THE MECHANISM OF CYCLOALKYLCARBINYL β-SCISSION

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

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by

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Department of Organic Chemistry

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CONTENTS

SUMMARY

The β-scission reactions of cycloalkylcarbinyl radicals have been investigated.

The kinetics of the ring opening reactions of a series of substituted cyclopropylcarbinyl and cyclobutylcarbinyl radicals have been determined through product studies of the reaction of the appropriate halide with tri-*n*-butyl- or triphenylstannane. The data show that no single factor determines the facility of the ring opening process but, rather, a complex interplay of electronic, polar, stereoelectronic and steric terms. The results are discussed in relation to previous studies of radical cyclisation reactions.

The behaviour of α-hydroxycyclopropylcarbinyl radicals and of the corresponding radical anions has also been examined. The generation of either intermediate in the sample cavity of the e.p.r. spectrometer leads to the formation of the corresponding 4-hydroxybut-3-enyl radical.

STATEMENT

This thesis contains no material previously submitted for a 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.

GRAEME MOAD

ACKNOWLEDGEMENTS

I should like to express my sincere gratitude to Professor A.L.J. Beckwith whose guidance and encouragement during the supervision of this work have proven invaluable. I am also thankful for the help of other members of the Organic Chemistry Department during the years. In particular I am indebted to Drs. G.E. Gream, D.P.G. Hamon and Mr. E.H. Williams.

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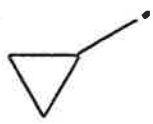
INTRODUCTION

CHAPTER 1

The Mechanism of the Ring Opening β-scission Reaction of Cycloalkylcarbinyl and Cycloalkyl Radicals.

Free radical rearrangement reactions and in particular those which involve ring formation through intramolecular addition to an unsaturated linkage and the reverse process, ring cleavage, have been extensively studied[1-4]. Recently several groups have published[5-12] accounts of their investigations into the factors which determine the rate and mode of radical cyclisation. As yet no comparable study of the fragmentation process has appeared.

The interconversion of various cyclopropylcarbinyl and allylcarbinyl radicals has been reported by many workers[1,2,4]. The parent cyclopropylcarbinyl radical (1)[13] and a number of alkylated derivatives (2-7)[14] have been generated in the sample cavity of the e.p.r. spectrometer through the reaction of *t*-butoxy radicals with the appropriate hydrocarbon. The radicals (1-5) were shown[13,14] to be stable below -140°C; above this temperature their rapid rearrangement



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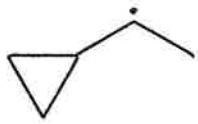

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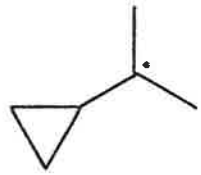

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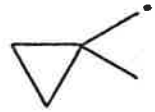

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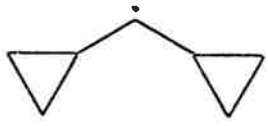

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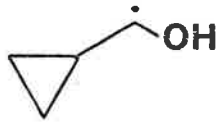

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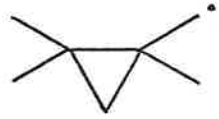

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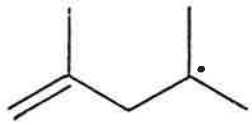
into the corresponding allylcarbinyl radical was observed. No evidence for the reverse reaction, known[15,16] to occur under other conditions, was found.

The (1,2,2-trimethylcyclopropyl)carbinyl radical (7) was not observed[14,17] even at -160°C. The spectrum recorded when a mixture of 1,1,2,2-tetramethylcyclopropane and di-*t*-butylperoxide is photolysed has been identified with the allylcarbinyl radical (8) arising through preferential cleavage of the more substituted βγ-bond[17]. A greater rate of ring fission for the formation of a tertiary radical is indicated.



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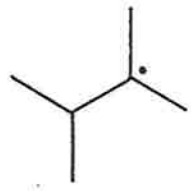

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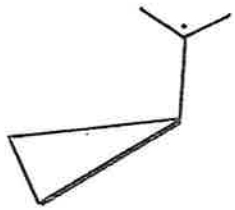
E.p.r. studies also indicate that the cyclopropylcarbinyl radical exists preferentially in the bisected conformation (10)[13,14,18-21]. It was suggested[13] that this conformation (10) may derive a degree of stabilisation through the interaction of the p orbital containing the free spin with an anti-bonding ring orbital antisymmetric with respect to the plane of symmetry of the molecule[22]. A later study[18,19], however, which compared the β-methyl hyperfine coupling constant of (4)

with that of the acyclic analogue (9), showed that >95% of the free spin was localised on the α-carbon. Hehre[23] has calculated that the bisected conformation (10) should be preferred over the orthogonal conformation (11) to the extent of 1.4 kcal/mole, a value consistent with that predicted on the basis of the e.p.r. results[18]. A substantially higher estimate (7.2 kcal/mole) was provided by Danen[24]. A variety of experimental evidence both for[25-29] and against[30-33] their being some form of stabilising interaction between a radical centre and an adjacent cyclopropane ring has also been reported. Some of these results will be discussed in the subsequent text.



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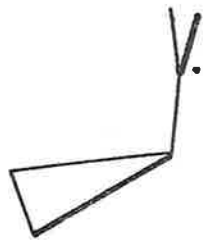

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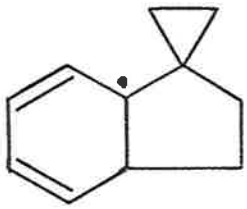
Kochi, Krusic and Eaton[14] have also suggested that the activation process required for ring cleavage is associated with a Π/2 rotation about the $\dot{C}R_2$-cyclopropyl bond. Such a transformation would leave the semi-occupied orbital in a position to interact with an antibonding ring orbital symmetric with respect to the plane of symmetry of the

molecule[22]. The fact that the radical (12) may not readily assume this conformation without incurring considerable strain has been cited[34] as a possible reason for its resistance to rearrangement. An alternative explanation in terms of the low unpaired electron density at the cyclopropylcarbinyl position due to delocalisation of the free spin into the π-system was also suggested[34]. That the radicals (13-15), generated during a free radical chlorination reaction[30], or by photolysis of the appropriate azo-compound[31], do rearrange supports the latter proposal. All four radicals (12-15) are held in the preferred bisected conformation through steric restraints inherent in the molecules. The ability of unsaturated substituents to stabilise a cyclopropylcarbinyl radical and thus retard or prevent β-scission has also been noted by other workers[35-37].



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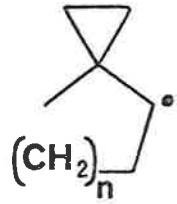
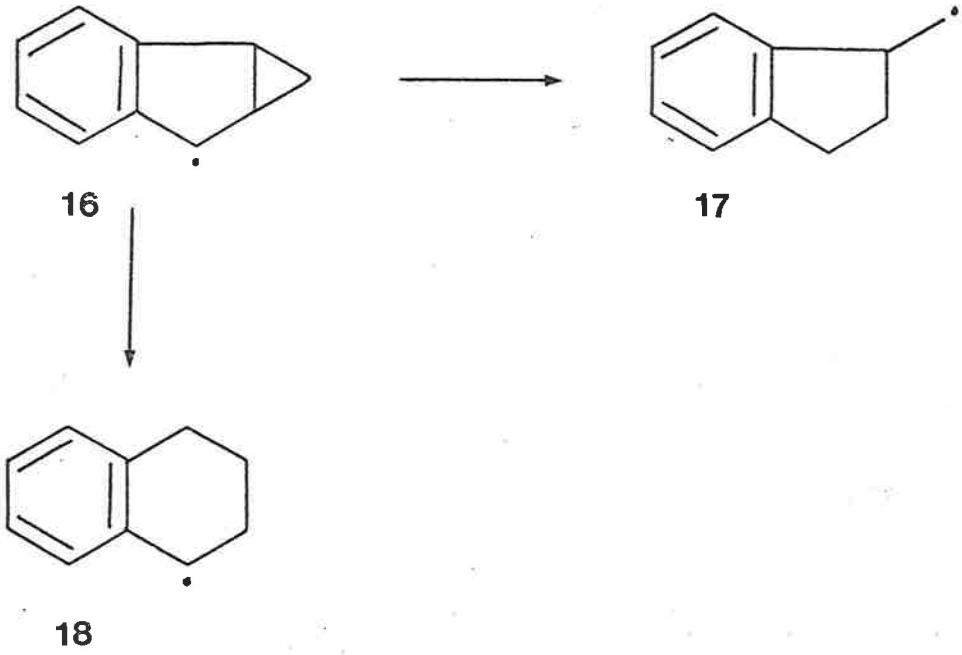


13 n = 1

14 n = 2

15 n = 3

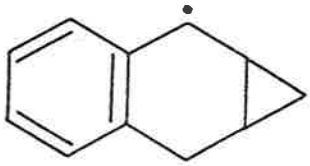
Homolytic β-elimination reactions of acyclic substrates invariably proceed *via* the most exothermic pathway possible[38-41] and, indeed, the course of the ring cleavage reactions of γ-substituted cycloalkylcarbinyl radicals may often be predicted on the basis of the relative thermodynamic stability of the product radicals. A number of notable exceptions to this general rule have, however, been reported[42-53].



Scheme 1

In several polycyclic systems rearrangement is seen to proceed preferentially to the less stable radical[42-50]. An example of such behaviour is provided by the radical (16) which undergoes ring scission to afford the primary radical (17) in preference to the secondary

benzylic radical (18)[42]. A similar ring opening reaction is observed for each of (19-21)[43-45] and related radicals[46-49]. The larger ring radical (22), however, undergoes a specific rearrangement with cleavage of the internal cyclopropane bond[54].



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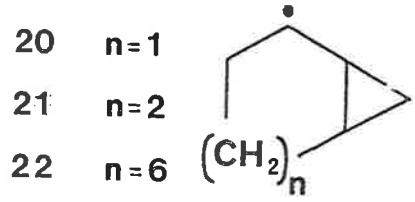
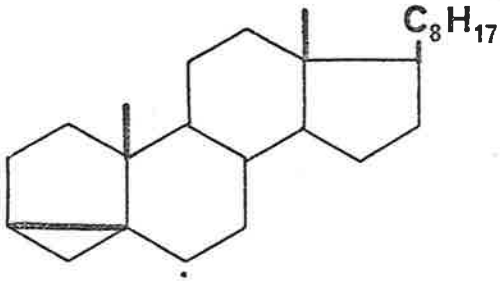


An explanation to take into account each of these examples proposes that the ring opening is subject to stereoelectronic influences[2,49,50]. The product distribution being determined by which βγ-bond (or its σ* orbital) is able to attain the more favourable overlap with the semi-occupied orbital. The most clear cut demonstration of this overlap control mechanism was provided by Beckwith and Phillipou[50]. The 3β,5-cyclocholestan-6-yl radical (23) and the isomeric radical (25)[55] each undergo ring fission with complete specificity to afford (24) and (26) respectively. An examination of molecular models of the two radicals (23) and (25) shows that only that bond cleaved preferentially is able to lie close to the plane containing the semi-occupied p orbital.



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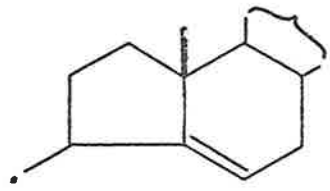

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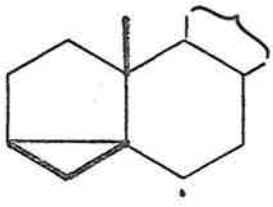

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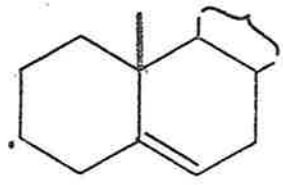

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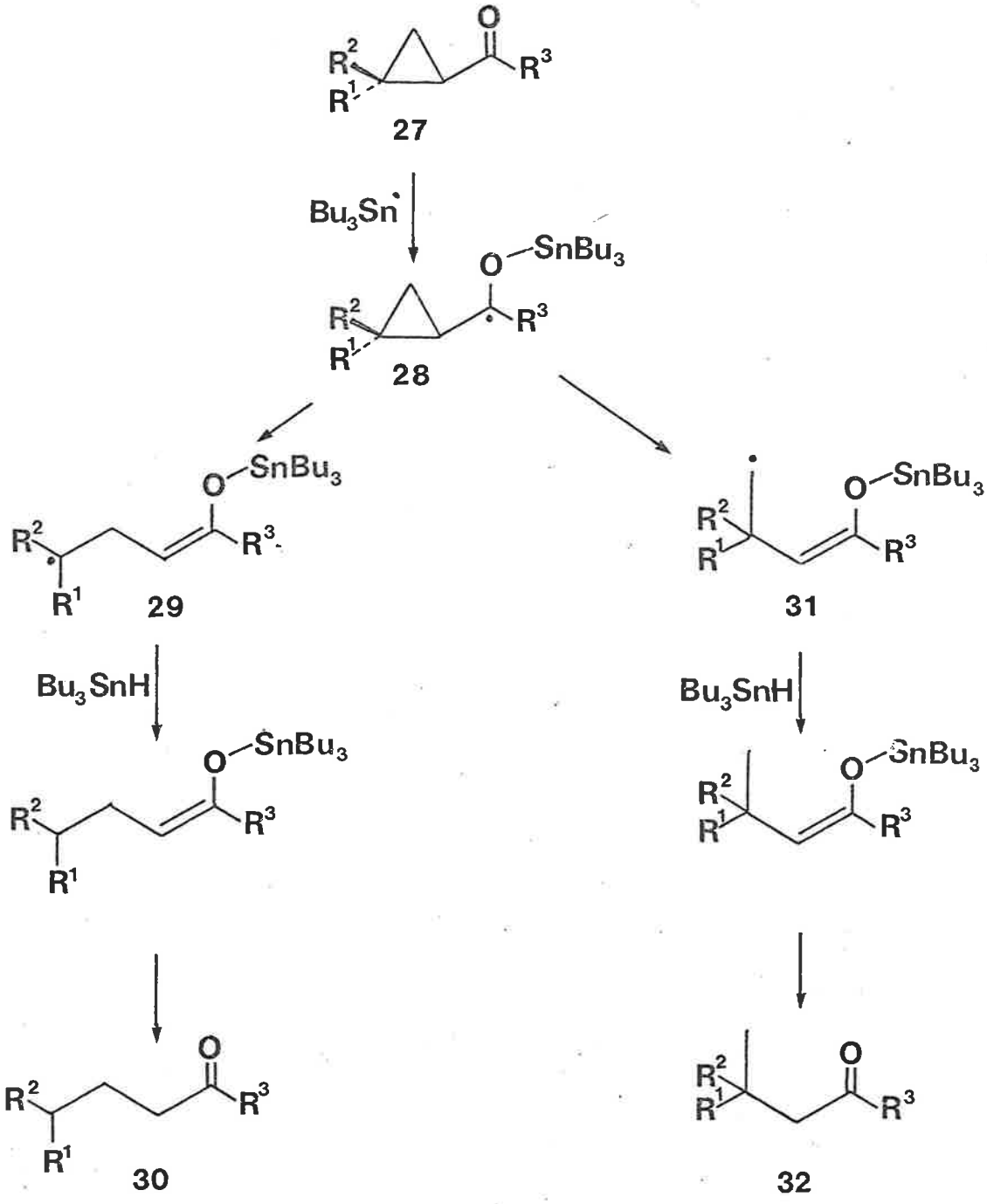
Conformationally mobile (*trans*-2-methylcyclopropyl)carbinyl radicals bearing an α-hydroxy[51] or stannyloxy[52,53] substituent may also be observed to undergo β-scission with a high degree of selectivity to afford the less stable primary radical under conditions of kinetic control. Godet and Pereyre[52,53] investigated the reduction of a series of cyclopropyl ketones (27) with tri-*n*-butylstannane (their results have been summarised in table 1). They advanced[52,56] a rationalisation for the apparently anomalous behaviour of the *trans*-2-methylated systems in terms of polar effects. The methyl substituent is considered[52] to destabilise the transition state leading to the secondary radical (29)



Scheme 2

Table 1

Distribution of products from the reduction of cyclopropyl ketones (27) with tri-*n*-butylstannane[52,53].

R^1	R^2	R^3	(30)	(32)
CH_3	H	H	8%	92%
CH_3	H	CH_3	15%	85%
CH_3	H	n-C_4H_9	35%	65%
CH_3	H	i-C_3H_7	35%	65%
CH_3	H	i-C_4H_9	38%	62%
CH_3	H	t-C_4H_9	45%	55%
H	CH_3	CH_3	90%	10%
H	CH_3	n-C_4H_9	97%	3%
H	CH_3	i-C_3H_7	98%	2%
H	CH_3	t-C_4H_9	100%	0%
Ph	H	CH_3	100%	0%
H	Ph	CH_3	100%	0%

relative to that leading to the primary radical (31) due to the partial negative charge born by the γ-carbon*. Thus cleavage of the less substituted βγ-bond is favoured. The known[15] reversibility of cyclopropylcarbinyl radical β-scission may account for the preponderance of products derived from the secondary radical (29) under other conditions[57,58].

In contrast to the above, the β-scission reactions of (*cis*-2-methylcyclopropyl)carbinyl radicals invariably involve preferential cleavage of the more substituted βγ-bond[52,53,57,58]. This result has been interpreted[52,53] in terms of a steric effect destabilising the transition state leading to the primary radical (31) (compare (33) and (34)). Steric factors may also provide an explanation for the dependence of the selectivity of these reductions on the nature of the α-substituent (R^3, see table 1). The steric bulk of the tri-*n*-butylstannyl group is thought[53] to cause the preferential adoption of a "transoid"[60] geometry for the transition state. Repulsion between R^3 and the 2-methyl group will then increasingly favour overlap of the semi-occupied orbital with the more substituted βγ-bond (compare (33) and (34), and (35) and (36)), and thus the formation of (30), as the steric bulk of R^3 increases.

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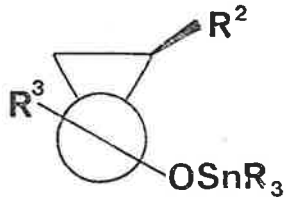
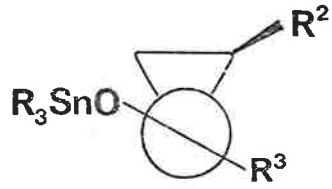
* Although in the original work[52,53] Godet and Pererye favoured the possibility of the ring opening reaction occurring simultaneously with the addition of the stannyl radical to the carbonyl group, more recent studies[59] have established the cyclopropylcarbinyl radical as a discrete intermediate.





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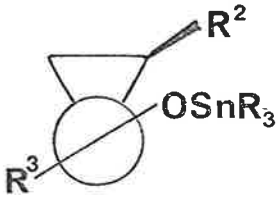

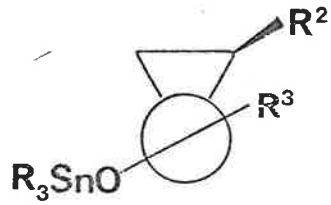

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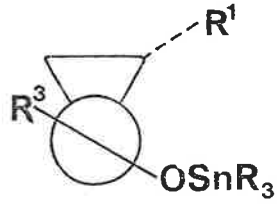

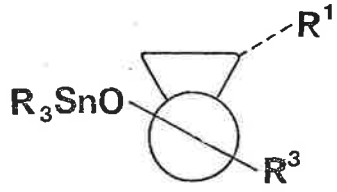

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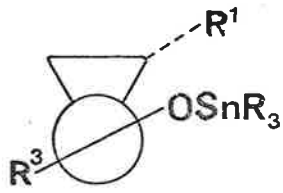

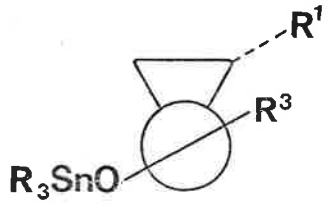

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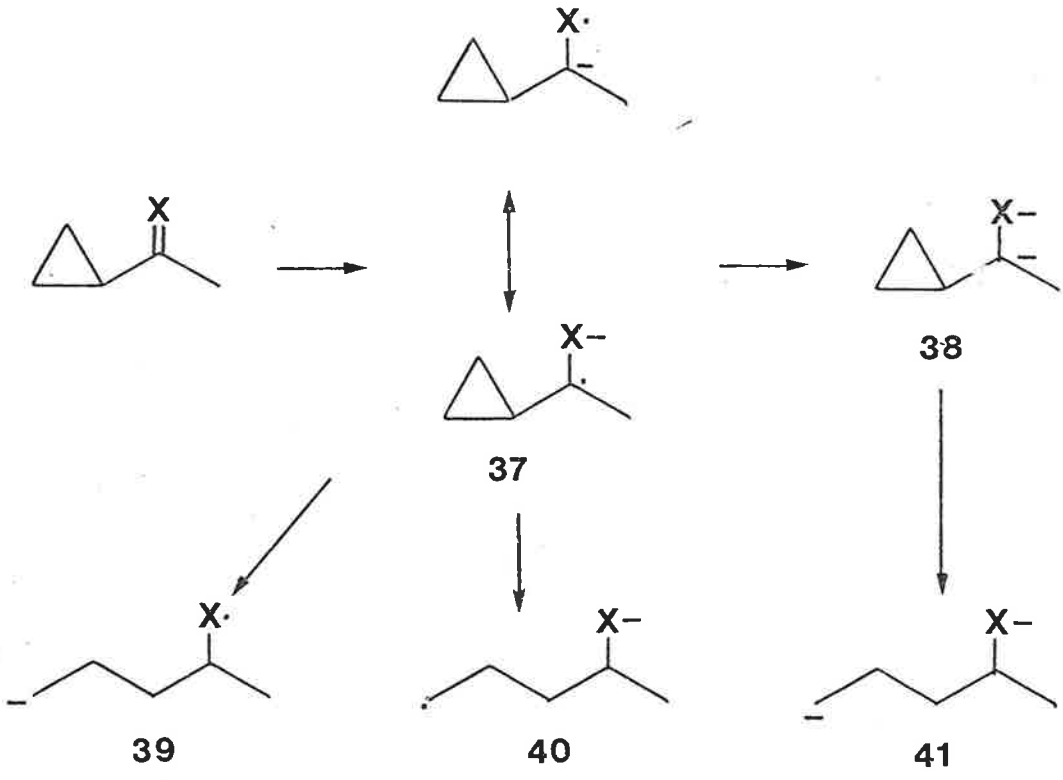
The reductive cleavage of conjugated cyclopropyl rings by dissolving metals[61] may also proceed *via* a cyclopropylcarbinyl radical intermediate (see scheme 3). The reduction of vinyl- and phenylcyclopropanes most likely involves the initial transfer of an electron from the metal (usually lithium or sodium) to generate a radical anion intermediate (37) followed by ring opening *via* either an anionic or free radical mechanism[61,62]. With cyclopropyl ketones and highly conjugated systems, however, the transfer of a second electron from the metal may

become competitive with fragmentation and part or all of the product may be derived from cleavage of the dianion (38).

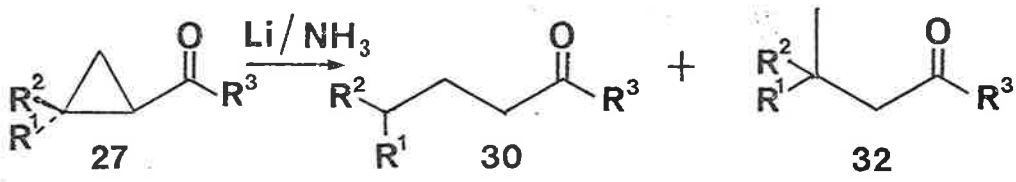


Scheme 3

Despite the extensive research[61,63-72] that has been devoted to the elucidation of the mechanism of the metal-ammonia reduction of cyclopropyl ketones the precise nature of the intermediates involved in the reaction remains unclear. Almost all studies have been carried out with rigid or semi-rigid systems in which the mode of ring cleavage is

determined primarily by stereoelectronic factors[61,63-68]. Recently, however, several groups[58,68,69] have reported the metal-ammonia reduction of the acyclic cyclopropyl alkyl ketones (27). It was reasoned[58,68,69] that the conformational mobility of these compounds would render stereoelectronic influences of little importance and that the product distribution observed would thus reflect the relative stability of the cleavage products. The observation that the reductive cleavage of (27, $R^1=CH_3$) proceeded with preferential opening of the less substituted $\beta\gamma$-bond was therefore interpreted by these workers[58,68,69] in terms of the involvement of either or both of the intermediates (39) and (41) but not (40) in the reaction pathway.

The recent demonstration[51-53] of similar selectivity in the ring opening of free radical systems bearing an α-oxygen substituent indicates, however, that such a conclusion is not justified on this evidence alone. Although other data consistent with an anionic ring cleavage mechanism has been reported[58,61,70-72] none would appear conclusive and clearly further work is required to elucidate the full details of the mechanism.



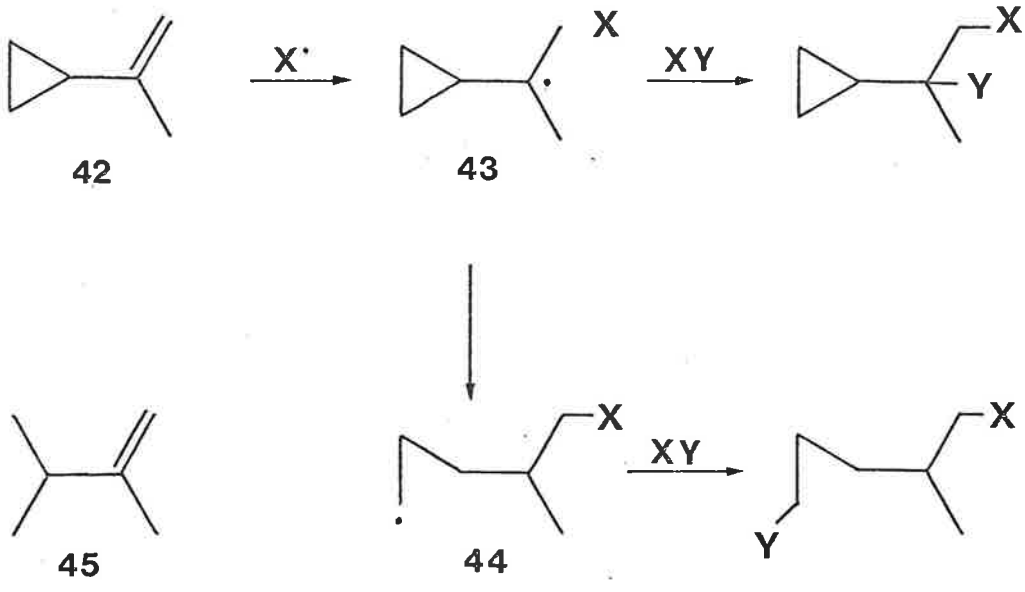
Scheme 4

Table 2

Distribution of products from the lithium-ammonia reduction of cyclopropyl ketones (27)[68,69].

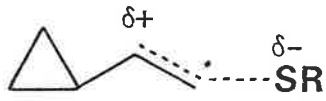
R^1	R^2	R^3	(30)	(32)
CH_3	H	CH_3	6%	94%
CH_3	H	n-C_4H_9	12%	88%
H	CH_3	CH_3	95%	5%
H	CH_3	n-C_4H_9	91%	9%
CH_3	CH_3	CH_3	76%	24%
CH_3	CH_3	n-C_4H_9	81%	19%
Ph	H	CH_3	100%	0%

The reactions of radical addends with vinylcyclopropane derivatives have been studied in detail[1,28,73-76]. The addition of thiols[28,73], halomethanes[28], methyl hypochlorite[74] and iodobenzene dichloride[74] to (42) has been shown to proceed *via* the free radical chain mechanism shown below (scheme 5). The distribution of products was found to vary according to the chain-transfer ability of the particular reagent and the concentration of the reactants thus indicating the discrete existence of the radical intermediates (43) and (44).



Scheme 5

An enhanced rate of consumption of (42) with respect to the acyclic compound (45) may imply some special stabilisation for the cyclopropylcarbinyl radical intermediate (43). The result might also reflect a degree of charge polarisation in the transition state (46). The ability of a cyclopropane ring to stabilise an adjacent positive charge is well known[77,78] and even a small degree of charge separation would be sufficient to explain the observed result[25,28].



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Lishanskii and co-workers[73,75] have investigated the addition of thiophenol to an extensive series of vinylcyclopropane derivatives (47) in connection with studies of the radical polymerisation of similar monomers. From their results[73] the conjugative ability of the cyclopropyl function is apparent (see table 3). Vinylcyclopropanes γ-substituted with a variety of conjugating groups were found to exhibit an increased reactivity toward thiophenol with respect to the parent compound (47, $R^1=R^2=R^3=R^4=H$). That the electron withdrawing cyano and carbethyoxy substituents effect an increase in reactivity would suggest

that there is not a significant degree of charge polarisation in the transition state for thiophenol addition[79].

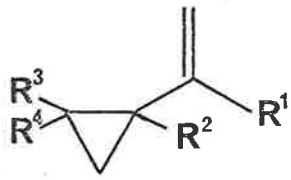

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Table 3

Relative reactivity (RR) of vinylcyclopropane derivatives (47) towards thiophenol[73].

R^1	H	H	H	H	CH_3	H	CH_3	H	H
R^2	H	H	H	H	H	CH_3	CH_3	H	H
R^3	H	Cl	H	H	H	H	H	H	H
R^4	H	Cl	OPh	CO_2Et	CO_2Et	CO_2Et	CO_2Et	CN	Ph
RR	1.0	1.75	1.9	3.0	9.5	2.8	7.8	4.9	9.0

Similarly faster rates have been observed for several other reactions which produce cyclopropylcarbinyl radical intermediates. These include the thermal decomposition of azo compounds[25] and *t*-butyl peresters[26] and free radical chlorination[29] and bromination[27] reactions (see tables 4-6).

Table 4

Kinetics of the thermal decomposition of azo compounds

$R(c\text{-}C_3H_5)_2C\text{-}N{=}N\text{-}C(c\text{-}C_3H_5)_2R$ [25].

R	$k(135^{\circ}C)$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
	$sec^{-1} \times 10^{4}$	kcal mol^{-1}	cal mol^{-1} K^{-1}
	2.7	38.0	17.6
	23.9	34.3	12.8

Table 5

Kinetics of the thermal decomposition of *t*-butyl peresters

$R\text{-}CO_3tBu$ [26].

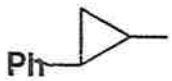
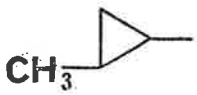
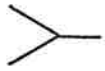
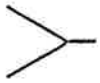
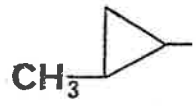
R	$k(90^{\circ}C)$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
	$sec^{-1} \times 10^{-5}$	kcal mol^{-1}	cal mol^{-1} K^{-1}
	2.18	33.4	11.6
	2.40	32.9	10.7
	2.73	31.6	7.34
	1.17	32.0	6.54

Table 6

Relative reactivity of benzylalkanes $PhCH_2$-R towards N-bromosuccinimide bromination[27].

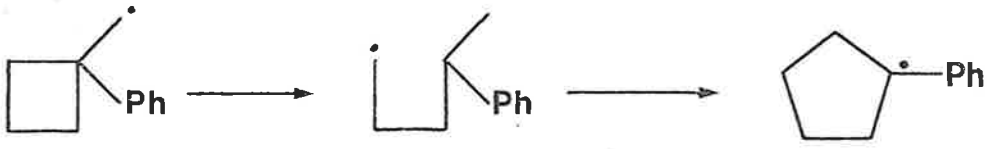
R			
k/k_{tol} [a]	9.35	30.08	42.4

[a] Rate constant for α-hydrogen atom abstraction from benzylalkane relative to that for abstraction from toluene.

Although the preceding results would certainly indicate that some form of special stabilisation exists for a cyclopropylcarbinyl radical, a more accurate view of the magnitude of this effect can be gained by consideration of the appropriate bond dissociation energies. McMillen, Golden and Benson[32], utilizing a kinetic iodination technique, were able to determine ΔH_f^o and $DH^o_{(\triangleright CH_2\text{-}H)}$ for the cyclopropylcarbinyl radical and hence obtain a value of 0.4 ± 1.6 kcal/mole for the stabilisation afforded this radical with respect to other primary radicals. Such a value is consistent with molecular orbital treatments of the cyclopropylcarbinyl radical[23,32] which indicate only minimal interaction between a radical centre and an adjacent cyclopropane ring and with the e.p.r. results already mentioned[18,19].

The rearrangement reactions of cyclobutylcarbinyl radicals have been less extensively studied than their cyclopropylcarbinyl analogues. It is evident, however, that the β-scission reactions of these radicals will proceed readily under certain conditions.

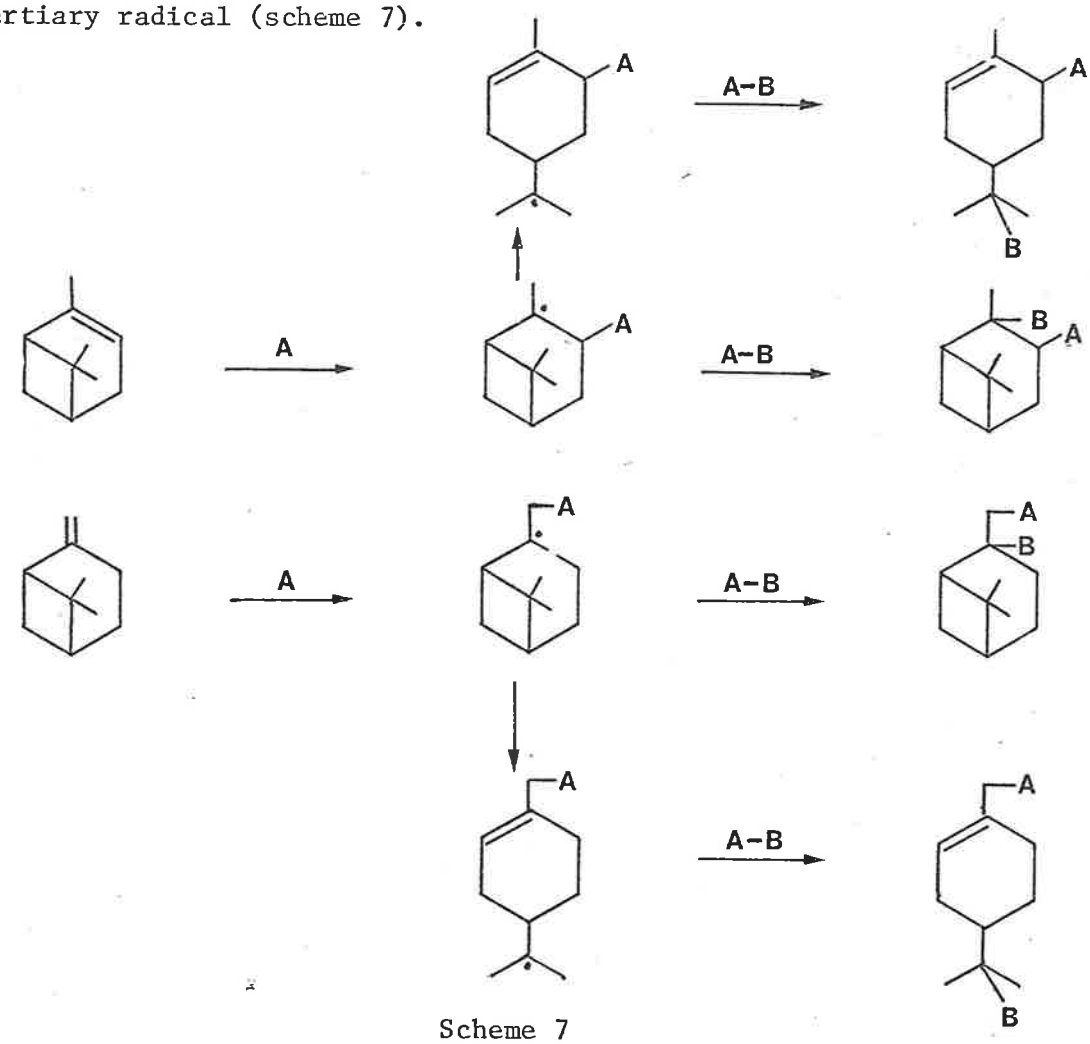
Kaplan[80] generated the parent cyclobutylcarbinyl radical in an attempt to observe a 1,2-alkyl radical shift. Although the desired ring expansion did not occur, the radical did rearrange by ring opening. The (1-phenylcyclobutyl)carbinyl radical does afford a significant amount of phenylcyclopentane amongst other products[81]. It seems likely, however, in view of the fact that no unequivocal example of a 1,2-alkyl radical shift has been reported[1] and the known reaction of pent-4-enyl radicals to afford cyclopentane derivatives[82-85], that this rearrangement occurs *via* the elimination-readdition sequence shown (scheme 6)[81].



Scheme 6

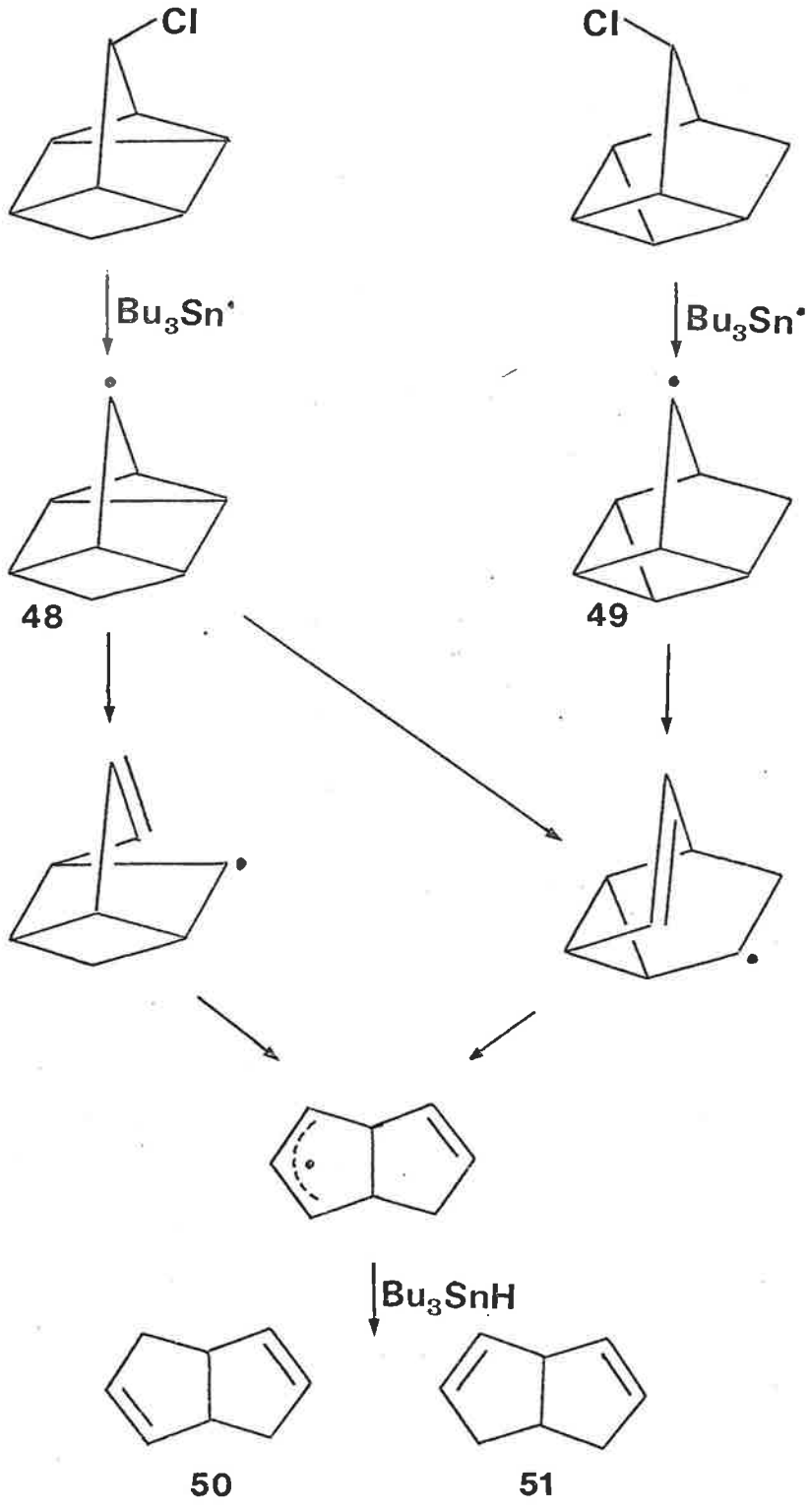
The reactions of various radical addends with both α- and β-pinene have been studied[1,86,87]. Opening of the cyclobutane ring is

frequently observed as a consequence of addition and occurs with specific cleavage of the more substituted βγ-bond to generate a tertiary radical (scheme 7).



