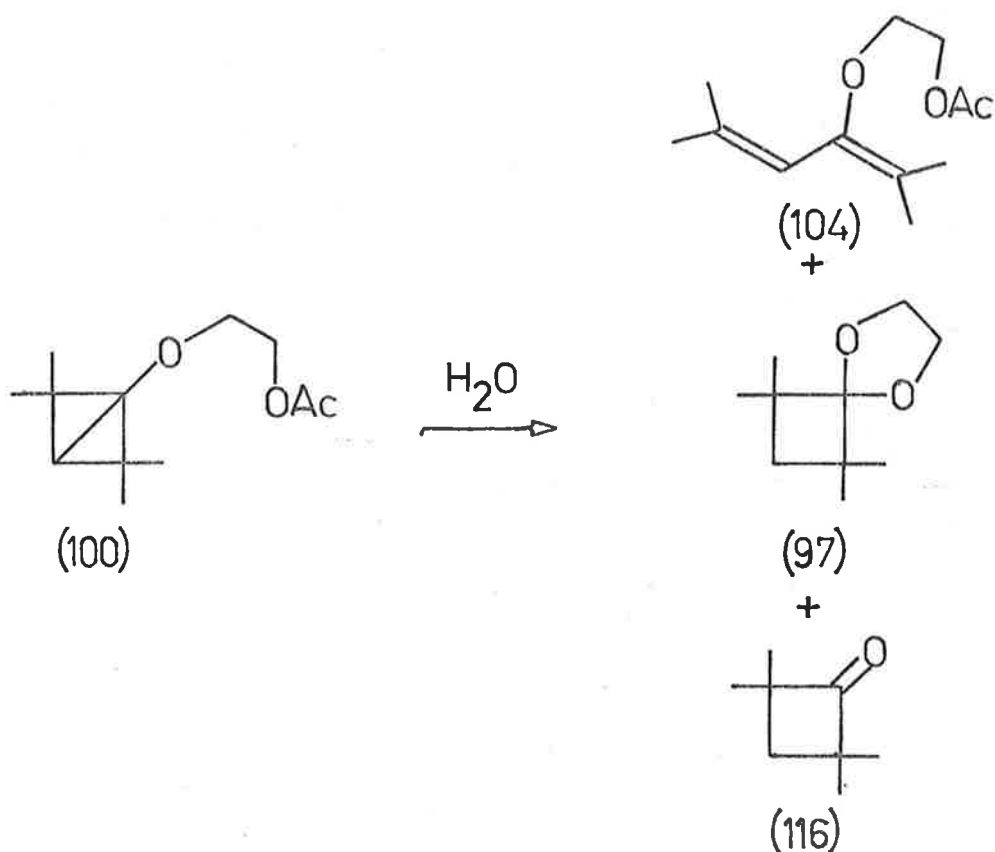


Diag. 5

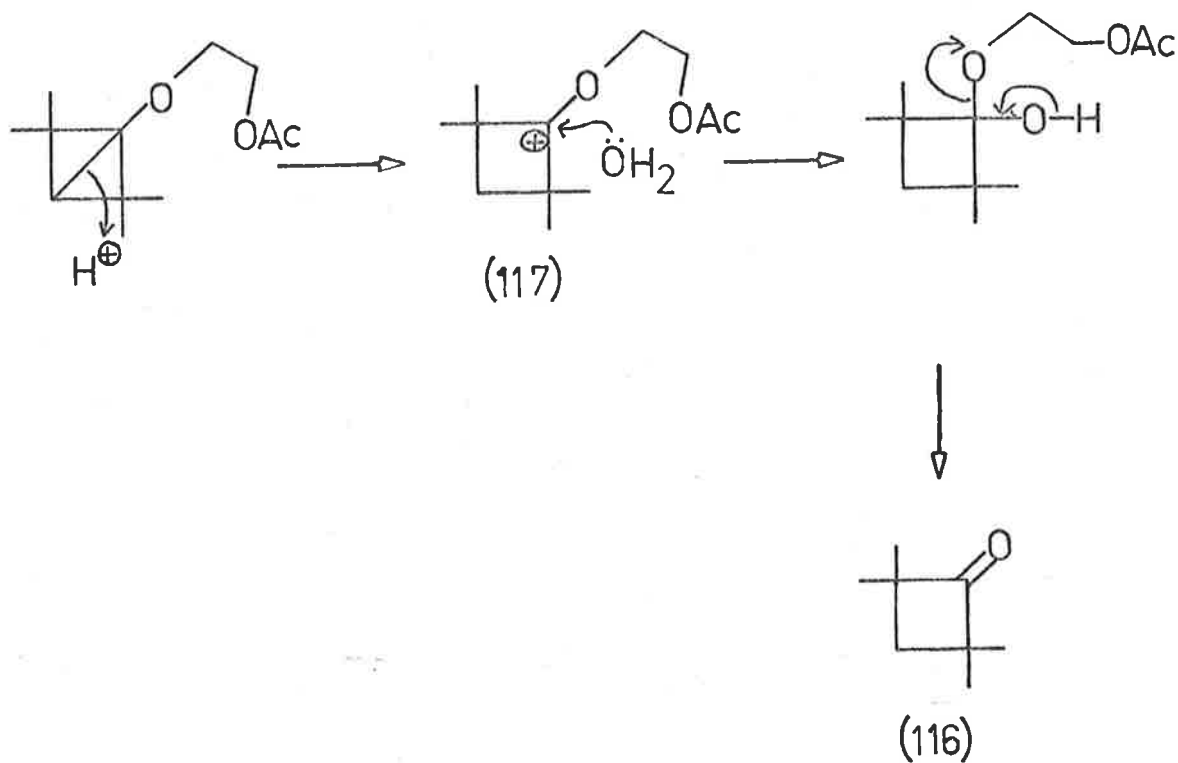


Diag. 6

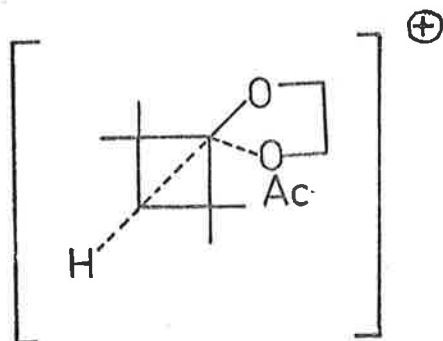
in Diag. 5 at δ 1.13 and 1.20 are due to the ring methyls of the bicyclobutane (100) and the absorption at δ 1.10 is due to the ketal (97). The cyclobutanone (116) could have been formed by addition of a proton to



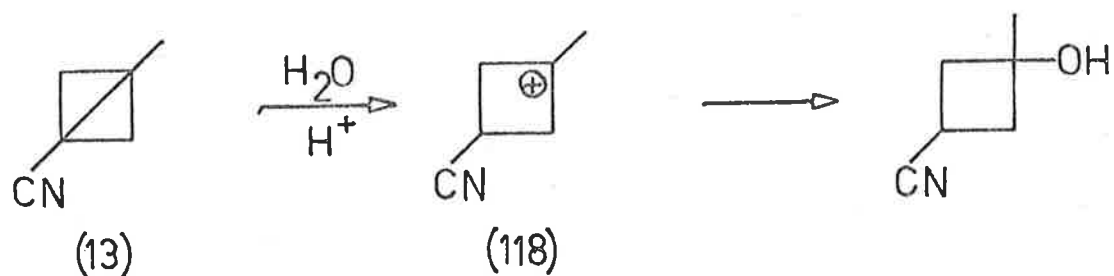
the central bond of the bicyclobutane (100) followed by hydrolysis of the ethylenedioxy group as shown in Scheme 26. This reaction would be catalysed by the presence of acetic acid from the hydrolysis of excess acetic anhydride. It is interesting to speculate whether the acetate group might participate to some extent in the solvolysis of the bicyclobutane (100) as shown below.



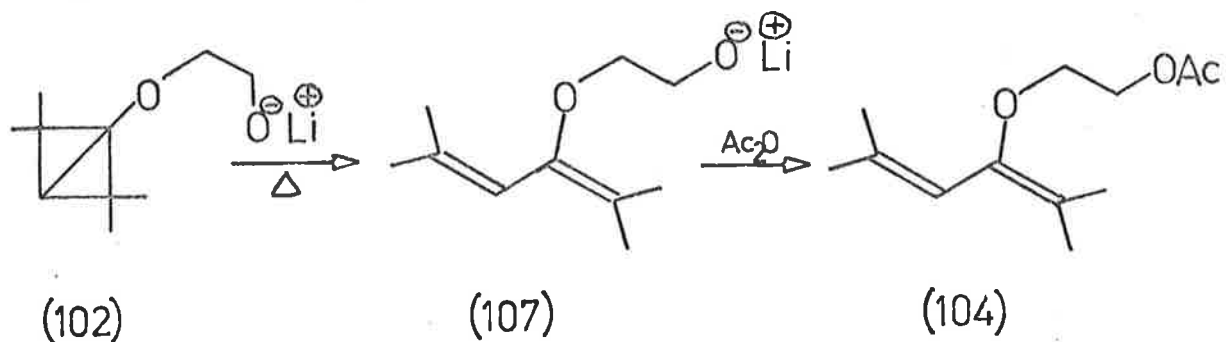
Scheme 26.



The presence of the angular oxygen function would be expected to stabilise the carbonium ion (117). It has been reported¹⁹ that the bicyclobutane (13) gives products derived from the carbonium ion (118), which would be stabilised by the methyl group, when treated with acid.



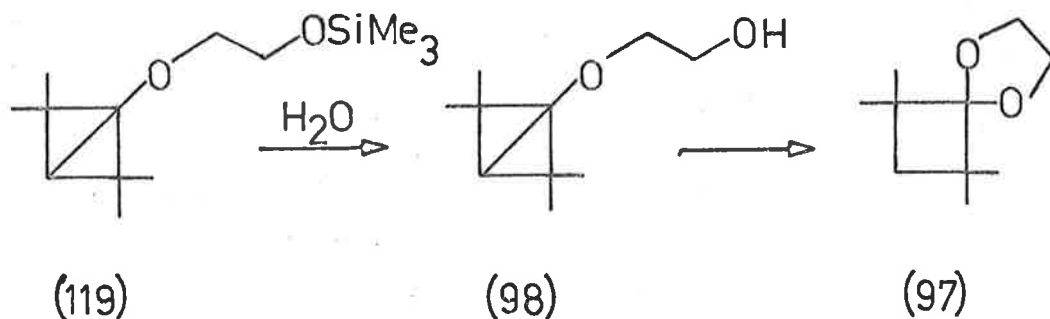
Because of the apparent stability of the carbonium ion (117) it was considered unlikely that the diene acetate (104) was formed by a protonolysis reaction. When a solution of the anion was heated under reflux briefly and its n.m.r. spectrum observed peaks at δ 1.53, 1.67, and 1.82 (1:2:1) were the major absorptions present. These peaks are attributed to the methyls of the diene anion (107). Support for this assignment was given by the repetition of this reaction on a larger



scale. Acetylation of the product while still in solution resulted in the formation of the diene acetate (104) as the major product. This result adds support to the hypothesis that the diene (104) is formed from the bicyclobutane (100) by a thermolytic reaction. The presence

of solvent and lithium salts is a complicating factor, however.