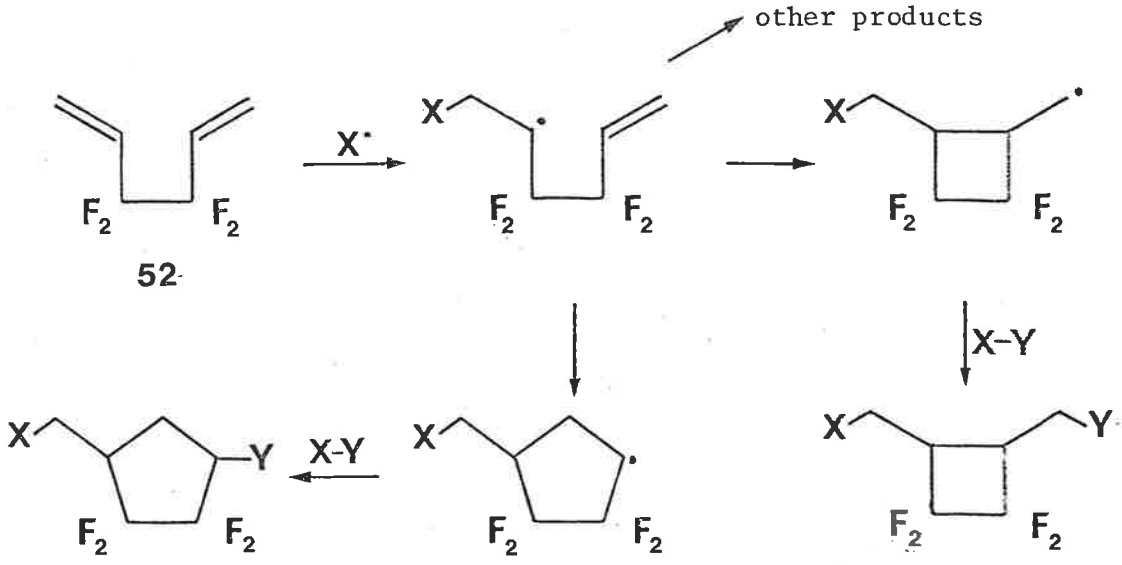
Scheme 7

Rearrangement[88] of the tetracyclic radicals (48) and (49) involves two successive β-scission reactions of cyclobutylcarbinyl and cyclopropylcarbinyl radical intermediates (scheme 8). In each case the reaction may be seen to proceed by the most exothermic pathway (the isomeric bicyclo[3.3.0]octadienes (50) and (51) are the only products of rearranged structure obtained from these reductions).



Scheme 8

All available evidence is in accordance with a view that the fragmentation reactions of cyclobutylcarbinyl radicals are irreversible. The parent pent-4-enyl radical has been generated under a variety of conditions[89-92]; under no circumstance, however, could any cyclic compound (either cyclobutane or cyclopentane derivative) be detected in the reaction product. The fluorinated radical (52)[93] affords a small yield of cyclobutane derivatives amongst other products, presumably as shown in scheme 9. As such it is the only known example of cyclisation to a cyclobutylcarbinyl radical.



Scheme 9

The β-scission reactions of the cyclopentylcarbinyl radical, its simple alkyl derivatives and larger ring analogues are endothermic; consequently, it is not surprising that ring opening is not a feature of their solution chemistry[1-12]. The reaction has only been observed when the system is subject to particularly favourable structural[94] or electronic[1-4,95,96] influences.

The reverse reaction, however, occurs readily and has been extensively studied[1-12]. A detailed discussion of radical cyclisation is clearly beyond the scope of the present work. However, inasmuch as those factors which are considered to affect the transition state of the addition reaction must logically also influence radical fragmentation, certain features of the process deserve mention.

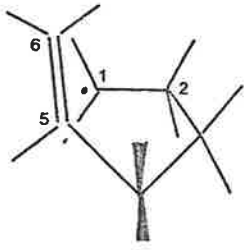
The hex-5-enyl radical undergoes intramolecular addition to afford almost exclusively the cyclopentylcarbinyl radical under conditions of kinetic control[1-4,8-12]. Several hypotheses have been advanced to account for the preferential formation of the less thermodynamically stable product.

Since e.p.r. studies[12] have demonstrated the discrete existence of both the hex-5-enyl and cyclopentylcarbinyl radicals, those hypothetical schemes involving non-classical intermediates[91,97] may be discounted.

A more favourable entropy change should be associated with closure to the smaller ring system[98]. However, it is difficult to imagine this factor being solely responsible for the observed specificity of the reaction. Indeed, a recent estimate[8] of the activation parameters for alkenyl radical cyclisation shows the enthalpy term to be of greater significance than the entropy term.

Beckwith[2,99] has proposed that the observed selectivity reflects a requirement for maximum overlap of the p orbital bearing the free spin and the vacant π^* orbital in the transition state. That such a stereoelectronic requirement should be of importance would follow from the demonstration[50] of a similar influence in the reverse reaction. The hypothesis has also received support from a recent molecular orbital treatment[100] of the addition of methyl radical to ethylene.

An examination of molecular models reveals that a transition state with the triangular array of centres dictated by these overlap requirements is more readily attained during the formation of a five membered ring. Furthermore, this model of the transition state satisfactorily accounts for the similar selectivity seen in the reactions of the allylcarbinyl radical[15], the very slow rate of cyclisation of pent-4-enyl radicals[82-85,89-92] (also to give cyclopentane derivatives preferentially[82-85]) and the observation that hept-6-enyl may afford products derived from both the cyclohexylcarbinyl and cycloheptyl radicals[8,84,101].



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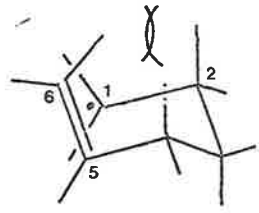

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A stereochemical factor may also be important in hindering six membered ring formation. Julia[3,10,11] has suggested that a non-bonded interaction between the pseudo-axial hydrogen at C_2 and the *trans*-hydrogen at C_6 may contribute to raising the energy of the transition state for 1,6-cyclisation (54) above that for 1,5-cyclisation (53). However, it is difficult to assess the significance of this factor without a more precise knowledge of the transition state.

Nevertheless, steric factors would appear to have a profound influence on radical cyclisation. Consider, for example, the results of Beckwith, Blair and Phillipou[5] which are summarised in table 7. Substituents at C_5 are seen to reduce dramatically the rate constant for 1,5-cyclisation (see table 7, compare $k_{1,5}$ for radicals (55a) and (55j-o)) whilst effecting only a minimal change in $k_{1,6}$ (the results of Julia[10,11] would suggest that *trans*-substitution at C_6 similarly

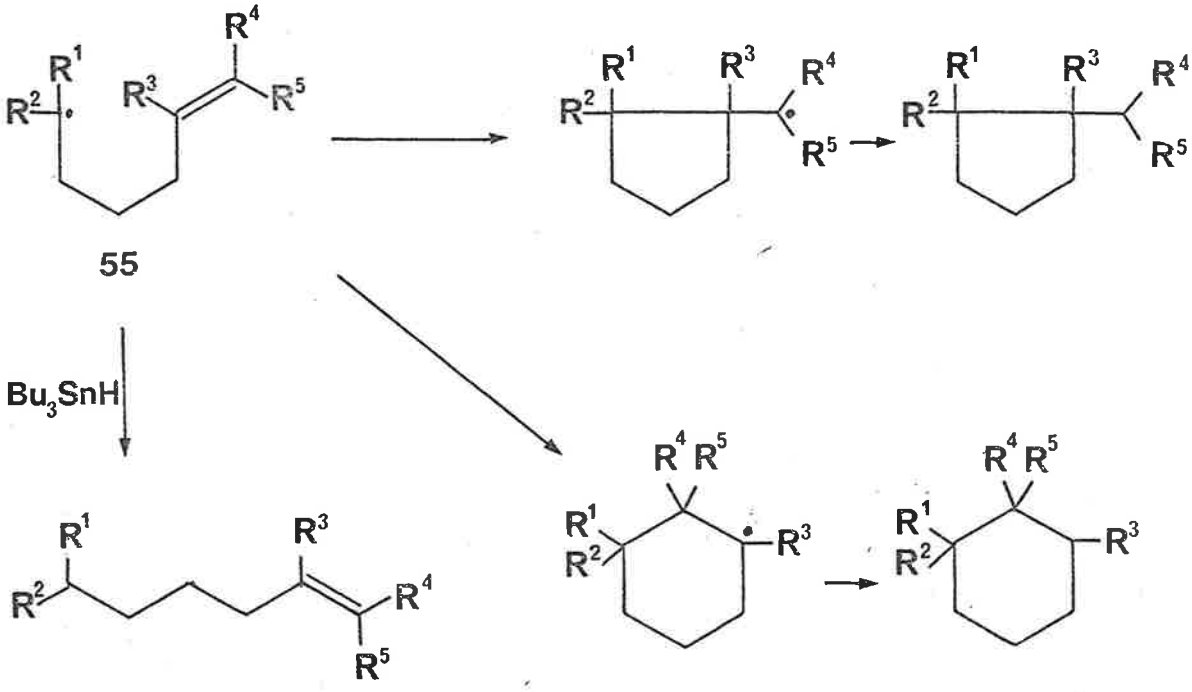
Table 7

Relative rate constants for cyclisation of substituted hex-5-enyl radicals at 65°[5].

Radical	R_1	R_2	R_3	R_4	R_5	$k_{1,5}/k_H$	$k_{1,6}/k_H$	$k_{1,5}/k_{1,6}$	$k_{1,5}$ (rel)[a]	$k_{1,6}$ (rel)[a]
(55a)	H	H	H	H	H	0.22	0.0046	48	1.0	0.02
(55b)	CH_3	H	H	H	H	0.26	0.0033	78	1.4	0.02
(55c)	*n*-C_3H_7	H	H	H	H	0.29	0.0014	206	1.6	0.008
(55d)	CH_3	CH_3	H	H	H	0.41	0.006	68	1.4	0.02
(55e)	$-(CH_2)_4-$		H	H	H	0.28	*ca.* 0.02[b]	*ca.* 14[b]	0.94	*ca.* 0.07[b]
(55f)	H	H	H	3-butenyl	H	0.38	< 0.002	> 200	1.7	< 0.009
(55g)	H	H	H	H	3-butenyl	0.30	< 0.0015	> 200	1.4	< 0.007
(55h)	H	H	H	CH_3	CH_3	0.52	< 0.0025	> 200	2.4	< 0.011
(55i)	H	H	H	$-(CH_2)_5-$		0.21	< 0.002	> 100	0.94	< 0.009
(55j)	H	H	CH_3	H	H	0.005	0.008	0.62	0.022	0.04
(55k)	H	H	*i*-C_3H_7	H	H	0.005	0.016	0.31	0.022	0.07
(55l)	H	H	$-(CH_2)_3-$		H	0.025	0.006	4.2	0.114	0.03
(55m)	H	H	$-(CH_2)_4-$		H	0.015	0.012	1.2	0.068	0.05
(55n)	H	H	CH_3	CH_3 / H	H / CH_3	0.024	0.004	5.4	0.11	0.02
(55o)	CH_3	CH_3	CH_3	H	H	$< 5 \times 10^{-5}$	0.005	< 0.01	< 0.0002	0.02

[a] Rate constant relative to $k_{1,5}$ for radical (55a).

[b] The yield of 1,6-cyclised product did not vary with Bu_3SnH in the expected manner; its formation may proceed in part by polar mechanisms.



Scheme 10

retards 1,6-cyclisation). Repulsion between the reacting centres cannot, however, completely explain this result, since, if such were the case, substituents at C_1 should exert a similar influence (see table 7, compare $k_{1,5}$ for radicals (55a-e)). The observation was, therefore, interpreted in terms of the steric compression (B strain), engendered between the substituents at C_5 on change to sp^3 hybridisation, being of greater importance than the interaction between these same substituents and those at C_1.

That steric factors should so significantly affect the rate constant for cyclisation, whilst electronic factors have only a marginal influence, is consistent with an unsymmetrical transition state involving considerable breakage of the π bond but little formation of the new σ bond.

Finally the effect of polar factors should be considered. Recent investigations[102] of intermolecular addition reactions suggest that the transition state may involve a significant degree of charge polarisation.

For the addition of nucleophilic radicals (*e.g.* methyl) a charge transfer structure (56) involving the transfer of an electron to the double bond may make a contribution to the transition state. Similarly, for the addition of electrophilic radicals (*e.g.* trifluoromethyl) an alternative charge transfer state (57) in which the radical accepts and electron from the double bond may contribute. Molecular

56

57

orbital treatments[100,102] support this view and depict[100] the transition state for the addition of methyl radical to ethylene as involving a positively charged radical centre and a negatively charged double bond.

If it is reasonably assumed that a similar charge polarisation will appear in the transition state for radical cyclisation, then the presence of electron donating alkyl substituents at the radical centre will stabilise the transition state and hence facilitate the reaction and similar substitution at the double bond will destabilise the transition state and retard the reaction. This provides an alternative interpretation of the results of Beckwith, Blair and Phillipou[5] (see table 7 and the associated discussion).

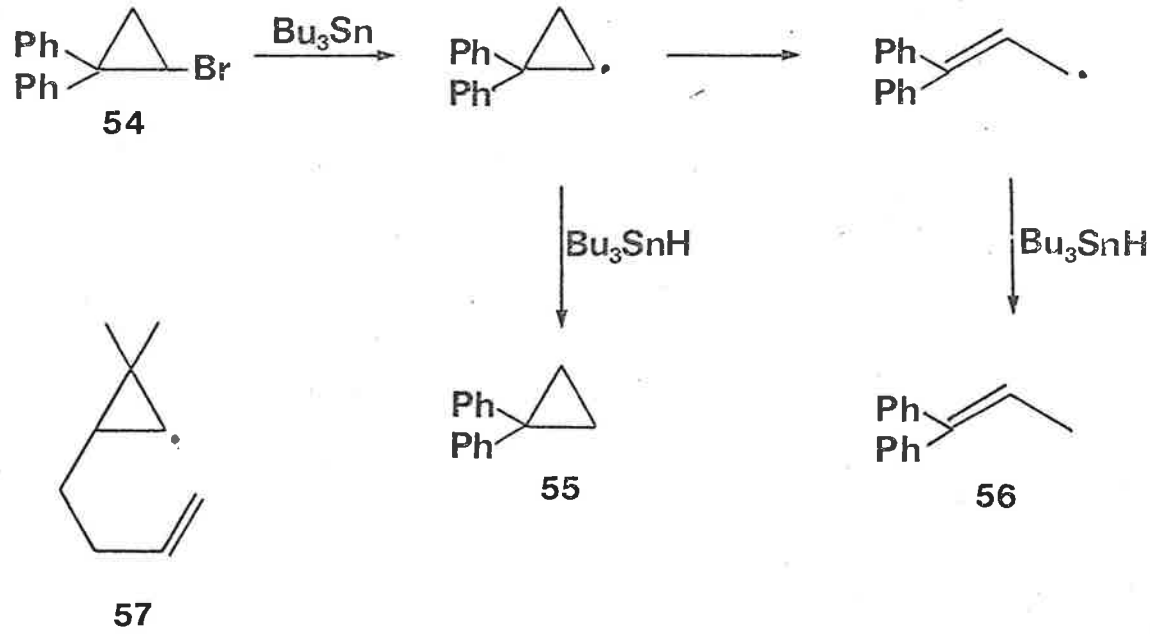
Both fragmentation of and ring closure to cycloalkyl radicals is seldom observed except under forcing conditions[1-4]. Ring opening of the cyclopropyl radical is exothermic to the extent of *c*. 30 kcal/mole[103]. Despite this fact cyclopropyl radicals are frequently observed to undergo intermolecular reactions without affording significant amounts of acyclic products[104,105].

A number of theoretical treatments of the cyclopropyl-allyl isomerisation have been carried out[106-108]. All indicate a high barrier to ring opening, consistent with the experimental results[109] and most[107,108] favour a disrotatory mode of cleavage.

Chemical activation techniques[110,111] have shown the ring cleavage reactions of cyclobutyl and cyclopentyl radicals to have similarly high activation energies. Although several reports of cyclobutyl radical ring opening in solution have appeared[112,113], the possibility that the rearranged products may have arisen *via* ionic intermediates cannot be excluded[114].

Some insight into the reasons behind the unexpectedly high activation energies for the ring opening reactions of cycloalkyl radicals may be gained by consideration of the previously mentioned stereoelectronic requirements for β-scission[2,50]. The orbital containing the free spin is in these radicals constrained to occupy a position in space orthogonal to the plane of the ring system, and to the σ orbital of the bond to be cleaved. Thus the transition state, which requires the interaction of these orbitals, must of necessity involve the development of considerable strain.

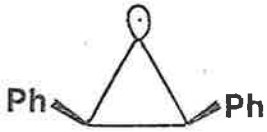
Certain arylcyclopropyl radicals are known[115-121] to undergo ring opening reactions. Reduction of the bromide (54) with tri-*n*-butylstannane in benzene affords, in addition to the expected 1,1-diphenylcyclopropane (55), a small yield of the ring opened product (56)[115]. The product distribution was found to vary with stannane concentration and temperature in a manner consistent with the mechanism shown below (scheme 11). Similar ring opening reactions have been reported by Walborsky and Chen[116,117] under somewhat different conditions.



Scheme 11

Each of these authors propose the stabilisation afforded the product allyl radical by the phenyl substituents as the major factor facilitating the ring cleavage.

It may be noted, however, that geminal methyl substituents also apparently lower the activation barrier for ring opening. The radical (57) is observed[122] to afford a significant proportion of products in which the cyclopropane ring has been cleaved. The analogous radical without the methyl substituents is stable to ring cleavage[122].



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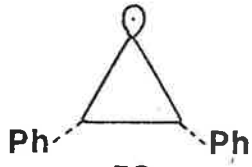

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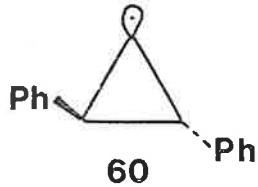

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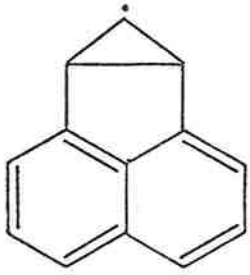

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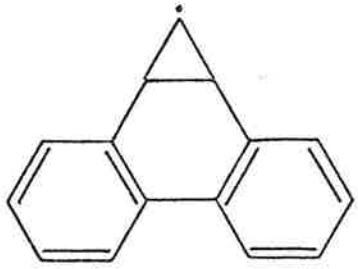

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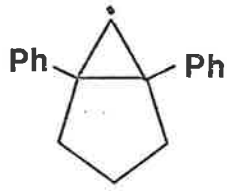

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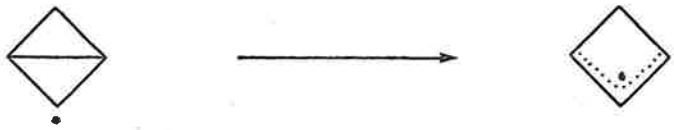
Rüchardt and co-workers[118,119] generated the stereoisomeric radicals (58-60) with the aim of determining the preferred mode of ring cleavage. Their results may be interpreted in terms of a favoured disrotatory ring opening. The possibility of a nonstereospecific cleavage could not, however, be eliminated. A subsequent study[120] involving the polycyclic radicals (61-63) showed that the reaction may follow a disrotatory mechanism. Each of the radicals (61-63) is

prevented from opening *via* a conrotatory mechanism by the structural restraints inherent in the molecules. However, a slower rate of cleavage for (63) with respect to the monocyclic radicals (58-60) may indicate the availability of an alternate ring cleavage mechanism, namely conrotatory, to the latter[120].

Ring opening of the cyclopropyl radical is also facilitated by certain structural features. For instance, the bicyclobutyl radical (64) is known[123], from e.p.r. experiments, to undergo a facile ring cleavage reaction at temperatures above $-100^{o}C$ (scheme 12). Further examples, where the relief of ring strain is thought to provide the driving force for the ring opening reaction, have been reported by Sustmann and Gellert[124].



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Scheme 12

It is evident from the preceding discussion that, despite the extensive research applied to the investigation of the β-scission reactions of cycloalkyl and cycloalkylcarbinyl radicals, many aspects of the mechanism are as yet uncertain. It is also apparent that a

knowledge of the effect of substituents on the kinetics of the ring opening process would aid significantly in the understanding of these reactions.

Recently, methods which permit the rate constants of free radical rearrangement reactions to be evaluated have been developed and have seen application in the study of radical cyclisation[4-9,125,126]. It would seem a logical development to utilize these same techniques to conduct a systematic study of the reverse reaction, namely radical fragmentation.

Furthermore, as the transition state for β-scission must be of similar structure to that for radical cyclisation, those factors which are thought to influence the energy of the transition state of the latter process must also influence the former process. A study of the kinetics of the ring opening reaction should, therefore, provide a test of the validity of many of the arguments developed to rationalise the features of alkenyl radical cyclisation.

Thus an investigation of the fragmentation reactions of cyclopropylcarbinyl and cyclobutylcarbinyl radicals was instigated.

RESULTS AND DISCUSSION

CHAPTER 2

Kinetics and Mechanism of the Reduction of Halocompounds with Trialkylstannanes.

Previous work[4-11,50,125] has demonstrated that the reduction of an alkyl halide with a trialkyl- or triarylstannane is a simple and convenient procedure for generating free radicals under controlled conditions.

Initiation

$$\text{initiator} \longrightarrow R^{\bullet}$$

Propagation

$$R^{\bullet} + R'_3SnH \longrightarrow RH + R'_3Sn^{\bullet}$$

$$R'_3Sn^{\bullet} + RX \longrightarrow R'_3SnX + R^{\bullet}$$

Termination

$$R^{\bullet} + R^{\bullet} \longrightarrow \left.\begin{array}{l} \\ \\ \end{array}\right\} \text{inactive products}$$

$$R^{\bullet} + R'_3Sn^{\bullet} \longrightarrow$$

$$R'_3Sn^{\bullet} + R'_3Sn^{\bullet} \longrightarrow$$

Scheme 12

The kinetics and mechanism of the process have been investigated by Carlsson and Ingold[125], who were able to establish the validity of the free radical chain mechanism (scheme 12) originally proposed by Kuivila and co-workers[127]. Several facts to emerge from their[125]

study deserve emphasis:

(i) The kinetics of reduction exhibit a first order dependence on either the stannane or the halide concentration over a wide range of relative and absolute reactant concentrations.

(ii) The reactions behave normally throughout their entire course, continuing until one of the reactants is consumed.

(iii) For the reduction of alkyl bromides and of methyl iodide the rate controlling propagation step is hydrogen atom abstraction from the stannane; chain termination occurs by the self reaction of two alkyl radicals.

(iv) For the reduction of alkyl chlorides the rate controlling propagation step is the abstraction of chlorine by the stannyl radical; chain termination occurs by the self reaction of two stannyl radicals.

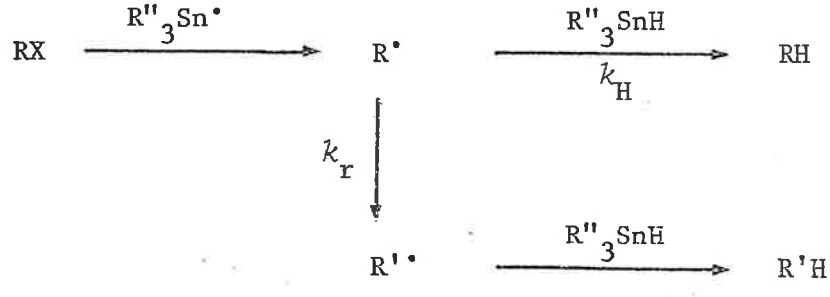
(v) The rate constant for hydrogen atom abstraction from tri-*n*-butylstannane is relatively insensitive to the nature of the abstracting radical, showing only a marginal increase in the series: *t*-butyl < *n*-hexyl ≲ *c*-hexyl < methyl (see table 8). Triphenylstannane is roughly four times more active as a hydrogen atom donor than is tri-*n*-butylstannane.

Table 8

Absolute rate constants for hydrogen atom transfer from stannane (k_H) in cyclohexane at 25°C[125].

Reaction	k_H (1 mol^{-1} sec^{-1})	
$(CH_3)_3C^\bullet$ + n-Bu_3SnH	$7.4 \times 10^5 = .74 \times 10^6$	1
c-$C_6H_{11}^\bullet$ + n-Bu_3SnH	1.2×10^6	1.62
$CH_3(CH_2)_4CH_2^\bullet$ + n-Bu_3SnH	1.0×10^6	1.35
$CH_3^\bullet$ + n-Bu_3SnH	5.8×10^5	7.84
$(CH_3)_3C^\bullet$ + Ph_3SnH	3.1×10^6	4.19

One additional feature of this procedure for generating free radicals, which is of particular relevance to the present study, is that the rate constant for any isomerisation reaction undergone by the initially generated radical may be estimated. Consider the general reaction shown in scheme 13.



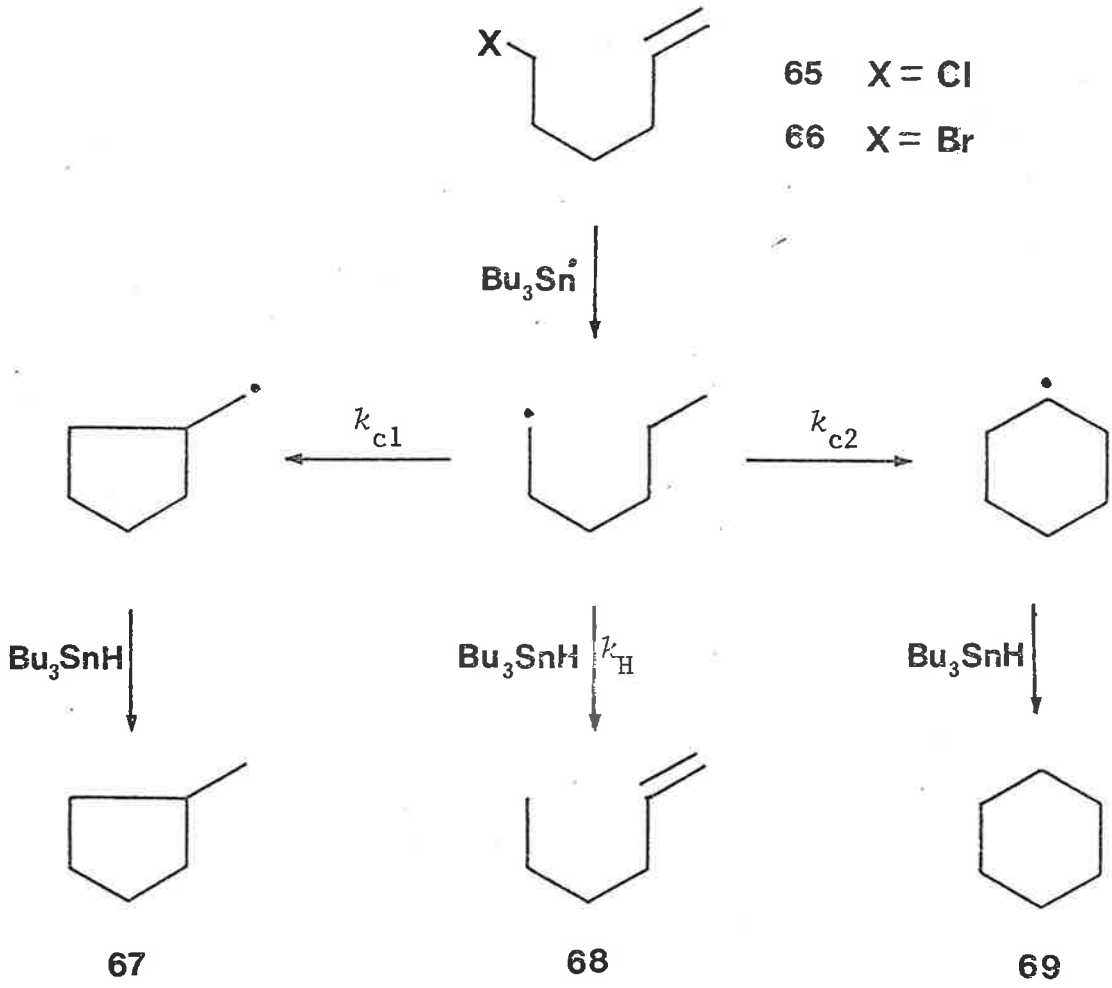
Scheme 13

If the reduction is assumed to be a long chain process and the rearrangement irreversible, then the usual steady state treatment may be applied to derive the following integrated rate expression (1)[9].

$$[R'H] = k_r/k_H\{\ln([S]_o + k_r/k_H) - \ln([S]_F + k_r/k_H)\} \qquad (1)$$

Thus, if the initial and final stannane concentration ($[S]_o$ and $[S]_F$ respectively) and the distribution of products are known, the rate constant for the isomerisation process (k_r) relative to that for hydrogen atom transfer from stannane (k_H) can be calculated. Furthermore, if the data given in table 8 are taken as reasonable values of k_H, then absolute values of k_r for reactions involving simple alkyl radicals may be estimated at 25°C. However, the determination of k_r at other temperatures requires that further assumptions be made.

Recently, Ingold and co-workers[126] have applied an e.p.r. spectroscopic technique to evaluate the kinetics of the cyclisation of hex-5-enyl radical to cyclopentylcarbinyl. Their results, in conjunction with the kinetic data which may be obtained through product studies of the reaction of a 1-halohex-5-ene with tri-*n*-butylstannane (see scheme 14), permit the derivation of activation parameters for the hydrogen atom transfer reaction.



Scheme 14

Most previous quantitative investigations of rearrangement reactions during stannane reduction have employed alkyl bromides. In the present work, however, due to the lability of halomethylcyclopropanes and halomethylcyclobutanes, the use of the alkyl chloride offers distinct advantages.

An examination of the kinetic scheme (scheme 13) shows that the formation of rearranged product is dependent only on k_H, k_r and the stannane concentration. The origin of the radical R$^\bullet$ should not have influence on the kinetics of the rearrangement reaction.

However, a halogen leaving group effect has recently been noted in the reductive rearrangement of γ- and δ-silyl halides with tri-*n*-butylstannane[128]. Also, it is known[125,127] that alkyl bromides and alkyl chlorides differ markedly in their reactivity towards stannane, and that different rate controlling propagation steps and chain termination reactions are involved in their reduction.

It was, therefore, clearly desirable to establish that chloro-compounds as well as bromo-compounds were suitable for the investigation of the kinetics of the rearrangement reactions of simple alkyl radicals.

The stannane reduction of 1-bromohex-5-ene (66) in benzene has been reported by Walling[9,91], Beckwith[8] and Julia[10,11] and their associates, but as there is some discrepancy between their results (see table 9) it was felt that a reinvestigation of the reaction was warranted.

1-Chloro- and 1-bromohex-5-ene (65) and (66) were reduced with tri-*n*-butylstannane in benzene and in decalin (benzene and other more volatile solvents were found to be unsatisfactory for reduction of

chloromethylcyclopropanes and chloromethylcyclobutanes due to problems associated with the gas chromatographic determination of the reaction products). Product analysis and treatment of the results as previously described[8,9] afforded the data given in table 9 (full details of the procedure used and the results obtained are given in the experimental section) which are in reasonable agreement with those of Beckwith[8]. In accord with the proposed kinetic scheme (scheme 14) the nature of the halide employed for the reaction (either chloride or bromide) was found to have no influence on the rate data obtained.

Table 9

Relative kinetic parameters[a] for hex-5-enyl radical cyclisation to cyclopentylcarbinyl (scheme 14).

$k_{Cl}/k_H(70^\circ)$ M^{-1}	$\Delta\Delta H^{\ddagger}$ [b] kcal mol^{-1}	$\Delta\Delta S^{\ddagger}$ [b] cal mol^{-1} K^{-1}	solvent	ref.
0.15	2.4	3.3	benzene	9
0.17	-	-	benzene	10,11
0.22[c]	3.0	5.7	benzene	8
0.20[c]	3.3 ± 0.1	6.3 ± 0.4	benzene	this work
0.17[c]	3.4 ± 0.1	6.2 ± 0.4	decalin	this work

[a] Uncertainties are expressed as the standard deviation from mean.

[b] $\Delta\Delta H(S)^{\ddagger} = H(S)^{\ddagger}_{Cl} - \Delta H(S)^{\ddagger}_{H}$

[c] Extrapolated on the basis of the activation parameters shown.

The relative rate constant for hex-5-enyl radical cyclisation (k_{cl}/k_H) is slightly lower in decalin than in benzene (see table 9). This result is contrary to what might be expected on the basis of the relative viscosity of the two solvents ($\eta(25^o)$: benzene, 0.61 cP; decalin, 1.75 cP). However, the work of Carlsson and Ingold[125] has indicated that solvent viscosity should have little influence on the propagation rate constants for the reduction.

The possibility that the lower k_{cl}/k_H may reflect some hydrogen atom donating ability of decalin is discounted by the fact that the product distribution was found to vary in the expected manner (according to equation (1)) over a ten-fold range of stannane concentration (see the experimental section).

A reasonable explanation of the solvent effect may lie with the ability of benzene to solvate free radicals. It is well known[129-132] that aromatic solvents are able to interact with radical intermediates and influence their stability and the rate of their reactions. Although most investigations have concerned polar species, there is some kinetic evidence[133,134] to suggest that benzene is able to specifically solvate alkyl radicals. That an aromatic system may interact with an alkyl radical centre is also implied by the effect which remote aryl and vinyl substituents have on radical conformation[135]. Solvation of the hex-5-enyl radical (and the cyclopentylcarbinyl and cyclohexyl radicals) can be expected to result in a reduced rate constant for

hydrogen atom transfer from stannane and hence an enhanced value of k_{cl}/k_H.

The absolute values of the activation parameters for hex-5-enyl cyclisation ($\Delta H(S)^{\ddagger}_{cl}$) and those derived for hydrogen atom transfer reaction with tri-*n*-butylstannane ($\Delta H(S)^{\ddagger}_{H}$) are given in table 10. The $\Delta S^{\ddagger}_{H}$ term corresponds to an *A*-factor of $10^{8.8 \pm 1.0}$ 1 mol^{-1} sec^{-1} which is reasonable for a simple metathesis reaction[136].

Table 10

Absolute activation parameters[a].

$\Delta H^{\ddagger}_{cl}$ [b]	$\Delta S^{\ddagger}_{cl}$ [b]	$\Delta H^{\ddagger}_{H}$ [c]	$\Delta S^{\ddagger}_{H}$ [c]
kcal mol^{-1}	cal mol^{-1} K^{-1}	kcal mol^{-1}	cal mol^{-1} K^{-1}
7.3 ± 0.5	-11.0 ± 2.5	3.9 ± 0.6	-17.2 ± 2.9

a Uncertainties are expressed as the standard deviation from mean.

b Determined by a least squares analysis of the rate data of Ingold and co-workers[126].

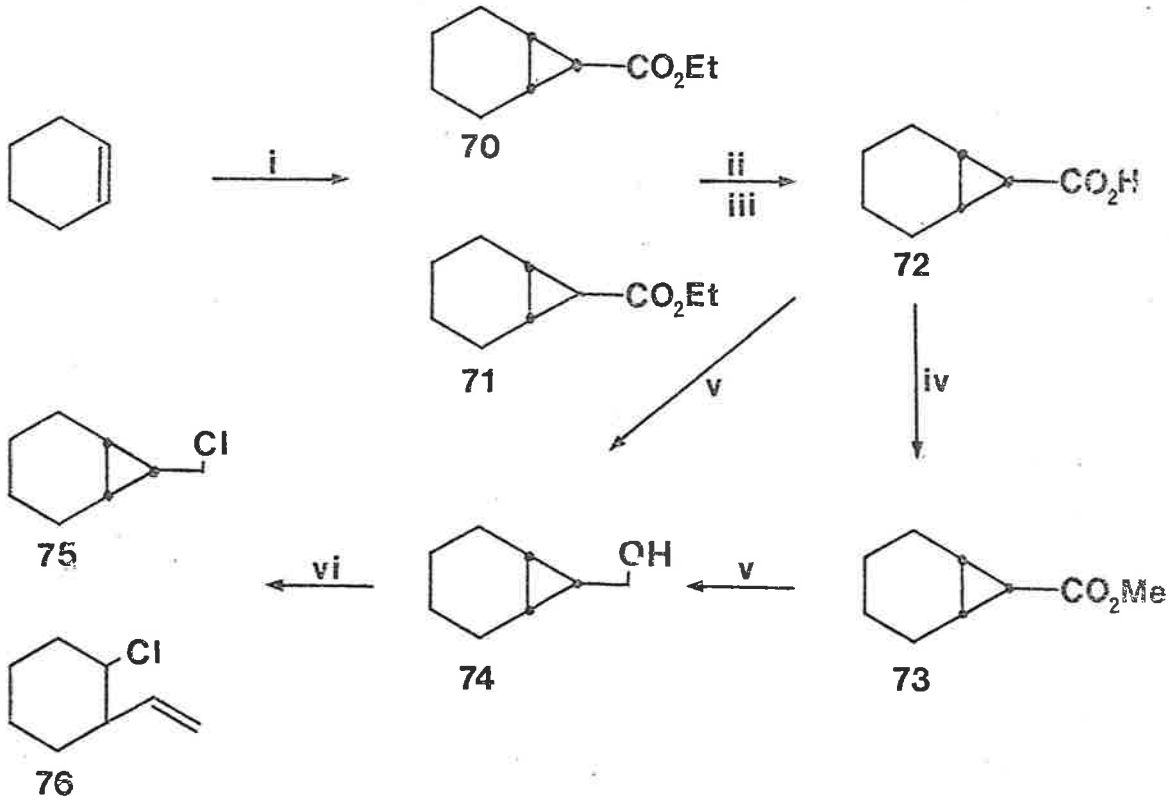
c $\Delta H(S)^{\ddagger}_{H} = -(\Delta\Delta H(S)^{\ddagger} - \Delta H(S)^{\ddagger}_{cl})$

Although the errors associated with this data are large, the results remain useful in that they permit the absolute magnitude of the activation parameters for the fragmentation reactions described in the subsequent text to be estimated.

CHAPTER 3

The Synthesis of Chloromethylcyclopropanes.

The immediate precursors of many of the chloromethylcyclopropane derivatives were obtained through the direct application of literature procedures; consequently, their preparation will not, in general, be described. Full mention of these compounds is, however, given in the experimental section.



Scheme 15

Reagents: i, N_2CHCO_2Et-$Cu^{I}[P(OMe)_3]I$-$(PhCO_2)_2$; ii, NaOH-H_2O; iii, recryst. *n*-hexane; iv, CH_2N_2-Et_2O; v, $LiAlH_4$-Et_2O; vi, see table 11.

The reaction of ethyl diazoacetate with cyclohexene was conducted according to a procedure adapted from that of Peace and Wulfman[137] to afford ethyl bicyclo[4.1.0]heptane-7-carboxylate as a mixture of the *exo*- and *endo*-isomers (70) and (71) in the ratio 13:1. Saponification of the ester mixture and recrystalisation of the crude acid from *n*-hexane afforded the pure *exo*-acid (>99.5% (72)).

Several procedures were used in an attempt to prepare the chloride (75), however, each was complicated by the formation of significant quantities (8-25%, see table 11) of the unsaturated isomer (76), presumably *via* a carbonium ion mechanism.

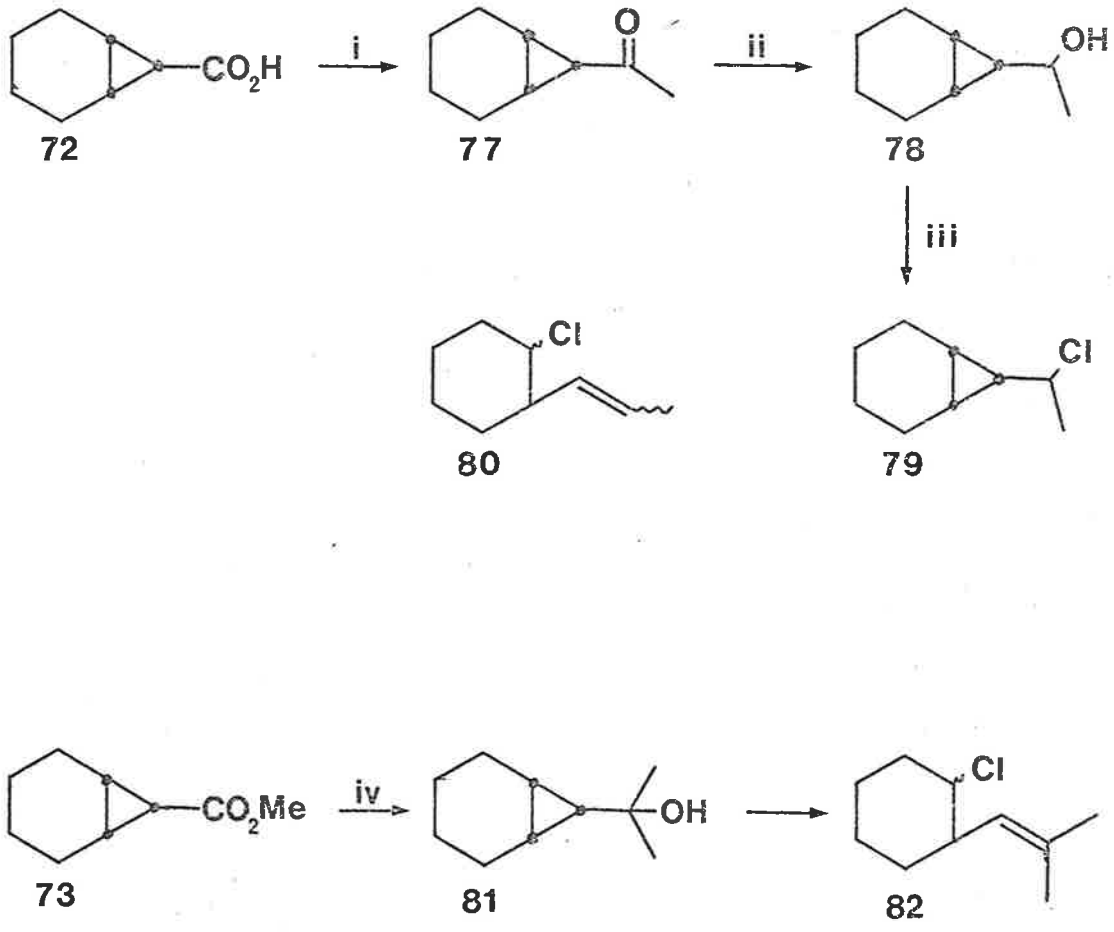
Table 11

Relative and absolute yields of products from the chlorination of *exo*-7-hydroxymethylbicyclo[4.1.0]heptane (64).

Reagent	(75)	(76)	Overall yield
i, TsCl-pyridine ii, pyridinium chloride-DMF	92%	8%	18%
$SOCl_2$-Et_2O, -78°C	75%	25%	89%
NCS-PPh_3-THF	85%	15%	97%

The chloride (75) proved to be unstable to the conditions required for preparative gas chromatography and attempts to separate the isomers using a spinning band column were unsuccessful. The

required compound (75) was obtained in a pure state by carrying out the low temperature ozonolysis of the chloride mixture; the chloride (75) being readily isolated from the ozonolysis product by distillation.



Scheme 16

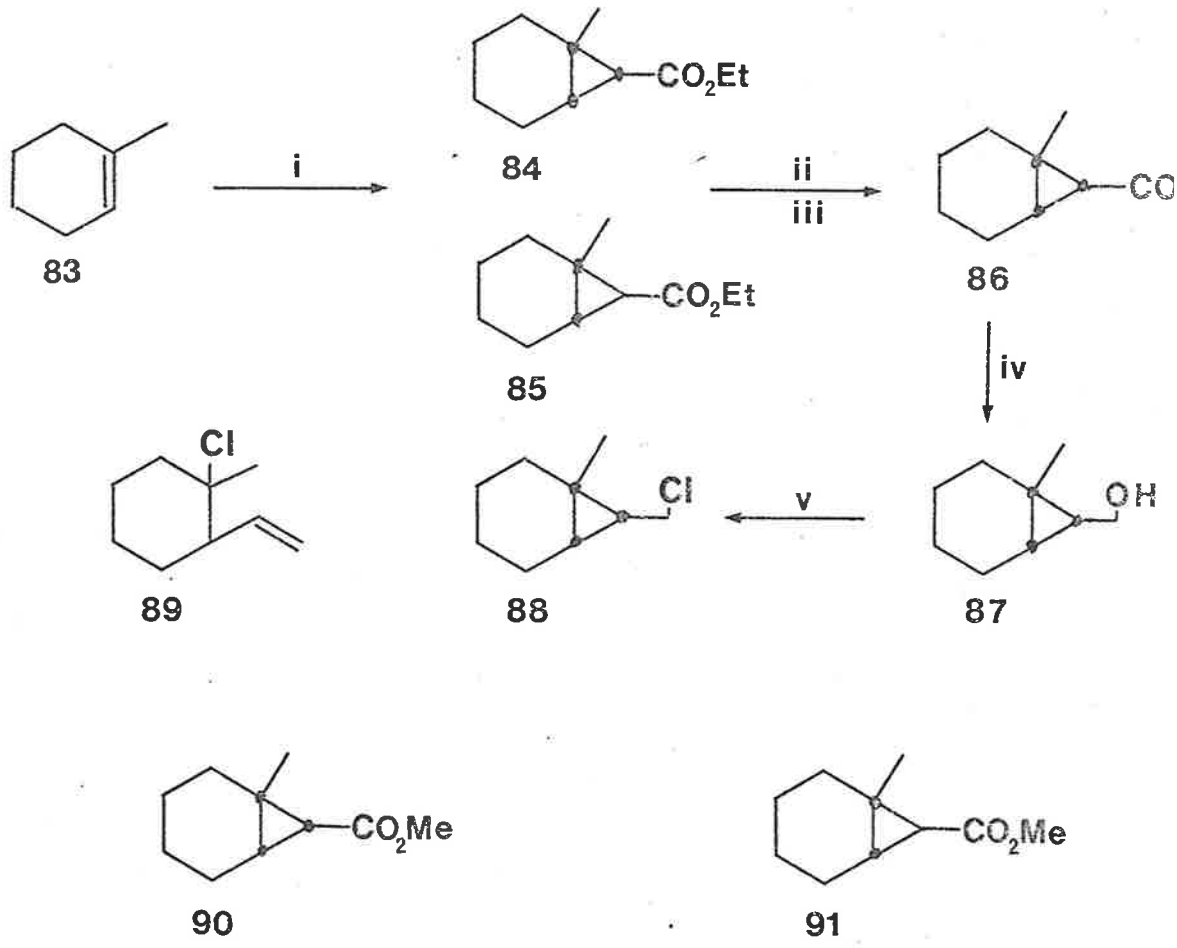
Reagents: i, $MeLi-Et_2O$; ii, $LiAlH_4-Et_2O$; iii, see text; iv, $MeMgI-Et_2O$.

All attempts to convert the secondary and tertiary alcohols (78) and (81) into the corresponding chlorides were unsuccessful. Treatment of the alcohol (78) with thionyl chloride in ether at $-78^{o}C$[50] or with phosphorous pentachloride, either in pentane at $-20^{o}C$[138] or in methylene chloride at $-78^{o}C$, afforded only an unsaturated chloride which was identified as (80) on the basis of its spectral properties and analytical data. The reaction of the alcohol (78) with the reagent derived from the addition of triphenyl phosphine to *N*-chlorosuccinimide[139] did afford the required chloride (79) as the minor (15%) product (as evidenced by n.m.r. data). However, the lability of this compound (79) prevented its isolation in a pure state.

The preparation of *exo*-7-chloromethyl-6-methylbicyclo[4.1.0] heptane (88) involved a similar sequence of reactions to that employed in the synthesis of the chloride (75). However, since only a limited quantity of 1-methylcyclohexene (83) was available, the reaction of this olefin with ethyl diazoacetate required the use of a suitable co-solvent.

The reaction was conducted in methylcyclohexane to afford the *exo*- and *endo*-cyclopropane esters (84) and (85), in yields of 50% and 16% respectively, and a small amount of an unsaturated by-product thought to be the product of allylic insertion. A previous experiment, in which cyclohexane was used as the co-solvent, led to the formation of the same three compounds in yields of 30%, 10%, and 5%. That the use

of a higher boiling solvent should result in a more efficient reaction is consistent with previous observations[137,140].



Scheme 17

Reagents: i, N_2CHCO_2Et-$Cu^I[P(OMe)_3]I$-$(PhCO_2)_2$-MCH; ii, NaOH-H_2O; iii, recryst. *n*-hexane; iv, $LiAlH_4$-Et_2O; v, NCS-PPh_3-THF.

The assignment of the *exo*-configuration to the major product of the reaction of ethyl diazoacetate with 1-methylcyclohexene (83) is based on the following n.m.r. data:

(i) The CH_2X hydrogens of the alcohol (87) and of the chloride (88) are magnetically non-equivalent and appear as the AB part of an ABX system. By analogy with the reported[141] spectra of structurally related compounds, the CH_2X hydrogens of bicyclo[4.1.0]heptane derivatives of the *endo*-configuration are expected to appear as a simple doublet.

(ii) The resonance attributable to the C_6 methyl group of the *exo*-ester (90) appears to lower field (0.04 ppm in CCl_4, 0.4 ppm in benzene) of that of the *endo*-ester (91). Previous studies[141,142] have established that, in compounds of related structure, methyl groups *cis* to a carbmethoxy group are deshielded with respect to those *trans* to a carbmethoxy group.

(iii) The spectra of the methyl esters (90) and (91) were also recorded in the presence of the n.m.r. shift reagent tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctan-4,6-dionato)praseodymium ($Pr(fod)_3$). Unfortunately, due to problems associated with assessing the position of the metal ion in the adducts between the esters (90) and (91) and $Pr(fod)_3$, it was not possible to unequivocally assign the ring hydrogens. It was noted, however, that the isotopic shift of the C_6 methyl group of the *exo*-ester (90) is

significantly larger than that of the *endo*-ester (91) and, although the precise geometry of the metal complex is unknown, it is apparent that the C_6 methyl-metal centre distance will be greater for the compound of *endo*-configuration (91).

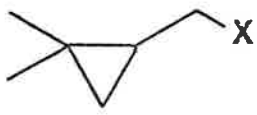
The stereochemical assignment is also consistent with chemical expectations. An examination of molecular models shows that those steric factors thought to be responsible for preferential formation of the *exo*-ester (70) from the reaction of ethyl diazoacetate with cyclohexene[140,143] should also favour the formation of the *exo*-compound (84) from the same reaction with 1-methylcyclohexene (83).

Treatment of the alcohol (87) with the reagent derived from the reaction of triphenyl phosphine with *N*-chlorosuccinimide in tetrahydrofuran afforded a mixture containing the chlorides (88) and (89) in the ratio 3:2. Subjection of this mixture to the ozonolysis procedure developed for the purification of (75) afforded the chloride (88) in a pure state (>99%, as evidenced by n.m.r. spectroscopy).

This compound (88) proved to be very prone to rearrangement, and was rapidly converted into the isomeric chloride (89) in the presence of trace amounts of acid. A significant degree of rearrangement was noted on dissolution in chloroform. The chloride (88) did, however, appear to be stable in both carbon tetrachloride and pentane (containing triphenyl tin chloride (5%)); no isomerisation was observed in either case after a period of 48 hours.

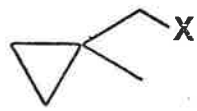
A convenient preparation of the monocyclic chloride (93) involved treatment of the alcohol (92) with thionyl chloride in ether at -78°C. However, although this procedure produced the required chloride (93) selectively (as evidenced by gas chromatographic analysis of the reaction mixture prior to work up), the isolated product contained 15% of rearranged material. The use of *n*-butane as solvent for the reaction permitted the work up procedure to be readily conducted at a low temperature. As a result of this modification the chloride (93) isolated was of >97% purity.

This same procedure ($SOCl_2$-butane) was employed in the successful preparation of the chlorides (95), (97), (99), and (101). The secondary chloride (103) was prepared according to Hanack and Eggensperger[137] by treatment of the alcohol (102) with phosphorous pentachloride in *n*-pentane at -20°C. Attempts to apply either this (PCl_5-pentane) or the preceding ($SOCl_2$-butane) method to the synthesis of the chloride (105) were unsuccessful.



92 X = OH

93 X = Cl



94 X = OH

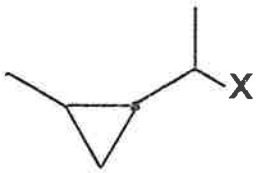
95 X = Cl

96 X = OH

97 X = Cl

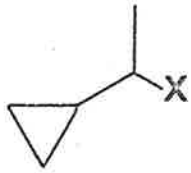
98 X = OH

99 X = Cl



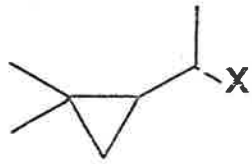
100 X = OH

101 X = Cl



102 X = OH

103 X = Cl



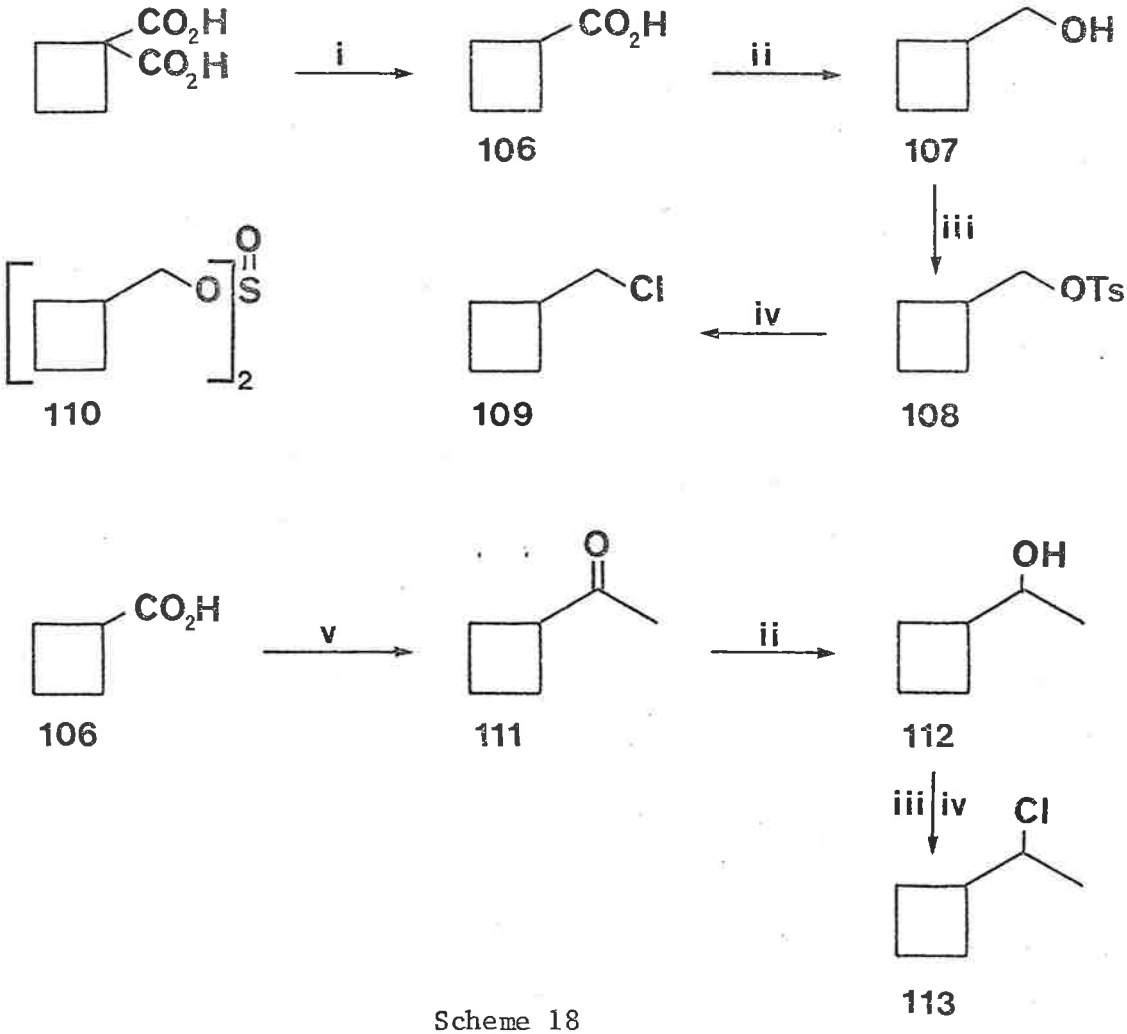
104 X = OH

105 X = Cl

CHAPTER 4

The Synthesis of Chloromethylcyclobutanes.

Procedures previously described in the literature[144-148] for the preparation of chloromethylcyclobutane derivatives often afford significant amounts of rearranged material. In order to avoid problems arising in the purification of the chlorides a search for a general synthetic method of greater selectivity was instigated.



Scheme 18

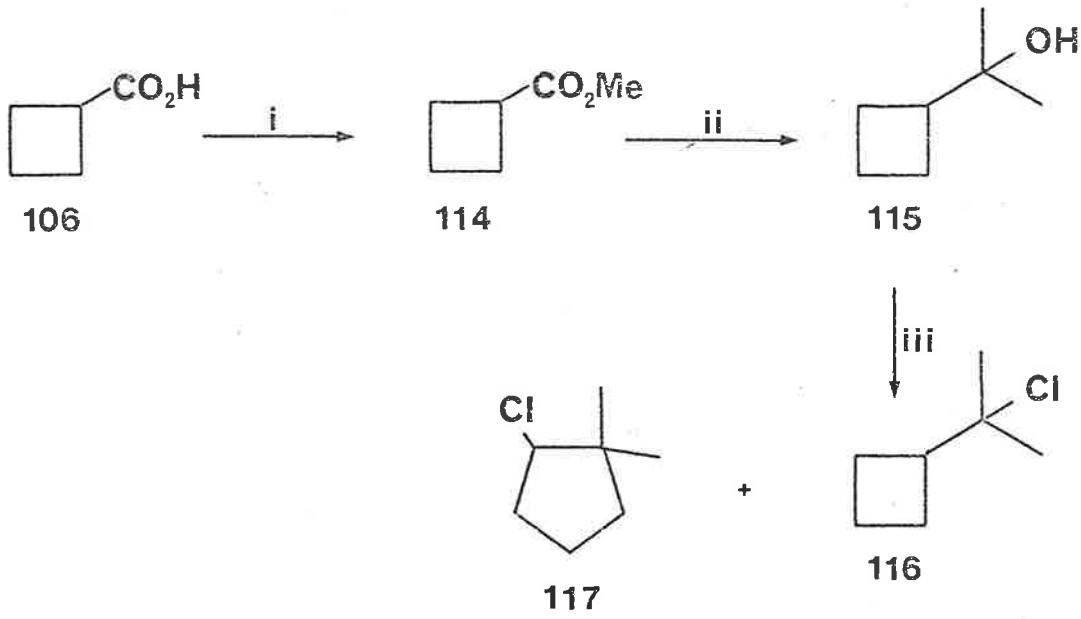
Reagents: i, Δ; ii, $LiAlH_4$-Et_2O; iii, TsCl-pyridine; iv, LiCl-HMPT; v, MeLi-Et_2O.

The reaction of the alcohol (107) with thionyl chloride in *n*-butane at -78°C, a procedure which has been used successfully for the preparation of chloromethylcyclopropanes (see chapter 3), afforded the dialkyl sulphite (110) as the only isolable product in 76% yield.

Previous work[101,172] has established that displacement of the appropriate toluene-*p*-sulphonate constitutes an excellent procedure for the preparation of halides without rearrangement. Thus, cyclobutylemethanol (107) was converted into its toluene-*p*-sulphonate (108), subsequent treatment of which with lithium chloride in hexamethylphosphorictriamide (HMPT) afforded chloromethylcyclobutane (109) in high yield (96%). When *N*,*N*-dimethylformamide (DMF) was used as solvent under similar conditions only 50% conversion into the chloride (109) was effected. The greater efficiency of HMPT in accomplishing the desired transformation is in accord with previous observations[101,149]. This same procedure (LiCl-HMPT) proved successful for the preparation of each of the primary and secondary chlorides required.

Although a variety of halogenation procedures were examined, the tertiary chloride (116) could not be obtained free of the isomeric 1-chloro-2,2-dimethylcyclopentane (117). The most convenient preparation of (116) involved treatment of the alcohol (115) with one equivalent of dry hydrogen chloride to give a mixture of the chlorides (116) and (117) in the ratio 4:1. This mixture was then subjected to preparative gas chromatography, and, although the compounds (116) and

(117) were not completely resolved, partial purification was achieved to afford material containing only 8% of the impurity (117).

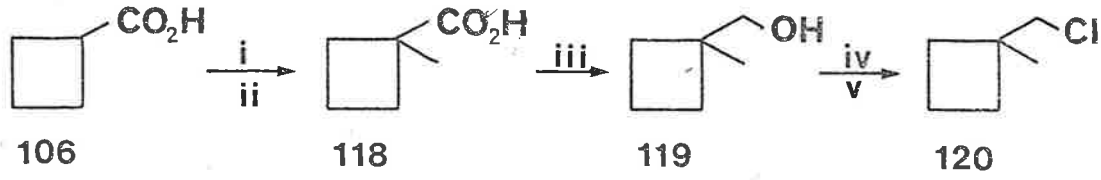


Scheme 19

Reagents: i, CH_2N_2-Et_2O; ii, MeMgI-Et_2O; iii, HCl-pentane.

Successive treatment of cyclobutanecarboxylic acid (106) with lithium *N*-cyclohexyl-*N*-isopropylamide or lithium *N*,*N*-diisopropylamide and methyl iodide[150] afforded the alkylated acid (118) in good yield (88%) but contaminated with some starting material (2-10% (106)). The acid could be resubjected to the alkylation procedure. However, it proved more convenient to subject the mixture of acids to the remaining steps of the sequence (scheme 20) and to purify the chloride (120) by preparative gas chromatography. The present synthesis offers

a shorter and more efficient route to the acid (118) than those previously reported[151,152].



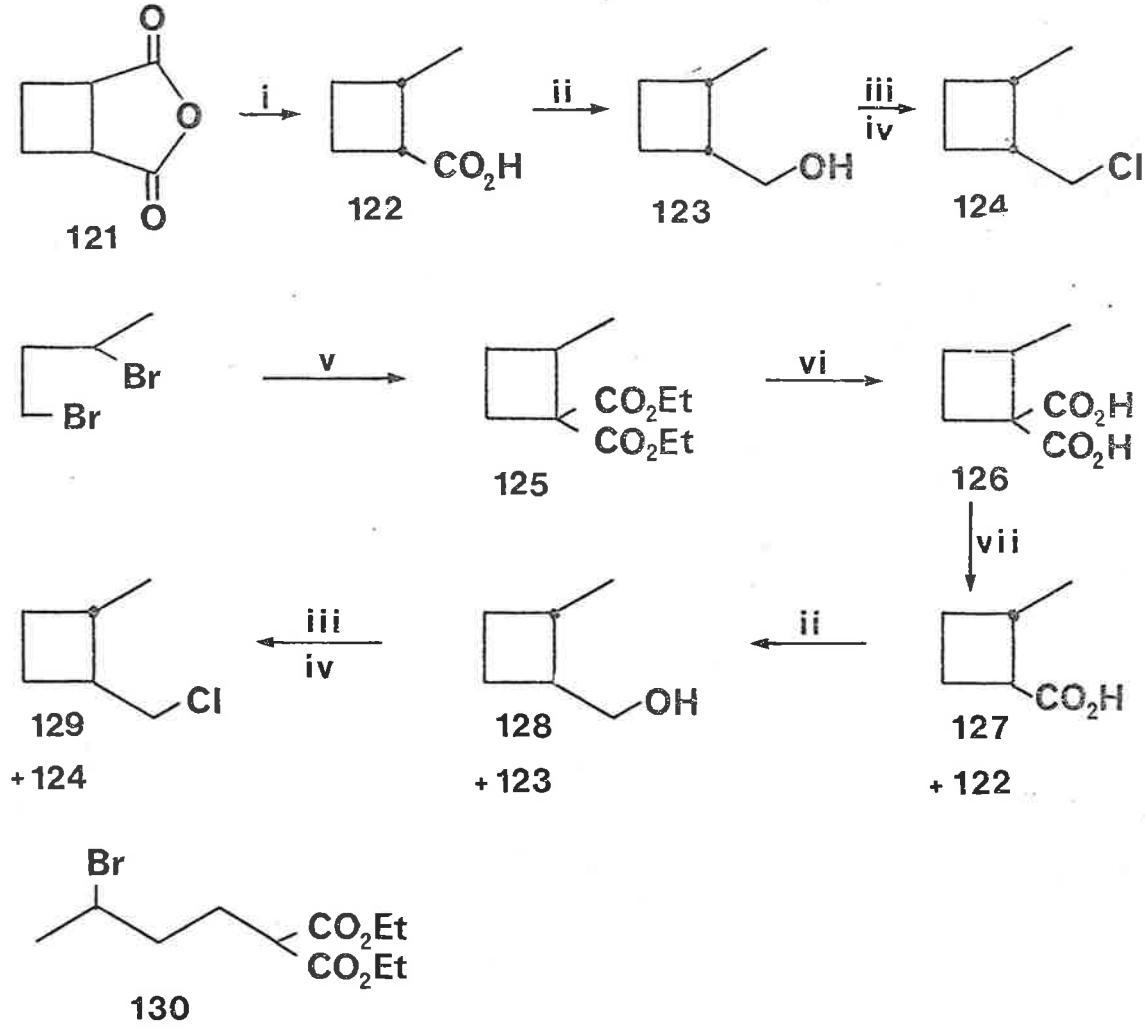
Scheme 20

Reagents: i, $LiNR_2$-THF-pentane; ii, MeI; iii, $LiAlH_4$-Et_2O; iv, TsCl-pyridine; v, LiCl-HMPT.

Cis-2-methylcyclobutanecarboxylic acid (122) was available from the hydrogenation[153] of the anhydride (121). The *trans*-acid (127), however, could not be obtained selectively. A mixture (1:3) of the *cis*- and *trans*-acids (122) and (127) was obtained from the decarboxylation[154] of the diacid (126). Both the alcohols (123) and (128) and the chlorides (124) and (129) were readily separable by preparative gas chromatography.

A useful modification of the malonic ester synthesis[154,155] involves the use of sodium hydride as base in *N*,*N*-dimethylformamide (DMF) solution. Although the yield of diester (122) obtained under these conditions shows only a marginal improvement over that formed by the

conventional procedure[154,155], the product contains little (<3%) unchanged diethyl malonate or unsaturated by-products. Thus the required compound (122) is readily obtained in a pure state.



Scheme 21

Reagents: i, H_2-PtO_2-EtAc; ii, $LiAlH_4$-Et_2O; iii, TsCl-pyridine; iv, LiCl-HMPT; v, $CH_2(CO_2Et)_2$-NaH-DMF; vi, HCl-H_2O; vii, Δ.

The major by-product of the reaction was identified as the bromoester (130) on the basis of spectral data. This result contrasts with a recent report[146] that the use of sodium hydride in DMF affords major amounts of elimination products (no experimental details were given).

The aluminium chloride promoted addition of olefins to methyl acrylate in ethylene chloride-nitromethane has been reported[156] to afford cyclobutane derivatives. The reaction appeared to provide a simple and convenient preparation of several of the compounds required.

The reaction of isobutylene with ethyl acrylate was conducted under the conditions previously described[156] to afford a mixture of products in the ratio 8:1. The major component was identified as the olefinic ester (131), which gave positive tests for unsaturation and afforded ^{1}H n.m.r. data in accord with the proposed structure. The minor component was tentatively assigned the structure (133) on the basis of a low field n.m.r. resonance at $\delta 4.65$, characteristic of the terminal methylene group, and the fact that hydrogenation of the mixture of esters (131) and (133) afforded a single product.*

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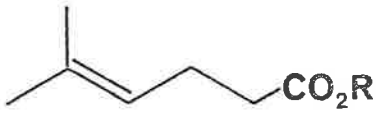
* Subsequent experiments conducted in these laboratories[157] have provided an authentic sample of the ester (133) which was shown to have identical spectral properties and g.l.c. retention time to the compound obtained by the above route.



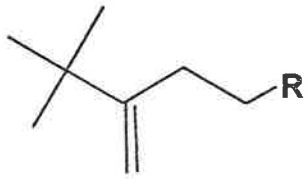
131 R = H

132 R = Et

133

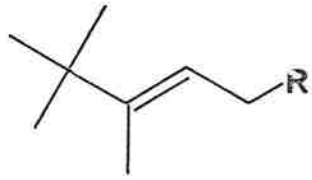
Saponification of the ester (131) afforded the acid (132) which had physical and spectral properties identical with those of the authentic compound[158]. These properties are quite different to those of 2,2-dimethylcyclobutanecarboxylic acid (156) which has been prepared by an unambiguous route (scheme 22).

Similarly the aluminium chloride promoted addition of tetramethylethylene to ethyl acrylate failed to afford any cyclobutane compounds. The product (36%) was shown by gas chromatography to contain four components in the ratio 10:44:34:12, identified as (134), (135), (136), and (137) respectively, on the basis of their spectral properties and analytical data.



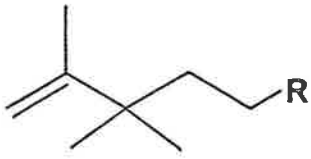
134 R=CO_2Et

138 R=CH_2OH



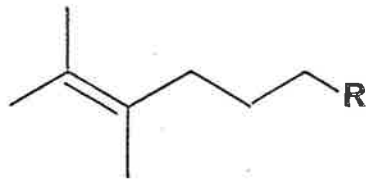
135 R=CO_2Et

139 R=CH_2OH



136 R=CO_2Et

140 R=CH_2OH



137 R=CO_2Et

141 R=CH_2OH

Reduction of the mixture of esters (134), (135), (136), and (137) with lithium aluminium hydride afforded a mixture of the corresponding alcohols (138), (139), (140), and (141). The observed and calculated ^{13}C shieldings for the two major products (139) and (140), which were separated from the mixture by preparative gas chromatography, are reported in tables 12 and 13. The data are consistent with the proposed structures. Additional evidence for the nature of the alcohol (140) comes from the fact that the product of its hydrogenation is identical to the compound (143) obtained from the hydroboration-oxidation of the olefin (142).

Table 12

^{13}C shieldings for 2,2,3-trimethylpent-3-ene (144) and 4,5,5-trimethylhex-3-en-1-ol (139)[a].

compound	(144)[b,c]	(139) obs.[c]	(139) calc.[c,d]
C_1	-	62.4	62.8
C_2	12.3	31.9	31.3
C_3	114.6	116.3	117.9[e]
C_4	143.8	146.7	143.0[e]
C_5	29.0	29.1	29.1
C_6	13.5	12.9	13.9
C_7	36.0	36.2	36.4

a δ_c, ppm from TMS.

b Similar data (± 1.0 ppm) have been reported by de Haan and van de Ven[159].

c The numbering scheme shown below has been adopted.

d Calculated shieldings are based on the spectrum of compound (144) and the additivity parameters given in refs. 160 and 161.

e The failure of the additivity parameters to accurately predict the shieldings for C_3 and C_4 is not unexpected. A similar variance (in both sign and magnitude) between the observed and calculated shieldings is seen for the γ and δ carbons of other substituted alcohols[161].

Table 13

^{13}C shieldings for 2,3,3-trimethylpent-1-ene (145) and 4,4,5-trimethylhex-5-en-1-ol (140)[a].

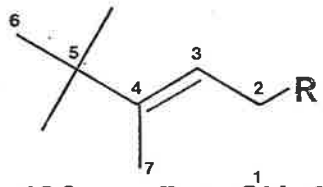
compound	(145)[b]	(140) obs.[b]	(140) calc.[b,c]
C_1	-	63.5	63.0
C_2	8.8	28.1	27.8
C_3	33.1	36.7	38.3[d]
C_4	38.9	38.4	36.7[d]
C_5	109.5	109.8	109.7
C_6	151.9	151.6	152.5
C_7	26.7	27.2	27.1
C_8	19.3	19.3	19.4

a δ_c, ppm from TMS.

b The numbering scheme shown below has been adopted.

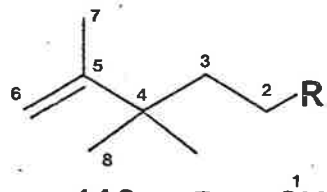
c Calculated shieldings are based on the spectrum of compound (145) and the additivity parameters given in refs. 160 and 161.

d See footnote e to table 12.



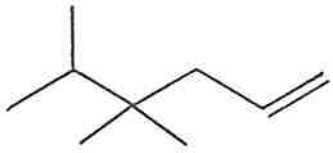
139 R = CH_2OH (1)

144 R = H



140 R = CH_2OH (1)

145 R = H



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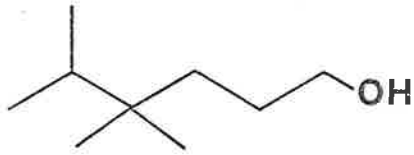


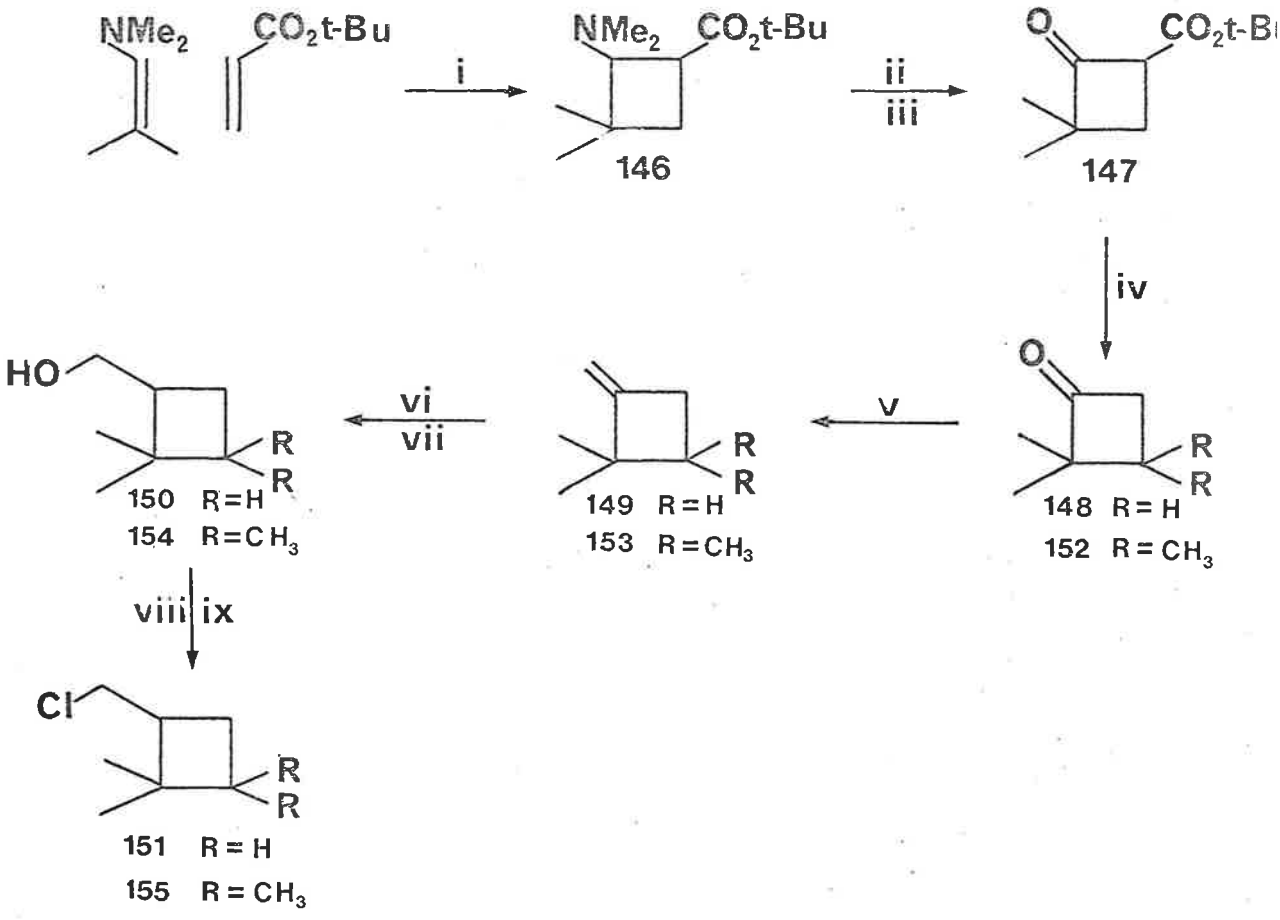
143

These results clearly show that in two cases the aluminium chloride promoted addition of olefins to ethyl acrylate afford only unsaturated esters. It appears that in the previous work[156] the products were erroneously assigned cyclobutane structures.

Subsequent experiments conducted in these laboratories[157] have shown that the reaction between isobutylene and ethyl acrylate in benzene solution affords only the terminally unsaturated ester (133). This reaction is thought to proceed *via* an aluminium chloride catalysed ene reaction[162]. It has also been demonstrated[157] that the ester (133), when dissolved in ethylene chloride-nitromethane containing aluminium chloride (the conditions of the experiment approximating those of the addition reactions described above), undergoes rearrangement, presumably *via* a carbonium ion intermediate, to afford the ester (131) amongst other products.

It seems likely, therefore, that the reactions of isobutylene and tetramethylethylene with ethyl acrylate in ethylene chloride-nitro-

methane also proceed *via* an ene reaction to form initially the esters (131) and (136) which, being unstable to the reaction conditions, are isomerised to afford the observed product mixtures.



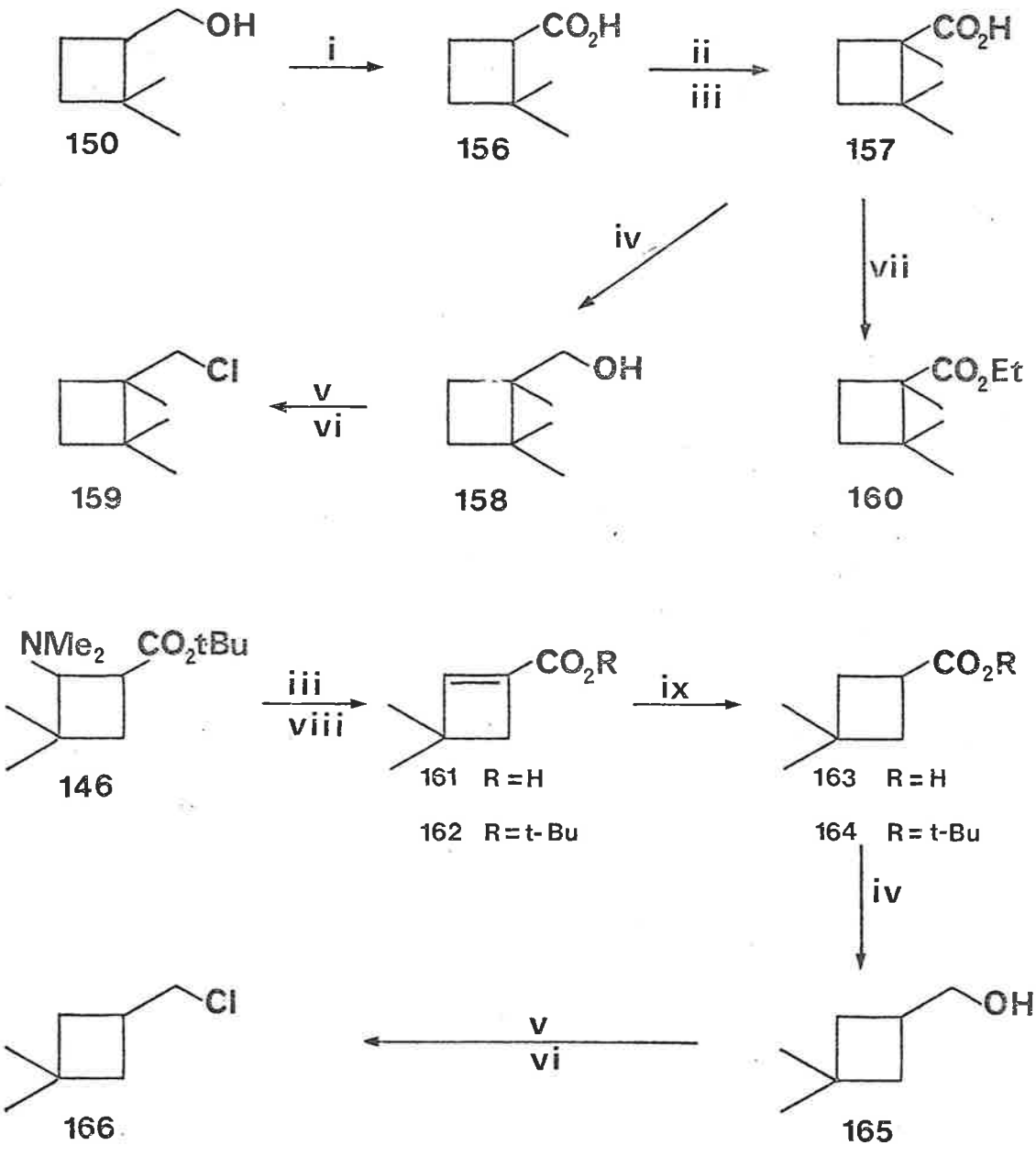
Scheme 22

Reagents: i, Δ-CH_3CN; ii, Br_2-H_2O; iii, Zn; iv, TsOH-Δ; v, CH_2PPh_2-DMSO; vi, B_2H_6-THF; vii, H_2O_2-NaOH; viii, TsCl-pyridine; ix, LiCl-HMPT.