Addition of trimethylsilyl chloride to a solution of the anion in the n.m.r. tube led to the formation of the silyl ether (119) as judged from the appearance of the spectrum of this solution (δ 1.13, 1.20, 0.01; 2:2:3). The ketal (97) was the major compound formed when water was added to this silyl ether. Trimethylsilyl ethers are

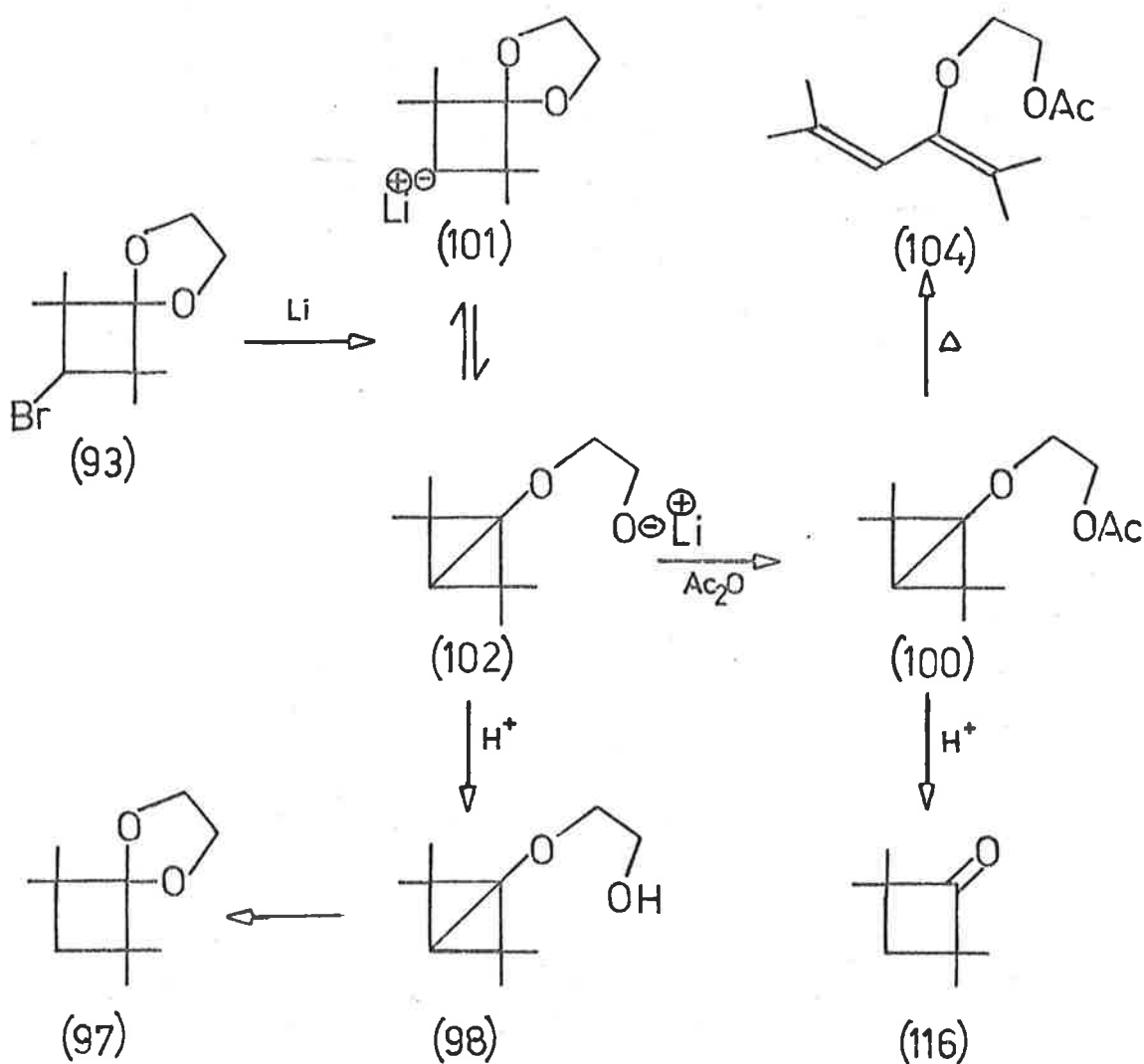


rapidly hydrolysed in either acidic or basic solutions.¹²¹ Hydrolysis of the silyl ether would produce the alcohol (98) which could form the ketal as previously discussed. The presence of hydrochloric acid from the hydrolysis of excess trimethylsilyl chloride could have catalysed the reaction.

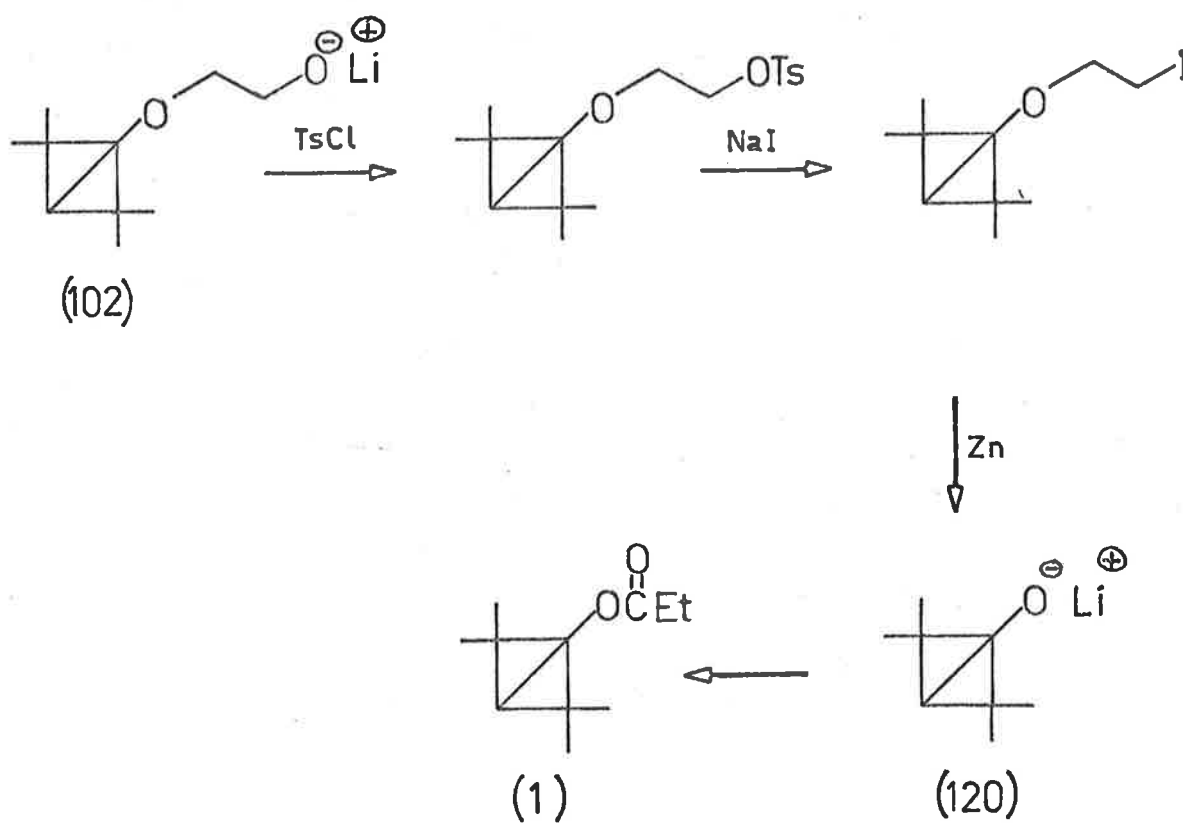
In order to avoid the presence of acid which could have catalysed the decomposition of the bicyclobutane the anion was allowed to react with methyl iodide and also with benzyl bromide. It was anticipated that the product could be separated from the salts by filtration and then isolated by evaporation of the solvent. However, neither reacted appreciably with the anion as judged from the appearance of the n.m.r.

spectra of the reaction mixtures. Similar difficulty has been reported with other alkoxides of lithium presumably due to their covalent nature.⁸⁸

From the appearance of the n.m.r. spectrum of the anion formed from the reaction of lithium with the ketal (93) and the reactions undergone by this anion it appears that bicyclobutanes with angular oxygen functions have been formed but are unstable under the conditions employed. Some of the reactions are summarised below.



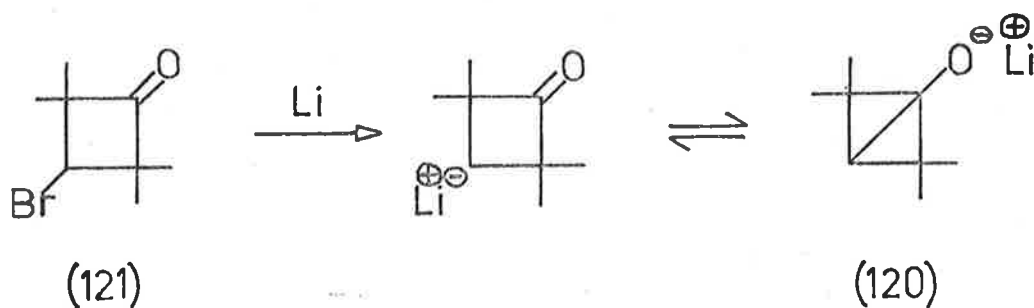
The proposed route to the sex-attractant of the American cockroach shown below is thus also unsuitable (Scheme 27).



Scheme 27.