A convenient route to the chlorides (156) and (157) was provided by the availability of the cyclobutanones (148)[163] and (152)[164] (see scheme 22). Intermediates in this synthesis of (148) also provided routes to two of the other compounds required (160) and (166) (see scheme 23).

An attempt to prepare 1,2,2-trimethylcyclobutanecarboxylic acid (157) directly from the olefin (149) *via* carbonylation with nickel carbonyl[152,165] led to the formation of only a poor yield (10%) of a mixture of the required acid (157) and its ethyl ester (160). A more efficient route to (157) involves alkylation of the acid (156) using a procedure similar to that described for the preparation of 1-methylcyclobutanecarboxylic acid (118). The acid (156) was available in high yield (90%) from the oxidation of the alcohol (150) with potassium permanganate using a phase transfer technique[166].

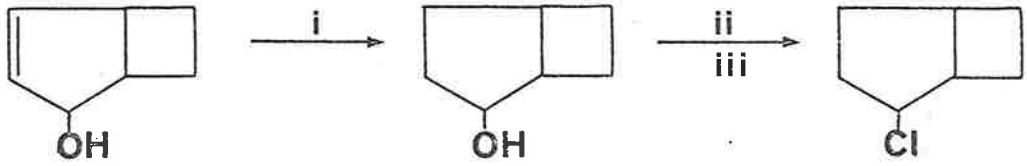
Exo-bicyclo[3.2.0]hept-3-en-2-ol (167), prepared according to the procedure of Winstein and Stafford[167], was hydrogenated to afford the saturated alcohol (168). The reaction of this alcohol (168) with the reagent derived from the addition of triphenyl phosphine to *N*-chlorosuccinimide in tetrahydroforan afforded the required chloride (169). However, the volatility of (169) and the consequent problems encountered in its isolation made this procedure unsatisfactory. Displacement of the toluene-*p*-sulphonate of the alcohol (168) through treatment with lithium chloride in HMPT gave a mixture of the *endo*-chloride (169) and



Scheme 23

Reagents: i, $KMnO_4$-R_4NCl-benzene-H_2O; ii, $LiNR_2$-THF-Et_2O; iii, MeI; iv, $LiAlH_4$-Et_2O; v, TsCl-pyridine; vi, LiCl-HMPT; vii, CH_3CHN_2-Et_2O; viii, NaOH-H_2O; ix, H_2-PtO_2-Et_2O.

the elimination product, bicyclo[3.2.0]hept-2-ene, in yields of 65% and 35% respectively. Both of the above-mentioned procedures proceeded with inversion of configuration at C_2 (as evidenced by n.m.r. spectroscopy[147,168,169]) and produced no (<1%) products of rearranged structure; a serious complication with the previously reported syntheses of 2-halobicyclo[3.2.0]heptanes[147,168].

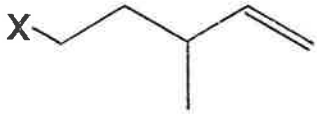


167 168 169

Scheme 24

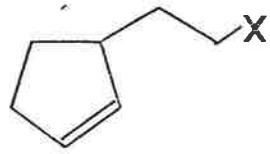
Reagents: i, H_2-PtO_2-Et_2O; ii, TsCl-pyridine; iii, LiCl-HMPT.

The chlorides (171) and (173), required to test the irreversibility of cyclobutylcarbinyl radical β-scission, were available in high yield from the alcohols (170)[170] and (172)[171] by treatment of their respective toluene-*p*-sulphonates with lithium chloride in DMF.



170 X = OH

171 X = Cl



172 X=OH

173 X=Cl

CHAPTER 5

Product Studies of the Reduction of Chloromethylcyclopropanes with Stannane; the Kinetics of Cyclopropylcarbinyl β-scission.

It will be apparent from the preceding discussion (chapter 1) that the ring opening β-scission reaction undergone by cyclopropylcarbinyl radicals is a very facile process.

Recently Ingold and co-workers[172] have applied a kinetic e.p.r. technique to determine the rate constant (k_f) for opening of the parent radical (1) to be 1.3×10^8 sec^{-1} at ambient temperature. On the basis of CIDNP experiments Kaptein[173] has estimated k_f for the same reaction at 80°C to be 3×10^7 sec^{-1}. He indicated, however, that, because of certain assumptions inherent in the calculation[173], this value may represent only a lower limit for k_f.

However, in spite of the extremely facile nature of the ring opening reaction, the rate of hydrogen atom transfer from stannane is sufficient that a cyclopropylcarbinyl radical intermediate may be trapped prior to its undergoing fragmentation[43,50,55,125,174]. Beckwith and Phillipou[50] have generated the 3β,5-cyclocholestan-6-yl radical (23) through reduction of the appropriate chloride with triphenylstannane in pentane. By means of an accurate product stuey they were able to determine the ratio k_f/k_H for the radical (23) to be *ca.* 7.5 mol l^{-1} at 25°C and, by taking k_H as 5×10^6 1 mol^{-1} sec^{-1} [125], the absolute value of k_f to be *ca.* 4×10^7 sec^{-1} at 25°C. A similar k_f has been estimated[50,125] for the isomeric radical (25).

Carlsson and Ingold[125] utilized product data[174] for the reduction of nortricyclyl bromide with triphenylstannane to show that the ring opening reaction of the nortricyclyl-norbornenyl isomerisation (scheme 25) occurs with a rate constant of *ca.* 10^8 sec^{-1} at 45°C. A later study[175] concerning the 7-acetoxynorbornenyl radical ((174) X=OAc) indicated that the reverse, ring closing, reaction proceeds with a similar rate constant (4×10^7 sec^{-1} at 20°C).

174

Scheme 25

Though our fears were later shown to be groundless, it was anticipated that the application of these methods (see chapter 2) to the investigation of the parent cyclopropylcarbinyl system might be complicated by difficulties in the determination of the highly volatile reaction products. Accordingly an initial study concerned the (bicyclo[4.1.0]hept-7-yl)carbinyl system.

Exo-7-chloromethylbicyclo[4.1.0]heptane (75) and its 6-methyl derivative (88) were reduced with triphenylstannane in pentane or in decalin at temperatures in the range 0-25°C. Tables 14 and 15 list

the relative and absolute yields of products obtained from these experiments together with estimates of the ratio k_f/k_H derived by the application of equation (1)†.

Unfortunately, the compounds with the cyclopropane ring intact (176) and (180) constituted only a small proportion of the reduction product (<5% from (75); <2% from (88)) even when very high concentrations of triphenylstannane were used. This fact severely limits the accuracy with which values of k_f/k_H can be determined and makes a detailed study of the effect of substituents on the kinetics of the ring opening process impracticable in this system.

The value of k_f/k_H for the radical (175) of *ca.* 55 mol l^{-1} at 25°C corresponds to a k_f of *ca.* 3×10^8 sec^{-1} at 25°C (by taking k_H as 5×10^6 1 mol^{-1} sec^{-1} [125]). The rate constant may thus be seen to be greater than that for the parent cyclopropylcarbinyl radical (1), a fact which probably reflects the greater strain energy inherent in the bicyclic ring system* and, perhaps, that fragmentation of (175) leads to the formation of a secondary radical.

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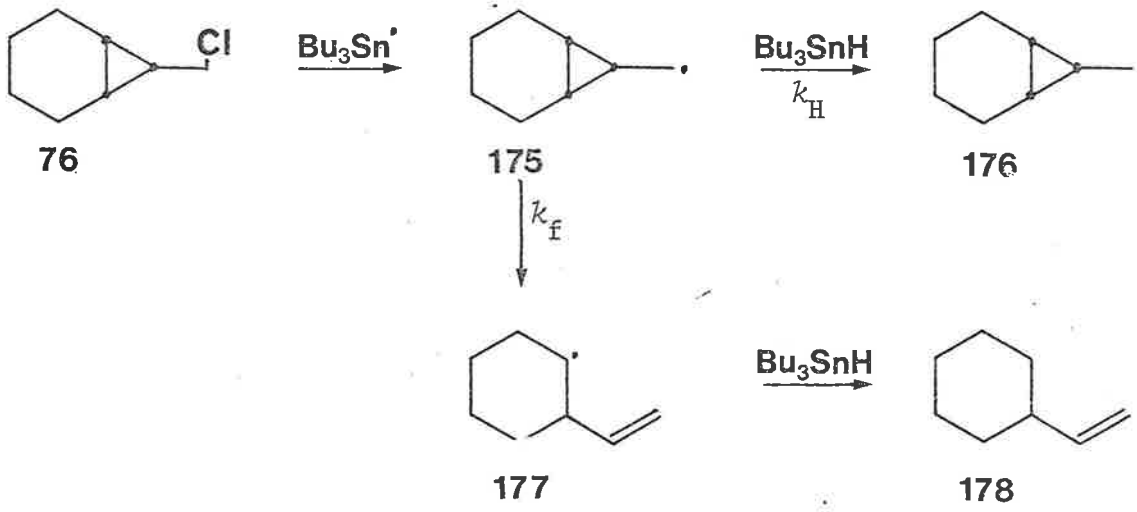
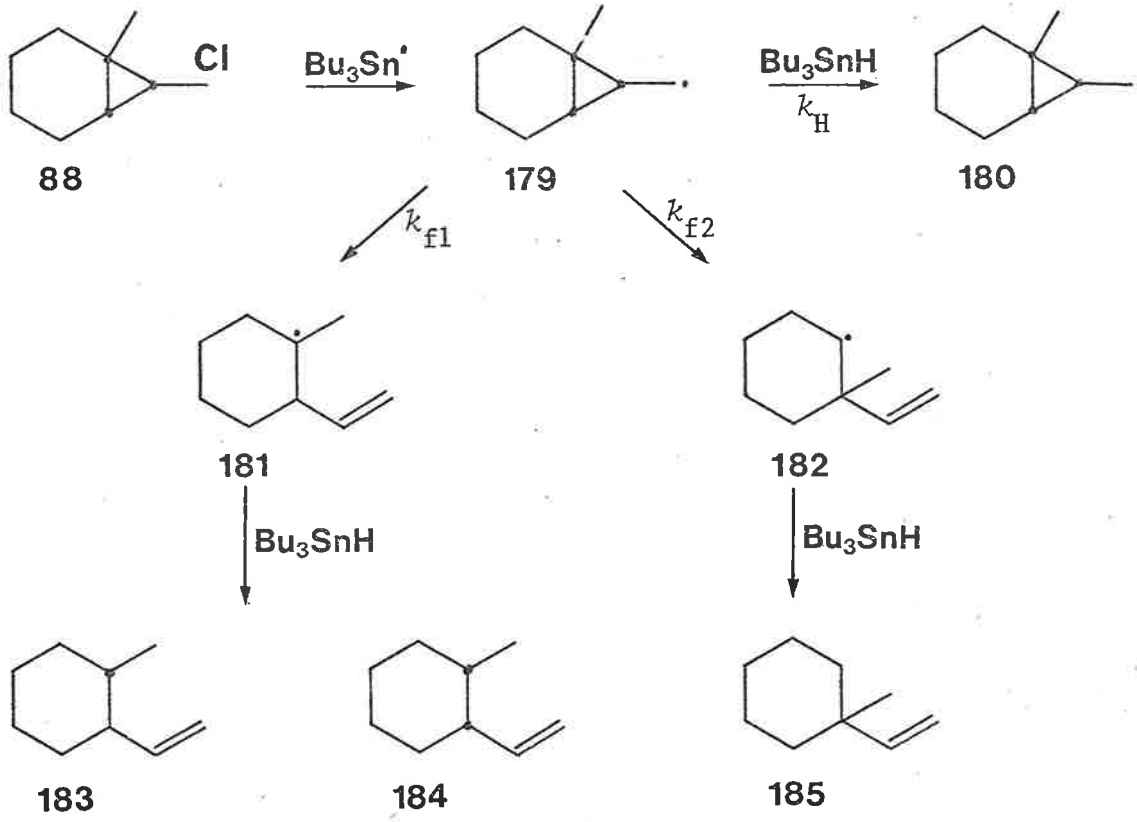
† General details of the procedure for obtaining kinetic data from product studies of the reduction of alkyl halides with stannane are given in chapter 2. For details of the conditions under which the reductions were conducted see the experimental section.

* The strain energy inherent in the bicyclo 4.1.0 heptane skeleton has been calculated[176] to be 30.29 kcal mol^{-1} which compares with a value of 28.13 kcal mol^{-1} for cyclopropane.



Scheme 26



Scheme 27

Table 14

Reduction of *exo*-7-chloromethylbicyclo[4.1.0]heptane (75) with triphenyl stannane in pentane[a].

Temperature	$[Ph_3SnH]_0$	Relative yield		Total yield	k_f/k_H
°C	mol l^{-1}	%(176)	%(178)	%	mol l^{-1}
25	1.71[b]	1.55 ± 0.02	98.45	100	54 ± 2
26	2.11[c]	3.8 ± 0.4	96.2	36	53 ± 6
26	3.10[c]	4.9 ± 0.4	95.1	40	60 ± 6
26	3.28[c]	4.8 ± 0.2	95.2	39	64 ± 3
10	1.07[c]	4.0 ± 0.2	96.0	30	23 ± 3
0	-	-	-	-	14[d]

[a] Uncertainties are expressed as the standard deviation from mean.

[b] Reaction conducted in decalin solvent.

[c] Stannane present in excess - halide concentration 0.035, 0.035, 0.073 and 0.30 mol l^{-1} respectively.

[d] Extrapolated value - an attempt to conduct the reduction at 0°C led to only a 7% yield of hydrocarbon products.

Table 15

Reduction of *exo*-7-chloromethyl-6-methylbicyclo[4.1.0]heptane (88) with triphenylstannane in pentane at 0°.

$[Ph_3SnH]_0$	Relative yield				(183)/(184)	Total yield
mol l^{-1}	%(180)	%(183)	%(184)	%(185)		%
0.66[a]	1[c]	48	27	24	1.8	34
1.06[a]	2[d]	50	26	23	1.9	28
ca. 1.27[a,b]	2	50	25	24	2.0	32

[a] Stannane present in excess - halide concentration 0.008, 0.009 and 0.013 mol l^{-1} respectively.

[b] Triphenylstannane was not completely soluble in pentane at concentrations above 1.0 mol l^{-1} at 0°.

[c] 1.2 ± 0.5 corresponds to k_f/k_H of *ca.* 50 mol l^{-1}

[d] 1.7 ± 0.8 corresponds to k_f/k_H of *ca.* 60 mol l^{-1}

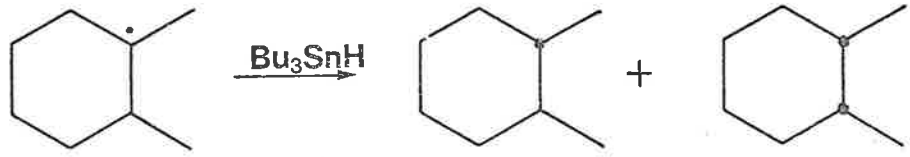
The radical (179) opens to afford a major amount of the products (183) and (184) derived from the more stable tertiary radical (181) (k_{f1}/k_{f2} = 3.2, see table 15) and, although absolute values of the rate constants for this reaction could not be determined precisely, it is clear that the selectivity observed is due primarily to an enhanced rate constant (k_{f1}) for cleavage of the more substituted bond. The value of k_{f2}/k_H of *ca.* 12 mol l^{-1} at 0°C being of similar or greater magnitude than k_f/k_H for the unsubstituted radical (175) (*ca.* 7 mol l^{-1} at 0°C if statistically corrected). This fact indicates that steric interactions between the hydrogens at the radical centre and the *cis*-methyl group are not sufficiently large to favour overlap of the semi-occupied orbital with that cyclopropane bond being preferentially cleaved. Further mention of this feature will be made in the subsequent text.

The value of the *trans*:*cis* isomer ratio ((183):(184), see table 15) and its marginal dependence on the concentration of triphenylstannane (which is within the limits of experimental error) may indicate the trapping of a *trans*-radical intermediate produced from the fragmentation reaction*. However, previous work[99,177-180] would suggest that the rate of hydrogen atom transfer from stannane is not sufficient to trap a radical intermediate (with the exception of cyclopropyl[105]) prior to

---

* Control experiments (see the experimental section) showed both *cis*- and *trans*-2-methylvinylcyclohexane to be configurationally stable under the reaction conditions.

its losing configurational integrity (if, indeed, the radical (181) is pyramidal). It is also noteworthy that the reaction of the radical (186) with tri-*n*-butylstannane[180] proceeds to afford a similar ratio of *trans*- and *cis*-products which is independent of stannane concentration.



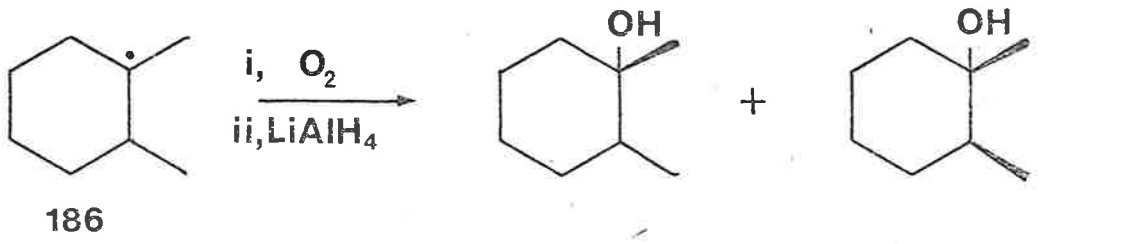
186

Relative yield	63%	37%

In contrast to these results, Miyajima and Simamura[181] have reported the reaction of the radical (186) with oxygen to afford a slight preponderance of product in which the methyl groups bear a *cis*-relationship to each other. In addition Boldt and co-workers[182] found the addition of bromodicyanomethane to 1-methylcyclohexene (which should form initially the radical (187)) to afford mainly the product resulting from *trans*-addition to the double bond*.

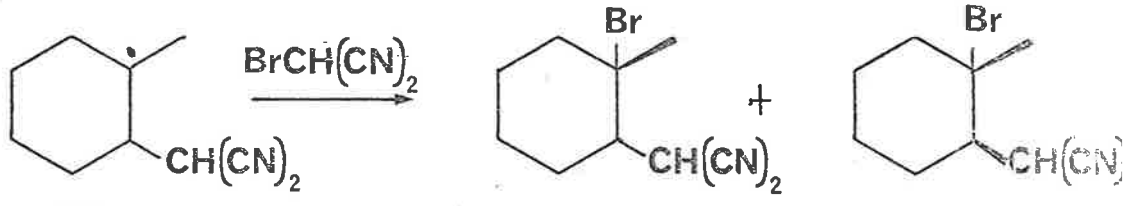
---

* Reactions involving the addition of trichlorosilyl radicals[183] and bromine atoms[184,185] to 1-methylcyclohexene also proceed *via* a *trans*-mechanism. However, the selectivity in these cases may result from a bridged radical intermediate[19,186].



186

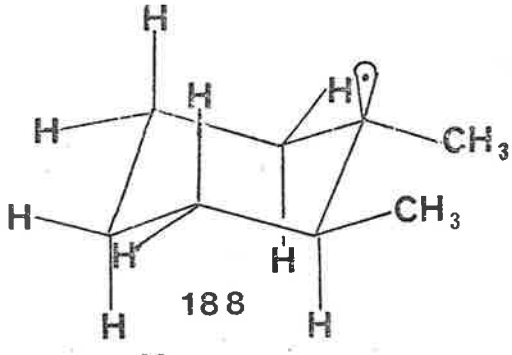
Relative yield	46%	54%



187

Relative yield	22%	78%

Recent e.p.r.[187,188] and photoelectron spectroscopy[189] results indicate a significantly non-planer equilibrium geometry for the *t*-butyl radical (though a low barrier to inversion of 400-600 cal mol^{-1}). In addition molecular orbital calculations[190] suggest the cyclohexyl radical to deviate slightly from planarity. On this basis it seems reasonable to assign a pyramidal geometry to the tertiary radicals in question. An examination of molecular models then shows the most stable conformation of these radicals to be (188) which should react to form a *trans*-disubstituted cyclohexane.



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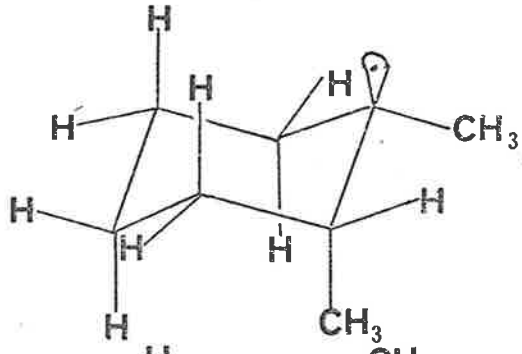
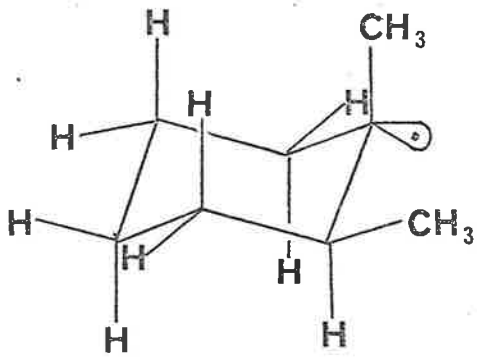
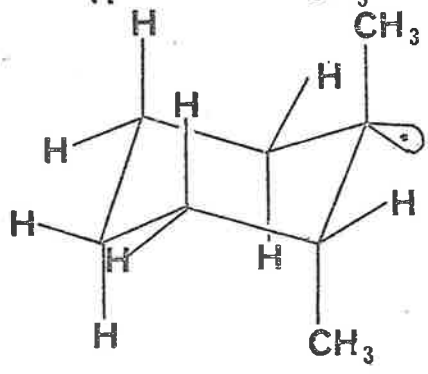




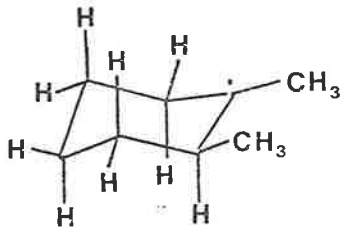


However, depending on the steric requirements of the incoming group the transition state for a less hindered equatorial attack may be of lower energy than that for axial attack. Unfortunately, available data does not allow the degree of bonding and hence the steric factors involved in the transition states for the three reactions to be adequately assessed. Nevertheless, it is worthwhile noting that there appears to be a direct relationship between the size of the incoming group and the distribution of products.

If we consider the radicals to adopt a planer ground-state geometry, the arguments given above do not have to be altered

substantially inasmuch as the transition state must involve a change to sp^3 hybridisation at the reacting centre. Some difficulty does arise, however, if we attempt to interpret our results in terms of the steric arguments proposed by Boldt and co-workers[182] to rationalise the product distribution from the reaction with bromodicyanomethane.

If a planer geometry is assumed for the radical centre and the ring adopts a chair conformation, then an examination of molecular models shows that attack of a reagent from the less hindered side of either of the two possible conformers (192) or (193) should favour the formation of a *cis*-disubstituted cyclohexane. This is not consistent with the product distribution observed from the reactions with stannane. Jenson and co-workers[191] have suggested that torsional interactions between the incoming group and the pseudo-axial hydrogens of the adjacent carbons may be important in determining the product distribution for reactions which are "less" exothermic and involve a substantial degree of bonding in the transition state (hydrogen atom



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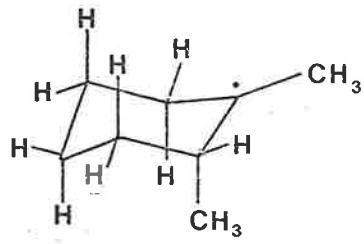
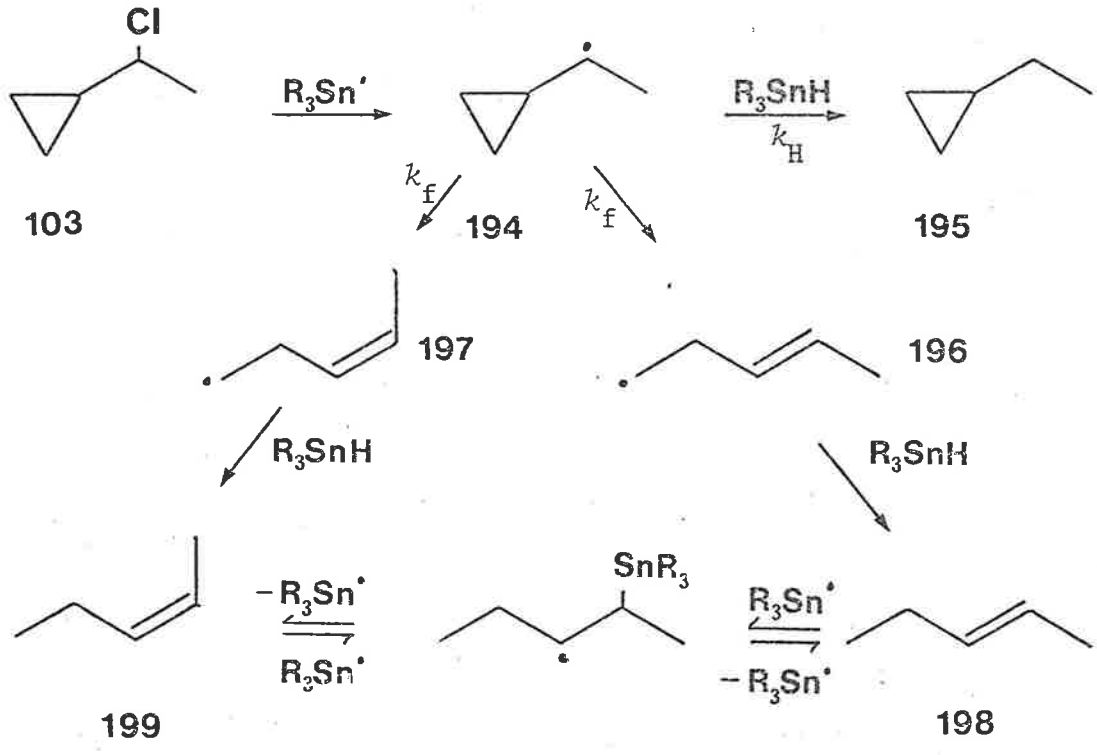


193

transfer from stannane should be exothermic to the extent of 4-5 kcal mol^{-1} (see chapter 2) which compares with *ca.* 28 kcal mol^{-1} for the reaction of an alkyl radical with oxygen[192]). The conceptual difficulty with such an argument, however, is that if there is a substantial degree of bonding in the transition state, there must logically also be a substantial change to sp^3 hybridisation, which should relieve the torsional interactions.

The problems entailed in obtaining accurate kinetic data for the opening of (bicyclo[4.1.0]hept-7-yl)carbinyl radicals prompted us to examine the reactions of the monocyclic chlorides (93), (95) and (103) with triphenylstannane.



Scheme 28

Table 16

Reduction of (1-chloroethyl)cyclopropane (103)

with triphenylstannane in decalin at 0°C.

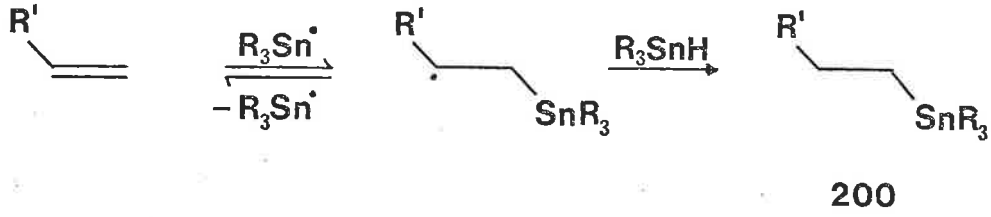
$[Ph_3SnH]_0$	Relative yield			(198)/(199)	Total yield	k_f/k_H
mol l^{-1}	%(195)	%(198)	%(199)		%	mol l^{-1}
1.49[a]	43.4	46.3	10.3	4.5	83	1.96
1.16[a]	37.7	51.7	10.7	4.8	81	1.90
0.30[a]	13.4	69.7	16.9	4.1	82	1.94
0.70[a,b]	*ca.* 2	80.1	17.9	4.5	53	-
0.14[a,b]	*ca.* 0.5	68.7	30.8	2.2	44	-

[a] Stannane present in excess - halide concentration 0.06, 0.08, 0.01, 0.16 and 0.03 mol l^{-1} respectively.

[b] $[Bu_3SnH]_0$

The reduction of (1-chloroethyl)cyclopropane (103) with triphenylstannane in decalin at 0°C proceeded according to scheme 28 to afford a high yield of hydrocarbon products of which the cyclopropane (195) made up a significant proportion (k_f/k_H = 1.9 l mol^{-1} at 0°C, see table 16). However, when the primary chlorides (93) and (95) were reduced under similar conditions only a poor yield of products resulted.

Control experiments, in which 2-chlorobutane was reduced with triphenylstannane in the presence of either 2-methylbut-1-ene or hex-1-ene, showed the olefins to be consumed under the reaction conditions, presumably as shown in scheme 29*. Interestingly, the recovery of olefin depended markedly on the conditions of analysis.



200

Scheme 29

* It is well known[193] that stannyl radicals undergo a rapid, though reversible, addition to olefins.

When the gas chromatograph was operated at relatively high temperatures a near quantitative yield could be obtained. Thus, it seems the alkylstannane (200) is thermally unstable and decomposes to regenerate the original olefin*.

Similar experiments showed the vinylcyclohexanes (178), (183), (184), and (185) to be much more stable to the reaction conditions (indeed, the recovery of olefins appeared to be quantitative (100 ± 3%) within the limits of experimental error). Nevertheless, in view of the above-mentioned results it would seem possible that a small proportion of the olefinic product from the reduction of the chlorides (75) and (86) could be converted into the corresponding alkylstannane. This would provide an explanation for the small dependence of the observed distribution of products from the reduction of (86) on the concentration of triphenylstannane (see table 15).

Trans- and *cis*-pent-2-ene (198) and (199), though not consumed under the reaction conditions, were isomerised to afford an equilibrium mixture of isomers (*trans/cis* = 4.8). For this reason the ratio of *trans*- and *cis*-pent-2-ene obtained from the reduction of (1-chloroethyl)cyclopropane (103) with triphenylstannane most likely does not represent the isomer distribution formed from the fragmentation

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* Thermal degradation of tetraalkylstannanes is known[194] to proceed, at least in part, by a β-elimination process to afford olefinic products.

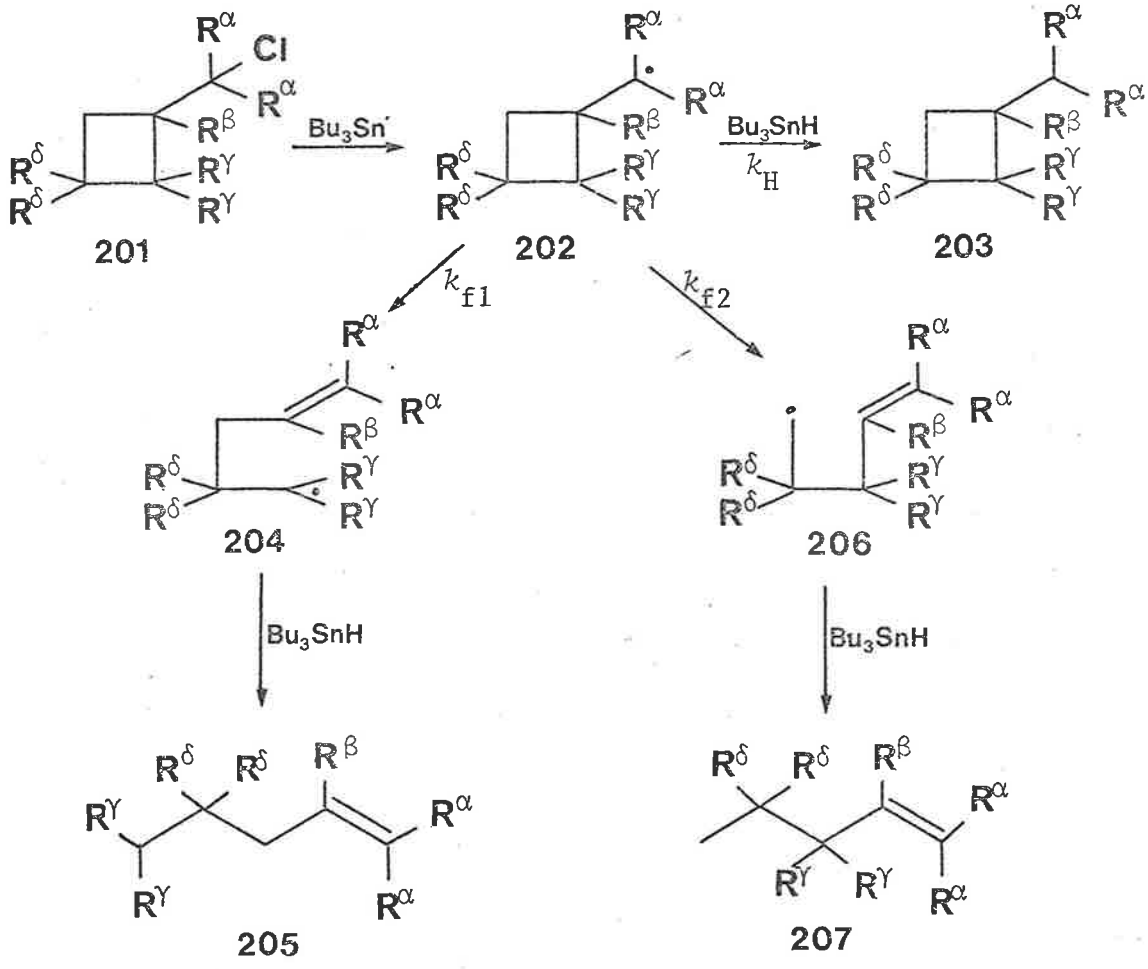
reaction. To determine this ratio several experiments were conducted in which the chloride (103) was reduced with the less reactive tri-*n*-butylstannane. Although the olefin was configurationally labile in the presence of a large excess of this reagent, control experiments demonstrated its stability both under conditions of high dilution and when an excess of the chloride was used. The value of the isomer ratio determined in this manner (*trans/cis* = *ca.* 2.2, see table 16) indicates that the fragmentation reaction is not as selective as previous work[195] would suggest.

It will be evident that product studies of the reduction of chloromethylcyclopropanes with triphenylstannane do not constitute a suitable method for examining the effect of substituents on the kinetics of the β-scission reactions of cyclopropyl carbinyl radicals. Although further work could be done to elucidate details of the reactions described in this chapter, such studies are beyond the scope of the present work. Accordingly, our attention turned to the study of the β-scission reactions of cyclobutylcarbinyl radicals, to which our present methods are more readily applicable.

Recent advances in the field of e.p.r. spectroscopy[126,196] may provide a more suitable means for examining the reactions of cyclopropylcarbinyl radicals.

CHAPTER 6

Product Studies of the Reduction of Chloromethylcyclobutanes with Stannane; the Kinetics of Cyclobutylcarbinyl β-scission.



Scheme 30

Reduction of the chloromethylcyclobutanes ((201), see chapter 4) with tri-*n*-butylstannane in decalin proceeded to afford a high yield of hydrocarbon products according to scheme 30. The relative and absolute yields of products were determined by gas chromatography (full details of the techniques used and the results obtained are presented in the experimental section). Utilization of these data in the appropriate integrated rate expression (equation 1, see chapter 2) enabled values of the rate constant ratio k_f/k_H to be calculated. A summary of the kinetic data in form of values of $k_f/k_H(60^0)$ and of

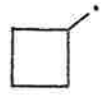
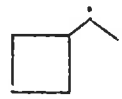
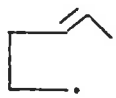
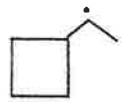
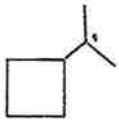
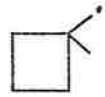
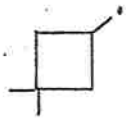
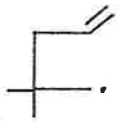
$\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ (the activation parameters for ring opening relative to those for hydrogen atom transfer from tri-*n*-butylstannane) is given in table 17.

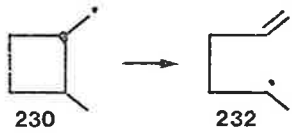
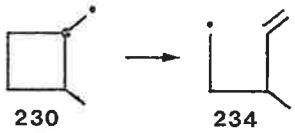
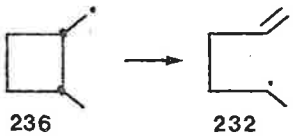
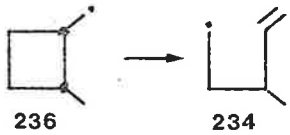
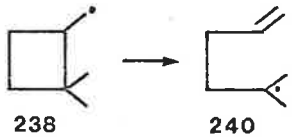
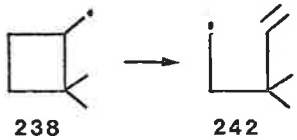
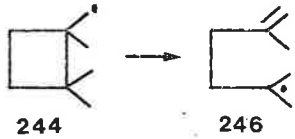
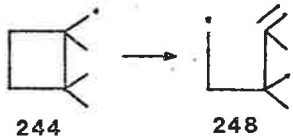
It should be pointed out at this stage that, because of the rather narrow temperature range (50-110°C) in which experiments could be successfully conducted, the errors associated with the activation parameters may be significantly larger than the standard deviations shown in table 17. It was found that only a poor yield of products (<60%) formed when the reduction was conducted at temperatures below 50°C; a result of the low reactivity of the chlorides towards tri-*n*-butylstannane. At high temperatures, above 110°C, though the reduction proceeded smoothly, consistent values of k_f/k_H could not be obtained. This latter observation is believed to be a consequence of the reduction initiating before the reaction mixture has attained thermal equilibrium. Nevertheless, the values of $\Delta\Delta H^{\ddagger}$ can be considered accurate to ± 0.5 kcal mol^{-1} and those of $\Delta\Delta S^{\ddagger}$ to ± 1 cal mol^{-1} K^{-1} and thus meaningful arguments may be based on these parameters.

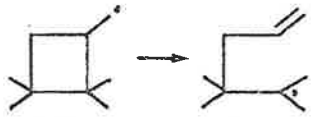
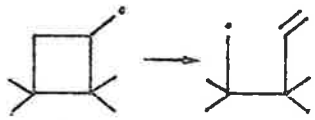
Table 18 relates the changes observed in $\Delta\Delta H^{\ddagger}$ with increasing methyl substitution of the cyclobutylcarbinyl radical to those in the enthalpy of reaction (ΔH^{o}_{r}) for the ring opening process. Thermochemical data for the majority of the olefins (205) and (207) are available[197,198] and have been used to derive the enthalpies of formation of the olefinic radicals (204) and (206). However, little

Table 17

Kinetic data for ring opening of substituted cyclobutylcarbinyl radicals[a].

	Reaction	$k_f/k_H(60^o)$[b]	$\Delta\Delta H^{\ddagger}$	$\Delta\Delta S^{\ddagger}$
		mol l^{-1} x 10^4	kcal mol^{-1}	cal mol^{-1} K^{-1}
(A)	 208  210	4.7 ± 0.2	9.1 ± 0.2	16.7 ± 0.6
(B1)	 212  214	3.3 ± 0.2	9.2 ± 0.2	16.3 ± 0.5
(B2)	 212  216	1.1 ± 0.2	9.9 ± 0.2	16.2 ± 0.5
(C)[d]	 218  220	2.6 ± 0.1	-	-
(D)	 222  224	2.5 ± 0.1	9.9 ± 0.2	17.8 ± 0.4
(E)	 226  228	2.7 ± 0.1	10.5 ± 0.2	19.9 ± 0.5

Reaction	$k_f/k_H(60^o)$ [b]	$\Delta\Delta H^{\ddagger}$	$\Delta\Delta S^{\ddagger}$
	mol l^{-1} x 10^4	kcal mol^{-1}	cal mol^{-1} K^{-1}
(F1) [c]  230 232	15.5 ± 0.2	8.5 ± 0.1	17.2 ± 0.2
(F2) [c]  230 234	1.9 ± 0.1	9.6 ± 0.1	16.4 ± 0.3
(G1) [c]  236 232	92.6 ± 0.9	7.6 ± 0.1	18.1 ± 0.2
(G2) [c]  236 234	2 ± 1	9.9 ± 0.9	16.8 ± 0.3
(H1)  238 240	700 ± 20	6.3 ± 0.2	18.2 ± 0.4
(H2)  238 242	< 4	-	-
(I1)  244 246	900 ± 20	6.2 ± 0.2	18.4 ± 0.4
(I2)  244 248	< 1	-	-

Reaction	$k_f/k_H(60^o)$[b]	$\Delta\Delta H^{\ddagger}$	$\Delta\Delta S^{\ddagger}$
	mol l^{-1} x 10^4	kcal mol^{-1}	cal mol^{-1} K^{-1}
(J1)  250 252	310 ± 10	7.0 ± 0.2	18.8 ± 0.4
(J2)  250 254	< 1	-	-

a Uncertainties are expressed as the standard deviation from mean.

b Values of $k_f/k_H(60^o)$ calculated on the basis of the activation parameters shown.

c The reduction of *cis*- and *trans*-1-chloro-2-methylcyclobutane with tri-*n*-butylstannane in benzene at 80^o has been reported by Hill and co-workers[146]. Analysis of their rather limited data suggests a slightly higher value of k_f/k_H. The discrepancy may reflect a solvent effect (see chapter 2).

d In the present study it has been assumed that the previously determined values of k_H for *n*-hexyl, cyclohexyl and *t*-butyl radicals (see table 8) provide reasonable indices of the relative reactivity of primary, secondary and tertiary radicals respectively. For the purposes of calculating k_f(rel) (see table 18): k_H(primary) = k_H(secondary) = 1.35 x k_H(tertiary).

Table 18

Kinetic and thermochemical data for ring opening of substituted cyclobutylcarbinyl radicals.

Reaction	ΔH_r^o	$\Delta(\Delta H_r^o)$ [a]	$\Delta(\Delta\Delta H^{\ddagger})$ [a]	k(rel) [a]
	kcal mol^{-1}	kcal mol^{-1}	kcal mol^{-1}	
(A)	-4.7	(0.0)	(0.0)	(1.0)
(B1)	-3.1	-1.6	-0.1	0.70
(B2)	-2.7	-2.0	-0.8	0.23
(C)	-1.4	-3.3	-	0.75 [b]
(D)	-6.9	2.2	-0.8	0.53
(E)	-3.1	-1.6	-1.4	0.57
(F1)	-5.8	1.1	0.6	3.30
(F2)	-4.2	-0.5	-0.5	0.40
(G1)	-6.8	2.1	1.5	19.6
(G2)	-5.2	0.5	(-0.8)	(0.4)
(H1)	-7.4	2.7	2.8	150
(H2)	-	-	-	<0.8
(I1)	-10.0	5.3	2.9	190
(I2)	-	-	-	<0.3
(J1)	-	-	2.1	66
(J2)	-	-	-	<0.3

[a] Parameter relative to that for reaction (A).

[b] See footnote d to table 17.

data for cyclobutane derivatives have been reported[199,200]; consequently the enthalpies of formation of the cyclobutylcarbinyl radicals (202) were calculated directly by the group additivity method of Benson and O'Neal[136,201]. This procedure predicts the enthalpies of formation of alkyl-cyclohexanes, -cyclopentanes, and -cyclopropanes to within ± 0.6 kcal mol^{-1} and there seems no reason to believe it will be any less accurate with respect to alkylcyclobutanes. No attempt was made to calculate the enthalpies of formation of the olefinic radicals containing two adjacent highly substituted carbons since the group additivity method is known to break down for such compounds. The errors associated with ΔH_r^o are possibly in excess of ± 2 kcal mol^{-1}; however, since the same assumptions are inherent in each calculation the uncertainty in $\Delta(\Delta H_r^o)$ should be significantly less.

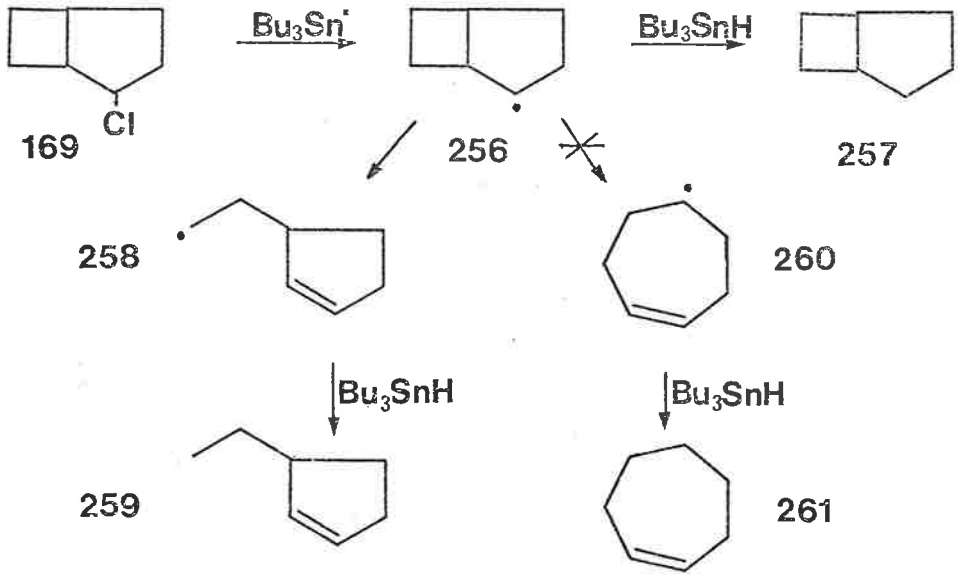
An estimate of the absolute magnitude of the activation parameters may be gained by adding 4 kcal mol^{-1} to $\Delta\Delta H^{\ddagger}$ and -17 cal mol^{-1} K^{-1} to $\Delta\Delta S^{\ddagger}$ (see chapter 2). The ring opening process thus has an appreciable enthalpy of activation (10-14 kcal mol^{-1}) and a very low entropy of activation (0-2 cal mol^{-1} K^{-1}) indicating a very rigid transition state. It is of interest to note that the latter term corresponds to an *A*-factor of 10^{13} - 10^{14} sec^{-1} which is of similar magnitude to the *A*-factors determined for the gas phase unimolecular decomposition reactions of acyclic alkyl radicals ($10^{13.5 \pm 1.0}$)[202,203]. These reactions are considered to have a relatively tight transition state (*i.e.* resembling the reactant radical).

To facilitate interpretation of the kinetic data it is clearly desirable that we first establish (i) whether the ring opening of the cyclobutylcarbinyl radical is an irreversible process, and (ii) whether the ring opening is, like that of the cyclopropylcarbinyl radical (see p. 6), subject to stereoelectronic control.

The first would appear to follow from the fact that the product distribution from the reductions exhibits the expected dependence on the concentration of stannane (the reductions were routinely conducted using at least a five fold range of stannane concentrations). In addition, as mentioned in the introduction (see p. 23), though the pent-4-enyl radical has been generated under a variety of conditions, its cyclisation to cyclobutylcarbinyl has not been observed. However, in order to provide further proof of the irreversible nature of cyclobutylcarbinyl opening it was decided to generate the 3-methylpent-4-enyl radical (234). It will be noted that even if this radical undergoes cyclisation in a reversible fashion, the subsequent fragmentation reaction should yield the hex-5-en-2-yl radical (232) preferentially. In the event, treatment of 5-chloro-3-methylpent-1-ene (170) with tri-*n*-butylstannane in decalin at 60°C or at 100°C afforded 3-methylpent-1-ene as the sole product.

It was proposed to test the stereoelectronic requirements for cyclobutylcarbinyl radical β-scission with the generation of the bicyclo[3.2.0]hept-2-yl radical (256). By analogy with the behaviour

of the *cis*-2-methylcyclobutylcarbinyl radical (236) which undergoes fragmentation to afford predominantly the secondary radical (232) we would expect that, in the absence of any stereoelectronic requirements, this radical (256) would open preferentially to the more stable* cyclohept-3-enyl radical (260). However, the semi-occupied orbital in the bicyclic radical (256) is constrained to occupy a position orthogonal to the internal cyclobutane bond and consequently the proposed orbital overlap conditions[50] cannot be met in the formation of (260) without considerable strain being incurred.



Scheme 31

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* By application of the free radical group values suggested by Benson and O'Neal[201] the enthalpies of formation of the (cyclopent-2'-en-1'-yl)eth-2-yl (258) and cyclohept-3-enyl (260) radicals are calculated to be 42.8 and 40.6 kcal mol^{-1} respectively.

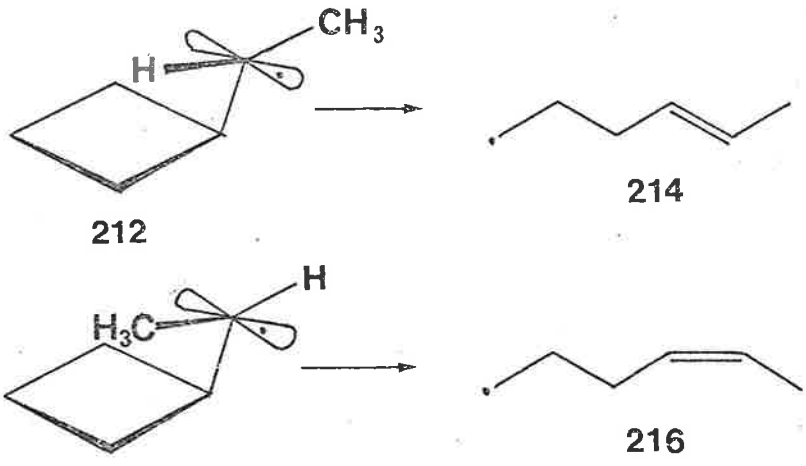
Reduction of the chloro-compound (169) with tri-*n*-butylstannane in decalin at 80°C or at 100°C proceeded smoothly to afford a mixture of bicyclo[3.2.0]heptane (257) and 2-ethylcyclopentene (259). Cycloheptene (261) was not detected amongst the reaction products (we estimate that as little as 0.1% of cycloheptene could have been detected). Very recently Hill and co-workers[147] have reported the reduction of the corresponding bromo-compound with similar results. They were also able to confirm that the cyclohept-3-enyl radical (260) is stable to the reaction conditions. On the basis of these results it must be concluded that the ring opening of the cyclobutylcarbinyl radical is subject to stereoelectronic influences.

In order to simplify presentation we shall first consider the effects of substituents at each of the α, β (and δ), and γ positions individually in terms of steric and electronic factors alone. However, it should be pointed out that whilst these factors undoubtedly influence the ring opening reaction, they do not necessarily provide a complete picture of the transition state.

Methyl substitution at the radical centre effects little change in the rate constant for the ring opening reaction (see table 18, compare k_f(rel) for reactions (A), (B1 + B2), and (C)). Indeed, though the β-scission reaction of the secondary radical ((212), reaction (B)) is calculated to be some 1.4 kcal mol^{-1} less favourable than that of the parent radical ((208), reaction (A)), the enthalpies of activation for

the two reactions are of comparable magnitude* (see table 18). These results suggest that the transition state for the fragmentation reaction resembles the cyclobutylcarbinyl radicals and involves little bond rupture.

The secondary radical (212) is observed to afford a preponderance of *trans*-olefinic product (*trans/cis* = 3.1 at 60°C). The major factor influencing the isomer distribution is probably the degree of steric crowding in the transition state. If the stereoelectronic requirements for β-scission are to be met then the transition state for the formation



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* It has been assumed that the kinetic parameters for the reaction of the primary radical (208) and of the secondary radical (212) with tri-*n*-butylstannane are the same. Whilst available data[125] would suggest that this is indeed the case, that there is not some small variation in the reactivity of the two radicals cannot be rigorously excluded. Since on thermochemical grounds it would be expected that hydrogen atom transfer to the secondary radical would be less favourable, it is possible that the values of k_f(rel) and of $\Delta(\Delta\Delta H^{\ddagger})$ for reaction (B) are only an upper limit.

of the *cis*-radical (216) must involve an eclipsed non-bonded interaction between the radical centre-methyl bond and one of the βγ-cyclobutane bonds. The effect of this interaction will be to raise the energy of the transition state leading to the *cis*-radical (216) above that leading to the *trans*-radical (214).

It will be remembered that the analogous cyclopropylcarbinyl radical also cleaves afford a preponderance of *trans*-product (see chapter 5). The slightly lower *trans/cis* isomer ratio observed in that case (2.2 at $0^{o}C$) is probably indicative of the more exothermic nature of the reaction.

Hill and co-workers[144] have suggested that the α-methylcyclobutylcarbinyl radical may be the precursor of the predominantly *cis*-olefinic product which arises during Grignard formation from (1-chloroethyl)-cyclobutane. However, the anomalous isomer distribution would argue against the intermediacy of a *free* radical species in the reaction.

The introduction of methyl groups either β or δ to the radical centre also has little influence on the kinetics of the ring opening process (see tables 17 and 18, compare data for reactions (A) and (D), (A) and (E), (H) and (I), and (H) and (J)). On the basis of enthalpy of reaction calculations (see table 18) the small δ-substituent effect seems reasonable. However, on the same basis the opening of the (1-methylcyclobutyl)carbinyl radical ((218), reaction (D)) would be predicted to be amongst the most facile of the reactions examined.

In fact, β-substitution of the cyclobutylcarbinyl radical effectively halves the observed rate of ring opening.

It is of interest at this stage to note that the rate of ring closure of hex-5-enyl radicals substituted at the point of attack on the double bond (to form a β-substituted cyclopentylcarbinyl radical) is strongly retarded with respect to unsubstituted systems (see p. 26). The rate of retardation has been attributed[5] to two causes;
(i) increased steric repulsion between the reacting centres and
(ii) steric compression (B-strain) engendered at the olefinic carbon on change towards sp^3 hybridisation. An apparent lack of influence of substitutents at the radical centre on the rate of ring closure suggests that the latter factor is of major importance[5].

Since the ring opening reaction must involve the reverse bonding changes it may be predicted that the above-mentioned factors should result in β-substitution effecting a significant enhancement in the rate at which the cyclobutylcarbinyl radical undergoes fragmentation. The fact that no rate enhancement is observed must therefore mean either that the transition state is reactant-like and involves little rehybridisation of the β-carbon, or that some other factor is important in retarding the rate of ring opening of the β-substituted radicals (the influence of polar factors will be considered later in this chapter).

An ability of alkyl groups, and in particular *geminal* alkyl groups, to both stabilise and aid in the formation of ring systems has been recognised for many years. This influence of alkyl groups on the rate of ring closing and ring opening reactions, termed the *gem*-dialkyl effect, has been attributed to a number of causes[204-209]. However, most studies have concerned ring closing reactions or situations where an equilibrium between ring opened and ring closed products exists. Consequently many explanations which are based on these investigations are not of direct relevance to the present discussion of an irreversible ring opening reaction. The Thorpe-Ingold hypothesis of valency deviation does warrant mention*, however, because of its applicability to reactions involving small ring systems[204,209].

It has been argued[204,209] that if one or more of the groups attached to a tetrasubstituted carbon is more bulky than the others or is in some way constrained, then a degree of angular deformation should occur such that the most efficient use of the available space is made. Available molecular structure data[209] would support a small effect of this nature. Geminal alkyl groups would therefore, by favouring a smaller angle between the two ends of an alkyl chain, have a stabilising influence on a small ring system. Simple calculations[209] based on this hypothesis predict the Thorpe-Ingold contribution to the

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* The Thorpe-Ingold effect has previously been considered with relation to the kinetics of ring opening reactions of methylated cyclobutylcarbinyl[145] and cyclopropylcarbinyl[211] Grignard reagents.

stability of 1,1-dimethylcyclobutane to be of the order of 1 kcal mol^{-1}. This is consistent with the small δ-substituent effect observed. Unfortunately, however, thermodynamic data for cyclobutane derivatives are not available to support this prediction.

Another related steric factor can perhaps be considered with relation to the β-substituted systems. Steric repulsion between the geminal substituents may restrict rotation about the $\dot{C}H_2$-cyclobutyl bond and thus hinder the radical assuming that conformation required for maximum overlap of the semi-occupied orbital with the bond being cleaved*. However, an inspection of molecular models does not reveal a severe interaction and, in the case of the trisubstituted radical (244) interactions with the vicinal substituents would seem to be of greater significance.

The ring opening reactions of the γ-substituted cyclobutylcarbinyl radicals (reactions (F)-(J)) proceed with preferential cleavage of the more substituted βγ-bond to generate the more stable radical product. This observation may be interpreted in terms of a more product-like transition state (for these reactions there is generally a good correlation between the values of $\Delta(\Delta\Delta H^{\ddagger})$ and $\Delta(\Delta H^{\circ}_{r})$; see table 18). However, the fact that there appears to be no significant increase in the entropy of activation for the ring opening process on the

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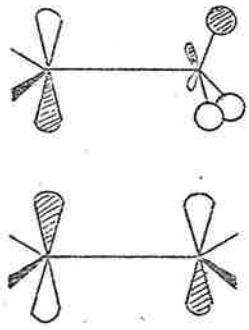
* Such an argument has been proposed to account for the resistance to fragmentation of more highly functionalised systems[211].

introduction of a substituent suggests that the structure of the transition state is not significantly different from that for the reactions already considered.

The ring opening reaction of the (*cis*-2-methylcyclobutyl)carbinyl radical ((236), reaction (G)) is significantly more selective than that of its *trans*-isomer ((230), reaction (F)). The additional strain inherent in that bond undergoing preferential cleavage due to steric repulsion between the *vicinal* substituents may account for a greater value of k_f(rel) for reaction (G1). Notably the value of k_f(rel) for reactions (F2) and (G2) is the same (within the limits of experimental error), and also of similar magnitude to k_f(rel) for the parent cyclobutylcarbinyl radical (statistically corrected). However, that the presence of an additional *cis*-interaction in the tri-substituted radical (244) results in only a marginal increase in the rate of ring opening (see table 18, compare k_f(rel) for reactions (H1) and (I1) suggests that factors other than bond strain may be of importance.

One additional factor to consider arises from the observation that the hept-6-en-2-yl radical and related species undergo ring closure to afford preferentially the *cis*-disubstituted cyclopentane derivative[212,213] An explanation of this unexpected behaviour has been advanced in terms of orbital symmetry considerations[212]. Thus, a secondary orbital interaction between the olefinic system and a modified delocalised orbital arising from a hyperconjugative mixing of the semi-occupied

p orbital with the σ and σ* orbitals of the adjacent C-H is considered to derive a net stabilisation for the transition state (see (262))



262

leading to the *cis*-product. This same feature may also serve to lower the energy of the transition state for the ring opening reaction of cyclobutylcarbinyl radicals which bear a *cis*-γ-substituent.

As mentioned above, the kinetics of opening of the less substituted cyclobutane bond are not affected by the introduction of a γ-substituent* This suggests that steric interactions between the vicinyl substituents are in these systems not of a magnitude to restrict rotation about the $\dot{C}H_2$-cyclobutyl bond and favour overlap of the semi-occupied orbital with that bond preferentially cleaved. Orbital overlap considerations are thus not a significant factor in determining the greater regio-specificity of the reactions of cyclobutylcarbinyl radicals bearing a *cis*-γ-substituent.

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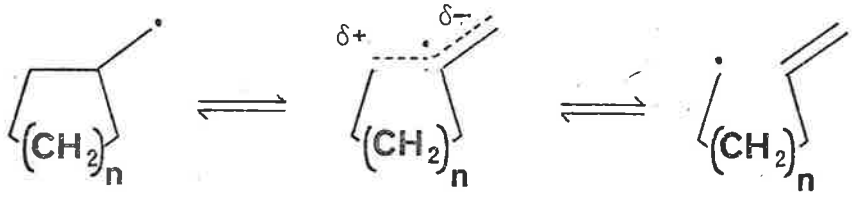
* The same feature has been noted in cyclopropylcarbinyl systems (see p. 81).

To summarise the main features of the kinetic data; it is found that the ring opening reaction is relatively insensitive to the presence of substituents at either of the α- or β-positions, whilst γ-substitution effects a marked acceleration in the rate of reaction. A consideration of the latter two results leads to the proposal that the transition state is unsymmetrical and involves little formation of the new π bond but, at the same time, considerable rupture of the βγ-bond. This picture of the transition state is similar to that recently proposed by Beckwith, Blair and Phillipou[5] for the cyclisation of the hex-5-enyl radical in order to rationalise the effect of substituents in that system. However, as was mentioned in the introduction (see p.29), the results of the cyclisation studies have an alternative interpretation in terms of a charge polarised transition state; the same is true of the present data for the ring opening process.

If we consider the transition state for radical fragmentation-cyclisation to be charge polarised as indicated (scheme 32), then it can be expected that the presence of electron-donating alkyl substituents either at the β-position of the cycloalkylcarbinyl radical, or at the point of attack on the double bond of the alkenyl radical, will destabilise the transition state and retard the reaction. Similarly, substituents at the γ-position of the cycloalkylcarbinyl radical, or

at the radical centre of the alkenyl radical, will stabilise the transition state and facilitate the reaction.



Scheme 32

It will be seen that in the case of the ring opening reaction of a β-substituted cyclobutylcarbinyl radical, and also in the case of the cyclisation of a 1-substituted 5-hexenyl radical, polar effects will act in opposition to what might be expected on the basis of a consideration of radical stabilities. Polar influences do not provide an explanation of the α-substituent effect. However, as noted on p. 102 there is a greater uncertainty associated with these data.

Whilst the present results clearly do not establish beyond doubt that the transition state for radical fragmentation-cyclisation has polar character, that such is the case does provide a consistent picture of the transition state which is not reliant on a consideration of seemingly minor steric influences. The effect of polar influences will be considered further in the subsequent chapter.

CHAPTER 7

The β-scission Reaction of α-oxygen Substituted Cyclopropylcarbinyl Radicals.

In the previous chapter we have seen how a consideration of polar influences in the transition state is able to provide a reasonable explanation of the main features of the kinetics of radical fragmentation and cyclisation reactions in all carbon systems. In the light of this result we may anticipate that the introduction of a polar substituent into the system should exert a significant effect on the course of these reactions.

The apparently anomalous ring opening reaction of *trans*-2-methylcyclopropylcarbinyl radicals which bear an α-stannyloxy or hydroxy substituent (to form the less stable radical product under conditions of kinetic control) was mentioned in the introduction (see p. 7). However, at the time of commencing the present work, the recent studies of Godet and Pereyre[59] establishing the cyclopropylcarbinyl radical to be a discrete intermediate in the stannane reduction of cyclopropyl ketones, and the recent e.p.r. study of Davies and Muggleton[51], had not appeared. Thus, a desire to further elucidate the influence of polar factors on the course of radical fragmentation, and an interest in the mechanism of the metal-ammonia reduction of cyclopropyl ketones (see p. 11), prompted a study of the influence of an α-oxygen substituent on cyclopropylcarbinyl radical β-scission.

Our initial aim was to examine the ring opening reaction under conditions where there could be no doubt as to whether discrete free

radical intermediates were involved. With this in mind we investigated the possibility of generating α-hydroxycyclopropylcarbinyl radicals in the sample cavity of the e.p.r. spectrometer.

A well established technique for generating radicals in the sample cavity of the e.p.r. spectrometer involves the use of the flow technique[214]. α-Hydroxyalkyl radicals may be generated by the interaction of hydroxyl radicals (produced by a redox reaction of titanium(III) ions with hydrogen peroxide) with the appropriate alcohol[215]. The mechanism of the reaction is as follows:

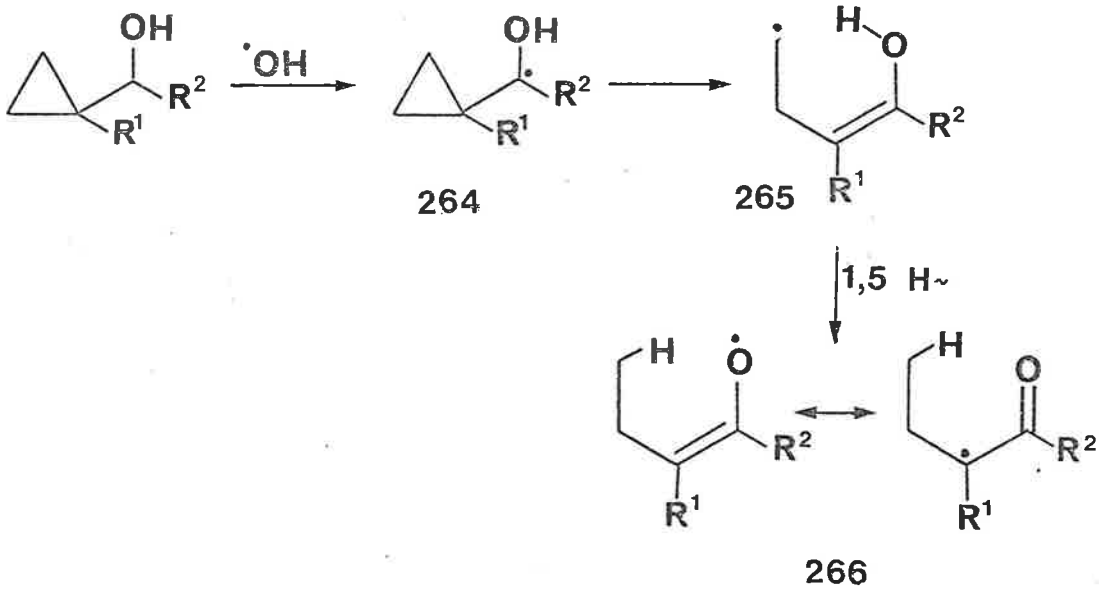
$$Ti^{III} + H_2O_2 \rightarrow Ti^{IV} + HO^- + HO^{\cdot}$$

$$HO^{\cdot} + RH \rightarrow R^{\cdot} + H_2O$$

Although the hydroxyl radical has been reported[214] to show poor selectivity in abstracting hydrogen from alcohols with more than three carbons, it was reasoned that this would not be a serious complication in the present investigation because of a relatively high cyclopropane C-H bond strength.

The alcohols (94), (100), and (102) were available from our previous studies (see chapter 3), in addition cyclopropylmethanol was readily obtained from the lithium aluminium hydride reduction of cyclopropanecarboxylic acid. The features of the spectra recorded when these alcohols are allowed to interact with hydroxyl radicals in the flow cell of the e.p.r. spectrometer at 6^{o} are as follows (see also table 19)

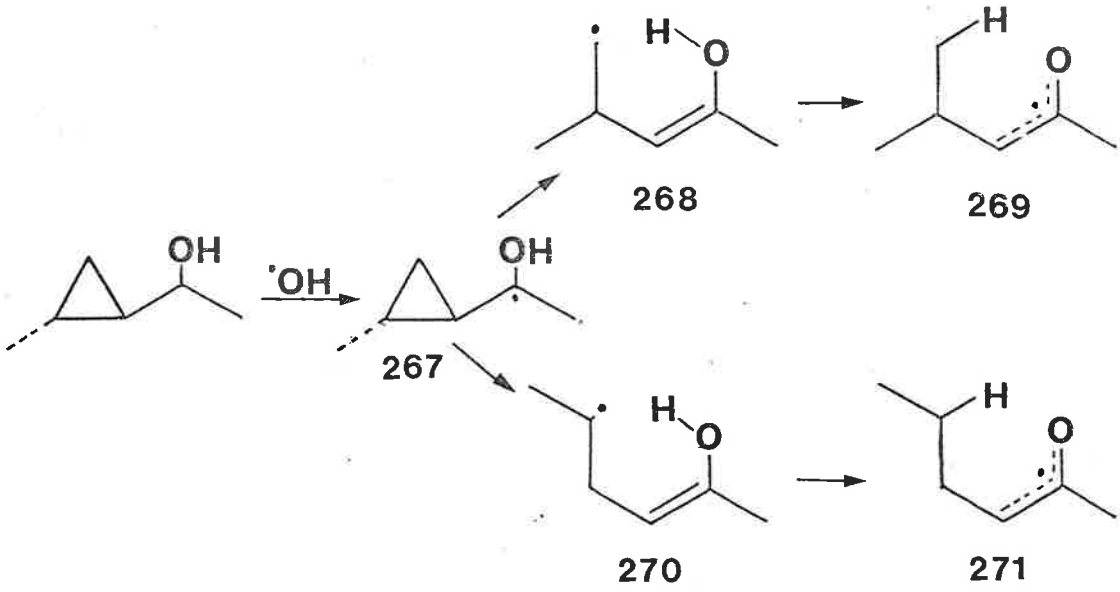
(i) *Cyclopropylmethanol*, 1-*methylcyclopropylmethanol* (94), *and* 1-*cyclopropylethanol* (102). - The spectra consist of a superimposition of the individual spectra of the appropriate 4-hydroxybut-3-enyl (265) and enoxyl (266) radicals. In each case the enoxyl radical (266) is present only in relatively low concentration. The radicals (265) and (266) may be considered to arise as indicated in scheme 33[51,216].



Scheme 33

It is noteworthy that when the α-hydroxycyclopropylcarbinyl radical is generated (by the photolysis of di-*t*-butylperoxide in the presence of cyclopropylmethanol) in cyclopropane solvent at similar temperatures only the spectrum of the enoxyl radical (266; R^1, R^2 = H) is observed[51,216]. The variation may indicate a different rate of destruction of the two radicals under our conditions. An alternative explanation is that the hydrogen atom transfer reaction proceeds at a slower rate in aqueous solution.

(ii) 1-(trans-2'-*Methylcyclopropyl*)*ethanol* (100). - A very complex spectrum is observed and the presence of at least four radical species is indicated. The spectrum of the primary radical (268) could be identified by means of the previously reported coupling constants[51]. This radical (268) is present only in low concentration. The major portion of the spectrum, consisting of a doublet of triplets of quartets, we attribute to the secondary radical (270).



This result contrasts with the recent findings of Davies and Muggleton[51], who generated the radical (267) in cyclopropane solvent and observed only the spectrum of the primary radical (268) at low temperatures (-86°) and that of the corresponding enoxyl radical (269) at higher temperatures (-9°). It would seem that at low temperatures

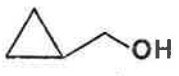
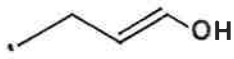
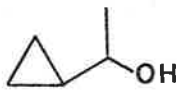
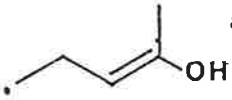
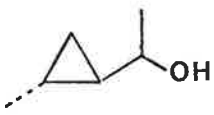
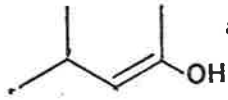
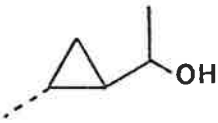
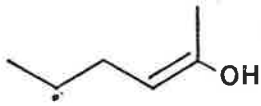
in cyclopropane solvent the kinetic product (268) of the ring opening reaction is observed whilst at higher temperatures, in aqueous solution, the reaction is reversible and the thermodynamic product (270) is observed. That no trace of the secondary radical (270) is observed when the radical (267) is generated in cyclopropane solution at higher temperatures indicates that, under these conditions, the 1,5-hydrogen atom transfer process is more favourable than ring closure, and that the primary product of the reaction maybe trapped efficiently. On the other hand, in aqueous solution, possibly due to solvation of the enolic hydrogen, the atom transfer process is less favourable and the equilibrium, (268)⇌(267)⇌(270), can be established.

As an alternate source of α-hydroxycyclopropylcarbinyl radicals, we also investigated the reaction of carbon dioxide radical anion (generated by the reaction of hydroxyl radicals with formate ion) with cyclopropyl ketones and aldehydes. Anderson and co-workers[217] have reported the reduction of acetaldehyde, propionaldehyde and acetone to the corresponding α-hydroxyalkyl radical with carbon dioxide radical anion. The mechanism of the reaction is believed[217] to involve one-electron transfer, to generate a radical anion intermediate, followed by protonation as indicated below:-

$$R^1R^2C{=}O + CO_2^{\bullet-} \rightarrow R^1R^2\dot{C}{-}\bar{O} + CO_2\uparrow \rightarrow R^1R^2\dot{C}{-}OH$$

Table 19

E.p.r. parameters of substituted 4-hydroxybut-3-enyl radicals.

Source	Radical	$a(H_\alpha)$ G	$a(H_\beta)$ G	g
	 [a,c,d] **265** $R^1=H, R^2=H$	22.1	28.5	2.0026
 **94**	 [b] **265** $R^1=H, R^2=CH_3$	22.1	27.1	2.0026
 **102**	 [a,e] **265** $R^1=CH_3, R^2=H$	22.0	28.8	2.0026
 **100**	 [a,e] **267**	21.5	24.0	2.0026
 **109**	 [a,e] **270**	21.2	21.2(CH_2)[f] 25.2(CH_3)	2.0026

[a] The corresponding enoxyl (266) radicals were also present but in too low a concentration to permit an unambiguous assignment of coupling constants.

[b] The enoxyl radical (266; $R^1=H$, $R^2=CH_3$) had $a(H_\beta)$ = 21.2(CH_3), 13.4(CH_2), 2.9(CHO) G, g = 2.0044.

[c] $a(H_\gamma) \sim 0.8$ G.

[d] The presence of both the *cis* and *trans* forms was apparent from the spectrum but the resolution did not permit the accurate assignment of coupling constants to the minor isomer.

[e] Relatively broad resonances indicating unresolved γ coupling and/or the presence of both *cis* and *trans* forms of the radical were observed.

[f] Tentative value.

An attempt to generate the radical anion of methyl *trans*-2-methylcyclopropyl ketone by this method failed; only the signal due to $CO_2^{\bullet-}$ was observed. Cyclopropanecarboxaldehyde was reduced, however, to give a spectrum identical to that observed when cyclopropylmethanol is allowed to react with hydroxyl radicals. That a higher concentration of the enoxyl reduced was not observed indicates that the intermediate radical anion does not open *via* an anionic mechanism. Of course, the radical anion intermediate is likely to have a very short lifetime in aqueous solution and it is quite possible that protonation will occur prior to ring cleavage. The result does, however, question the proposal[72] that the reductive cleavage of cyclopropyl ketones by dissolving metals, in the presence of a proton source, involves protonation of the γ-carbon of the radical anion intermediate and concerted ring opening. The mechanism of the metal ammonic reduction of cyclopropyl ketones will be considered in more detail in the subsequent text.

As a final experiment cyclobutanecarboxaldehyde was reduced under similar conditions. The spectrum recorded appeared as a doublet of doublets of quintets* and is attributed to the α-hydroxycyclobutyl-

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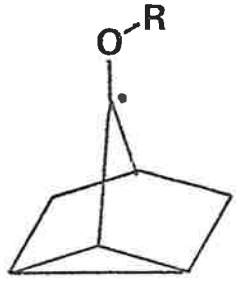
* $a(H_\alpha)$ = 13.4 G, $a(H_\beta)$ = 15.5 G, $a(H_\gamma) \sim$ 1.5 G; g = 2.0036 (Relatively broad resonances and a slight departure from the expected 1:4:6:4:1 intensity ratio for the quintet coupling were observed. This is probably due to a slight inequivalence of the γ coupling to the *cis*- and *trans*-cyclobutyl hydrogens.)

carbinyl radical. No ring opened products were observed. This is consistent with previous observations[218,219] which indicate that the α-hydroxycyclobutylcarbinyl radical opens at a very slow rate with respect to its smaller ringed analogue.

A previous attempt to generate the same spectrum, through the interaction of hydroxyl radicals with cyclobutylmethanol (107), led to a very complex spectrum in which only the signals due to the α-hydroxycyclobutylcarbinyl radical could be unambiguously assigned. The abstraction of cyclobutyl ring hydrogens is indicated under these conditions.

It is clear from the e.p.r. data, and from the studies of Godet and Pereyre[52,53,59] (see p. 7), that (*trans*-2-methylcyclopropyl)carbinyl radicals which bear an α-oxygen substituent will afford the less stable radical product under conditions of kinetic control. The explanation for this selectivity is, however, not straight-forward, since to evaluate the importance of the various steric, polar, and electronic effects which may influence the reaction, we require a knowledge of the conformation which the radical assumes in the transition state.

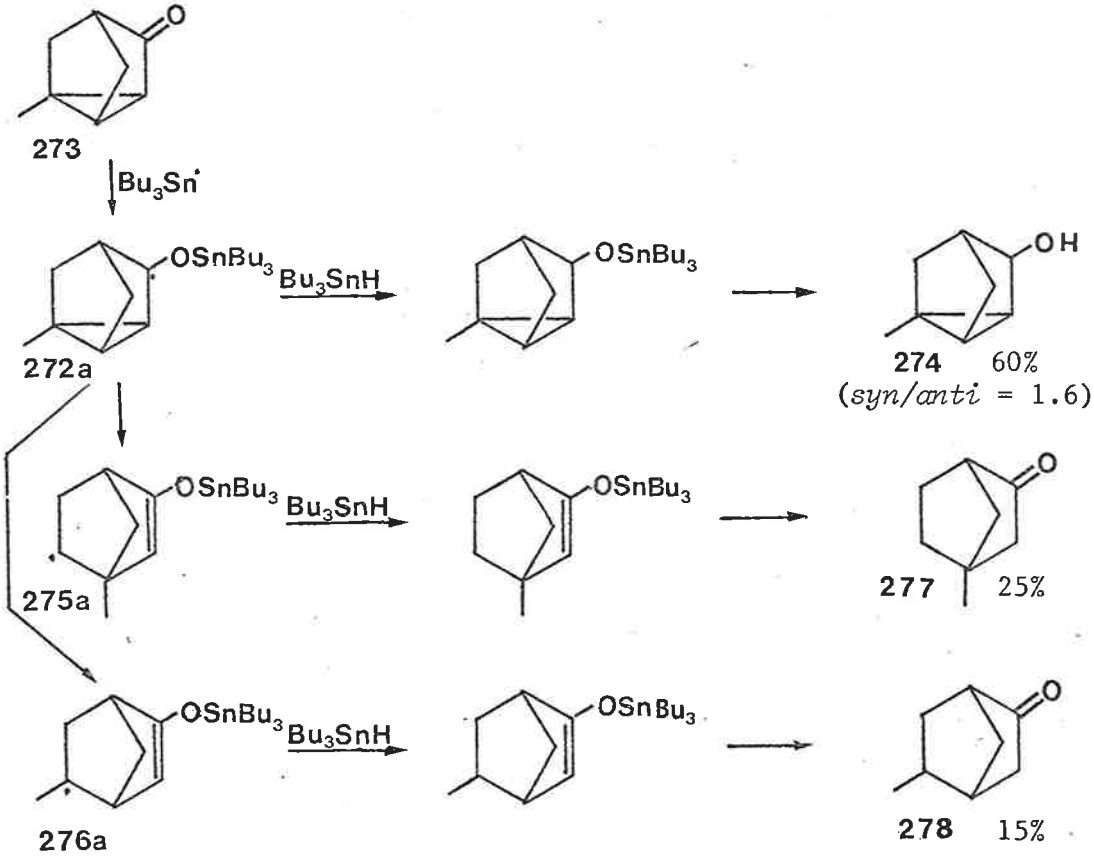
In an effort to clarify the situation the study of the radical (272) was proposed. It was reasoned that the rigid stereochemistry of the nortricyclene system (and of the products of ring opening) would render steric factors of little influence (see, however, p. 126) and allow the nature of the transition state to be more precisely defined.



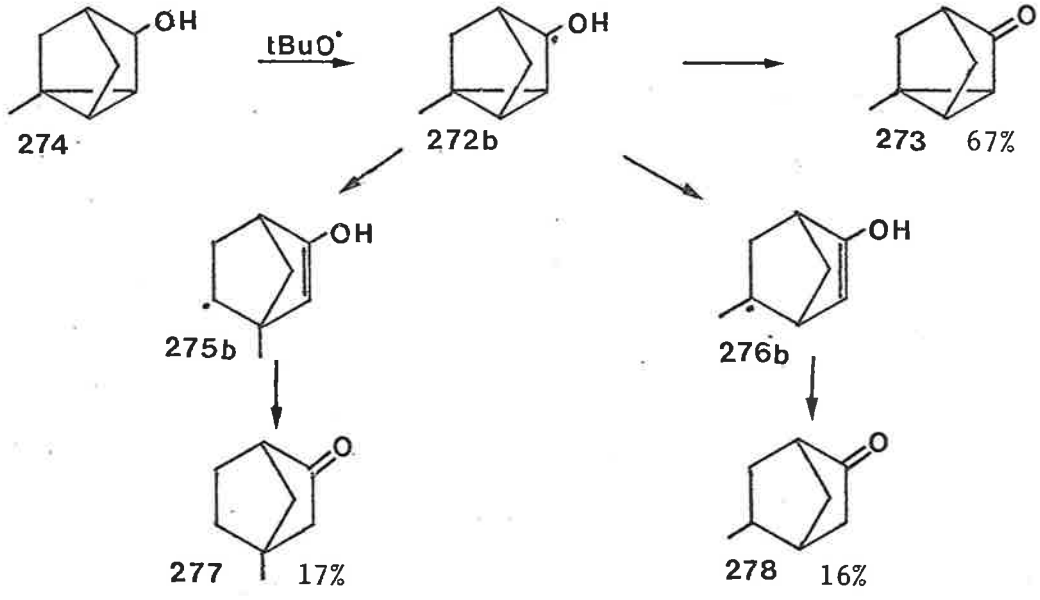
272

The radical (272) was generated in three ways; (a) by the photoreduction[49] of 1-methylnortricyclen-3-one (273) in isopropanol, (b) by reducing the ketone (273) with tri-*n*-butylstannane[59] (see scheme 34), and (c) by heating the corresponding alcohol (274) with di-*t*-butylperoxide[220] (see scheme 35).