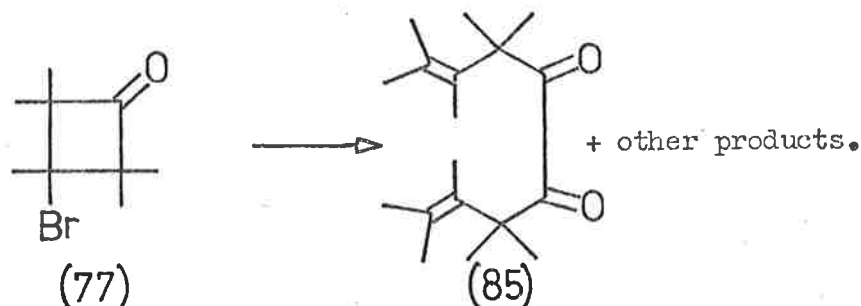
2.4. 3-Bromo-2,2,4,4-tetramethylcyclobutanone.

It seemed possible that the anion (120) could be prepared by the reaction of a metal with the title bromoketone (121) as shown in Scheme 4. This method would avoid the series of reactions outlined

Scheme 4.

in Scheme 27 for the preparation of this anion.

Previous attempts to carry out this type of reaction with the bromoketone (77) had been unsuccessful due to reduction of the carbonyl



group. It was expected that reduction of the bromine might be more favourable in the case of the secondary bromide (121) because of the

smaller amount of steric hindrance.

The bromoketone (121) was prepared by hydrolysis of the bromoketal (93) using 10% methanolic hydrochloric acid. It was obtained as an oil which was purified by preparative v.p.c. It could also be prepared by the Cristol-Firth¹⁰⁶ modification of the Hunsdiecker reaction from the known¹²² ketoacid (122). The n.m.r. spectrum (Table 16) supported the structural assignment.

Table 16.

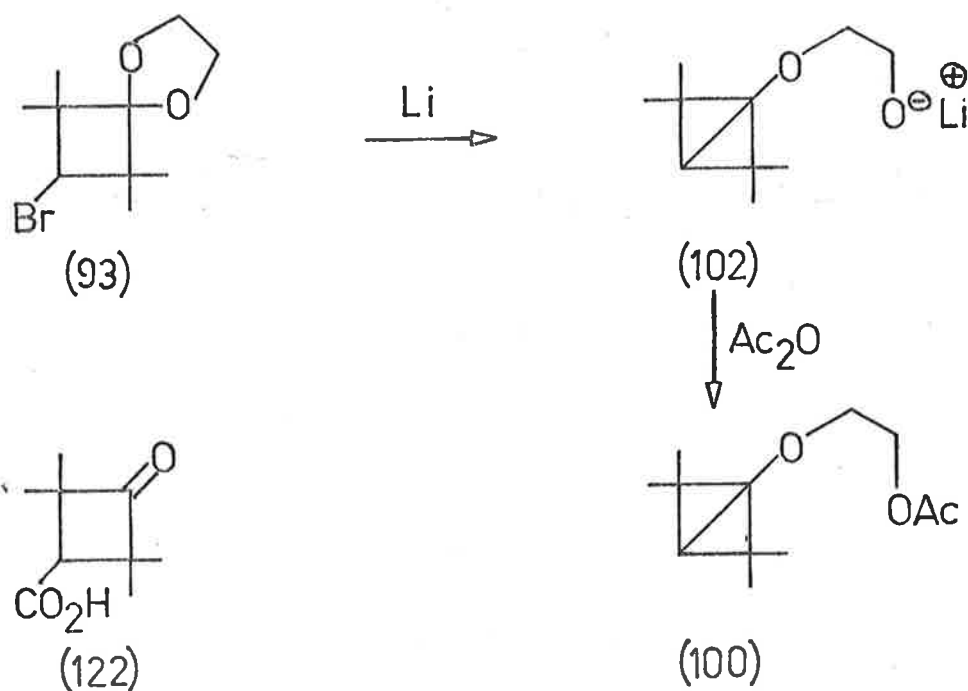
N.m.r. spectrum (CCl_4) of 3-Bromo-2,2,4,4-tetramethylcyclobutanone.

δ (p.p.m.)	Appearance	Proton Count	Assignment
1.25	singlet	12	ring Me_4
4.05	singlet	1	C-3 H.

Reaction of this bromoketone with lithium in dimethoxyethane and addition of acetic anhydride to the solution gave a mixture of at least twenty compounds by v.p.c. analysis. An examination of the n.m.r. of the solution before the addition of acetic anhydride was uninformative because of the broad nature of the peaks present. The mixture of products may have been due to the decomposition of the anion (120) and/or reduction of the carbonyl group as well as the bromine atom as observed for the bromoketone (77).

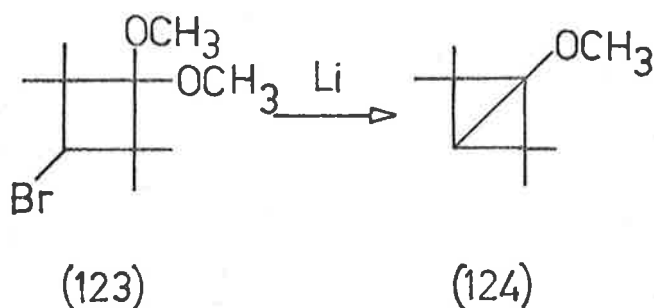
2.5 Attempted preparation of 1-bromo-3,3-dimethoxy-2,2,4,4-tetra-
methylcyclobutane.

Following the difficulty encountered with the reaction of bromo-
ketones with lithium it was decided to return ^{to} the other approach to
the bicyclobutane ring which had been partially successful. This
approach, the reaction of a bromoketal with a metal, had several
drawbacks. The addition of acetic anhydride to the anion (102) in

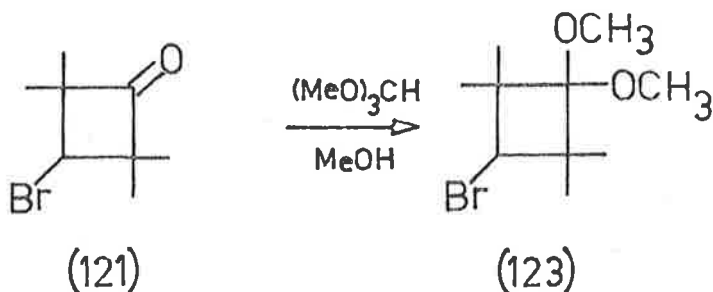


order to trap it led to difficulties in the work-up of the reaction
mixture. Because of the instability of the bicyclobutane ring
unnecessary handling of the compound was to be avoided. The possi-
bility that the acetate group participated in the decomposition of
the ring as previously discussed was also a problem. If an acyclic

ketal such as the title compound (123) could be prepared then both of these problems might be avoided. If this ketal were to react with lithium as shown then it should only be necessary to filter the



solution to remove the salts and then remove the solvent to isolate the bicyclobutane (124). The preparation of the bromoketone (121) made the synthesis of the required bromoketal (123) feasible by the route shown. It was envisaged that severe 1,2-interactions between the ring



methyl groups and the methoxyl groups which are not present in the parent ketone would make the ketal difficult to prepare.¹²³ Indeed, the only tetrasubstituted cyclobutanone ketals reported have been prepared by cycloaddition reactions between the dimethyl ketal of certain ketenes and olefins.^{124,125}

The reaction of the bromoketone (121) with trimethyl orthoformate and methanol in the presence of dry hydrogen chloride¹²⁶ was unsuccessful. Starting material was isolated on careful work-up of the reaction mixture. A similar reaction using 2,2,4,4-tetramethylcyclobutanone (116) as the ketone was carried out at the same time. The product from this reaction showed no carbonyl absorption in its infrared spectrum. Its n.m.r. spectrum (Table 17) is in accord with that expected for the dimethylketal of this ketone.

Table 17.

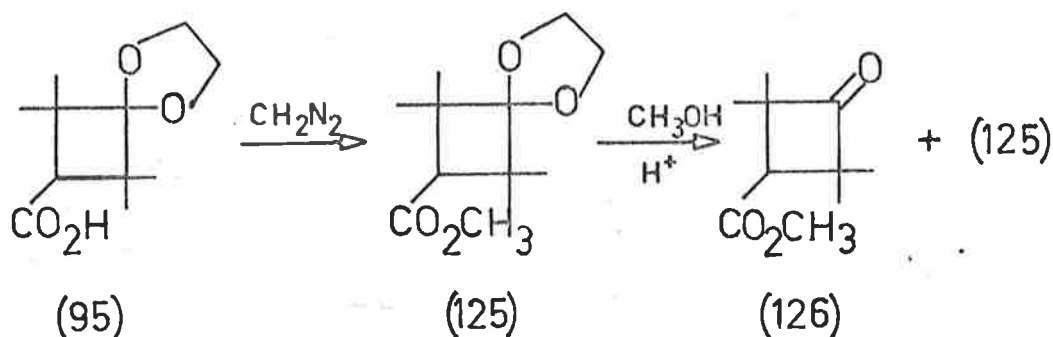
N.m.r. spectrum of 1,1-dimethoxy-2,2,4,4-tetramethylcyclobutane.

δ (p.p.m.)	Appearance	Proton Count	Assignment
1.10	singlet	12	ring Me ₄
1.63	singlet	2	C-3 H
3.27	singlet	6	methoxyls

The formation of the ketal suggests that 1,3-steric interaction between the bromine atom and the methoxyl group is an important factor in decreasing the stability of the bromoketal and thus preventing its formation in this equilibrium reaction.

The use of a high temperature and pressure to force the equilibrium between the ketone and the ketal in favour of the ketal was considered necessary. Under these conditions 2,2,4,4-tetramethyl-

cyclobuta-1,3-dione has been shown to ring open.¹²⁷ The bromoketone (121) might be expected to behave in a similar manner. The ester (125) was chosen for the reaction because the $\text{CH}_3\text{O}-\overset{\text{O}}{\parallel}{\text{C}}$ group would be expected to be a poor leaving group thus preventing ring opening. A ketal exchange was attempted in order to prevent water, which is



produced when a ketone is ketalised, from interfering with the reaction.

The ester (125) was prepared from the corresponding acid (95) by reaction with diazomethane. It was envisaged that the ester group could be converted to an acid group under basic conditions which should allow the ketal to survive. Subsequent conversion of the acid to a bromide by means of a Hunsdiecker reaction should lead to the formation of the required bromoketal (123).

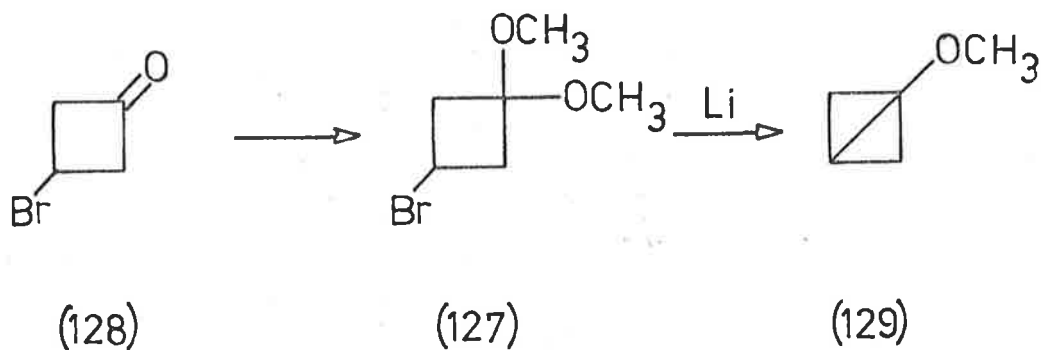
Treatment of the ester (125) with methanol and trifluoroacetic acid as catalyst at 170° in a "bomb" resulted in the formation of the ketone (126) and starting material in the ratio of about 1:4 as shown by v.p.c. analysis of the reaction mixture. Work-up of the reaction

mixture and an examination of the n.m.r. spectrum of the product confirmed this estimate. An authentic sample of the ketoester (126) was prepared from the ketal (95) by means of methanol and hydrochloric acid. The presence of the ketone in the product was apparently due to moisture being present despite precautions to exclude it. Apparently, the strain involved in the formation of the ketal is such that the equilibrium lies strongly in favour of the ketone (126) and the ester (125).

2.6 1-Bromo-3,3-dimethoxycyclobutane.

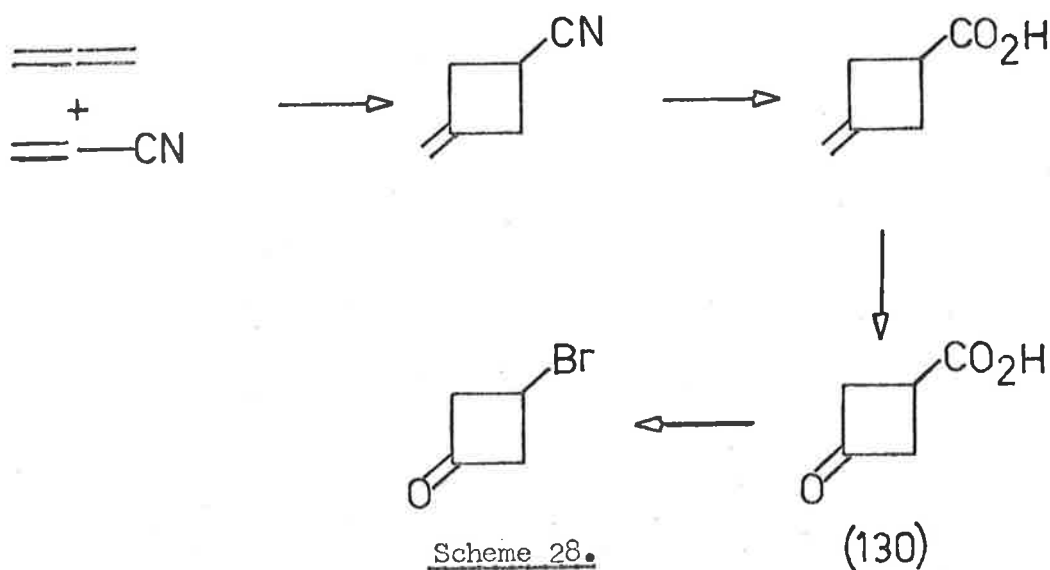
This section contains the results of a preliminary study of a suitable method for the preparation of the title compound (127).

The difficulty experienced in the preparation of 1-bromo-3,3-dimethoxy-2,2,4,4-tetramethylcyclobutane (123) was apparently due to the steric repulsions involved in converting a trigonal center of the molecule to a tetrahedral center. The dimethyl ketal of cyclobutanone itself is easily prepared.¹²⁸ It was therefore decided to prepare 3-bromocyclobutanone (128) in anticipation that it could be converted to the ketal (127). Treatment of this bromoketal with lithium was



expected to give the bicyclobutane (129). It was considered that the formation of a cyclobutene by the elimination of hydrogen bromide from the ketal (127) might be a problem in this approach. Slow addition of the bromoketal to the lithium was expected to reduce this side reaction.

Roberts and co-workers^{129,130} had reported the preparation of the ketoacid (130) by the route shown in Scheme 28. The dimerisation



Scheme 28.

of allene and acrylonitrile in the absence of a solvent¹³¹ resulted in an explosion which destroyed the bomb being used. The use of toluene as a solvent and an efficient means of stirring¹³¹ overcame this problem. The ketoacid (130) was allowed to react with bromine under the conditions of the Cristol-Firth¹⁰⁶ modification of the Hunsdiecker reaction. An oil whose infrared spectrum showed an absorption at 1785 cm^{-1} and no absorption due to a carboxylic acid group was isolated from the reaction mixture. It gave a positive Bielstein test. The n.m.r. spectrum of this oil consisted of two complex multiplets in the regions $\delta 3.80-4.73$ and $\delta 3.40-3.80$, and a third smaller multiplet in the region $\delta 2.07-3.40$. The ratio of the areas of these multiplets was approximately 1.5:3:1. It might be expected that the protons of this ketone would exhibit an A_2B_2X type spectrum. No attempt was made to analyse the spectrum. The presence of impurities may have contributed to the complexity of the spectrum. The oil rapidly darkened in colour at room temperature possibly due to the elimination of hydrogen bromide. It was allowed to stand at room temperature overnight with trimethyl orthoformate in methanol into which dry hydrogen chloride had been bubbled. Careful work-up of the reaction mixture produced an oil whose infrared spectrum showed no absorption due to a carbonyl group. The oil was purified by evaporative distillation. It gradually darkened at room temperature possibly due to an impurity which was not removed by distillation. The n.m.r. spectrum of the oil (Table 18) was in

accord with that expected for the bromoketal (127). The mass spectrum of the oil showed no peaks in the region of m/e 195, the molecular weight of the ketal (127). A base peak at m/e 115 expected for an ion produced from the molecular ion of (127) by loss of a bromine radical was present. A doublet at m/e 163, 165 suggested the presence of bromine in an ion which could have arisen by loss of a methoxyl radical from the molecular ion.¹³²

Table 18.

N.m.r. spectrum (CCl_4) of 1-bromo-3,3-dimethoxycyclobutane.

δ (p.p.m.)	Appearance	Proton Count	Assignment
2.20-3.00	complex multiplet	4	ring methylenes
3.10	singlet	6	methoxyls
3.67-4.33	multiplet	1	C-1 H

A preliminary experiment in which the bromoketal was allowed to react with lithium resulted in a product whose n.m.r. spectrum (CCl_4) exhibited broad absorption in the region δ 0.67-3.83. An absorption attributable to a methoxyl group was present at δ 3.03. The spectrum was not altered by the addition of deuterium oxide to the solution in the n.m.r. tube. Bicyclo[1.1.0]butane itself has a spectrum with three

multiplets at $\delta 0.44$, 1.37 , and 1.47 with relative areas of $1:1:1$.⁹

The appearance of the spectrum of the product obtained suggests that none of the bicyclobutane (129) was present.

EXPERIMENTAL

General.

Melting points were determined on a Kofler heating stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 or a Unicam SP200 spectrometer. N.M.R. spectra were recorded on a Varian D.P.60 or a D.A.-60-I.L. spectrometer operating at 60 Mc/sec using tetramethylsilane as an internal standard unless otherwise indicated. Mass spectra were recorded on a Perkin-Elmer Hitachi RMU 6D instrument. Analyses were carried out by the Australian Microanalytical Service, Melbourne.

Vapour phase chromatography was carried out with a Perkin-Elmer 800 gas chromatograph. The carrier gas was nitrogen and the flow rate was 30 ml/min. Preparative vapour phase chromatography was carried out using a Varian Aerograph 705 instrument.

Organic extracts were dried over magnesium sulphate.

Ether and 1,2-dimethoxyethane (D.M.E.) were dried by distillation from sodium.

The term "petroleum ether" refers to reagent grade material boiling in the range 40-60°. Whatman Sorbsil was used as adsorbant for column chromatography.

All glassware for reactions involving metals was flame dried under vacuum.

All peaks in the n.m.r. spectra reported were singlets which integrated for the correct number of protons, unless otherwise indicated.

Work described in Chapter 1.

3-Hydroxy-2,2-dimethylpropan-1-al (49).

(a) Condensation of isobutyraldehyde with formalin⁵⁵ resulted in variable yields of the hydroxyaldehyde (49) b.p. 60-90°/10 mm (lit.⁵⁵ b.p. 83-86°/15 mm), m.p. 99-101° (lit.⁵⁵ m.p. 96-97°). On several occasions 2,2-dimethylpropan-1,3-diol b.p. 208-210° (lit.⁵⁷ b.p. 176-205°), m.p. 123-127° (lit.⁵⁷ m.p. 130°) was obtained as a waxy solid.

(b) A Liebig condenser (2 cm x 50 cm) fitted with a sinter was charged with a solution of Amberlite IRA400 resin (40 g) in water. Hot water (60°) was continuously pumped through the jacket. A solution of 10% sodium carbonate (1 l) was run through the column. Isobutyraldehyde (41.6 g) and 40% formalin (36 g) were added to the top of the column in a dropwise manner over eight hours. The oily solution which collected at the bottom of the column was extracted with ether. Removal of solvent from the dried ether solution gave the hydroxyaldehyde (49) (14.5 g, 25%) b.p. 90-100°/25 mm (lit.⁵⁸ b.p. 90-95°/15 mm).

2,2-Dimethylpropan-1,3-diol (50).

Condensation⁵⁷ of isobutyraldehyde with formalin produced the diol (50) (56%) as a waxy solid m.p. 123-127°, b.p. 208-210° (lit.⁵⁷ m.p. 130°, b.p. 176-205°).

3-Bromo-2,2-dimethylpropan-1-ol (51).