The method (a) produced a complex mixture of products of which the expected ring opened compounds (277), (278) and (279) made up only a small fraction (<20%). Analysis of the mixture by g.l.c.-mass spectrometry indicated the four major products of the reaction (*ca.* 75% of the mixture) to have a molecular weight of 182. On this basis they have been tentatively identified as isomeric pinacol-type products arising from a coupling reaction of the radicals (272), (275) and (276) with the ketyl of isopropanol. This reaction was not subjected to further investigation.



Scheme 34



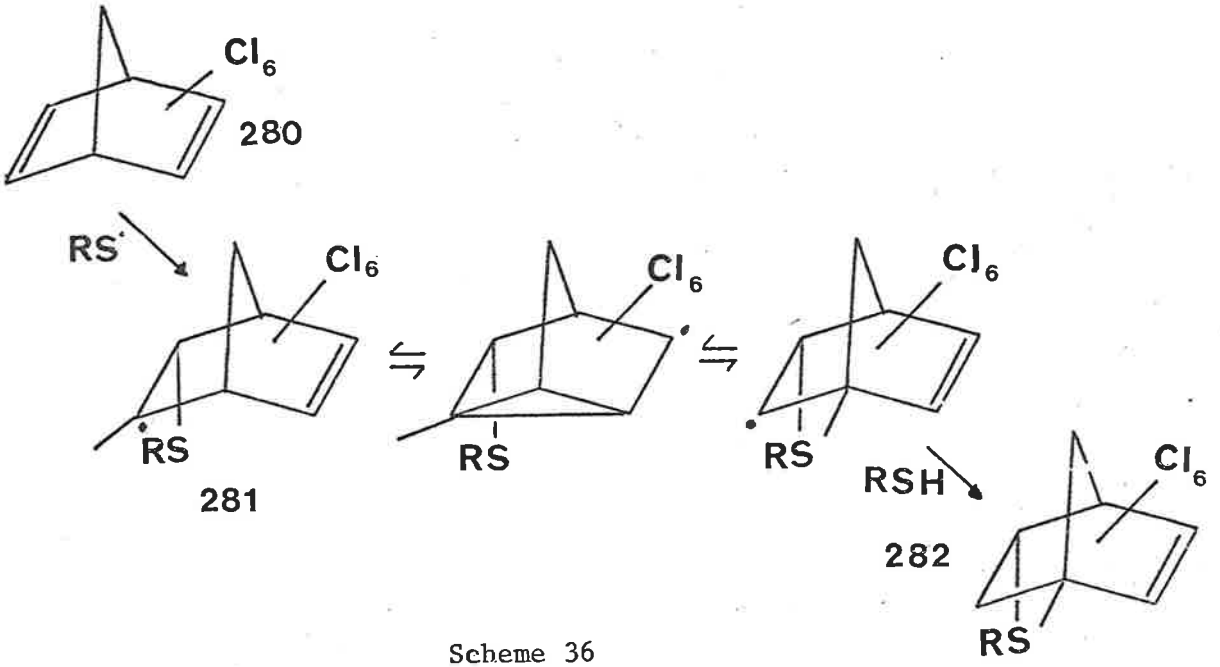
Scheme 35

* *exo*-5-Methylnorborn-5-en-2-one (279) if formed constituted <3% of the reaction product.

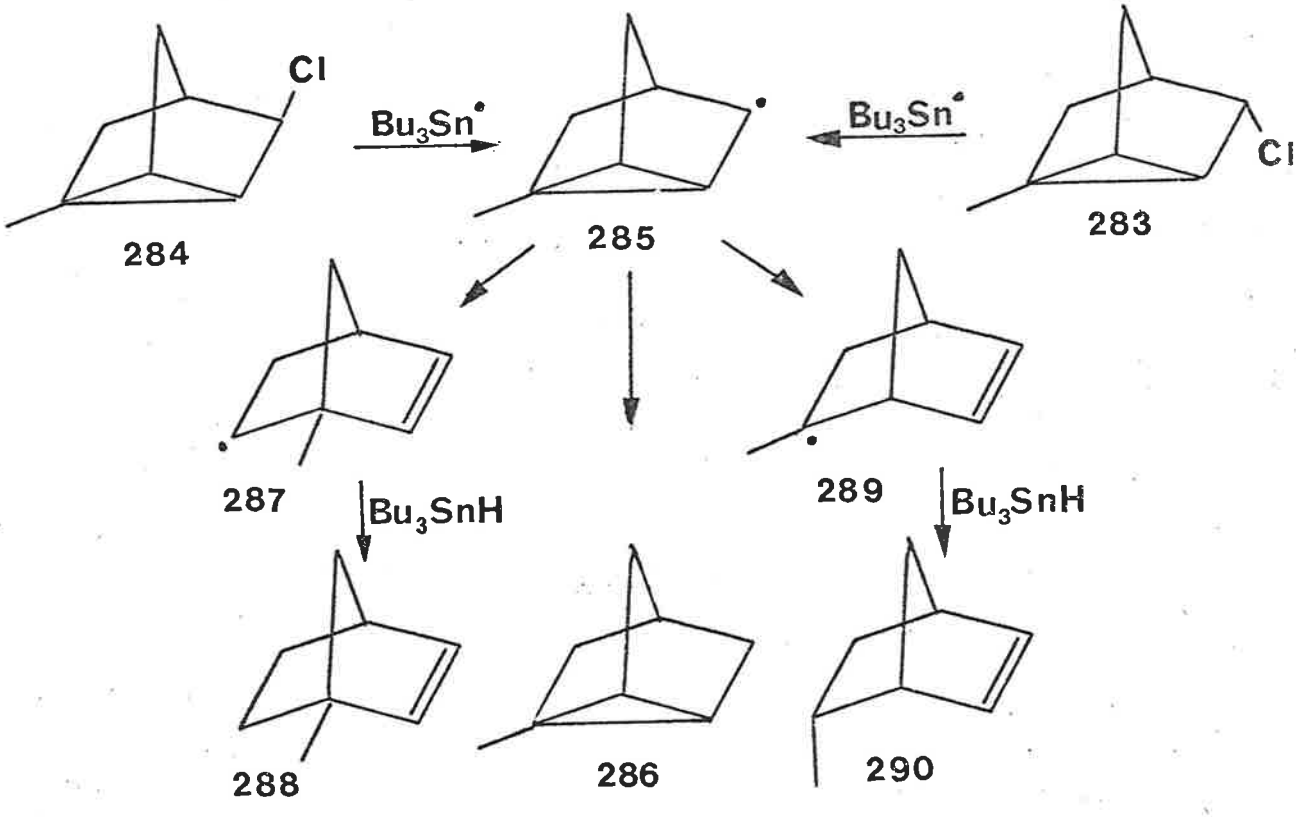
The procedures (b) and (c) proceeded smoothly to afford a mixture of products as indicated in schemes 34 and 35 respectively. Interestingly, the major product of these reactions contained the cyclopropane ring intact. This indicates the tricyclic radical (272) to be significantly more stable to ring cleavage than analogous monocyclic radicals[59,220]. Though the selectivity is not great, the major ring opened product formed is that derived from cleavage of the less substituted cyclopropane bond (*i.e.* from the less stable secondary radical (275)).

The selectivity observed in these reactions is not entirely unprecedented[221,222]. For example, the free radical addition of thiols to the chlorinated norbornadiene derivative (280) affords solely the rearranged adduct (282) presumably *via* the mechanism indicated (scheme 36). An explanation based on the reactivity of the radical intermediates (281) and (282) both towards rearrangement and towards the chain transfer reagent was advanced[221] to explain this result.

In order to establish that our results reflect the influence of the α-oxygen substituent and not simply the relative reactivity of the secondary and tertiary radicals (275) and (276) towards tri-*n*-butylstannane, it was decided to examine the ring opening reaction of the parent radical (285). In the event, reduction of either *syn*- or *anti*-3-chloro-1-methylnortricyclene (283) or (284) with tri-*n*-butylstannane in hexane afforded a mixture of three hydrocarbon products, of which



Scheme 36



Scheme 37

Table 20

Reduction of *syn*-3-chloro-1-methylnortricyclene (183) with tri-*n*-butylstannane in hexane.

Temperature	$[Bu_3SnH]_o$	Relative yield			Total yield
°C	mol l^{-1}	%(286)	%(288)	%(290)	%
60	0.01	14.8	9.0	76.1	78.6
60	0.05	14.5	9.1	76.4	85.6
60	0.01[a]	14.6	9.0	76.4	86.7
80	0.01	16.8	9.9	73.3	68.3
100	0.01	17.9	10.7	71.4	86.5

[a] Reduction of *anti*-3-chloro-1-methylnortricyclene (184).

the product derived from the more stable tertiary radical (289) was the major constituent (see table 20). The product distribution was found to be independent of stannane concentration indicating that the equilibrium, (287)⇌(285)⇌(289), is established under the reaction conditions*. An attempt to examine the reaction under conditions of kinetic control by conducting the reduction in the presence of a high concentration of triphenylstannane was unsuccessful because of the reactivity of the olefins (287) and (288). Nevertheless, it is clear that the relative reactivity of secondary and tertiary radicals towards tri-*n*-butylstannane does not provide an explanation of the product distribution observed from the reduction of 1-methylnortricyclen-3-one (274).

We mentioned previously that the ring opening reaction of the tricyclic radical (272) should be insensitive to steric factors; this may not be the case if the radical centre adopts a pyramidal configuration. A "bent" geometry for the radical centre might be expected since e.p.r. studies have shown:

(i) That structurally related bicyclic radicals possess a slightly pyramidal equilibrium geometry[19,226].

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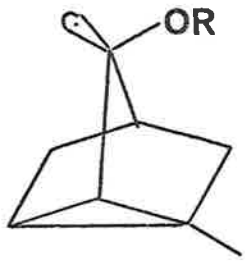
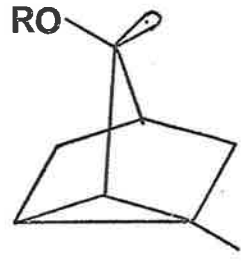
* The reversible nature of the norborenyl-nortricyclyl rearrangement is well known[1,223-225] and rate constants for both the ring opening and ring closing reactions have been estimated[125,175] to have $k \sim 10^8$ sec^{-1}.

(ii) That tertiary radicals bearing an α-oxygen substituent are pyramidal[227,228].

On this basis, it is likely that, rather than dealing with a single radical, we are dealing with two rapidly interconverting conformers (290) and (291). By application of the orbital overlap criteria[50], it may be seen that the ring opening reaction of the more stable conformer (291), that in which steric interactions between the methyl and -OR groups are minimized, should afford the less stable secondary radical (286). However, it seems unlikely that the barrier to interconversion of the conformers (290) and (291) would be of sufficient magnitude (with respect to the activation energy for the ring opening process) to influence the course of reaction, particularly in the case where R = hydrogen.



290



291

A consideration of polar factors in the transition provides an alternative explanation for the selectivity observed. That polar influences might account for the course of the ring opening reaction

observed during the reduction of *trans*-2-methylcyclopropyl ketones with tri-*n*-butylstannane was recognised in the original work of Godet and Pereyre[52,56] (see p. 7). However, the mechanism of the reaction was considered to involve addition of a nucleophilic stannyl radical to the carbinyl group and concerted bond rupture. More recent studies[59] have shown the reaction to involve a discrete cyclopropylcarbinyl radical intermediate. Nevertheless, polar influences, however, cannot be ignored.

The influence which polar factors are likely to have on the transition state may be more readily appreciated in a consideration of the reverse ring closure reaction. Whereas, the transition state for the addition of an alkyl radical to an hydrocarbon double bond may involve a contribution from a charge transfer structure in which an electron transfers from the radical to the double bond (see pp. 29 and 109), for addition to a more nucleophilic enol double bond an alternative charge transfer structure* involving the loss of an electron from the double bond may contribute.

That a charge polarised transition state of this type should be involved in the addition of radicals to oxygen substituted double bonds is not a new idea. Such charge transfer structures are thought to be

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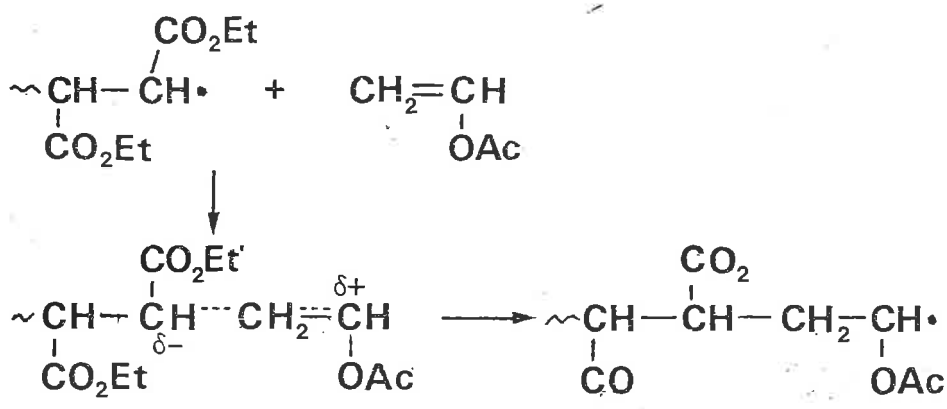
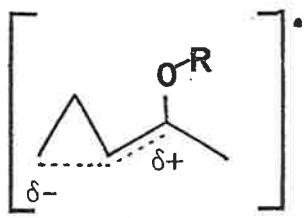
* A charge transfer transition state of this nature is thought[102] to be of significance in the addition of electrophilic trifluoromethyl radicals to hydrocarbon double bonds (see p. 29).

involved[229] in vinyl copolymerisation and account for the frequently observed tendency for a growing polymer chain to alternate when two monomers are present in the feed. This is illustrated in the co-polymerisation of vinyl acetate with ethyl fumarate (scheme 38).



Scheme 38

On this basis it does not seem unreasonable to consider the transition state for the reaction under consideration to be charge polarised as indicated (scheme 39), the influence of alkyl substituents



Scheme 39

on the kinetics of reaction should then be the reverse of that observed in all carbon systems (see chapter 6). Namely, the presence of alkyl groups at the radical centre should stabilise the transition state and facilitate reaction whilst those of the γ position should destabilise the transition state and hinder reaction as, indeed, is observed.

Finally, it is of interest to consider the preceding results with relation to the mechanism of the reductive cleavage of cyclopropyl ketones by dissolving metals. The over-all reaction involves the addition of two electrons by a metal and two protons by some donor with concomitant opening of one of the two βγ-cyclopropane bonds. If we assume that the first stage in the mechanism is the addition of electron to the carbonyl group to form a radical anion intermediate, we can envisage at least five separate mechanisms for the ring opening step:

(i) The radical anion may open with the development of a free-radical centre at the γ-carbon.

(ii) The radical anion may open with the development of a carbanionic centre at the γ-carbon. (This mode of ring opening must be considered unlikely since it involves the complete removal of an electron from the influence of the electronegative oxygen atom.)

(iii) The radical anion may be protonated by some donor (*e.g.* an alcohol) to form an α-hydroxycyclopropylcarbinyl radical which may undergo ring opening.

(iv) The radical anion may be protonated at the γ-carbon with concerted opening of the cyclopropane ring.

(v) The radical anion may accept a second electron from the metal to form a dianion intermediate which may then undergo ring opening.

On the basis of observations (a) that unsymmetrically substituted cyclopropyl ketones in which the βγ cyclopropane bonds are equivalent, or differ only marginally, with respect to overlap with the carbinyl π-system undergo reduction with preferential opening of the less substituted bond* [58,61,68,69,71,72], (b) that the reaction proceeds with inversion of stereochemistry at the γ-carbon (in the absence of an excess of a proton donor)[70-72], and (c) that the reduction involves the overall addition of 2 electrons[58], it has been concluded that the mechanism does not involve the development of a radical centre at the γ-carbon (*i.e.* that the ring opening occurs by either of the mechanisms (ii), (iv) or (v)). However, the results described in this chapter

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* Consistent with these observations we have found the lithium-ammonia reduction of the ketone (273) to afford exclusively (277).

clearly show that (a) cannot be used as a basis for distinguishing whether the ring opening occurs *via* a free radical or an anionic mechanism. Furthermore, though (b) is certainly more in keeping with a carbanionic than a free radical intermediate being involved. Inasmuch as the behaviour of free radicals under similar conditions is unknown*, this result in itself cannot be regarded as a sufficient basis on which to draw conclusions as to the nature of the reaction mechanism.

We have shown (see p. 119) that a radical anion intermediate generated in aqueous solution will open to afford a 4-hydroxybut-3-enyl radical. Following up this observation, several experiments were designed to examine the possibility that a similar free radical intermediate might play a significant role in the metal-ammonia reduction of cyclopropyl ketones in the absence of a proton source.

Bellamy and co-workers[58] have reported that products characteristic of a free radical dimerisation reaction are formed when a solution of lithium in ammonia is titrated with methylcyclopropyl ketone. We conducted the reduction of lithium was maintained at a low level. However, under optimum conditions the yield of decan-2,9-dione formed amounted to <10% of the product (the remainder being butan-2-one).

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* Interestingly, the product obtained from the opening of the radical (272) is totally of *endo* configuration (*i.e.* inversion has occurred at the γ carbon). This may reflect the steric requirements of the atom transfer reaction.

We therefore decided to carry out the reduction in the presence of isobutylene with the expectation that at least a portion of any free radical intermediate formed during the reaction would be trapped in an addition reaction with the olefin*. The reaction produced a significant quantity (*ca.* 15% of the total product) of involatile product; however, analysis of the mixture by g.l.c.-mass spectrometry showed that no adducts to isobutylene were formed. The four major involatile products of the reaction, which gave molecular ions at m/e 150, 150, 152, and 152 respectively and constituted *ca.* 90% of the mixture, could not be unequivocally identified but may well arise *via* the reduction and elimination of the dimeric product decan-2,9-dione. A small quantity (∿ 3%) of decan-2,9-dione was present in the reaction mixture. That the reaction should form a significant quantity of dimeric product and yet no adducts to isobutylene indicates either that the olefin is unsuitable as a radical trapping agent under these conditions, or that other than a free radical mechanism is responsible for the formation of decan-2,9-dione. Clearly, further work is required to elucidate the full details of the mechanism of this reaction.

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* The use of more efficient radical trapping agents was precluded by their reactivity towards lithium-ammonia solutions.

AFTERWARD

It is generally found that the course and facility of intermolecular radical reactions is predictable from a consideration of enthalpy factors We have seen in the previous chapters that this situation does not pertain to intramolecular radical reactions and, in particular, to radical fragmentation and cyclisation. In a number of cases the deviation from "expected" behaviour is clearly attributable to an inability to meet the stereoelectronic requirements for reaction due to structural restraints inherent in the molecule. In other cases, however, the situation is less clear. Explanations in terms of steric factors are often possible. We have seen, however, that the influence of polar factors in the transition state must also be considered.

In the present study we have been unable to accurately assess the relative importance of the various steric and polar influences which may afford the reaction and obviously further work is required to this end.

This may involve an investigation of the influence of trifluoromethyl and *t*-butyl or isopropyl groups on the kinetics of radical fragmentation or cyclisation using similar techniques to those used in the present study to provide information on the effects of polar and steric factors respectively.

EXPERIMENTAL

CHAPTER 8

The Synthesis of Halocompounds.

General

Melting points were determined using a Kofler hot stage and are uncorrected.

Microanalyses were carried out by the Australian Microanalytical Service, Melbourne.

Light petroleum refers to the fraction of b.p. 30-40°.

Reactions were conducted under an atmosphere of dry nitrogen unless otherwise stated.

Organic extracts were dried over magnesium sulphate.

Spectroscopic

Infrared spectra were recorded on an Unicam SP200 or a JASCO IRA-1 spectrophotometer.

^{1}H n.m.r. spectra were recorded in either carbon tetrachloride or deuteriochloroform solution, containing tetramethylsilane as an internal standard, with an Varian T60 spectrometer operating at 60 MHz; data are reported in the order: value, integral, multiplicity, coupling constant, assignment.

^{13}C n.m.r. spectra were recorded in deuteriochloroform solution with a Bruker HX90-E spectrometer fitted with a Nicolet B-NC12 Fourier

system and a Bruker B-SV3PM pulse unit.

Mass spectra were determined with a Perkin-Elmer-Hitachi RMU-6D instrument operating at 70eV.

Gas chromatography

Analytical gas chromatography was conducted using a Perkin-Elmer 881 or 990 instrument.

Preparative separations were achieved using a Pye-Unicam 104 or 105 instrument.

The following columns were used:

A 6.3m x 3.2mm, $\frac{3}{4}$% FFAP on Varaport 30 (100-120 mesh).

B 3m x 7mm, 14% Carbowax 20M-TPA on Chromasorb A (40-60 mesh).

C 2m x 7mm, 20% QF1 on Varaport 30 (70-80 mesh).

D 6.1m x 3.2mm, 20% Carbowax 20M on Varaport 30 (100-120 mesh).

E 6m x 8mm, 30% QF1-NPGS (2:1) on Chromasorb A (40-60 mesh).

F 4.6m x 2.1mm, 5% Apiezon M on Varaport 30 (100-120 mesh).

G 3m x 3.2mm, 5% PDEAS on Varaport 30 (100-120 mesh).

H 3m x 3.2mm, 3% NPGS-XE60 (1:1) on Varaport 30 (80-100 mesh).

I 70m x 0.5mm, Carbowax 20M, Surface Coated Open Tubular Column.

J 6m x 7mm, 20% OV1 on Chromasorb W (80-100 mesh).

K 1.4m x 7mm, 17% FFAP on Varaport 30 (70-80 mesh).

L 2m x 3.2mm, 40% $AgNO_3$-benzyl cyanide on Chromasorb W (80-100 mesh).

M 6m x 3.2mm, $\frac{3}{4}$% Squalane on Varaport 30 (100-120 mesh).

N 3m x 3.2mm, 20% Dimethylsulpholane on Chromasorb W (80-100 mesh).

O 6m x 3.2mm, 20% Propylenecarbonate on Varaport 30 (100-120 mesh).

P 70m x 0.5mm, Squalane Surface Coated Open Tubular Column.

Columns A, D, H, and L were constructed of stainless steel and the remainder were of glass.

Nomenclature

For ease of reference cyclopropyl- and cyclobutylmethanol derivatives have been named after the same system as that used for the chlorides (e.g. cyclobutylmethanol = hydroxymethylcyclobutane).

1-*Chlorohex*-5-*ene* (65)

Hex-5-en-1-ol was converted into its toluene-*p*-sulphonate (98%) according to the general procedure described by Fieser[230]. A solution of the toluene-*p*-sulphonate (3.0g) was stirred with lithium chloride (1.0g) in *N*,*N*-dimethylformamide (30ml) at ambient temperature for 48h. The mixture was then poured into water and extracted with light petroleum. The organic layer was washed thoroughly with water, dried, and distilled to afford the required chloride (1.2g, 86%), b.p. 135° (block), (lit.[231,232] 128-130°, 132-134°), n_D^{17} 1.4412 (lit.[231,232] n_D^{24} 1.4320, n_D^{20} 1.4382).

1-*Bromohex*-5-*ene* (66)

According to the foregoing procedure the toluene-*p*-sulphonate of hex-5-en-1-ol (8.5g) was treated with lithium bromide (3.5g) in *N*,*N*-dimethylformamide (50ml) to afford the required bromide (4.9g, 90%), b.p. 55-57°/20mm (lit.[233] 47-51°/16mm). The product was shown by g.l.c. (column A, 70°) to contain *ca.* 5% of the corresponding chloride (65). Pure 1-bromohex-5-ene, n_D^{17} 1.4701 (lit.[233] n_D^{25} 1.4632), was obtained by preparative gas chromatography (column B, 120°, N_2 70ml min^{-1}

Ethyl bicyclo[4.1.0]*heptane*-7-*carboxylate* (70) *and* (71)

A solution of (trimethyl phosphite)copper(I) iodide[143] (650mg) and benzoyl peroxide (260mg) in cyclohexene (250ml) was heated at reflux whilst a solution of ethyl diazoacetate[143] (35g) in cyclohexene (250ml)

was added at a rate of *ca.* 6 drops/min. After 18h at reflux, the mixture was cooled, filtered and the excess of cyclohexene then removed by distillation. The residual oil was distilled under vacuum to afford the required ester (41g, 69%), b.p. 86-88°/2mm (lit.[234] 109-110°/18mm), as a mixture of *exo*- and *endo*-isomers in the ratio 13:1 (g.l.c., column A, 200°).

Bicyclo[4.1.0]*heptane*-exo-7-*carboxylic acid* (72)

Saponification[235] of the foregoing ester mixture (40g) was effected with aqueous sodium hydroxide. Two recrystalisations from *n*-hexane afforded the pure *exo*-acid* (25g, 75%), m.p. 97-99° (lit.[235] 98-99°).

Methyl bicyclo[4.1.0]*heptane*-exo-7-*carboxylate* (73)

The foregoing acid (2.5g) was treated with an ethereal solution of diazomethane[236] to afford the required methyl ester (2.7g, 92%), b.p. 100-102°/22mm (lit.[236] 99°/15mm). The product was shown by g.l.c. (column A, 150°) to be of >99.5% purity.

exo-7-*Hydroxymethylbicyclo*[4.1.0]*heptane* (74)

A solution of bicyclo[4.1.0]heptane-*exo*-7-carboxylic acid (10.0g) in ether (50ml) was added to a stirred suspension of lithium aluminium hydride (3.0g) in ether (200ml) at a rate to maintain gentle reflux.

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* >99.5%, determined by g.l.c. analysis of the methyl ester (73).

After being heated under reflux for 16h the mixture was cooled to 0°C and hydrolysed by the addition of water (1.5ml), 10% sodium hydroxide solution (3ml), and water (3ml). The precipitated salts were filtered off and the ethereal solution distilled to give the required alcohol (7.7g, 85%), b.p. 92-93°/8.5mm (lit.[237] 106-107°/17mm). G.l.c. analysis (column A, 150°) showed the product to be homogeneous.

exo-7-*Chloromethylbicyclo*[4.1.0]*heptane* (75)

(a) Thionyl chloride (5.0g) was added to a solution of the foregoing alcohol (5.2g) in ether (20ml) at -78°. After 10 min. the solvent was removed *in vacuo* at 0°C and the residue dissolved in pentane. After percolation through a short column of calcium carbonate the solution was evaporated and distilled to afford a mixture (5.2g, 89%), b.p. 39-41°/1.2mm, which was shown by g.l.c. (column A, 110°) to contain approximately 75% of the required chloride (75) and 25% of 1-chloro-2-vinylcyclohexane (76).

Ozonized oxygen was passed through a solution of the foregoing chloride mixture (2.7g) in methylene chloride (50ml) at -78°C until the solution assumed a permanent blue colour (*ca.* 2h), then hexamethylphosphorictriamide (2g) was added. The mixture was then allowed to warm to 0°C and the solvent removed *in vacuo*. The residual oil was taken up in pentane, washed thoroughly with ice-cold water, dried and distilled to afford pure exo-7-*chloromethylbicyclo*[4.1.0]*heptane*,

b.p. 40° (block)/1.0mm, n_D^{22} 1.4482 (Found: C, 66.7; H, 9.0. $C_8H_{13}Cl$ requires C, 66.4; H, 9.1%); n.m.r. ($CDCl_3$) δ0.7 - 2.5 (11H, complex), 3.5 (2H, d, *J*=7Hz, CH_2Cl).

(b) A solution of triphenyl phosphine (1.3g) in tetrahydrofuran (5ml) was slowly added to a stirred solution of *N*-chlorosuccinimide (1.8g) in tetrahydrofuran (30ml) at room temperature; a white precipitate formed during the addition. The alcohol (74) (0.8g) in tetrahydrofuran (12ml) was then added and stirring continued until most of the solid went into solution (*ca.* 2h). The mixture was then stripped of solvent on the rotary evaporator and the residue treated with ether and water. The organic layer was separated, dried, and chromatographed on Florisil. Elution with light petroleum afforded a colourless oil (0.7g 97%) which was shown by g.l.c. (column A, 110°) to comprise 85% of the required chloride and 15% of the isomeric chloride (75).

(c) The alcohol (74) (2.05g) in pyridine (10ml) was treated with solution of toluene-*p*-sulphonyl chloride (6.2g) in pyridine (15ml) at 0°C. After being allowed to stand at 0°C for 2h the mixture was poured into ice-water and extracted with ether. The organic layer was washed successively with 5% aqueous hydrochloric acid, 5% sodium bicarbonate solution and water, dried and evaporated. The n.m.r. spectrum showed the crude toluene-*p*-sulphonate (1.4g) to be contaminated with *ca.* 30% of a *ca.* 1:4 mixture of the chlorides (75) and (76). The contaminants were removed by distillation (0°/0.1mm).

A solution of the toluene-*p*-sulphonate (1.2g), pyridinium chloride (1.2g) and *N*,*N*-dimethylformamide (30ml) was stirred at room temperature for 24h. The mixture was then poured into ice-cold water and extracted with light petroleum. The organic layer was washed thoroughly with ice-cold water, dried and evaporated. G.l.c. analysis (column A, 110°) showed the residual oil to contain approximately 90% of the required chloride (75) and 10% of 1-chloro-2-vinylcyclohexane (76).

exo-7-*Acetylbicyclo*[4.1.0]*heptane* (77)

An ethereal solution of methyllithium (60ml; 1.5M) was added dropwise during 10min to a stirred solution of bicyclo[4.1.0]heptane-*exo*-7-carboxylic acid (5.0g) in ether (30ml) at 0°. After the addition, the mixture was stirred at room temperature for 30min, then poured on to crushed ice (100g). Extraction of the mixture with ether and distillation of the dried extract under reduced pressure afforded the required ketone (4.2g, 80%), b.p. 67-69°/2.5mm (lit.[238] 98°/20mm). ν_{max} (film) 1680 cm^{-1}; n.m.r. ($CDCl_3$) δ 0.9 - 2.0 (11H, complex), 2.2 (3H, s, CH_3).

exo-7-(1'-*Hydroxyethyl bicyclo*[4.1.0]*heptane* (78)

The foregoing ketone (3.0g) in ether (30ml) was added to a stirred suspension of lithium aluminium hydride (1.3g) in ether (20ml) and the mixture was then stirred at room temperature for 16h. Work up in the usual way afforded exo-7-(1'-*hydroxyethyl*)*bicyclo*[4.1.0]*heptane* (3.0g, 98

b.p. 81-83°/5mm (Found: C, 77.2; H, 11.6. $C_9H_{16}O$ requires C, 77.2; H, 11.5%). ν_{max} (film) 3350 cm^{-1}; n.m.r. ($CDCl_3$) δ 0.3 - 2.1 (11H, complex), 1.2 (3H, d, *J*=7Hz, CH_3), 3.1 (1H, m, CHO). G.l.c. analysis (column A, 150°) showed the alcohol to be of >99% purity.

Attempted preparation of exo-7-(1'-*chloroethyl*)*bicyclo*[4.1.0]*heptane* (79) (a) The foregoing alcohol (1.8g) was added to a stirred suspension of phosphorous pentachloride (2.8g; freshly sublimed) in pentane (15ml) at -20°. The resulting mixture was stirred for a further 1h at -20°, then ice-water (20ml) was added. The pentane layer was separated, then washed successively with water, saturated sodium bicarbonate solution and water. Evaporation of the dried pentane solution and distillation of the residual oil afforded a mixture (1.8g, 88%), b.p. 35-37°/0.5mm, which was shown by analysis of n.m.r. spectrum to contain 10% of unchanged alcohol and 90% of unsaturated chlorides tentatively identified as a mixture of stereoisomeric 1-chloro-2-(prop-1'-enyl)-cyclohexanes (80). A sample of the chloro-olefin (80) separated by preparative g.l.c. (column C, 80°, N_2 70ml min^{-1}) had b.p. 40° (block)/ 1mm (Found: C, 68.6; H, 9.6. Calc for $C_9H_{15}Cl$ C, 68.2; H, 9.5%), n.m.r. (CCl_4) δ 0.9 - 2.5 (12H, complex, 3.6 (1H, m, CHCl), 5.5 (2H, complex, CH=CH).

Treatment of the alcohol (78) with either phosphorous pentachloride in methylene chloride at -78°, or thionyl chloride in pentane at -78° also afforded the chloro-olefin (80).

(b) Using the procedure (b) described for the preparation of the chloride (78), *exo*-7-(1'-hydroxyethyl)bicyclo[4.1.0]heptane (0.8g) was treated with the reagent derived from the addition of triphenyl phosphine to *N*-chlorosuccinimide in tetrahydrofuran to afford a colourless liquid (0.3g, 33%), b.p. 40° (block)/0.5mm. Analysis of the n.m.r. spectrum indicated the presence of 85% of the chloro-olefin (80) and 15% of a compound believed to be the required chloride (79) by virtue of an enhanced CHCl multiplet at δ 3.6, and resonances in the region δ 0.3 - 2.1 characteristic of the bicyclo[4.1.0]heptane skeleton (the absence of the alcohol (78) was demonstrated by infra red and g.l.c. analysis).

Attempts to purify the chloride using the ozonolysis procedure described for the purification of the chloride (75) were unsuccessful.

exo-7-(2'-*Hydroxyprop*-2'-*yl*)*bicyclo*[4.1.0]*heptane* (81)

Treatment of methyl bicyclo[4.1.0]heptane-*exo*-7-carboxylate (2.5g) with methyl magnesium iodide as previously described[239] afforded the required alcohol (1.95g, 78%), b.p. 45-50°/0.2mm, ν_{max} 3350 cm^{-1}, n.m.r. ($CDCl_3$) δ 0.4 - 2.2 (12H, complex), 1.1 (6H, s, CH_3). G.l.c. analysis (column G, 100°) showed the alcohol to be contaminated with *ca.* 4% of an unidentified impurity.

Attempted preparation of exo-7-(2'-*chloroprop*-2'-*yl*)*bicyclo*[4.1.0]*heptane* (82)

Treatment of the foregoing alcohol with either thionyl chloride in ether at -78°[50], phosphorous pentachloride in methylene chloride at -78°[180], or successively with methyllithium, *p*-toluenesuphonyl chloride and lithium chloride in hexamethylphosphorictriamide[240] afforded only an unsaturated chloride tentatively identified as 1-chloro--2-(2'-methylprop-1'-enyl)cyclohexane (82), b.p. 45° (block)/2mm, n.m.r. (CCl_4) δ 0.9 - 2.6 (15H, complex), 3.6 (1H, m, CHCl), 5.0 (1H, br d, =CH) mass spectrum m/e 172, 174 (M^+).

1-*Methylcyclohexene* (83)

Dehydration of 1-methylcyclohexanol by distillation from iodine as described by Mosher[241] gave the required olefin (90%), b.p. 110-112° (lit.[242] 110.0°). G.l.c. (column D, 120°) showed the product to be contaminated with *ca.* 2% of methylenecyclohexane.

Ethyl 6-*methylbicyclo*[4.1.0]*heptane*-7-*carboxylate* (84) *and* (85)

A solution of (trimethyl phosphite)copper(I) iodide (575mg), benzoyl peroxide (230mg) and 1-methylcyclohexene (16g) in methylcyclohexane (200ml) was heated under reflux whilst a solution of ethyl diazoacetate (26.1g) and 1-methylcyclohexene (15g) in methylcyclohexane (200ml) was added at a rate of *ca.* 6 drops/min. After the addition the mixture was heated under reflux for 18h, then cooled and evaporated.

Distillation of the residual oil afforded a mixture (38g, 65%), b.p. 80-82°/2.5mm, containing 77% of the *exo*-ester (84), 22% of the *endo*-ester (85) and 1% of an unsaturated by-product deemed to be the product of allylic insertion. A pure sample of the *exo*-ester obtained by preparative g.l.c. (column E, 180°, N_2 70ml min^{-1}) had b.p. 85° (block)/2.5mm (Found: C, 72.2; H, 10.2. Calc for $C_{11}H_{18}O_2$ C, 72.5; H, 10.0%). ν_{max} 1720 cm^{-1}; n.m.r. ($CDCl_3$) δ 1,1 - 2.2 (16H, complex), 4.2 (2H, q, *J*=7Hz, CH_2O).

A previous experiment in which the reaction was conducted under similar conditions but using cyclohexane as solvent led to the formation of the same three products in yields of 30%, 10% and 5% respectively.

6-*Methylbicyclo*[4.1.0]*heptane*-exo-7-*carboxylic acid* (86)

The foregoing ester mixture was saponified with aqueous sodium hydroxide to give a solid which was recrystalised three times from *n*-hexane to afford the required *exo*-acid (45%), m.p. 121-124° (lit.[243] 121-123°). ν_{max} 1700 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.0 - 2.0 (13H, complex), 13.5 (1H, br s, COOH). The acid was shown to be of >99% purity by g.l.c. analysis (column A, 180°) of its ethyl ester (84) (prepared by treatment of the acid with an ethereal solution of diazoethane).

exo-7-*Hydroxymethyl*-6-*methylbicyclo*[4.1.0]*heptane* (87)

A solution of the foregoing acid (8g) in ether (20ml) was added to a stirred suspension of lithium aluminium hydride (2.2g) in ether (50ml) and the mixture then heated under reflux for 16h. Work up in the usual way afforded the *required alcohol* (6.8g, 93%), b.p. 82-85°/3.5mm (Found: C, 76.8; H, 11.6. $C_9H_{16}O$ requires C, 77.0; H, 11.5%). ν_{max} 3370 cm^{-1}; n.m.r. ($CDCl_3$) δ 0.3 - 2.1 (11H, complex), 1.1 (3H, s, CH_3), 3.6 (2H, m, appears as the AB portion of ABX system with $J_{AB} \sim$ 10Hz, CH_2OH). G.l.c. (column A, 160°) showed the product to be homogeneous.

exo-7-*Chloromethyl*-6-*methylbicyclo*[4.1.0]*heptane* (88)

Using the procedure (b) described for the preparation of the chloride (76), the reaction of the alcohol (87) (1.3g) with the reagent derived from the addition of triphenyl phosphine to *N*-chlorosuccinimide afforded a mixture (0.8g, 55%) containing approximately equal amounts of the required chloride (88) and an unsaturated chloride tentatively identified as 1-chloro-1-methyl-2-vinylcyclohexane (89).

A sample of the chloride mixture (0.7g) was subjected to the ozonolysis procedure described for the purification of the chloride (76) to afford pure *exo*-7-chloromethyl-6-methylbicyclo[4.1.0]heptane (0.3g) b.p. 80-81° (block)/4mm. n.m.r. (CCl_4) δ 0.4 - 2.2 (10H, complex), 1.2 (3H, s, CH_3), 3.6 (2H, m, appears as the AB portion of an ABX system with $J_{AB} \sim$ 10Hz, CH_2Cl). Due to its high lability a satisfactory analys

could not be obtained for the chloride (88); however, the compound was shown to be of >99% purity by its n.m.r. spectrum and by g.l.c. (column F, 120°).

Methyl 6-*methylbicyclo*[4.1.0]*heptane*-exo-7-*carboxylate* (90) *and* *methyl* 6-*methylbicyclo*[4.1.0]*heptane*-endo-7-*carboxylate* (91)

The mother liquors left after crystalisation of bicyclo[4.1.0] heptane-*exo*-7-carboxylic acid were evaporated and the residual oil (2.0g) treated with an ethereal solution of diazomethane to afford a mixture (2.1g, 95%) which was shown by g.l.c. (column A, 170°) to contain approximately 40% of the *exo*-ester (90) and 60% of the *endo*-ester (91). This mixture was subjected to preparative gas chromatography (column C, 140°, N_2 70ml min^{-1}) to afford samples of (i) *methyl* 6-*methylbicyclo*-[4 1.0]*heptane*-exo-7-*carboxylate* (90), b.p. 70° (block)/2mm (Found: C, 71.8; H, 9.7. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.6%), n.m.r. (CCl_4) δ 1.0 - 2.2 (10H, complex), 1.1 (3H, s, CH_3), 3.6 (3H, s, CH_3) (The methyl singlet at δ 1.1 is displaced to δ 1.4 in benzene solution.), and (ii) *methyl* 6-*methylbicyclo*[4.1.0]*heptane*-endo-7-*carboxylate* (91), b.p. 70° (block)/2mm (Found: C, 71.6; H, 9.9. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.6%), n.m.r. (CCl_4) 0.9 - 2.2 (10H, complex), 1.06 (3H, s, CH_3), 3.6 (3H, s, OCH_3) (The methyl singlet at δ 1.06 is displaced to δ 1.02 in benzene solution).