Treatment⁵⁹ of the diol (50) with hydrogen bromide and acetic acid produced the bromoalcohol (51) (83%) as a colourless oil b.p. 92-98°/26 mm (lit.⁵⁹ b.p. 76-80°/13 mm).

Attempted oxidation of the bromoalcohol (51).

(a) Oxidation of the alcohol (51) with chromium trioxide in sulfuric acid⁶¹ or pyridine⁶² resulted in oils after the usual work-up. The infrared spectra of these oils showed broad absorptions in the region near 1700 cm⁻¹.

(b) Treatment of the alcohol (51) with dimethyl sulfoxide and acetic anhydride⁶³ produced an oil, ν_{\max} 1735, 1220 cm⁻¹ ($\text{-O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$). This oil had a strong odour and its infrared spectrum was different from that of the acetate of the bromoalcohol (51).⁵⁹

(c) Phosgene (13 g) was bubbled into an ice-cooled, stirred solution of ether (100 ml). To this was added, in one lot, the bromoalcohol (51) (10 g) in ether (25 ml). Several drops of quinoline were added to the solution until a slight precipitate formed. After 4 hr the solution was filtered and solvent and excess phosgene removed under vacuum. The chloroformate ester, ν_{\max} (film) 1780, 1150 cm⁻¹, was transferred to a three-necked flask fitted with a calcium chloride tube, a dropping funnel, and a thermometer. Dry dimethyl sulfoxide (10 ml) was added

slowly to the stirred and cooled ($0-5^{\circ}$) oil. After a short time bubbles formed in the solution and the mixture solidified. The flask was immediately cooled with dry ice-acetone to keep the temperature at 5° . The remaining dimethyl sulfoxide was added causing the solid to break up. After all the gas had stopped forming the mixture was stirred at room temperature for $1/4$ hr. Triethylamine (10 ml, 20% excess) was added to the mixture with cooling (10°). After $3/4$ hr at room temperature the mixture was diluted with water and the aqueous solution was extracted with ether. The ethereal layer was washed with dilute hydrochloric acid and water and dried. Removal of the solvent gave 3-bromo-2,2-dimethylpropan-1-al (5 g, 50%) b.p. $62-68^{\circ}/23$ mm. (Found: C, 36.0; H, 5.5. C_5H_9BrO requires C, 36.4; H, 5.5%). The oil was stable for about 3 months if stored in a refrigerator.

3-p-Toluenesulfonyloxy-2,2-dimethylpropan-1-al (53).

Tosylation⁶⁷ of 3-hydroxy-2,2-dimethylpropan-1-al (49) produced (53) (77%) as a colourless solid m.p. $65-66^{\circ}$ (lit.⁶⁷ $61-63^{\circ}$).

3-Bromo-2,2-dimethylpropan-1-al (48).

A mixture of the tosylaldehyde (53) (1.7 g) and sodium bromide (0.7 g) in dimethyl sulfoxide (20 ml) was stirred at 80° for 12 hr. The cooled mixture was diluted with water and the aqueous solution extracted with ether. The ethereal layer was washed exhaustively with water and dried. Removal of solvent gave an oil (0.75 g, 69%) whose

infrared spectrum was identical to that of 3-bromo-2,2-dimethylpropan-1-al previously obtained.

Reaction of 3-bromo-2,2-dimethylpropan-1-al (48) with lithium.

The bromoaldehyde (48) (1 g) in ether (25 ml) was added to a stirred suspension of finely cut lithium (0.2 g) in ether (15 ml) during 6 hr. The solution was kept at 10° under nitrogen. Excess lithium was removed by filtration through glass wool and the resulting solution was added to an excess of acetic anhydride. A white precipitate formed. After 1/4 hr a solution of pyridine in water (10 ml, 50%) was added and the mixture stirred vigorously for 1/4 hr. The mixture was extracted with ether and the ethereal layer washed with water to remove any excess pyridine. Removal of solvent from the dried ether solution gave 2,2-dimethylcyclopropyl acetate (0.52 g, 67%) b.p. 40°/26 mm. ν_{\max} (film) 1740, 1230 cm^{-1} ($-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$). An analytical sample was prepared by preparative v.p.c. (5' SE30, 20%) (Found: C, 65.5; H, 9.4. $\text{C}_7\text{H}_{12}\text{O}_2$ requires C, 65.6; H, 9.4%).

A sample of the anion prepared as above but in 1,2-dimethoxyethane as solvent was pipetted into an n.m.r. tube and its n.m.r. spectrum observed.

2,2-Dimethylcyclopropylmethyl ketone (56).

Addition⁶⁹ of trimethylsulfoxonium ylide to mesityl oxide produced this ketone as a colourless liquid (50%) b.p. 46-50°/45 mm (lit.⁶⁹

b.p. 69-71°/80-85 mm).

Baeyer-Villiger oxidation¹³³ of 2,2-dimethylcyclopropyl methyl ketone.

Hydrogen peroxide (0.5 ml, 86%) and freshly distilled trifluoroacetic anhydride (1.5 ml) were heated under reflux in dichloromethane (5 ml) for $\frac{1}{2}$ hr. The solution was added to a stirred solution of the ketone (56) (1.2 g) and disodium hydrogen phosphate (3 g) in dichloromethane (20 ml). This mixture was heated under reflux for 2 hr. The cooled solution was filtered and washed with a saturated solution of sodium bicarbonate. Removal of solvent from the dried dichloromethane solution gave 2,2-dimethylcyclopropyl acetate (0.5 g, 40%) which was contaminated by a trace of starting material. The infrared and n.m.r. spectra were identical to those of the acetate previously obtained other than for peaks due to starting material.

3-Hydroxy-2,2-dimethylpropiophenone (61).

Condensation⁷² of isobutyrophenone¹³⁴ and formalin gave this ketone as an oil (20%) b.p. 104-107°/0.3 mm (lit.⁷² b.p. 138°/1 mm).

Isobutyrophenone.

This compound b.p. 118°/25 mm (lit.¹³⁴ b.p. 217°) was prepared according to the literature.¹³⁴



3-Bromo-2,2-dimethylpropiophenone (59).

Treatment of the alcohol (61) with hydrogen bromide in ether⁵¹ gave the bromoketone (59) as an oil (60%) b.p. 88°/0.3 mm (lit.⁵¹ b.p. 110-111°/0.5 mm).

Reaction of 3-bromo-2,2-dimethylpropiophenone with lithium.

The bromoketone (59) was reacted with lithium under conditions similar to those for the bromoaldehyde (48). 2,2-Dimethyl-1-phenylcyclopropyl acetate (60) (40%) was obtained as an oil b.p. 90-95°/1 mm whose infrared spectrum was identical to that of an authentic sample⁷¹ b.p. 70-72°/0.5 mm prepared from β,β -dimethylacrylophenone.¹³⁵

The n.m.r. of a solution of the anion in D.M.F. was observed. The solution resulting from addition of acetic anhydride (2 drops) to the n.m.r. tube was diluted with water and extracted with ether. Removal of solvent from the dried ether solution gave an oil whose infrared and n.m.r. spectra were identical to that of an authentic sample of 2,2-dimethyl-1-phenylcyclopropyl acetate (60).

Reaction of 3-p-toluenesulfonyloxy-2,2-dimethylpropan-1-al (53) with lithium.

A solution of the tosylaldehyde (53) (0.25 g) in ether (5 ml) was slowly added to a stirred suspension of lithium (0.1 g) in ether

(5 ml). The solution was maintained under nitrogen at room temperature. After 16 hr the filtered solution was added to acetic anhydride (0.5 ml). No precipitate formed. Work-up of the reaction in the normal way gave a solid (0.22 g, 88%) which was identical to starting material in every respect.

Work described in Chapter 2.

3-Hydroxy-2,2,4,4-tetramethylcyclobutanone.

2,2,4,4-Tetramethylcyclobuta-1,3-dione (Koch-Light) was hydrogenated at 40° and 70 p.s.i. in 40 g lots in ethanol (250 ml) as solvent.¹²⁷ Raney nickel¹³⁶ (4 g) was used as a catalyst. The hydroxyketone was obtained as a solid m.p. 110° (lit.¹²⁷ 114°) in 60% yield.

3-Tetrahydropyranyloxy-2,2,4,4-tetramethylcyclobutanone.³³

The hydroxyketone (50 g) obtained from the previous experiment was suspended in a cooled (5°) solution of dihydropyran (56 g) and *p*-toluenesulfonic acid (20 mg). After 18 hr the solution was poured into a 10% solution of sodium carbonate and the aqueous solution extracted with ether. Removal of solvent from the dried ethereal solution gave an oil which was dried by azeotroping with benzene and distilled. The fraction boiling at greater than 90° was collected. The yield (92 g, 115%) suggested that an impurity was present.

2,2,4,4-Tetramethyl-3-methylene-1-tetrahydropyranyloxycyclobutane.

This compound was obtained from the above ketone by the use of methylenetriphenylphosphorane in ether³³ as a liquid which was subjected to methanolysis without further purification.

1-Hydroxy-2,2,4,4-tetramethyl-3-methylenecyclobutane (80).

This alcohol (80) was obtained from the corresponding tetrahydro-pyranyl ether by methanolysis⁶ as a solid b.p. $88^{\circ}/18$ mm, m.p. $46-48^{\circ}$ (lit.⁶ m.p. $48-49^{\circ}$) in 65% yield.

2,2,4,4-Tetramethyl-3-methylenecyclobutanone (78).

This ketone was obtained from the corresponding alcohol by oxidation⁶ using "Jones⁶¹ Reagent" as a volatile solid m.p. 42° (lit.⁶ m.p. $42-43^{\circ}$) in a 50% yield. Attempted oxidation of the alcohol using ruthenium dioxide and sodium metaperiodate⁹⁸ or dimethyl sulfoxide and acetic anhydride⁶³ resulted in high recoveries of starting material.

Attempted Wittig reaction at -60° .