1-*Hydroxymethyl*-2,2-*dimethylcyclopropane* (92)

2,2-Dimethylcyclopropanecarboxylic acid[244] (3.8g) was reduced with lithium aluminium hydride in the usual way[246] to afford the required alcohol (2.8g, 84%), b.p. 62-66°/25mm (lit.[245] 93-94°/118mm). G.l.c. analysis (column A, 110°) showed the product to be homogeneous.

1-*Chloromethyl*-2,2-*dimethylcyclopropane* (93)

Thionyl chloride (2.3g) was added in one portion to a stirred solution of 1-hydroxymethyl-2,2-dimethylcyclopropane (2.0g) in *n*-butane (20ml) at -78°. After 5min at -78° the solvent was removed *in vacuo* at 0°. The residual oil was distilled under reduced pressure to afford the required chloride (1.9g, 82%), b.p. 55-60°/100mm, n.m.r. ($CDCl_3$) δ 0.6 - 1.8 (3H, complex), 1.08 (3H, s, CH_3), 1.12 (3H, s, CH_3), 4.05 (2H, m, CH_2Cl). The n.m.r. spectrum and g.l.c. analysis (column A, 50°) showed the product to be contaminated with *ca.* 3% of an unsaturated chloride, tentatively identified as 4-chloro-4-methylpent-1-ene. The lability of the chloride (93) prevented its purification by preparative g.l.c.

1-*Hydroxymethyl*-1-*methylcyclopropane* (94)

The alcohol prepared according to the sequence of reactions described by Siegel and Bergstrom[246] had b.p. 55-58°/80mm (lit.[246] 124.5 - 126°).

1-Chloromethyl-1-methylcyclopropane (95)

Using the procedure described for the preparation of 1-chloromethyl-2,2-dimethylcyclopropane the foregoing alcohol (1.5g) was converted into the required chloride (1.5g, 82%), b.p. 32-35° (block)/30mm (lit.[247] 96°), n_D^{20} 1.4335 (lit.[247] n_D^{20} 1.4329).

cis- *and* trans-*1-Hydroxymethyl-2-methylcyclopropane* (96) *and* (98)

Methylene iodide (70g) was added dropwise to a stirred suspension of zinc-copper couple (prepared from zinc powder (27.5g) and cuprous chloride (4.2g) in ether (150ml) according to the procedure of Rawson and Harrison[248]) during 30min. After the addition the mixture was heated under reflux for 2h, then crotyl alcohol (10.2g; a mixture of *cis*- and *trans*-isomers in the ratio 2:1) was added slowly during 30min. The mixture was heated under reflux for a further 2h, then cooled to room temperature and saturated ammonium chloride solution was added. The ethereal slurry was decanted into a separating funnel and the precipitated salts washed with several portions of ether. The combined ether solutions were washed successively with saturated ammonium chloride solution, saturated sodium bicarbonate solution and saturated brine, and dried. Distillation of the ether solution afforded 1-hydroxymethyl-2-methylcyclopropane (10.0g, 82%), b.p. 95-100°/15mm (lit.[249] 134-135°), as a mixture of the *cis* and *trans* isomers in the ratio 1:2 (g.l.c. column A, 80°). Samples of the *cis*- and *trans*-alcohols separated by preparative g.l.c. (column B, 130°, N_2 70ml min^{-1}) showed identical n.m.r. spectra to those previously reported[249].

cis- *and* trans-1-*Chloromethyl*-2-*methylcyclopropane* (97) *and* (99)

Using the procedure described for the preparation of 1-chloromethyl-2,2-dimethylcyclopropane (93) the foregoing mixture of alcohols (2.0g) was treated with thionyl chloride in *n*-butane at -78° to afford a mixture of *cis*- and *trans*-1-chloromethyl-2-methylcyclopropane (1.7g, 72%). The product was subjected to preparative g.l.c. (column B, 80°, N_2 60ml min^{-1}) to afford (i) a pure sample of *cis* chloride (97), n_D^{20} 1.4358 (lit.[247] n_D^{22} 1.4363), and (ii) a sample of the *trans* chloride containing *ca.* 5% of an unidentified impurity, n_D^{20} 1.4290 (lit.[247] n_D^{22} 1.4302). The n.m.r. spectra of the chlorides were identical to those previously recorded[247].

trans-1-(1'-*Hydroxyethyl*)-2-*methylcyclopropane* (100)

Utilizing the procedure described for the preparation of *cis*- and *trans*-1-hydroxymethyl-2-methylcyclopropane (96) and (98) *trans*-pent-2-en-3-ol (12g) was converted into the required alcohol (10.0g, 79%), b.p. 87-89°/100mm (lit.[250] 81-83°/93mm). G.l.c. (column I, 60°C) showed the product to be a *ca.* 1:1 mixture of the two possible diastereoisomers. The absence of the *cis*-isomer was established by analysis of the n.m.r. spectrum[250].

trans-1-(1'-*Chloroethyl*)-2-*methylcyclopropane* (101)

The foregoing alcohol (1.6g) was treated with thionyl chloride in butane at -78° to afford a colourless liquid (0.8g, 44%). G.l.c. showed the product to comprise 95% of a *ca.* 1:1 mixture of the two possible diastereoisomers of *trans*-1-(1'-chloroethyl)-2-methylcyclopropane and

5% of unsaturated impurities. Samples of the two diastereoisomers were isolated in >90% purity by preparative g.l.c. (column B, 120°, N_2 60ml min^{-1}). The diastereoisomer of longer retention time had (Found: C, 61.3; H, 9.6. $C_6H_{11}Cl$ requires C, 60.8; H, 9.4%) n.m.r. δ 0.3 - 1.2 (3H, complex, ring H), 1.1 (3H, d, *J*=5Hz, CH_3), 1.6 (3H, d, *J*=6Hz, CH_3), 3.4 (1H, m, CHCl). (The spectra of the diastereoisomers were identical apart from small variations in the pattern in the region δ 0.3 - 1.2.)

(1-*Hydroxyethyl*)*cyclopropane* (102)

Reduction of acetylcyclopropane (15g) with lithium aluminium hydride in the usual way afforded the required alcohol (13.9g, 90%), b.p. 71-72°/100mm (lit.[139] 121-122°).

(1-*Chloroethyl*)*cyclopropane* (103)

Using the procedure of Hanack and Eggensperger[139] (1-hydroxyethyl-cyclopropane (6.2g) was treated with phosphorous pentachloride in pentane to afford a mixture (5,6g, 74%), b.p. 100-102° (lit.[137] 100-102°), of the required chloride (95%) and 5-chloropent-2-ene (5%). Pure (1-chloroethyl)cyclopropane (103) was obtained by preparative gas chromatography (column B, 50°, N_2 50ml min^{-1}).

1-(1'-*Hydroxyethyl*)-2,2-*dimethylcyclopropane* (104)

1-Acetyl-2,2-dimethylcyclopropane[251] (3.2g) was reduced with lithium aluminium hydride in the usual way to afford the required alcoho (2.7g, 95%), b.p. 61-62°/20mm. (Found: C, 73.8; H, 12.3. Calc for

$C_6H_{14}O$ C, 73.6; H, 12.4%), as a mixture of diastereoisomers in the ratio 10:1 (g.l.c. column A, 90°C).

Attempted preparation of 1-(1'-*chloroethyl*)-2,2-*dimethylcyclopropane* (105

Treatment of the foregoing alcohol with either phosphorous pentachloride in pentane at -20° or with thionyl chloride in butane at -78° afforded a mixture of unsaturated chlorides, the major component of which has been tentatively identified as 5-chloro-5,5-dimethylhex-2-ene, n.m.r. ($CDCl_3$) δ 1.5 (6H, s, CH_3), 1.7 (3H, m, CH_3), 2.4 (2H, m, CH_2), 5.6 (2H, m, CH=CH).

Hydroxymethylcyclobutane (107)

Cyclobutanecarboxylic acid[252] (3.9g) was reduced with lithium aluminium hydride in ether in the usual way to afford hydroxymethylcyclobutane (3.2g, 97%)as a colourless liquid,b.p. 70-71°/35mm (lit.[253] 142-143°/750mm).

Chloromethylcyclobutane (109)

A solution of toluene-*p*-sulphonyl chloride (12.6g) in pyridine (40ml) was added to a solution of hydroxymethylcyclobutane (2.9g) in pyridine (15ml) at 0°. After 24h at 0°, the excess toluene-*p*-sulphonyl chloride was hydrolysed by the addition of water (5ml) in pyridine (5ml), and the mixture was then poured into ice-water and extracted with ether. The ether extracts were washed successively with ice-cold 2% aqueous hydrochloric acid, 10% sodium bicarbonate solution, and water and dried. Removal of the solvent under reduced pressure left the toluene-*p*-sulphona

(108) as a pale yellow oil (7.5g, 92%) which was used without further purification.

The toluene-*p*-sulphonate (108) (2.9g) was stirred with lithium chloride (1.8g) in hexamethylphosphorictriamide (25ml) at room temperature for 24h. After dilution with water, the mixture was shaken with light petroleum and the organic layer washed with water and dried. Distillation afforded 1-chloromethylcyclobutane (1.2g, 97%), b.p. 109-111° (lit.[144] b.p. 109.5-111°), n_D^{21} 1.448. The n.m.r. spectrum[144] and g.l.c. analysis (column A, 50°) showed the chloride to be free of impurities.

A previous experiment in which *N*,*N*-dimethylformamide was used as solvent led to only 50% conversion of the toluene-*p*-sulphonate (108) into the required chloride (109) after 84h.

Acetylcyclobutane (111)

Treatment[144] of cyclobutanecarboxylic acid (8g) with an ethereal solution of methyllithium (200ml, 0.8M) afforded the desired ketone (6g, 77%), b.p. 132-135° (lit.[144] 133-137°). G.l.c. (column H, 90°) showed the product to be contaminated with <4% of the tertiary alcohol (115).

(1-*Chloroethyl*)*cyclobutane* (113)

(1-Hydroxyethyl)cyclobutane (112) (6.5g) (prepared by the reduction[2] of acetylcyclobutane (111) with lithium aluminium hydride) was converted into (1-chloroethyl)cyclobutane (5.2g, 76%), b.p. 126-128° (lit.[144,145] 127-128°, 122-127.5°), n_D^{23} 1.444 (lit.[145] n_D^{23} 1.4408) by displacement of its toluene-*p*-sulphonate ester with lithium chloride in hexamethylphosphorictriamide. G.l.c. analysis (column A, 80°) showed the chloride to be >97% pure. The impurity, thought to be 1-chloro-2-methylcyclopentane[144], was removed by preparative g.l.c. (column B, 110°, N_2 60ml min^{-1}).

(2-*Hydroxyprop*-2-*yl*)*cyclobutane* (115)

Methyl cyclobutanecarboxylate[255] (7.2g) in ether (30ml) was slowly added to a solution of methyl magnesium iodide (from methyl iodide (30g) and magnesium (5g) in ether (150ml)). The mixture was then stirred at room temperature for 16h. Work up in the usual manner afforded (2-hydroxyprop-2-yl)cyclobutane (7.0g, 97%) as a colourless liquid, b.p. 123-126°/100mm (lit.[256] 144-145°); n.m.r. ($CDCl_3$) δ 1.1 (6H, s, CH_3), 1.25 (1H, br s, OH), 1.5 - 2.7 (7H, complex), ν_{max} 3400 cm^{-1}.

(2-*Chloroprop*-2-*yl*)*cyclobutane* (116)

(a) Hydrogen chloride gas (generated by the addition of concentrated hydrochloric acid (1.5ml; SG 1.19) to concentrated sulphuric acid (50ml; SG 1.84)) was slowly introduced into a solution of (2-hydroxyprop-2-yl)-cyclobutane (0.52g) in pentane (2ml) at 0° until g.l.c. analysis (column

A, 60°) indicated 95% conversion. The excess hydrogen chloride was then removed by gentle aspiration and the mixture dried over anhydrous potassium carbonate. The chloride, isolated by preparative g.l.c. (column B, 90°, N_2 60ml min^{-1}), was of 92% purity. The contaminant (8%) was identified as 1-chloro-2,2-dimethylcyclopentane (117) on the basis of spectral data and the fact that on reduction of the chloride mixture with tri-*n*-butylstannane an equivalent amount of 1,1-dimethylcyclopentane is formed. N.m.r. (CCl_4) [(2-chloroprop-2-yl)cyclobutane] δ 1.25 (6H, s, CH_3), 1.7 - 2.7 (7H, complex). N.m.r. (CCl_4) [1-chloro-2,2-dimethylcyclopentane] δ 1.05 (6H, s, CH_3), 1.4 - 2.4 (6H, complex, ring H), 3.8 (1H, t, *J*=6Hz, CHCl).

(b) The reaction of the alcohol (116) (0.5g) with phosphorous pentachloride in methylene chloride at -78° was conducted according to the procedure (a) described for the preparation of the chloride (79) to afford a mixture (0.45g, 77%) containing (2-chloroprop-2-yl)cyclobutane (60%) and 1-chloro-2,2-dimethylcyclopentane (40%).

1-*Methylcyclobutanecarboxylic acid* (118)

Cyclobutanecarboxylic acid (4g) was added to a cooled (-10°), stirred solution of lithium *N*,*N*-diisopropylamide (prepared by the addition of a pentane solution of *n*-butyllithium (96ml; 1M) to a solution of *N*,*N*-diisopropylamine (9.7g) in tetrahydrofuran (30ml) at -10°) at a rate so as to maintain the temperature at less than 0°. After the addition the mixture was stirred at room temperature for 30min, then

methyl iodide (6.8g) was added dropwise. The resultant pale yellow solution was stirred for a further 3h at room temperature, then acidified by the addition of 20% aqueous hydrochloric acid. The mixture was extracted with ether and the extracts washed with 10% aqueous hydrochlori acid and saturated brine, and dried. Evaporation of the ether solution and distillation of the residual oil under reduced pressure afforded 1-methylcyclobutanecarboxylic acid (4.0g, 88%), b.p. 101-105°/17mm (lit.[151] 98°/13mm). The presence of *ca.* 5% of unchanged acid was detected in the product by g.l.c. analysis (column A, 100°) of the ethyl ester obtained by treatment of the acid with diazoethane.

1-Methylcyclobutanecarboxylic acid of >98% purity could be obtained by resubjecting the crude acid to the alkylation conditions

1-*Hydroxymethyl*-1-*methylcyclobutane* (119)

Lithium aluminium hydride reduction[148] of the foregoing acid (3.2g) afforded the required alcohol (2.3g, 80%), b.p. 90-95°/50mm (lit.[148] 70-71°/32mm).

1-*Chloromethyl*-1-*methylcyclobutane* (120)

Using the procedure described for the preparation of chloromethyl-cyclobutane (109), 1-hydroxymethyl-1-methylcyclobutane (1.8g) was converted into its toluene-*p*-sulphonate and treated with lithium chlorid in hexamethylphosphorictriamide to afford the required chloride (2.0g, 93%). The only contaminant, chloromethylcyclobutane, was removed by

preparative g.l.c. (column E, 130°, N_2 60ml min^{-1}) to give pure 1-chloromethyl-1-methylcyclobutane, b.p. 125-130° (block) (lit.[148] 122-123°), n_D^{24} 1.445 (Found: C, 60.8, H, 9.3. Calc for $C_6H_{11}Cl$ C, 60.8; H, 9.4%).

cis-2-*Methylcyclobutanecarboxylic acid* (122)

Hydrogenation of *cis*-cyclobutane-1,2-dicarboxylic acid anhydride (121) using the procedure of McCrindle and co-workers[153] afforded the required acid (1.9g, 93%), b.p. 87-90°/6mm. G.l.c. analysis (column F, 150°) of the ethyl ester, prepared by esterification of the acid (122) with diazoethane, did not reveal any impurities.

cis-1-*Hydroxymethyl*-2-*methylcyclobutane* (123)

The foregoing acid (2.5g) was reduced with lithium aluminium hydride in the usual way to afford *cis*-1-hydroxymethyl-2-methylcyclobutane (1.9g, 87%), b.p. 70-70°/32mm (lit.[257] b.p. 82-83°/45mm).

cis-1-*Chloromethyl*-2-*methylcyclobutane* (124)

Using the procedure described for the preparation of chloromethylcyclobutane (109) *cis*-1-hydroxymethyl-2-methylcyclobutane (1.8g) was converted into its toluene-*p*-sulphonate and treated with lithium chloride in hexamethylphosphorictriamide to afford the required chloride (1.9g, 87%). G.l.c. analysis showed (column A, 65°) the product to be contaminated by a trace amount (<2%) of the *trans*-isomer. Pure *cis*-1-

chloromethyl-2-methylcyclobutane had n_D^{20} 1.443 (Found: C, 60.4; H, 9.3. Calc for $C_6H_{11}Cl$ C, 60.8; H, 9.4). The n.m.r. spectrum was in accord with that previously described[147].

Diethyl 2-methylcyclobutane-1,1-dicarboxylic acid (125)

Diethyl malonate (96g) was added dropwise to a stirred suspension of sodium hydride (29g; 50% dispersion in oil) in *N*,*N*-dimethylformamide (140ml) and the mixture stirred at room temperature until the evolution of hydrogen ceased (*ca.* 30min). The resultant black solution was transferred under nitrogen to a dropping funnel and added slowly with stirring to 1,3-dibromobutane (130g). After the addition, the mixture was stirred for a further 3h at room temperature, then sodium hydride (29g; 50% dispersion in oil) was added portionwise during 1h, stirring was then continued for 16h. The mixture was poured into water, extracted with ether, and the extracts washed thoroughly with water and saturated brine. Evaporation of the dried ether solution and distillation of the residual oil under reduced pressure afforded, after a small forerun (6.2g), the required diester (50.1g, 39%), b.p. 82-85°/0.3mm (lit.[154] b.p. 70-72.5°/1.0mm). G.l.c. analysis (column A, 160°) showed the diester to be of >98% purity.

2-Methylcyclobutanecarboxylic acid (122) *and* (127)

Utilizing the literature procedure[154] the foregoing diester (28g) was hydrolysed and the resultant diacid decarboxylated to give 2-methylcyclobutanecarboxylic acid (9g, 59%), b.p. 196-206° (lit.[154] 200°).

1-Hydroxymethyl-2-methylcyclobutane (123) *and* (128)

Reduction of 2-methylcyclobutanecarboxylic acid (8.2g) with lithium aluminium hydride in ether in the usual way afforded a mixture (7.0g, 97%), b.p. 80-86°/45mm, containing the *cis*- and *trans*-isomers of 1-hydroxymethyl-2-methylcyclobutane in the ratio 1:3 (g.l.c. column A, 140°).

trans-*1-Chloromethyl-2-methylcyclobutane* (129)

The foregoing alcohol (4.3g) was converted into its toluene-*p*-sulphonate and treated with lithium chloride in hexamethylphosphoric-triamide in the usual manner to afford a colourless liquid (4.7g, 92%), b.p. 123-128° (lit.[146] 124°), which was shown by g.l.c. (column A, 80°) to contain the *cis*- and *trans*-chlorides (124) and (129) in the ratio 1:3. The required *trans*-chloride (129) was obtained by preparative g.l.c. (column B, 85°, N_2 60ml min^{-1}), n_D^{19} 1.443 (Found: C, 61.3; H, 9.8. Calc for $C_6H_{11}Cl$ C, 60.8; H, 9.4%), and contained >0.5% of the *cis*-isomer (124).

The aluminium chloride promoted reaction of isobutylene with ethyl acrylate

The aluminium chloride promoted addition of isobutylene to ethyl acrylate in ethylene chloride-nitromethane was conducted under the conditions described by Sands[156] to afford a mixture (15g, 16%), b.p. 83-87°/18mm, comprising two ethyl esters in the ratio 8:1 (g.l.c. column I, 100°). The minor component had spectral properties and g.l.c. retention time identical to that of an authentic sample of ethyl 5-methylhex-4-enoate[157] (133).

The foregoing ester mixture was saponified according to the literature procedure[156] to afford a mixture of acids, b.p. 92-93°/2mm, n_D^{23} 1.447 (lit.[156] 80°/2mm, n_D^{23} 1.4492) [reported[158] for 5-methylhex-4-enoic acid (133) b.p. 98-99°/5mm, n_D^{20} 1.4470]. The n.m.r. spectrum of the major component (88%) was identical to that previously reported[158] for 5-methylhex-4-enoic acid (132).

Hydrogenation of a sample of the ester mixture (100mg) in the presence of Adams catalyst afforded a quantitative yield of a colourless liquid, b.p. 67-70° (block)/14mm [lit.[258] (for 5-methylhexanoic acid) 183.7°/750mm]. G.l.c. (column I, 150°) showed the product to be homogeneous.

The aluminium chloride promoted reaction of tetramethylethylene with ethyl acrylate

A solution of tetramethylethylene (10.0g) and ethyl acrylate (7.5g) was slowly added to a stirred solution of aluminium chloride (0.6g) in ethylene chloride (18ml) containing nitromethane (1.2ml). The mixture was stirred overnight at room temperature, then heated under reflux for 24h. The reaction mixture was then transferred to a separating funnel, washed with 5% sodium hydroxide solution and saturated brine, and dried. Evaporation of the solvent, and distillation of the residue under reduced pressure afforded a mixture (4.9g, 36%), b.p. 112-120°/20mm, consisting of four components (134), (135), (136), and (137) in the ratio 10:44:34:12 (g.l.c. column I, 150°).

Preparative g.l.c. allowed the separation of:

(i) Ethyl 4,5,5-trimethylhex-3-enoate (135) (Found: C, 71.8; H, 10.7. Calc for $C_{11}H_{20}O_2$ C, 71.7; H, 10.9%), n.m.r. ($CDCl_3$) δ 1.1* (10.2H, s, CH_3), 1.3 (3.6H, t, *J*=7Hz, OCH_2CH_3), 1.6 (3H, br s, CH_3), 2.3 - 2.6* (0.8H, complex, CH_2), 3.05 (2H, br d, *J*=7Hz, CH_2), 4.15* (3.6H, q, *J*=7Hz, OCH_2CH_3), 4.7 - 4.9* (0.4H, m, $=CH_2$), 5.95 (1H, br t, *J*=7Hz, =CH); ν_{max} 1750 cm^{-1}; mass spectrum m/e 184 (M^+);

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* These resonances have been attributed to the presence of ethyl 4-methylene-5,5-dimethylhexanoate (134) as an impurity (*ca.* 15%).

(ii) Ethyl 4,5,5-trimethylhex-5-enoate (136) (Found: C, 71.8; H, 10.7. Calc for $C_{11}H_{20}O_2$ C, 71.7; 10.9%), n.m.r. ($CDCl_3$) δ 1.1 (6H, s, CH_3), 1.3 (3H, t, *J*=7Hz, OCH_2CH_3), 1.5 - 2.5 (4H, complex) 1.7 (3H, br s, CH_3), 4.15 (2H, q, *J*=7Hz, OCH_2CH_3), 4.7 - 4.9 (2H, m, $=CH_2$); ν_{max} 1640 cm^{-1}, 900 cm^{-1}; mass spectrum m/e 184 (M^+);

(iii) Ethyl 5,6-dimethylhept-5-enoate (137) n.m.r. δ 1.1 - 2.3 (6H, complex) 1.3 (3H, *J*=7Hz, OCH_2CH_3), 1.6 (9H, s, CH_3), 4.15 (2H, q, *J*=7Hz, OCH_2CH_3), ν_{max} 1750 cm^{-1}; mass spectrum m/e 184 (M^+).

Reduction of the esters (134), (135), (136) *and* (137)

A solution of the foregoing ester mixture (1.3g) in ether (10ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.25g) in ether (10ml) and the resultant mixture then stirred for 16h at room temperature. Work up in the usual manner afforded a colourless oil (0.9g, 90%), b.p. 95-105°/20 mm. G.l.c. (column I, 160°) showed the product to consist of four components (139), (138), (140) and (141) in the ratio 44:10:34:12.

Subjection of the mixture of alcohols to preparative g.l.c. (column E, 180°, N_2 70ml min^{-1}) afforded samples of:

(i) 4,5,5-Trimethylhex-3-en-1-ol (139), n_D^{18} 1.4589 (lit.[259] n_D^{21} 1.4552, b.p. 92-93°/17mm) (Found: C, 75.9; H, 13.0. Calc for $C_9H_{18}O$ C, 76.0; H, 12.8), n.m.r. ($CDCl_3$), 1.1 (9H, s, CH_3), 1.3 (1H, br s, OH), 1.6 (3H, br s, CH_3), 2.3 (2H, m, CH_2), 3.7 (2H, br t, *J*=7Hz, CH_2O), 5.3 (1H, br t,

J=7Hz, =CH); ν_{max} 3390 cm^{-1}; mass spectrum m/e 142 (M^+);

(ii) 4,5,5-trimethylhex-5-en-1-ol (140), n_D^{18} 1.4569, (Found: C, 75.5; H, 13.0. Calc for $C_9H_{18}O$. C, 76.0, H, 12.8), n.m.r. ($CDCl_3$) δ 1.1 (6H, s, CH_3), 1.2 - 1.6 (5H, complex), 1.7 (3H, br s, 3H, CH_3), 3.6 (2H, m, CH_2O), 4.7 - 4.9 (2H, m, $=CH_2$); ν_{max} 3390 cm^{-1}, 1640 cm^{-1}, 895 cm^{-1}; mass spectrum m/e 142 (M^+);

(iii) 5,6-dimethylhept-5-en-1-ol (141), n_D^{18} 1.4633, n.m.r. ($CDCl_3$), 1.7 (9H, s, CH_3), 1.1 - 2.4 (7H, complex), 3.7 (2H, br t, CH_2O); ν_{max} 3390 cm^{-1}; mass spectrum m/e 142 (M^+).

The observed and calculated ^{13}C shieldings of the compounds (139) and (140) are reported in tables 12 and 13 (see pp. 66 and 67).

2,3,3-*Trimethylhex*-1-*ene* (142)

The preparation of this compound is described later (see (254)).

4,4,5-*Trimethylhexan*-1-*ol* (143)

The hydroboration-oxidation of 2,3,3-trimethylhex-1-ene (500mg) was conducted according to the general procedure described by Zweifel and Brown[260] to afford the required alcohol (400mg, 80%), b.p. 95-96°/20mm (Found: C, 74.9; H, 14.1. $C_9H_{20}O$ requires C, 74.9; H, 14.0); n.m.r. (CCl_4) δ 0.7 - 1.6 (18H, complex), 3.5 (2H, t, J=6Hz, CH_2O).

A compound with identical spectral properties and g.l.c. retention time (column I, 150°) was obtained from the hydrogenation of the alcohol (140).

2,2-Dimethyl-1-methylenecyclobutane (149)

The sequence of reactions described by Erickson[163] was employed to prepare 2,2-dimethyl-1-methylenecyclobutane, b.p. 80-90° (lit.[163] b.p. 80-95°). G.l.c. analysis (column D, 60°) showed the product to contain benzene (*ca.* 15%) as a contaminant.

1-Hydroxymethyl-2,2-dimethylcyclobutane (150)

A solution of diborane (23ml, 1.6M) tetrahydrofuran was added slowly to a stirred solution of the foregoing olefin (3.2g) in tetrahydrofuran (30ml). After the addition the mixture was stirred for 30min at room temperature then the excess of diborane decomposed by the cautious addition of water (0.7ml). A solution of 30% hydrogen peroxide (30ml) and aqueous sodium hydroxide (20ml; 6N) was then added slowly and the resultant mixture stirred at room temperature for 30min, and at 60° for 1 h. The mixture was then cooled, saturated with potassium carbonate and extracted with ether. The ether extracts were washed with saturated brine and dried. Evaporation of the solvent and distillation of the residual oil afforded 1-hydroxymethyl-2,2-dimethyl-cyclobutane (3.3g, 85%), b.p. 76-78°/17mm which was shown by g.l.c. (column A, 100°) to be of >98% purity. A sample purified by preparative g.l.c. (column C, 110°, N_2 70ml min^{-1}) had b.p. 80° (block)/17mm (Found: C, 73.8; H, 12.6. $C_7H_{14}O$ requires C, 73.6; H, 12.4)

n.m.r. ($CDCl_3$) δ 0.9 - 2.6 (6H, complex), 1.05 (3H, s, CH_3), 1.15 (3H, s, CH_3), 3.5 - 3.9 (2H, m, CH_2O).

1-*Chloromethyl*-2,2-*dimethylcyclobutane* (151)

Utilizing the procedure described for the preparation of the chloride (109) the foregoing alcohol (3g) was converted into its toluene-*p*-sulphonate and treated with lithium chloride in hexamethylphosphorictriamide to afford a liquid (3.6g, 94%) which was subjected to preparative g.l.c. (column B, 100°, N_2 50ml min^{-1}) to afford pure 1-*chloromethyl*-2,2-*dimethylcyclobutane*, n_D^{24} 1.446 (Found: C, 63.9; H, 9.8. $C_7H_{13}Cl$ requires C, 63.4; H, 9.9%); n.m.r. ($CDCl_3$) δ 1.05 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.3 - 2.6 (5H, complex), 3.4 (2H, m, CH_2Cl).

2,2,3,3-*Tetramethyl*-1-*methylenecyclobutane* (153)

Dimethylsulphoxide (12ml) was slowly added to sodium hydride (1.6g; 50% dispersion in oil), after the addition was complete the mixture was heated at 75° until hydrogen evolution ceased (1h). The mixture was then cooled to 0° and a solution of methyltriphenylphosphonium iodide (12.8g) in warm dimethylsulphoxide (30ml) added dropwise. The resultant yellow-red suspension was stirred at room temperature for 15min and then 2,2,3,3-tetramethylcyclobutanone[164] (1.6g) in dimethylsulphoxide (8ml) was added. The mixture was stirred for a further 16h at room temperature and then subjected to flash distillation (40°/12mm), the

volatile products being collected in a dry-ice acetone trap. The crude olefin (2.0g, 90%; contaminated with benzene (*ca.* 30%)) was used without purification. A pure sample of *the olefin*, n_D^{18} 1.4345 (Found: C, 87.2; H, 12.8. C_9H_{16} requires C, 87.0; H, 13.0%), was obtained by preparative g.l.c. (column H, 100°, N_2 70ml min^{-1}). N.m.r. ($CDCl_3$) δ 1.05 (12H, s, CH_3), 2.4 (2H, t, *J*=2Hz, CH_2), 4.8 (2H, m, CH_2).

1-*Hydroxymethyl*-2,2,3,3-*tetramethylcyclobutane* (154)

The procedure used to prepare 1-hydroxymethyl-2,2-dimethylcyclobutane (21) was employed to convert 2,2,3,3-tetramethyl-1-methylenecyclobutane (1.4g; containing *ca.* 30% benzene) into *the required alcohol* (1.0g, 89%), b.p. 95-100° (block)/20mm, n_D^{15} 1.4541 (Found: C, 75.7; H, 12.9. $C_9H_{18}O$ requires C, 76.0; H, 12.8%); n.m.r. ($CDCl_3$) δ 0.9 (3H, s, CH_3), 1.0 (6H, s, CH_3), 1.05 (3H, s, CH_3), 1.2 - 1.7 (2H, m, CH_2), 1.8 - 2.6 (1H, m, CH), 3.3 - 3.9 (2H, m, CH_2O); ν_{max} 3380 cm^{-1}.

1-*Chloromethyl*-2,2,3,3-*tetramethylcyclobutane* (155)

The foregoing alcohol (1.0g) was converted into its toluene-*p*-sulphonate and treated with lithium chloride in hexamethylphosphoric-triamide in the usual way to afford a colourless liquid (1.1g, 97%). The crude chloride was purified by preparative g.l.c. (column B, 120°, N_2 70ml min^{-1}) to afford pure 1-*chloromethyl*-2,2,3,3-*tetramethylcyclo butane* n_D^{22} 1.4351 (Found: C, 67.3; H, 10.6. $C_9H_{17}Cl$ requires C, 67.3; H, 10.7%);

n.m.r. ($CDCl_3$) δ 0.9 (3H, s, CH_3), 1.0 (6H, s, CH_3), 1.05 (3H, s, CH_3), 1.3 - 1.9 (2H, m, ring CH_2), 2.0 - 2.7 (1H, m, CH), 3.3 - 3.6 (2H, m, CH_2Cl).

2,2-Dimethylcyclobutanecarboxylic acid (156)

A solution of 1-hydroxymethyl-2,2-dimethylcyclobutane (3.2g) and tri-*n*-caprylmethylammonium chloride (0.3g) in benzene (35ml) was added to a vigorously stirred solution of potassium permanganate (8.9g) in water (100ml). After the addition the mixture was stirred at room temperature until g.l.c. analysis (column A, 100°) showed no unchanged alcohol to remain. Sodium sulphite was then added and the mixture acidified with 10% aqueous hydrochloric acid and extracted with ether. The ether solution was washed with 10% aqueous hydrochloric acid, dried, and evaporated. Distillation of the residual oil under reduced pressure afforded 2,2-*dimethylcyclobutanecarboxylic acid* (12.9g, 81%) b.p. 85-86°/1.5mm (Found: C, 66.0; H, 9.4. $C_7H_{12}O_2$ requires C, 65.6; H, 9.4%); n.m.r. ($CDCl_3$) δ 1.4 - 2.9 (4H, complex, CH_2), 2.9 (1H, t, J=4Hz, CH), 10.0 (1H, br s, COOH). G.l.c. analysis (column A, 150°) of the ethyl ester obtained by treatment of the acid with diazoethane showed the product to be pure.

1,2,2-*Trimethylcyclobutanecarboxylic acid* (157)

Using the procedure described for the preparation of 1-methylcyclobutanecarboxylic acid (118), 2,2-dimethylcyclobutanecarboxylic acid was alkylated to afford the required compound as a semi-crystaline oil (2.7g, 88%). A sample of the acid was treated with an ethereal solution of diazoethane to afford a mixture comprising 91% of ethyl 1,2,2-trimethylcyclobutanecarboxylate (160) and 9% of ethyl 2,2-dimethylcyclobutanecarboxylate. A pure sample of *the ester* (160) obtained by preparative g.l.c. (column C, 125°, N_2 60ml min^{-1}) had n_D^{18} 1.4331 (Found: C, 70.9, H, 10.7. $C_{10}H_{18}O_2$ requires C, 70.6; H, 10.7), n.m.r. ($CDCl_3$) δ 1.0 - 2.7 (4H, complex), 1.05 (6H, s, CH_3), 1.25 (3H, t, *J*=7Hz, OCH_2CH_3), 1.3 (3H, s, CH_3), 4.15 (2H, q, *J*=7Hz, OCH_2CH_3); ν_{max} 1740 cm^{-1}.

1-*Hydroxymethyl*-1,2,2-*trimethylcyclobutane* (158)

The foregoing acid mixture (2.4g) was reduced with lithium aluminium hydride in ether in the usual manner to afford a colourless oil (1.9g, 88%) a sample of which was purified by preparative g.l.c. (column C, 100°, N_2 60ml min^{-1}) to give a white waxy solid, m.p. 113-114° (Found: C, 75.7; H, 12.6. $C_8H_{16}O$ requires C, 74.9; H, 13.0%) n.m.r. δ 1.05 (9H, 3 partially resolved singlets, CH_3), 1.6 (4H, complex CH_2), 3.55 (2H, m, appears as the AB portion of an ABX pattern with $J_{AB} \sim$ 6Hz, CH_2O).

1-Chloromethyl-1,2,2-trimethylcyclobutane (159)

The foregoing alcohol (2.9g) was converted into its toluene-*p*-sulphonate, subsequent treatment of which with lithium chloride in hexamethylphosphorictriamide afforded a mixture (2.9g, 87%) of the required chloride (90%) and 1-chloromethyl-2,2-dimethylcyclobutane (151) (10%). The contaminant was removed by preparative g.l.c. (column B, 120°, N_2 70ml min^{-1} to afford *1-chloromethyl-1,2,2-trimethylcyclobutane* as a white waxy solid m.p. ∿ 40° (Found: C, 65.9; H, 10.1. $C_8H_{18}Cl$ requires C, 65.5, H, 10.3), n.m.r. (CCl_4) 1.4 (3H, s, CH_3), 1.5 (3H, s, CH_3), 2.0 (4H, m, CH_2CH_2), 3.85 (2H, m, appears as the AB portion of an ABX pattern with J_{AB} ∿ 5Hz, CH_2Cl).

3,3-Dimethylcyclobutanecarboxylic acid (161) *and t-butyl 3,3-dimethyl-cyclobut-1-enecarboxylate* (162)

A mixture of *t*-butyl 2-(dimethylamino)-3,3-dimethylcyclobutane-carboxylate (146)[163] (34g) and methyl iodide (27g) were heated at 80° for 4h. The excess of methyl iodide was then evaporated *in vacuo* and a solution of potassium hydroxide (22g) in water (60ml) was added. The mixture was maintained at 80° for 16h, then cooled and extracted with ether. The organic layer was washed with water, dried, and evaporated to afford the *t*-butyl ester (162) as a yellow oil (8.3g, 30%) which was used without purification.

The aqueous layer was acidified with 10% aqueous hydrochloric acid and extracted with ether. Removal of the solvent *in vacuo* left a semi-crystaline oil which was recrystalised twice from *n*-hexane to afford 3,3-dimethylcyclobut-1-enecarboxylic acid (161) (5g, 27%) as a crystaline solid m.p. 70-72° (lit.[261] m.p. 70-71°).

3,3-*Dimethylcyclobutanecarboxylic acid* (163)

3,3-Dimethylcyclobut-1-enecarboxylic acid (4.8g) in ether (50ml) was hydrogenated under 4 atm in the presence of Adams catalyst (PtO_2) to afford the saturated acid (4.3g, 88%), b.p. 103-106°/15mm (lit.[261] 98-99/9.5 - 10mm).

t-*Butyl* 3,3-*dimethylcyclobutanecarboxylate* (164)

The crude *t*-butyl ester (162) (8.3g) in ether (20ml) was hydrogenated under 3 atm in the presence of Adams catalyst (PtO_2) to afford *t*-butyl 3,3-dimethylcyclobutanecarboxylate (7.8g, 93%), of >98% purity. A sample of the ester purified by preparative g.l.c. (column K, 100° N_2 70ml min^{-1}) had n_D^{20} 1.562 (Found: C, 71.5; H, 11.0. $C_9H_{20}O_2$ requires C, 71.7; H, 10.9%); n.m.r. ($CDCl_3$) δ 0.95 (3H, s, CH_3), 1.0 (3H, s, CH_3), 1.3 (9H, s, CH_3), 1.7 - 2.1 (5H, complex, ring H).

1-Hydroxymethyl-3,3-dimethylcyclobutane (165)

3,3-Dimethylcyclobutanecarboxylic acid (4.2g) was reduced with lithium aluminium hydride in ether in the usual way to afford the required alcohol (3.6g, 76%), b.p. 67-70°/18mm (lit.[155] 71°/14mm).

1-Chloromethyl-3,3-dimethylcyclobutane (166)

Using the procedure described for the preparation of chloromethylcyclobutane the foregoing alcohol (1.75g) was converted into the required chloride (1.9g, 93%), b.p. 60° (block)/100mm, n_D^{21} 1.438 (Found: C, 63.8; H, 9.8. $C_7H_{13}Cl$ requires C, 63.4; H, 9.8%), n.m.r. ($CDCl_3$) δ 1.05 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.3 - 3.2 (5H, complex, ring H), 3.5 (2H, d, CH_2Cl).

exo-*Bicyclo*[3.2.0]*hept-3-en-2-ol* (167)

syn-Bicyclo-[2.2.1]-hept-2-en-7-ol, prepared according to Baird[262] was converted into its toluene-*p*-sulphonate in the usual manner. The ester was solvolysed[167] in 0.2N aqueous sodium bicarbonate at 100° for 72h to afford *exo*-bicyclo[3.2.0]hept-2-en-2-ol, b.p. 100-104/200mm, n.m.r. ($CDCl_3$) δ 0.9 - 3.0 (complex, 7H), 3.2 - 3.4 (m, 1H, CH), 4.5 (m, 1H, CHOH), 5.9 - 6.3 (m, 2H, CH=CH); ν_{max} 3300, 1600 cm^{-1}; mass spectrum m/e 110 (M^+).

exo-*Bicyclo*[3.2.0]*heptan*-2-*ol* (168)

The foregoing alcohol (5g) in ether (20ml) was hydrogenated in the presence of Adams catalyst (PtO_2) under 3 atm for 72h to afford the saturated alcohol (4.6g, 90%), b.p. 96-98°/20mm. G.l.c. (column F, 120°) showed the alcohol to be of >95% purity. The spectral properties of the alcohol were identical to those previously reported[168,169].

endo-2-*Chlorobicyclo*[3.2.0]*heptane* (169)

(a) The alcohol (2.0g) was converted into its toluene-*p*-sulphonate in the usual manner. Treatment of the ester with lithium chloride (8.8g) in hexamethylphosphorictriamide (20ml) according to the procedure described for the preparation of chloromethylcyclobutane (109) afforded a mixture of the required chloride (60%) and the elimination product, bicyclo[3.2.0]hept-2-ene (35%) together with some unchanged toluene-*p*-sulphonate. The chloride, b.p. 49-50° (block)/20mm, isolated by preparative g.l.c. (column B, 120°, N_2 70ml min^{-1}) had spectral properties consistent with those reported[147,168]. The olefin had b.p. 105° (block), n_D^{19} 1.4652 (lit.[263] b.p. 102.5 - 103°, n_D^{20} 1.4646) mass spectrum m/e 94 (M^+).