To a two-necked flask, fitted with a constant pressure dropping funnel and a thermometer, was added ether (100 ml), methyltriphenylphosphonium iodide (10.1 g) and potassium tertiary-butoxide (5.6 g). The solution was maintained under a pressure of nitrogen. The expected yellow colour of the phosphorane formed. The flask was cooled to -60° whereupon the yellow colour faded. It reappeared when the flask was allowed to warm temporarily to room temperature. A solution of 2,2,4,4-tetramethylcyclobuta-1,3-dione (1.6 g) in ether (25 ml) was added slowly to the cooled flask through a tube which was surrounded by a dry ice-acetone solution. After 5 hr at -60° the solution was diluted with water. At one stage the temperature rose to -40° . The ethereal

layer was separated and the solvent removed. The residual oil was dissolved in petroleum ether (100 ml) and the solution cooled in ice. The triphenylphosphine oxide which precipitated was removed by filtration. The petroleum ether solution was washed with 80% methanol (2 x 50 ml) and the methanol layers were combined and back-extracted with petroleum ether (100 ml). The petroleum ether extracts were combined and dried. Removal of the solvent gave a solid (2.0 g) m.p. 135-137° which had an infrared spectrum similar to that reported⁹⁴ for the product obtained from the reaction of 2,2,4,4-tetramethylcyclobuta-1,3-dione with this ylide at 65° (m.p. 139-140°).

6,6,8,8-Tetramethyl-11-dioxaspiro[4.3]octan-7-one.

Reaction of 2,2,4,4-tetramethylcyclobuta-1,3-dione with ethylene glycol and subsequent hydrolysis of the diketal formed¹⁰⁰ gave the required monoketal as a solid b.p. 84-87°/5 mm, m.p. 56-59° (lit.¹⁰⁰ b.p. 84-87°/5 mm, m.p. 56-57°) in 28% yield.

6,6,8,8-Tetramethyl-7-methylene-1,4-dioxaspiro[4.3]octane (82).

Methyltriphenylphosphonium iodide was prepared by adding methyl iodide (80 g) in benzene (100 ml) to a stirred solution of triphenylphosphine (131 g) in benzene (400 ml) during 2 hr. The mixture was heated under reflux for 2 hr. The solid which precipitated when the solution was cooled (10°) was collected by filtration. It was dried under vacuum for 5 days. The methyltriphenylphosphine iodide collected

(195.5 g, 97%) had m.p. 179-180° (lit.¹³⁷ m.p. 179-180°).

Potassium (22.5 g) was added to tertiary-butanol (250 ml) (distilled from calcium hydride) and the mixture heated under reflux until all the potassium had dissolved. Most of the excess alcohol was blown off the hot mixture with a stream of nitrogen. Ether (1 l) was distilled from sodium onto the white solid which remained. Triphenylphosphonium iodide (216 g) was added to the mixture with stirring under nitrogen. After 2 hr the ketal (80 g) previously prepared was added and the mixture heated under reflux for 18 hr. Work-up as previously described gave a solid (60.2 g, 78%) b.p. 87°/23 mm, m.p. 78-79° (lit.¹⁰⁰ 75-80°/5 mm). The difference in boiling points is presumably due to an error in the literature value. No melting point was recorded. The infrared and n.m.r. spectra are identical to those recorded.¹⁰⁰

2,2,4,4-Tetramethyl-3-methylenecyclobutanone (78).

The methyleneketal (82) (0.18 g) was dissolved in a mixture of methanol (10 ml) and dilute hydrochloric acid (5 ml) and the solution heated under reflux for 8 hr. The cooled solution was extracted with ether and the ethereal layer washed successively with sodium bicarbonate solution and water. Removal of solvent from the dried ether solution gave the methyleneketone (0.11 g, 85%) as a volatile solid m.p. 42-43° (lit.⁶ m.p. 42-43°).

2,2,4,4-Tetramethyl-3-phenyliminocyclobutanone¹⁰¹ (83).

Reaction of 2,2,4,4-tetramethylcyclobuta-1,3-dione with aniline in a Dean and Stark apparatus gave the monoimine (83) b.p. 112-115°/6 mm (lit.¹⁰¹ b.p. 124-125°/7 mm) in 37% yield.

2,2,4,4-Tetramethyl-1-methylene-3-phenyliminocyclobutane (84).

The monoimine (83) (2.0 g) in ether (10 ml) was added, in one lot, to a stirred suspension of methyltriphenylphosphonium iodide (4.2 g) and potassium tertiary-butoxide (1.2 g) in ether (50 ml), under nitrogen. The yellow solution was stirred 18 hr. Work-up of the reaction mixture as previously described gave an oil (1.9 g, 96%) which crystallised when scratched. 2,2,4,4-Tetramethyl-1-methylene-3-

phenyliminocyclobutane (m.p. 45-47°) was purified by evaporative distillation (60°/3 mm). The solid decomposed on standing to the methyleneketone (78) and aniline and this was probably the reason why accurate analysis figures could not be obtained (Found: C, 71.2; H,

7.8. C₁₅H₁₉N requires C, 84.5; H, 9.0%). ν_{\max} (Nujol) 3020(w), 1660, and 900 (C=CH₂), 1720 (C=N-), and 1600 cm⁻¹ (aromatic ring); n.m.r. (CCl₄) δ 1.10, 1.20 (ring Me₄), 4.83, 4.93 (2s, C=CH₂), 6.57-7.22 (m, aromatic protons).

2,2,4,4-Tetramethyl-3-methylenecyclobutanone (78).

The monoimine (84) (0.9 g) and 50% acetic acid (50 ml) were stirred and heated under reflux 1 hr. A solid collected in the condenser after a few minutes. The mixture was basified with sodium bicarbonate solution and extracted with ether. The ethereal extract was washed with dilute hydrochloric acid and worked up to give a solid (0.6 g, quantitative) m.p. 40-42° (lit.⁶ m.p. 42-43°). The infrared and n.m.r. spectra were identical to those previously obtained.

3-Bromo-2,2,3,4,4-pentamethylcyclobutanone (77).

Hydrogen bromide (Matheson) (5 ml) was condensed into a flask containing the methyleneketone (78) (0.9 g) by means of a dry ice-acetone trap which was connected to a decalin trap. The dry ice-acetone trap was allowed to warm to room temperature. After 3 hr the hydrogen bromide had evaporated leaving a white solid. The solid was dissolved in ether and the ethereal layer washed with sodium bicarbonate solution and water. Removal of solvent from the dried ether solution gave 3-bromo-2,2,3,4,4-pentamethylcyclobutanone (77) (0.9 g, 63%) as a white solid m.p. 65-66°. An analytical sample was obtained by column chromatography using petroleum ether as eluent and subsequent sublimation (60°/0.1 mm). (Found: C, 44.2; H, 6.2. C₉H₁₅BrO requires C, 49.3; H, 6.9%). A satisfactory analysis could not be obtained for this compound, although its n.m.r. spectrum and v.p.c. chromatogram indicated that it was a pure sample and had the assigned structure.

Its mass spectrum was also in accord with the assigned structure M^+ 189, 190, m/e 148(4), 150(4), 139(8), 111(45), and a base peak at m/e 70(100%).

Reaction of 3-bromo-2,2,3,4,4-pentamethylcyclobutanone (77) with lithium.

The bromoketone (77) (1.1 g) in ether (15 ml) was added, during 1.3 hr, to a stirred suspension of finely cut and beaten lithium (0.15 g) in ether (10 ml). The solution was maintained in a nitrogen atmosphere at room temperature. After 1/4 hr the solution was yellow and the lithium had a pink coating on its surface. The mixture was gently heated under reflux for 2 hr. The surface of the lithium became shiny and the metal was consumed. After a total of 4 hr the solution was filtered through glass wool and added to an excess of acetic anhydride. A thick yellow precipitate formed. Work-up as previously described gave an oil whose v.p.c. chromatogram showed many peaks. Preparative v.p.c. (5' SE30, 20%) gave octamethyldeca-2,8-diene-5,6-dione (85) (65 mg) as an orange solid m.p. 66-68°. (Found: C, 77.2; H, 11.4. $C_{18}H_{30}O_2$ requires C, 77.7; H, 10.9%).

7-Bromo-6,6,7,8,8-pentamethyl-1,4-dioxaspiro[4.3]octane (89).

A three-necked flask (100 ml) containing the methyleneketal (82) (2.0 g) was fitted with two dry ice-acetone condensers and a nitrogen inlet. Hydrogen bromide (Matheson) was condensed into the

flask through one of the condensers until it covered the solid ketal. The second condenser was fitted with a bunsen valve. After 1 hr the hydrogen bromide was blown off with a stream of dry nitrogen. Ammonia (50 ml) was distilled into the flask from potassium. The ammonia was then blown off with a stream of nitrogen. The solid which remained was sublimed ($120^{\circ}/20$ mm) to free it from ammonium bromide. Column chromatography of the solid using petroleum ether as eluent gave 7-bromo-6,6,7,8,8-pentamethyl-1,4-dioxaspiro[4.3]octane (89) (2.0 g, 70%) as a colourless solid m.p. $118-120^{\circ}$. An analytical sample was obtained by sublimation ($80^{\circ}/0.1$ mm) (Found: C, 50.4; H, 7.3). $C_{11}H_{19}BrO_2$ requires C, 50.2; H, 7.3%. ν_{max} (Nujol) 1030, 1065, and 1102 cm^{-1} (ketal). Later fractions from the column contained the bromoketone (77) (0.3 g) m.p. $63-65^{\circ}$.

Reaction of the bromoketal (89) with sodium-potassium alloy.

The bromoketal (89) (0.5 g) in benzene (2 ml) was added during $\frac{1}{2}$ hr to a stirred suspension of sodium-potassium alloy¹³⁸ (0.2 ml) in benzene (4 ml). The mixture was maintained in a nitrogen atmosphere at room temperature for 1 hr then at 48° during 10 hr. The remaining alloy was destroyed by careful addition of water to the solution (in an atmosphere of nitrogen!). The benzene solution was washed with water and dried. The n.m.r. spectrum of this solution showed peaks at $\delta 0.77, 0.88, 1.08, 1.13, 1.30, 2.53, 3.45, 5.50,$ and 5.62 . V.p.c. showed the presence of two compounds in the ratio of about 3:1. These

were shown to be 6,6,7,8,8-pentamethyl-1,4-dioxaspiro[4.3]octane (90) and 6,6,8,8-tetramethyl-7-methylene-1,4-dioxaspiro[4.3]octane (82) by their behaviour as compared with authentic compounds and by a comparison of n.m.r. spectral data. A solution of the anion was pipetted into an n.m.r. tube and the spectrum recorded. It was similar to that detailed above.

6,6,7,8,8-Pentamethyl-1,4-dioxaspiro[4.3]octane (90).

The methyleneketal (82) (1.8 g) and platinum oxide (11.7 mg) were stirred in ether (30 ml) in an atmosphere of hydrogen until the theoretical amount of hydrogen had been taken up ($1\frac{1}{2}$ hr). The ethereal solution was filtered and the solvent removed. The oily product was chromatographed using petroleum ether as eluent. 6,6,7,8,8-Pentamethyl-1,4-dioxaspiro[4.3]octane (90) (1.6 g, 90%) was obtained as a waxy solid m.p. $58-59^{\circ}$ after evaporative distillation ($90^{\circ}/25$ mm) (Found: C, 71.7; H, 11.1. $C_{11}H_{20}O_2$ requires C, 71.7; H, 10.9%). ν_{\max} (Nujol) 1060, 1080, 1165 cm^{-1} (ketal); n.m.r. (benzene) δ 0.80 (d, $J = 7$ Hz, C-7 Me), 1.08, 1.14 (C-2, C-4 Me₄), 1.59 (q, $J = 7$ Hz, C-7 H), and 3.43 (ketal protons). This compound has been prepared by this method but no details were given.⁹⁹

7-Hydroxymethyl-6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane (94).

Diborane, prepared from sodium borohydride (11 g) and iodine (28 g) in diglyme (100 ml),¹³⁹ was bubbled into a solution of the

methyleneketal (82) (19.5 g) in tetrahydrofuran (50 ml, distilled from calcium hydride) during $\frac{1}{2}$ hr. The solution was maintained at -78° in an atmosphere of nitrogen. During 12 hr the mixture was allowed to warm to room temperature. Sodium hydroxide (3N, 100 ml) was added carefully to the solution followed by hydrogen peroxide (30%, 40 ml). The solution was heated under reflux (2 hr), cooled, and diluted with saturated sodium chloride solution. This solution was extracted with ether and the ethereal layer washed with ferrous sulfate solution and water. Removal of solvent from the dried ether solution gave 7-hydroxy-methyl-6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane (94) (20.1 g, 93%) as a solid m.p. $75-77^{\circ}$. An analytical sample m.p. $79-80^{\circ}$ was prepared by preparative v.p.c. (5' SE30, 20%) (Found: C, 65.8; H, 10.0. $C_{11}H_{20}O_3$ requires C, 66.0; H, 10.1%). ν_{max} (Nujol) 3200 (OH), 1160, and 1030 cm^{-1} (ketal); n.m.r. (CCl_4) δ 1.01, 1.04 (ring Me_4), 1.57 (t, $J = 8$ Hz, C-7 H), 2.32 (OH), 3.58 (d, $J = 8$ Hz, $-CH_2-OH$ methylene protons), and 3.78 (ketal protons).

Oxidation of the alcohol (94).

"Jones⁶¹ reagent" (10 ml) was added over $\frac{1}{2}$ hr to a stirred solution of the alcohol (94) (5 g) in acetone (60 ml, distilled from potassium permanganate) at 0° . After a further $\frac{1}{4}$ hr the acetone was poured off the salts which had formed and diluted with ether. This ethereal solution was extracted with sodium hydroxide solution (1N, 3 x 50 ml). Removal of solvent from the dried ether solution gave a

solid which was chromatographed using petroleum ether as eluent.

7-(6,6,8,8-Tetramethyl-1,4-dioxaspiro[4.3]octane)methyl-6',6',8',8'-tetramethyl-1',4'-dioxaspiro[4.3]octane-7'-carboxylate (96) (0.6 g)

was obtained as a solid. An analytical sample m.p. 88-92° was obtained by evaporative distillation (120°/0.5 mm) (Found: C, 66.8; H, 9.2.

$C_{22}H_{36}O_6$ requires C, 66.6; H, 9.2%). ν_{max} (Nujol) 1720, 1230 ($\overset{O}{\parallel}C-O-$), 1170, 1140, and 1040 cm^{-1} (ketals). The sodium hydroxide layers were

combined, acidified with concentrated hydrochloric acid, and extracted with ether. Removal of solvent from the dried ether solution gave

6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane-7-carboxylic acid (95)

(3.6 g, 67%) as a white solid m.p. 128-129°. An analytical sample,

which had the same m.p. was prepared by sublimation (120°/0.01 mm).

(Found: C, 61.4; H, 8.6. $C_{11}H_{18}O_4$ requires C, 61.7; H, 8.5%). ν_{max}

(Nujol) 3200-2600 (carboxylic acid OH) 1695, 1275 ($\overset{O}{\parallel}C-O-$) 1140, and 1030 cm^{-1} (ketal).

7-Bromo-6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane (93).

A two-necked flask (100 ml) was fitted with a constant pressure dropping funnel and a Dean and Stark apparatus modified to be similar to a Quickfit WE7 type water estimator. The flask was charged with carbon tetrachloride (30 ml), red mercuric oxide (4.4 g), and the acid (95) (4.3 g) and covered with aluminium foil to exclude light. The contents of the flask were heated under reflux and stirred. Bromine

(4 g, washed with concentrated sulfuric acid and distilled) in carbon tetrachloride (10 ml) was added during $2\frac{1}{2}$ hr to the refluxing solution. After a further 1 hr the mixture was cooled and filtered. The filtrate was washed with sodium carbonate solution and water. Removal of solvent from the dried carbon tetrachloride solution gave a solid which was chromatographed using petroleum ether as eluent. 7-Bromo-6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane (93) (3.0 g, 60%) was obtained as a white solid m.p. $64-65^{\circ}$. An analytical sample was prepared by sublimation ($60^{\circ}/0.05$ mm) (Found: C, 48.4; H, 7.0. $C_{10}H_{17}BrO_2$ requires C, 48.2; H, 6.8%). ν_{\max} (Nujol) 1125, 1040, and 1020 cm^{-1} (ketal).

Reaction of the bromoketal (93) with sodium-potassium alloy.

The general procedure used was similar to that employed for the bromoketal (89). A temperature of 60° was used for the reaction. An n.m.r. spectrum of the product in the benzene solution showed peaks at $\delta 1.21$, 1.30 , and 3.42 in the ratio 6:1:2. Removal of solvent from the benzene solution gave an oil whose infrared and n.m.r. spectra were identical to those of an authentic sample of 6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane (97). An n.m.r. spectrum of the benzene solution before work-up was similar to that recorded above.

When cyclohexane was used as solvent with a temperature of 80° the major product obtained (after bulb to bulb distillation) was the ketal (97) (identical infrared and n.m.r. spectra). Work-up with deuterium oxide instead of water gave an oil whose n.m.r. spectrum

(CCl₄) showed peaks at δ 1.01, 1.25, and 3.73 in the ratio of about 12:13:4. ν_{\max} (film) 2200 (C-D), 1150, 1060, and 1035 cm⁻¹ (ketal).

2,2,4,4-Tetramethylcyclobutanone (116).

This ketone was prepared from 2,2,4,4-tetramethylcyclobuta-1,3-dione by the method of Herzog and Buchman.¹⁰⁸ The dione (14 g) gave the required ketone (116) (0.5 g, 4%) as a colourless liquid. ν_{\max} (film) 1765 cm⁻¹ (C=O); n.m.r. (D.M.E.) δ 1.10 (ring Me₄), 1.72 (C-3 protons). These values are in agreement with those reported for this compound.¹¹⁴

6,6,8,8-Tetramethyl-1,4-dioxaspiro[4.3]octane (97).

The ketone (116) (0.4 g) was heated under reflux in toluene (25 ml) with ethylene glycol (0.5 g) and *p*-toluenesulfonic acid (10 mg) using a Dean and Stark apparatus. After 16 hr the mixture was cooled and worked up in the normal way to give an oil (0.4 g) which was purified by preparative v.p.c. (20' SE30, 30%). 6,6,8,8-Tetramethyl-1,4-dioxaspiro[4.3]octane (97) was obtained as a clear liquid (Found: C, 70.7; H, 10.7. C₁₀H₁₈O₂ requires C, 70.5; H, 10.7%). ν_{\max} (film) 1150, 1055, and 1030 cm⁻¹ (ketal); n.m.r. (CCl₄) δ 1.01 (ring Me₄), 1.25 (C-7 protons), and 3.73 (ketal protons).

Reaction of the bromoketal (93) with lithium amalgam.

The bromoketal (93) (0.2 g) in cyclohexane (10 ml) was heated under reflux with lithium amalgam [from lithium (0.12 g) and mercury (25 g)] for 16 hr. The mixture was stirred with water until effervescence ceased then with ether. Removal of solvent from the dried ether solution gave a solid (0.19 g) which was chromatographed using petroleum ether as eluent. An analytical sample m.p. 113-114° was prepared by evaporative distillation (140°/0.1 mm) (Found: C, 44.7; H, 6.5. $C_{20}H_{34}O_4Hg$ requires C, 44.6; H, 6.4%). The demasking of potassium ferrocyanide¹¹¹ and the mass spectrum m/e 198, 199, 200, 201, 202, and 204 confirmed that the compound was 7,7'-di-(6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane) mercury (103).

Reaction of the bromoketal (93) with lithium.

The bromoketal (93) (0.7 g) in D.M.E. (4 ml) was added to a stirred suspension of lithium, (0.2 g, dispersion or 1 mm wire) in D.M.E. (4 ml). The solution was stirred in an atmosphere of nitrogen at 60° for 10 hr. Acetic anhydride (2 ml) was added to the filtered solution. A white precipitate formed and the mixture became warm. Work-up as previously described gave an oil (0.5 g) which was purified by preparative v.p.c. (5' UCON, 20%). An analytical sample of a compound was obtained by evaporative distillation (100°/18 mm) (Found: C, 66.7, 66.3; H, 9.1, 9.2. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5%). Spectral data (see Discussion) indicated that the compound was

3-(2'-acetoxy)ethoxy-2,5-dimethylhexa-2,4-diene (104). Hydrolysis

(10% aqueous methanolic hydrochloric acid for 2 hr and the usual work-up) gave 2,5-dimethylhex-2-ene-4-one (106) whose infrared and, n.m.r. spectra were identical to those reported for this compound.¹¹⁵ A

D.N.P. derivative of this ketone m.p. 112-114^o (lit.^{115,116} m.p. 112^o, 115-116^o) was prepared by addition of Brady's Reagent¹⁴⁰ to the diene (104).

N.m.r. Spectra of the anion (102).

The general procedure adopted for the observation of the spectrum of the anion was to allow the reaction mixture to settle, then pipette some of the solution into an n.m.r. tube. A spectrum was run about 5 mins after this transfer had been carried out.

(a) Addition of deuterium oxide to the anion.

Deuterium oxide (2 drops) was added to a solution of the anion in an n.m.r. tube and the mixture shaken. After an n.m.r. spectrum of the solution had been recorded, the contents of the tube were diluted with water and extracted with ether. Removal of solvent from the dried ether solution gave an oil whose n.m.r. spectrum was similar to that of the ketal (97). Several peaks due to impurities were present and it was difficult to tell how much deuterium was present at the 7-position.

(b) Addition of acetic anhydride to the anion.

The bromoketal (93) (0.2 g) was stirred with lithium wire (0.1 g) in ether (3 ml) at room temperature for 2 hr. The filtered solution was cooled to -78° and acetic anhydride (0.2 g) added with stirring. After 5 mins the solution was diluted with water and extracted with ether. Removal of solvent from the dried ether solution gave an oil whose n.m.r. spectrum (CCl_4) and v.p.c. chromatogram were recorded. The oil consisted of three main compounds in the ratio of 1:1:2. By comparison with authentic samples the compounds were shown to be the diene (104), the ketal (97), and the ketone (116). Several other smaller peaks due to impurities were present in the n.m.r. spectrum of the oil.

(c) Addition of acetic anhydride to a heated solution of the anion.

A solution of the anion in D.M.E. was prepared as previously described and after stirring at room temperature for 6 hr was refluxed for 5 mins. Acetic anhydride was added to the filtered solution with stirring. A white precipitate formed. The mixture was carefully diluted with sodium bicarbonate solution and extracted with ether. Removal of solvent from the dried ether solution gave an oil which consisted of two main compounds in the ratio of 2:1. The compounds were the diene (104) and the ketal (97) as shown by comparison with authentic samples.

(d) Addition of trimethylsilyl chloride to the anion.

Trimethylsilyl chloride was added to a solution of the anion in an n.m.r. tube as previously described. The n.m.r. spectrum of the solution was recorded. When water was added to this solution and the product isolated as previously described, an oil was obtained. This oil consisted of a mixture of compounds (v.p.c.). The major compound present (>60%) was shown to be the ketal (97) by comparison of its infrared and n.m.r. spectra with those of an authentic sample.

(e) Addition of benzyl bromide and methyl iodide to the anion.

The addition of benzyl bromide and methyl iodide to solutions of the anion in n.m.r. tubes had caused no appreciable change in the appearance of the spectra produced after $\frac{1}{2}$ hr.

Methyl 2,2,4,4-tetramethylcyclobutan-1-one-3-carboxylate (126).

The ketal (95) (0.3 g) was heated under reflux with a mixture of methanol (35 ml) and hydrochloric acid (1N, 7 ml) for 10 hr. The cooled solution was diluted with sodium bicarbonate solution and extracted with ether. Removal of solvent from the dried ether solution gave methyl 2,2,4,4-tetramethylcyclobutan-1-one-3-carboxylate (126)

(0.23 g, 90%) as a liquid b.p. $120^{\circ}/18$ mm (Found: C, 65.3; H, 8.9.

$C_{10}H_{16}O_3$ requires C, 65.2; H, 8.8%). ν_{\max} (film) 1770 (ring C=O),

1730 and 1210 cm^{-1} ($\overset{\text{O}}{\parallel}\text{C}-\text{OMe}$); n.m.r. (CCl_4) δ 1.25 (ring Me_4), 2.67

(C-3 H), and 3.65 (ester Me).

2,2,4,4-Tetramethylcyclobutan-1-one-3-carboxylic acid (122).

The ketoester (126) (0.4 g) was heated under reflux with 10% methanolic potassium hydroxide (30 ml) for 3 hr. The cooled mixture was acidified with hydrochloric acid and extracted with ether. Work-up of the ethereal extract afforded an oil (0.35 g, 94%), which crystallised on scratching to yield the ketoacid (122) m.p. 88-90° (lit.¹²² m.p. 93°). The infrared and n.m.r. spectra were identical to those of an authentic sample.¹²²

3-Bromo-2,2,4,4-tetramethylcyclobutan-1-one (121).

(a) The bromoketal (93) (1.0 g) was heated under reflux with methanol (20 ml) and hydrochloric acid (2N, 5 ml) for 40 hr. The cooled solution was diluted with sodium bicarbonate solution and extracted with ether. Work-up of the ethereal solution gave an oil (0.79 g) which was subjected to preparative v.p.c. (12' Carbowax).

3-Bromo-2,2,4,4-tetramethylcyclobutan-1-one (121) (0.5 g, 63%) was obtained as a liquid (b.p. 90°/25 mm) (Found: C, 46.9; H, 6.4. $C_8H_{15}BrO$ requires C, 46.9; H, 6.4%). ν_{max} 1770 and 1790 cm^{-1} (ring C=O).

(b) The ketoacid (122) (0.17 g) and red mercuric oxide (0.22 g) were heated under reflux in carbon tetrachloride (10 ml) using a modified Dean and Stark apparatus to remove water. Bromine (0.2 g) in

carbon tetrachloride (3 ml) was added to the mixture over 2 hr. Work-up as previously described gave an oil (0.19 g) whose infrared and n.m.r. spectra were identical to those previously obtained for the bromoketone (121).

Reaction of the bromoketone (121) with lithium.

The bromoketone (121) (0.12 g) in D.M.E. (2 ml) was added over 6 hr to lithium (0.1 g) in D.M.E. (2 ml) at room temperature. The mixture was stirred in an atmosphere of nitrogen. An n.m.r. spectrum of the solution contained many broad peaks. Addition of acetic anhydride to the filtered solution gave a precipitate. Work-up as previously described gave an oil (0.08 g) whose v.p.c. chromatogram showed twenty peaks of approximately equal size.

Attempted ketalisation of the bromoketone (121).

Trimethyl orthoformate b.p. $101-104^{\circ}$ (lit.¹⁴¹ $101-102^{\circ}$) was prepared from chloroform (150 g), sodium (69 g), and methanol (500 ml).

A solution of the bromoketone (0.3 g) and benzene (5 ml) was distilled briefly to remove any water present. Absolute methanol (5 ml), containing dry hydrogen chloride (Kipps), and trimethyl orthoformate (0.2 g) were heated under reflux with this dried solution for 10 hr. The mixture was carefully basified with solid potassium hydroxide, diluted with water, and extracted with ether. Removal of solvent from the dried ether solution gave an oil whose infrared spectrum was

identical to that of the bromoketone (121).

Treatment of 2,2,4,4-tetramethylcyclobutanone (0.13 g) under similar conditions to those described above gave an oil (0.12 g) whose n.m.r. spectrum (Table 17) suggested that it was 1,1-dimethoxy-2,2,4,4-tetramethylcyclobutane. $\nu_{\max}(\text{CCl}_4)$ 1060 and 1130 cm^{-1} (ketal).

Methyl 6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane-7-carboxylate (125).

The acid (95) (0.5 g) was treated with an excess of an ethereal solution of diazomethane to give a quantitative yield of methyl 6,6,8,8-tetramethyl-1,4-dioxaspiro[4.3]octane-7-carboxylate (125) which was evaporatively distilled (120°/18 mm) (Found: C, 63.6; H, 8.9. $\text{C}_{12}\text{H}_{20}\text{O}_4$ requires C, 63.1; H, 8.8%). ν_{\max} (film) 1730, 1230 ($\text{-}\overset{\text{O}}{\parallel}\text{C-OMe}$), 1140 and 1040 cm^{-1} (ketal); n.m.r. (CCl_4) δ 1.07, 1.15 (ring Me_4), 2.18 (C-7 H), 3.57 (ester Me), and 3.78 (ketal protons).

Attempted trans-ketalisation of the ketal (125).

The ketal (125) (0.1 g), absolute methanol (10 ml), and a mixture of trifluoroacetic acid and anhydride (1 drop) was heated in a "bomb" at 170° for 12 hr. A v.p.c. chromatogram of the cooled mixture showed the presence of two compounds, other than solvent, in the ratio 1:4. These were shown to be the ketone (126) and the starting ketal (125) by an examination of the n.m.r. and infrared spectra of the mixture, after the usual work-up.

3-Methylenecyclobutane-1-carbonitrile.

This compound was prepared by the cycloaddition of allene (from 2,3-dichloropropene)¹⁴² and acrylonitrile.¹²⁹ When no solvent was used an explosion occurred. The use of toluene as solvent and a Baskerville hydrogenation apparatus at 210° gave the nitrile as a liquid (5.8 g, 17%) b.p. 70°/30 mm (lit.¹²⁹ b.p. 74-76°/31 mm).

3-Methylenecyclobutane-1-carboxylic acid.

This compound was prepared by hydrolysis of the corresponding nitrile.¹²⁹ It distilled at 111°/19 mm (lit.¹²⁹ b.p. 99-101°/9 mm) (5.4 g, 7%).

3-Ketocyclobutane-1-carboxylic acid (130).

This compound was obtained as a colourless solid (1.0 g, 25%) m.p. 69-70° (lit.¹³⁰ m.p. 69-70°) by the method of Roberts and Caserio.¹³⁰

3-Bromocyclobutan-1-one (128).

Bromine (3.2 g) in carbon tetrachloride (8 ml) was added to a stirred mixture of the ketoacid (130) (1.8 g), red mercuric oxide (4.3 g), and carbon tetrachloride (30 ml) over 2 hr as previously described. The usual work-up gave an oil (1.0 g) whose v.p.c. chromatogram showed one main peak. The oil was evaporatively dis-

tilled ($80^{\circ}/25$ mm). It darkened in colour gradually. An examination of spectral data suggested that it was the bromoketone (128).

1-Bromo-3,3,-dimethoxycyclobutane (127).

The bromoketone (128) (0.3 g) was treated with trimethyl orthoformate at room temperature as previously described. An oil (0.27 g) was obtained after the usual work-up. An examination of spectral data (see Discussion); ν_{\max} (film) 1275, 1155, and 1040 cm^{-1} (ketal), suggested that the compound was the required bromoketal (127). It slowly decomposed at 5° .

Preliminary reaction of the bromoketal (127) with lithium.

The bromoketal (127) (0.05 g) in ether (2 ml) was added, during 1 hr, to a stirred suspension of lithium (0.1 g) in ether (2 ml) at room temperature. After a further 1 hr the solution was filtered and the solvent removed. An oil, whose n.m.r. spectrum (CCl_4) showed broad absorptions, was obtained.

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