5-Chloro-3-methylpent-1-ene (171)

Using the procedure described for the preparation of 1-chlorohex-5-ene (65), 3-methylpent-4-en-1-ol (1.8g) was converted into the required chloride (2.0g, 94%), b.p. 124-126° (Found: C, 61.1; H, 9.4. Calc for $C_6H_{11}Cl$ C, 60.8; 9.4%). The spectral properties of the chloride were consistent with those reported[264].

(2'-Hydroxyethyl)cyclopent-2-ene (172)

A sample of the alcohol was kindly provided by Dr. I. Buczynski.

(2'-Chloroethyl)cyclopent-2-ene (173)

The foregoing alcohol (0.5g) was converted into its toluene-*p*-sulphonate in the usual way and treated with lithium chloride in *N*,*N*-dimethylformamide using the procedure described for the preparation of 1-chlorohex-5-ene (65) to afford a liquid (0.3g, 51%). G.l.c. (column A, 80°) indicated the crude chloride to be contaminated with *ca.* 10% of an unidentified impurity which was removed by preparative g.l.c. (column B, 120°, N_2 70ml min^{-1}). Pure *(2'-chloroethyl)cyclopent-2-ene* had b.p. 40° (block)/50mm (Found: C, 64.6; H, 8.5. $C_7H_{11}Cl$ requires C, 64.4; H, 8.5%); n.m.r. (CCl_4) δ 1.4 -3.1 (7H, complex), 3.6 (2H, t, *J*=7Hz, CH_2Cl), 5.7 (2H, m, CH=CH).

CHAPTER 9

The Reduction of Chloromethylcyclopropanes with Triphenylstannane.

Kinetic methods.

(i) *Reduction of chloromethylcyclopropanes with triphenylstannane*

Triphenylstannane, the chloride (in excess; the concentration of halide employed is given as a footnote to the tables), and an internal standard were each accurately weighed into a volumetric flask which was then filled with solvent (decalin unless otherwise stated) to give the required concentration. This solution was then pipetted into ampoules (1ml, each containing a trace of azobisisobutyronitrile as radical initiator) which were cooled to -78^{o}, deoxygenated with a stream of nitrogen and sealed. The ampoules were then immersed in constant temperature baths at the required temperature ($\pm 0.2^{o}$) for 24h, at which time they were cooled, opened and the contents analysed by g.l.c. The results obtained have been compiled in tables 14-16. Each item of data is the result of two or more duplicate determinations.

(ii) *Product analysis* (for general details see chapter 12)

The vinylcyclohexanes were determined with column F, N or P. Analysis of the reduction products of 1-chloroethylcyclopropane necessitated the use of two columns: column O to separate *cis*-pent-1-ene and ethylcyclopropane from *trans*-pent-2-ene, and column L to determine the *cis*:*trans* isomer ratio.

(iii) *Control experiments*

Samples of the reaction mixtures to which no radical initiator had been added were wrapped in foil and immersed in the appropriate constant temperature bath for 48h. Analysis by g.l.c. indicated that no hydrocarbon products were formed.

2-Chlorobutane was reduced with triphenylstannane in the presence of samples of representative olefins (hex-1-ene, pent-2-ene, vinylcyclohexane, and *trans*-1-methyl-2-vinylcyclohexane), the conditions approximating those used for the kinetic runs. Hex-1-ene was quantitatively consumed under the reaction conditions. Pent-2-ene, vinylcyclohexane and *trans*-1-methyl-2-vinylcyclohexane were stable to reaction conditions. However, the disubstituted olefin was configurationally labile and was isomerised to afford an equilibrium mixture of isomers (see chapter 5).

(iv) For details of the calculation of rate data see chapter 12.

(v) *The synthesis of reference compounds*

exo-7-*Methylbicyclo*[4.1.0]*heptane* (176)

A solution of *exo*-7-chloromethylbicyclo[4.1.0]heptane (76) (0.5g) was added to a stirred suspension of lithium aluminium hydride (0.3g) in ether (30ml) and the mixture was heated under reflux for 24h. Work up in the usual way afforded a colourless liquid (0.4g) which was subjected to preparative g.l.c. (column B, 80°, N_2 40ml min^{-1}) to afford a sample of *exo*-7-methylbicyclo[4.1.0]heptane n_D^{25} 1.4504 (lit.[265,266] 1.4528, 1.4493), mass spectrum m/e 110 (M^+).

Vinylcyclohexane (178)

A suspension of methyltriphenylphosphonium iodide (2g) in ether (20ml) was cooled to 0° and treated with a hexane solution of *n*-butyllithium (3.2ml; 1.48M) and the resultant mixture stirred at room temperature for 2h. A solution of cyclohexanecarboxaldehyde[267] (0.5g) in ether (2ml) was then added. After being stirred at room temperature for 18h the mixture was diluted with water, and the ether layer washed with water, dried and evaporated. The residue was dissolved in light petroleum and chromotographed on silica gel. Distillation of the non-polar fraction afforded a liquid (0.45g), b.p. 133° (block) (lit.[268] 127°) which was >90% vinylcyclohexane. A sample of the olefin purified by preparative g.l.c. (column B, 80°, N_2 40ml min^{-1}) had n_D^{22} 1.4470 (lit.[268] n_D^{20} 1.4462).

6,7-*Dimethylbicyclo*[4.1.0]*heptane* (180)

Using the general procedure described by Ratcliffe and Rodehorst[269] a sample of 7-hydroxymethyl-6-methylbicyclo[4.1.0]heptane (87) (1.0g; a mixture of *exo*- and *endo*-isomers in the ratio 3:1) was oxidised with chromium trioxide and pyridine in methylene chloride to afford 6-methylbicyclo[4.1.0]heptane-7-carboxaldehyde (0.53g, 54%), b.p. 70° (block)/15mm (Found: C, 78.2; H, 10.7. Calc for $C_9H_{14}O$ C, 78.2; H, 10.2%).

A mixture of the aldehyde (0.4g), potassium hydroxide (0.32g), hydrazine hydrate (0.3ml) and ethylene glycol (3ml) was heated at 110° for 3h and the temperature was then raised to 190° and the excess of hydrazine hydrate, water, and the product were distilled from the reaction mixture. The distillate was extracted with pentane and the extract washed with water and dried. 6,7-Dimethylbicyclo[4.1.0]heptane, n_D^{20} 1.4520 (Found: C, 87.4; H, 13.0. Calc for C_9H_{16} C, 87.0; H, 13.0), a mixture of the *exo*- and *endo*-isomers in the ratio 4:1, was isolated by preparative g.l.c. (column B, 80°, N_2 50ml min^{-1}).

trans-1-*Methyl*-2-*vinylcyclohexane* (183)

Using the procedure described for the preparation of vinylcyclobutane (176), *trans*-2-methylcyclohexanecarboxaldehyde[270] was converted into the required olefin. G.l.c. (column D, 180°) showed the product to be a mixture of *cis*- and *trans*-isomers in the ratio 1:15. Pure

trans-1-*methyl*-2-*vinylcyclohexane*, n_D^{23} 1.4438 [lit.[271] (for *cis*- or *trans*-isomer) n_D^{20} 1.4510] (Found: C, 87.3; H, 12.9. C_9H_{16} requires C, 87.0; H, 13.0%); n.m.r. ($CDCl_3$) δ 0.8 - 2.0 (7H, complex), 4.8 - 5.2 (2H, m, $=CH_2$), 5.3 - 6.0 (1H, m, =CH); was isolated by preparative g.l.c. (column K, 80°, N_2 40ml min^{-1}).

cis-1-*Methyl*-2-*vinylcyclohexane* (184)

cis-2-Methylcyclohexylmethanol[272] was oxidised[269] with chromium trioxide and pyridine in methylene chloride to afford a sample of 2-methylcyclohexanecarboxaldehyde which was shown by g.l.c. (column A, 110°) to be a mixture of *cis*- and *trans*-isomers in the ratio 5:1.

A Wittig reaction of the crude aldehyde (0.8g) and methyltriphenylphosphorane (prepared by the addition of an ethereal solution of methyllithium (6.2ml; 1.3M) to methyltriphenylphosphonium iodide (3.2g) in ether (30ml)) afforded the olefin as a mixture of *cis*- and *trans*-isomers in the ratio 20:1. Preparative g.l.c. afforded a pure sample of cis-1-*methyl*-2-*vinylcyclohexane*, n_D^{22} 1.4519 [lit.[271] (for *cis*- or *trans*-isomer) n_D^{20} 1.4510] (Found: C, 87.2; H, 12.7. C_9H_{16} requires C, 87.0; H, 13.0%), n.m.r. ($CDCl_3$) δ 0.85 (3H, d, J=7Hz, CH_3), 1.5 (10H, br s, ring H), 4.8 - 5.2 (2H, m, $=CH_2$), 5.6 - 6.3 (1H, m, =CH).

1-Methyl-1-vinylcyclohexane (185)

Methyl 1-methylcyclohex-3-enecarboxylate[274] was quantitatively hydrogenated and the product reduced with lithium aluminium hydride in the usual way to afford 1-methylcyclohexylmethanol, b.p. 90-93°/20mm (lit.[274] b.p. 85°/14mm). The alcohol was oxidised[269] with chromium trioxide and pyridine in methylene chloride in the usual way to afford 1-methylcyclohexanecarboxaldehyde, b.p. 70-74°/25mm (lit.[275] 120°/546mm).

Using the procedure described for the preparation of *cis*-1-methyl-2-vinylcyclohexane the foregoing aldehyde (2.0g) was converted into the required olefin (0.4g, 20%), b.p. 136° (block). A sample purified by preparative g.l.c. (column K, 80°, N_2 40ml min^{-1}) had n_D^{20} 1.4565 (lit.[275] n_D^{21} 1.4570), n.m.r. ($CDCl_3$) δ 0.95 (3H, s, CH_3), 1.4 (10H, br s, ring H), 4.7 - 5.2 (2H, m, $=CH_2$), 5.7 - 6.0 (1H, m, appears as a doublet ($J \sim 17$Hz) of doublets ($J \sim 9$Hz), =CH).

Ethylcyclopropane (195)

The Wolff-Kischner reduction[276] of acetylcyclopropane afforded the required compound, n_D^{20} 1.3786 (lit.[276] n_D^{20} 1.3788).

CHAPTER 10

The Reduction of Chloromethylcyclobutanes with Tri-*n*-butylstannane.

Kinetic methods

(i) *The reduction of chlorides with tri-*n*-butylstannane*

Tri-*n*-butylstannane, the chloride (1.2-1.5 equivalents unless otherwise stated), and an internal standard were each accurately weighed into a volumetric flask which was then filled with solvent (decalin unless otherwise stated) to give the required concentration. This solution was then pipetted into ampoules (1ml, each containing a trace of azobisisobutyronitrile as radical initiator) which were cooled at -78°, deoxygenated with a stream of nitrogen and sealed. The ampoules were then immersed in constant temperature baths at the required temperature (± 0.2°) for 24h, at which time they were cooled, opened and the contents analysed by g.l.c. The results obtained have been compiled in tables 21-34. Each item of data is the result of two or more duplicate determinations.

(ii) *Identification of products*

Products of the free radical reaction were in each case identified by comparison of their g.l.c. retention times with those of authentic samples on at least two columns of widely different separation characteristics. In general, columns O and P were used for this purpose, though in specific cases, where the desired separation was not obtained, columns F, L and N were also used.

With one exception, the reference compounds required for product identification were either commercially available or were synthesised by unambiguous routes (see parts viii and ix). 3,3,4,4-Tetramethylpent-1-ene (255) was not available. However, there is evidence to show that it is not a product of reduction of 1-chloromethyl-2,2,3,3-tetramethylcyclobutane (155):

(a) Analysis of the product mixture using columns I, O, or P indicated the presence of 1,1,2,2,3-pentamethylcyclobutane (251), 4,4,5-trimethylhex-1-ene (253), and *n*-heptane (internal standard), and a small amount of the unchanged chloride. No other compounds were detected in the reaction mixtures.

(b) The ^{1}H n.m.r. spectrum of a mixture of the compounds (251) and (253), isolated from the reaction mixtures by preparative g.l.c. (column B, 60°, N_2 50ml min^{-1}), exhibited no resonances which could not be assigned to these compounds.

(iii) *Quantitative determination of the reaction products*

The product mixtures were analysed using that column (of O or P) which afforded the best separation of the reaction products. Mixtures containing accurately known amounts of each of the reaction products in decalin were also analysed to determine the molar response ratios. In no case was this ratio found to deviate more than ± 2% from unity.

The product ratios could, in general, be determined to be better than ± 1%. The errors were magnified in cases where a compound constituted <5% of the total hydrocarbon product. However, the total yield of products could not be determined to be better than ± 3%.

(iv) *Control experiments*

(a) Samples of the chlorides in decalin, containing tri-*n*-butyltin chloride, were heated at 60° or at 100° for 48h. G.l.c. analysis indicated a quantitative recovery of the chloride. No hydrocarbon products were formed from these reactions.

(b) A halide (either bromocyclohexane or 2-chlorobutane) was reduced with tri-*n*-butylstannane in the presence of samples of representative olefins (hex-1-ene, *cis*-hex-2-ene, *trans*-hept-2-ene, pent-2-ene, 2-methylhex-2-ene, 2-ethylcyclopentene and 4- and 5-methylnorbornene), the reaction conditions approximating those used for the kinetic runs.

A proportion of the terminal and cyclic olefins was consumed under conditions where a large excess of tri-*n*-butylstannane was used. The recovery of olefin depended on the relative and absolute concentration of tri-*n*-butylstannane and the conditions of analysis. This latter factor meant that no precise estimate of the amount of olefin consumed could be made. The olefins were stable in the presence of an excess of the halide.

Acyclic disubstituted and trisubstituted olefins were stable under all conditions used. However, they were found to undergo *cis-trans* isomerisation, tc form an equilibrium mixture of isomers, both when an excess of stannane was used. The olefins were configurationally stable in the presence of excess chloride at stannane concentrations below 0.1 mol l^{-1}.

(v) *Evaluation of rate constants*

Values of the rate constant ratio k/k_H were determined by solving equation (1) (see chapter 2) by a computer based iterative procedure.

For the reactions conducted under "normal" reduction conditions (i.e. in the presence of excess chloride) the total yield of hydrocarbon products was normalised to 100% for computational purposes; the final stannane concentration being assumed to be zero (residual halide was detected in the reaction mixtures; however, a precise determination could not be made). In an attempt to overcome any errors which might be introduced through this assumption the reduction of one chloride was conducted in the presence of a large excess (15 fold) of stannane. Under these circumstances the integrated rate expression (equation 1) reduces to the form:

$$k_f/k_H = [S]_{AV}[R'H] / [RH] \qquad (2)$$

the stannane concentration remaining essentially the same throughout the reaction. It was found, however, that in the presence of a large excess of stannane the olefinic product was consumed, the procedure was therefore unsatisfactory. Values of k/k_H calculated by making the assumption that the reduction proceeded in 100% yield, based on the initial chloride concentration (no residual chloride was detected in the reaction mixtures by gas chromatography), show close agreement with the data obtained under "normal" reduction conditions (compare tables 30 and 31).

(vi) *Calculation of activation parameters*

Values of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ were determined by a least squares treatment of the rate constants data using the ACTENG program[303]. The program was modified to permit the use of a ratio of rate constants. The values of the parameters and the associated standard deviations are given in table 17.

(vii) *Results*

Table 21

Reduction of 1-chlorohex-5-ene.

Temperature	$[Bu_3SnH]_o$	Relative yield			Total yield	$\Sigma k_f/k_H$
^oC	mol l^{-1}	%(68)	%(67)	%(69)	%	mol l^{-1}
60.2	0.028	8.6	90.6	0.8	89	0.15
60.2	0.067	17.0	81.7	1.3	97	0.15
60.2	0.087	22.9	75.7	1.3	95	0.15
60.2	0.141	29.4	69.4	1.2	93	0.15
60.2	0.262	43.0	55.9	1.1	93	0.14
80.1	0.262	38.2	60.8	1.0	94	0.19
97.5	0.141	21.0	77.8	1.2	90	0.25

Table 22

Reduction of 1-bromohex-5-ene

with tri-*n*-butylstannane in benzene.

Temperature	$[Bu_3SnH]_o$	Relative yield			Total yield	$\Sigma k_f/k_H$
°C	mol l^{-1}	%(68)	%(67)	%(69)	%	~~mol l^{-1}~~ l mol^{-1}
40.2	0.077	22.1	76.7	1.3	87	0.13
40.2	0.260	44.9	54.3	0.8	92	0.13
60.2	0.077	17.0	80.8	2.0	84	0.18
60.2	0.260	38.6	60.0	1.4	97	0.18
60.2[a]	0.286	40.6	58.2	1.3	91	0.18
80.1	0.077	13.5	84.6	1.9	86	0.24
80.1	0.260	33.0	65.4	1.6	96	0.23

[a] Reduction of 1-chlorohex-5-ene.

Table 23

Reduction of chloromethylcyclobutane (109).

Temperature	$[Bu_3SnH]_o$	Relative yield		Total yield	k_f/k_H
°C	mol l^{-1}	%(208)	%(210)	%	mol l^{-1} x 10^2
59.9	0.011	49.4	50.6	-	0.42
59.9	0.054	78.3	21.7	75.5	0.46
59.9	0.073	81.8	18.2	76.2	0.47
60.1	0.010	49.4	50.6	55.4	0.42
60.1	0.012	51.9	48.1	67.7	0.45
60.1	0.052	77.7	22.3	84.3	0.46
60.1	0.062	80.0	20.0	81.1	0.46
70.1	0.054	71.6	28.4	79.7	0.71
70.1	0.073	74.9	25.1	78.1	0.75
90.3	0.054	58.5	41.5	85.3	1.44
90.3	0.073	63.9	36.1	80.3	1.43

Table 24

Reduction of (1-chloroethyl)cyclobutane (113).

Temperature	$[Bu_3SnH]_o$	Relative yield		(214)/(216)	Total yield	$\Sigma k_f/k_H$
°C	mol l^{-1}	%(212)	%(214)+(216)		%	mol l^{-1} x 10
59.9	0.010	49.4	50.6	3.2	67.9	0.41
59.9	0.050	77.4	22.6	3.1	94.2	0.45
59.9	0.068	82.7	17.3	3.1	93.1	0.41
60.2	0.024	65.3	34.7	3.1	92.0	0.45
60.2	0.075	83.3	16.7	3.1	91.6	0.43
70.1	0.024	56.6	43.4	2.9	82.6	0.70
70.1	0.075	78.2	21.8	3.0	93.9	0.64
79.3	0.050	65.6	34.4	2.9	90.3	0.93
79.3	0.068	70.9	29.1	2.9	92.0	0.93
90.8	0.024	39.6	60.4	2.8	83.9	1.55
90.8	0.075	64.6	35.4	2.8	88.8	1.48
100.3	0.050	50.3	49.7	2.8	92.0	1.97
100.3	0.068	55.2	44.8	2.8	89.3	2.11

Table 25

Reduction of (2-chloroprop-2-yl)cyclobutane (116)[a,b].

Temperature	$[Bu_3SnH]_o$	Relative yield		Total yield	k_f/k_H
°C	mol l^{-1}	%(218)	%(220)	%	mol l^{-1} x 10^2
60.2	0.019	87.6	12.4	100	0.26
60.2	0.038	93.5	6.5	100	0.25
60.2	0.192	98.6	1.4	100	0.26
89.8	0.038	80.1	19.9	100	0.90
89.8	0.192	96.3	4.7	100	0.90

a Excess stannane - chloride concentration 0.0022, 0.0044 and 0.0218 mol l^{-1} respectively.

b The chloride was contaminated with 8% 1-chloro-2,2-dimethylcyclopentane (117), the same amount of 1,1-dimethylcyclopentane was observed in the reduction product.

Table 26

Reduction of 1-chloromethyl-1-methylcyclobutane (120).

Temperature	$[Bu_3SnH]_o$	Relative yield		Total yield	k_f/k_H
^oC	mol l^{-1}	%(222)	%(224)	%	mol l^{-1} x 10^2
59.9	0.011	61.6	38.4	68.5	0.24
59.9	0.014	65.4	34.6	72.4	0.26
59.9	0.027	77.7	22.3	83.3	0.24
59.9	0.055	85.8	14.2	83.8	0.25
80.7	0.027	63.1	36.9	84.5	0.58
80.7	0.055	74.8	25.2	83.7	0.59
104.9	0.027	44.1	55.9	82.2	1.44
104.9	0.055	57.7	42.3	87.4	1.51

Table 27

Reduction of 1-chloromethyl-3,3-dimethylcyclobutane (166).

Temperature	$[Bu_3SnH]_o$	Relative yield		Total yield	k_f/k_H
^oC	mol l^{-1}	%(226)	%(228)	%	mol l^{-1} x 10^2
60.2	0.012	60.2	31.8	62.4	0.29
60.2	0.016	68.3	31.7	76.1	0.26
60.2	0.031	77.0	23.0	75.1	0.29
60.2	0.046	83.2	16.8	90.3	0.27
60.2	0.060	85.3	14.7	88.1	0.28
60.2	0.062	86.2	13.8	73.8	0.27
69.9	0.016	57.1	42.9	66.0	0.46
69.9	0.046	77.3	22.7	87.9	0.42
69.9	0.060	80.0	20.0	86.9	0.45
79.6	0.031	61.8	31.2	68.4	0.70
79.6	0.062	75.6	24.4	71.6	0.64
90.7	0.046	63.7	36.3	88.0	0.95
92.0	0.016	42.3	57.7	75.8	0.96
92.0	0.060	66.0	34.0	88.3	1.08
100.3	0.031	45.9	64.1	64.1	1.50
100.3	0.062	60.1	39.9	74.4	1.53

Table 28

Reduction of *trans*-1-chloromethyl-2-methylcyclobutane (129).

Temperature	$[Bu_3SnH]_o$	Relative yield			Total yield	$\Sigma k_f/k_H$
^oC	mol l^{-1}	%(230)	%(232)	%(234)	%	mol l^{-1} x 10^2
60.2	0.024	37.2	35.9	6.9	76.4	1.8
60.2	0.048	51.8	42.9	5.3	74.1	1.8
60.2	0.121	69.9	26.8	3.3	81.9	1.8
79.3	0.048	36.6	55.7	7.7	74.0	3.6
79.3	0.121	55.8	38.8	5.4	79.5	3.7
100.3	0.048	24.0	66.2	9.8	75.2	7.0
100.3	0.121	41.5	51.0	7.5	86.5	7.2

Table 29

Reduction of *cis*-1-chloromethyl-2-methylcyclobtuane (124).

Temperature	$[Bu_3SnH]_o$	Relative yield			Total yield	$\Sigma k_f/k_H$
°C	mol l^{-1}	%(236)	%(232)	%(234)	%	mol l^{-1} x 10^1
60.6	0.020	8.7	89.8	1.5	74.9	0.96
60.6	0.098	31.2	67.9	0.9	81.2	0.95
60.6	0.196	45.3	53.6	1.1	80.1	0.97
79.6	0.098	20.2	78.4	1.4	78.2	1.79
79.6	0.196	32.3	66.6	1.1	82.5	1.80
101.4	0.098	12.2	85.6	2.2	81.2	3.38
101.4	0.098	21.4	76.3	1.8	82.4	3.34

Table 30

Reduction of 1-chloromethyl-2,2-dimethylcyclobutane (151)[a].

Temperature	$[Bu_3SnH]_o$	Relative yield		Total yield	k_f/k_H
°C	mol l^{-1}	%(238)	%(240)	%	mol l^{-1}
60.3	0.102	6.6	93.4	89.3	0.70
60.3	0.256	13.9	86.1	92.8	0.75
60.3	0.352	19.5	80.5	80.1	0.68
60.3	0.880	35.0	65.0	85.5	0.71
79.8	0.102	4.1	95.9	90.0	1.20
79.8	0.256	9.4	90.6	86.9	1.19
79.8	0.352	12.4	87.6	85.9	1.18
79.8	0.880	25.0	75.0	82.8	1.20
99.8	0.256	6.1	93.9	90.1	1.92
101.3	0.352	8.0	92.0	93.6	2.01
101.3	0.880	16.8	83.2	81.6	2.05

[a] 3,3-Dimethylpent-1-ene (242) was detected in the reaction mixtures but amounted to less than 0.5% of the total hydrocarbon product in each case.

Table 31

Reduction of 1-chloromethyl-2,2-dimethylcyclobutane (151)[a].

Temperature	$[Bu_3SnH]_o$[c]	Relative yield		Total yield	k_f/k_H
°C	mol l^{-1}	%(238)	%(240)	%	mol l^{-1}
60.2	0.108	13.2	86.8 (6.0)[b]	(100)	0.68
60.2	0.217	22.3	77.7 (8.9)	(100)	0.73
60.2	0.539	43.6	56.4(15.8)	(100)	0.67
60.2	1.078	57.4	42.6(26.6)	(100)	0.77
79.8	0.539	29.7	70.3(13.1)	(100)	1.23
79.8	1.078	45.2	54.8(23.7)	(100)	1.26
99.5	0.539	21.3	78.7(14.7)	(100)	1.92
99.5	1.078	32.8	67.2(19.4)	(100)	2.13

[a] No 3,3-dimethylpent-1-ene (242) was detected in the reaction mixtures.

[b] Amount of 5-methylhex-1-ene (240) consumed during the reaction assuming 100% reduction.

[c] Excess stannane - halide concentration 0.0073, 0.0146, 0.0367 and 0.0733 mol l^{-1} respectively.

Table 32

Reduction of 1-chloromethyl-1,2,2-trimethylcyclobutane (159)[a].

Temperature	$[Bu_3SnH]_o$	Relative yield		Total yield	k_f/k_H
°C	mol l^{-1}	%(244)	%(246)	%	mol l^{-1}
60.2	0.137	6.8	93.2	87.4	0.91
60.2	0.274	12.7	87.3	84.9	0.90
60.2	0.685	25.7	74.3	86.9	0.90
80.1	0.137	4.4	95.6	85.9	1.47
80.1	0.274	7.8	92.2	86.3	1.57
80.1	0.685	17.7	82.3	88.5	1.49
91.0	0.274	5.4	94.6	83.5	2.08
91.0	0.685	14.1	85.9	88.6	1.99

[a] 2,3,3-Trimethylpent-1-ene (248) was detected in the reaction mixtures but amounted to less than 0.1% of the total hydrocarbon product.

Table 33

Reduction of 1-chloromethyl-2,2,3,3-tetramethylcyclobutane (155)[a].

Temperature	$[Bu_3SnH]_o$	Relative yield		Total yield	k_f/k_H
°C	mol l^{-1}	%(250)	%(252)	%	mol l^{-1}
60.2	0.306	30.1	69.9	91.7	0.32
60.2	0.612	44.8	55.2	91.7	0.31
80.1	0.306	20.2	79.8	88.7	0.56
90.6	0.306	15.8	84.2	90.7	0.77

[a] 3,3,4,4-Tetramethylpent-1-ene (254) was not detected in the reaction mixtures (less than 0.1%).

Table 34

Reduction of 2-chlorobicyclo[3.2.0]heptane (169)[a,b].

Temperature	$[Bu_3SnH]_o$	Relative yield		Total yield	k_f/k_H
^oC	mol l^{-1}	%(257)	%(259)	%	mol l^{-1}
80.1	0.021	73.4	26.6	67.9	0.25
80.1	0.053	85.6	14.4	76.9	0.24
91.0	0.021	64.4	35.6	70.1	0.42
91.0	0.053	78.4	21.6	77.0	0.44

[a] Cycloheptene (261) was not detected amongst the reaction products.

[b] The reduction of (2'-chloroethyl)cyclopent-2-ene (173) with tri-*n*-butylstannane afforded 2-ethylcyclopentene (259) as the sole product.

(viii) *The synthesis of reference compounds - cyclobutanes*

Ethylcyclobutane (213)

The Wolff-Kishner reduction of acetylcyclobutane (111) was conducted as previously described to afford the required hydrocarbon, n_D^{20} 1.402 (lit.[278] n_D^{20} 1.4020); n.m.r. ($CDCl_3$) δ 0.75 (3H, t, *J*=7Hz, CH_3), 1.0 - 2.2 (9H, complex).

Isopropylcyclobutane (219)

Using the procedure described for the preparation of 2,2,3,3-tetramethylmethylenecyclobutane (153), acetylcyclobutane (111) (2g) was converted into isopropenylcyclobutane (1.4g, 68%). The crude olefin (1.4g) in ether (10ml) was hydrogenated under 2atm in the presence of adams catalyst (PtO_2) for 16h. The catalyst was then filtered off and the filtrate concentrated to *ca.* 2 ml. Preparative g.l.c. (column B, 40°, N_2 30ml min^{-1}) of the ether solution afforded the required hydrocarbon, n_D^{20} 1.4078 (lit.[279] n_D^{20} 1.4080); n.m.r. ($CDCl_3$) δ 0.8 (6H, umsym d, *J*=6Hz, CH_3), 1.2 - 2.2 (8H, complex).

1,1-*Dimethylcyclobutane* (223)

1,1-Dihydroxymethylcyclobutane (2g; prepared by reduction of cyclobutane-1,1-dicarboxylic acid[280]) was quantitatively converted into its ditoluene-*p*-sulphonate which was added in one portion to a stirred suspension of lithium aluminium hydride (3.2g) in diglyme (30ml). After being stirred at 50° for 16h, the mixture was heated to 140° and the product, which distilled from the mixture, was collected in a dry-ice

acetone trap. The crude product (1.2g, 67%) contained >95% of the required compound (g.l.c. column D, 40°). A pure sample of 1,1-dimethylcyclobutane, n_D^{20} 1.394 (lit.[281] 1.3936), was obtained by preparative g.l.c. (column B, 40°, N_2 40ml min^{-1}); n.m.r. ($CDCl_3$) δ 1.1 (6H, s, CH_3), δ 1.75 (6H, s, ring H).

The same three step procedure was used to prepare:

(i) 1,3,3-*Trimethylcyclobutane* (227) [from 3,3-dimethylcyclobutane-carboxylic acid (163)] n_D^{20} 1.402. (Found: C, 86.0; H, 14.3. C_7H_{14} requires C, 85.6 H, 14.4%); n.m.r. ($CDCl_3$) δ 0.95 - 1.15 (9H a doublet and two singlets partially resolved, CH_3) 1.0 - 2.7 (5H, complex, ring H);

(ii) trans-1,2-*Dimethylcyclobutane*[282] (231) [from *trans*-cyclobutane-1,2-dicarboxylic acid] n_D^{20} 1.389 (lit.[282] n_D^{20} 1.3896); n.m.r. ($CDCl_3$) δ 0.9 - 2.2 (complex, at δ 1.0, a partially resolved doublet, $J \sim 5$Hz).

(iii) cis-1,2-*Dimethylcyclobutane*[283] (237) [from *cis*-cyclobutane-1,2-dicarboxylic acid anhydride] n_D^{20} 1.403 (lit.[283] n_D^{20} 1.403); n.m.r. ($CDCl_3$) δ 0.95 (6H, d, J=6Hz, CH_3), 1.1 - 2.7 (6H, complex, ring H).

(iv) 1,1,2-*Trimethylcyclobutane* (239) [from 1-methylcyclobutane-2,2-dicarboxylic acid (126)] n_D^{20} 1.406, (Found: C, 85.9 H, 14.4. Calc C, 85.6, H, 14.4%); n.m.r. ($CDCl_3$) δ 0.7 - 1.0 (9H, a doublet and two singlets partially resolved, CH_3), 1.4 - 2.4 (5H, complex, ring H). The same hydrocarbon was obtained from the hydrogenation

of 2,2-dimethylmethylenecyclobutane (149).

1,1,2,2-*Tetramethylcyclobutane* (245)

Using the procedure described for the preparation of 6,7-dimethylbicyclo[4.1.0]heptane (186), the Wolff-Kishner reduction of 2,2,3,3-tetramethylcyclobutanone (152) afforded a mixture of the required hydrocarbon (*ca.* 60%) and unchanged ketone. The pure hydrocarbon was obtained as a white waxy solid m.p. $\sim 40^{\circ}$ (Found: C, 85.0; H, 14.4; C_8H_{16} requires C, 85.6; H, 14.4%) by preparative g.l.c. column B, 60°, N_2 40ml min^{-1}) n.m.r. ($CDCl_3$) 0.95 (12H, s, CH_3), 1.6 (4H, s, ring H).

1,1,2,2,3-*Pentamethylcyclobutane* (251)

A sample of 2,2,3,3-tetramethylmethylenecyclobutane (153) (300mg) in ether (20ml) was hydrogenated under 3 atm in the presence of Adams catalyst (PtO_2) for 16h. The catalyst was then filtered off and the filtrate concentrated to *ca.* 2ml. Preparative g.l.c. (column B, 60°, N_2 40ml min^{-1}) afforded a sample of the required hydrocarbon (Found: C, 86.0: H, 14.2. C_9H_{18} requires C, 85.6; H, 14.4%).

Bicyclo[3.2.0]*heptane* (257)

Bicyclo[3.2.0]hept-2-ene (0.5g) in ether (10ml) was hydrogenated under 3 atm in the presence of Adams catalyst (PtO_2) for 16h. The catalyst was filtered off and the filtrate concentrated to *ca.* 2ml by distillation. Preparative g.l.c. (Column B, 40°, N_2 40ml min^{-1}) afforded a sample of bicyclo[3.2.0]heptane n_D^{19} 1.4532 (lit.[163] n_D^{20} 1.4532).

(ix) *The synthesis of reference compounds - olefins*

cis-2-*Hexene* (217)

A suspension of methyltriphenylphosphonium iodide (40g) and potassium *t*-butoxide (11g) in diglyme (200ml) was stirred at room temperature for 1h. The resultant yellow solution was cooled to 0^{o} and treated with butanal (5.5g) and the mixture then stirred at room temperature for 36h. A mixture (8g) of hex-2-ene and *t*-butanol was isolated by distillation. The crude olefin was shown by g.l.c. (column D, 80^{o}) to be a mixture of *cis*- and *trans*-isomers in the ratio 8:1. A sample of pure *cis*-hex-2-ene, n_{D}^{20} 1.3974 (lit.[242] 1.3977), was isolated by preparative g.l.c. (column B, 30^{o} N_2 30ml min^{-1}).

2-*Methylhex*-2-*ene* (221)

A suspension of isopropyltriphenylphosphonium iodide (8.2g) and potassium *t*-butoxide (2.2g) in ether (30ml) was stirred at room temperature for 1h. The resultant deep red solution was cooled to 0^{o} and a solution of butanal (1.2g) in ether (10ml) was added. The mixture was then stirred at room temperature for 18h. Work up as described for vinylcyclohexane (178) afforded a sample of the required olefin (0.6g) which was of >95% purity (g.l.c. column D, 90^{o}). Pure 2-methylhex-2-ene n_{D}^{20} 1.4100 (lit.[242] 1.4106) was obtained by preparativ g.l.c. (column B, 30^{o}, N_2 40ml min^{-1}).

2-*Methylpent*-1-*ene* (225)

Using the procedure described for the preparation of 2,2,3,3-tetramethylmethylenecyclobutane (153), the reaction of butan-2-one (2.3g) with methyltriphenylphosphorane in dimethylsulphoxide afforded a sample of the olefin (2.6g) which was contaminated with benzene (*ca.* 30%). The crude olefin was purified by preparative g.l.c. (column B, 30°, N_2 40ml min^{-1}) to give pure 2-methylpent-1-ene, n_D^{20} 1.3935 (lit.[242] 1.3943).

4,4-*Dimethylpent*-1-*ene* (229)

t-Butylmagnesium chloride was coupled with allyl bromide following the procedure described by Whitmore and Homeyer[284] to give 4,4-dimethylpent-1-ene, b.p. 67-72° (lit.[284] 70.7-71.2). A sample of the olefin which was further purified by preparative g.l.c. (column K, 30°, N_2 40ml min^{-1} had n_D^{20} 1.3912 (lit.[242] 1.3911).

3-*Methylpent*-1-*ene* (235)

3-Methylpentan-1-ol[285] was converted into its acetate b.p. 71-73°/18mm (lit.[286] 65-73°/20mm) by treatment with acetic anhydride in pyridin in the usual way.

The foregoing acetate (0.5g) was pyrolysed by slow distillation (*ca.* 30°/1mm) through a 30cm silica column packed with silica beads which was heated at 500°. The crude pyrolysate (0.4g), consisting of the required olefin (60%) and unchanged acetate (40%), was subjected

to preparative g.l.c. (column B, 30°, N_2 40ml min^{-1}) to afford pure 3-methylpent-1-ene, n_D^{22} 1.3828 (lit.[242] 1.3830).

5-*Methylhex*-1-*ene* (239)

5-Methylhexanoic acid was reduced with lithium aluminium hydride in ether in the usual way and the product treated with acetic anhydride in pyridine to afford 5-methylhex-1-yl acetate, b.p. 62-63°/20mm.

Using the procedure described for the preparation of 3-methylpent-1-ene, the foregoing acetate (0.6g) was pyrolysed to afford a mixture (0.9g) of the required olefin (80%) and unchanged acetate (20%). Preparative g.l.c. (column B, 60°, N_2 40ml min^{-1}) afforded a pure sample of 5-methylhex-1-ene, n_D^{20} 1.3966 (lit.[242] 1.3966).

3,3-*Dimethylpent*-1-*ene* (241)

A solution of 3,3-dimethylbutanoic acid[274] (4.5g) was treated with an ethereal solution of methyllithium (90ml; 1M) and the resultant mixture was stirred at room temperature for 20min. Work up in the usual way afforded a sample of 3,3-dimethylpentan-2-one (4.0g, 90%), b.p. 128-129° (lit.[287] 128-129°/744mm), which was shown by g.l.c. (column D, 80°) to be of >98% purity.

The ketone was reduced with lithium aluminium hydride in ether in the usual way and the product alcohol, b.p. 145-150° (lit.[288] 147-148°) treated with acetic anhydride in pyridine to afford 3,3-*dimethyl*-

pent-1-yl acetate, b.p. 90-100° (block)/20mm, n_D^{18} 1.4192 (Found: C, 68.6; H, 11.2. $C_9H_{18}O_2$ requires C, 68.3; H, 11.5).

Pyrolysis of the foregoing acetate (0.8g) using the procedure described for the preparation of 3-methylpent-1-ene afforded a mixture (0.7g) of the required olefin (60%), unchanged acetate (20%) and several unidentified hydrocarbons (20%). A pure sample of 3,3-dimethylpent-1-ene, n_D^{20} 1.3980 (lit.[242] n_D^{20} 1.3984), was isolated by preparative g.l.c. (column B, 40°, N_2 40ml min^{-1}).

2,5-*Dimethylhex*-1-*ene* (245)

A solution of 2-methylprop-1-yl magnesium bromide (prepared from 1-bromo-2-methylpropane (9g) and magnesium turnings (3.7g) in tetrahydrofuran (20ml)) and 3-chloro-2-methylpropene (5.4g) was cooled to 0° and treated with a solution of lithium tetrachlorocuprate in tetrahydrofuran[289] (2ml; 0.1M). The resultant mixture was stirred for 3h at 0° then poured on to ice. Work up in the usual way afforded a mixture (3g, 45%) b.p. 112-115° (lit.[242] 111.6°) which contained >80% of the required hydrocarbon. A pure sample of 2,5-dimethylhex-2-ene, n_D^{20} 1.4085 (lit.[242] n_D^{20} 1.4080), was isolated by preparative g.l.c. (column B, 90°, N_2, 40ml min^{-1}).

2,3,3-*Trimethylpent*-1-*ene* (247) [(145)]

The olefin b.p. 104-107°, n_D^{20} 1.4183 (lit.[290] 106-106.7°, n_D^{20} 1.4179) was prepared by dehydration of 2,2,3-trimethylpentan-2-ol using the procedure described by Whitmore and Laughlin[291]. The ^{13}C n.m.r. spectrum of (247) is reported in table 13 (see p. 67).

4,5,5-*Trimethylhex*-1-*ene* (253) [(142)]

A solution of mesityl oxide (4.6g) and (trimethyl phosphite)copper(I) iodide (160mg) in ether (50ml) was added to a stirred solution of isopropyl magnesium bromide (prepared from isopropyl bromide (5.2g) and magnesium (1.2g) in ether (50ml)) at -10°. The resultant black solution was stirred at room temperature for 3h, then poured into ice-cold saturated ammonium chloride solution (200ml) and extracted with ether. The ether solution was washed successively with saturated sodium bicarbonate solution and water, dried, and evaporated. Distillation of the residual oil afforded 4,5,5-trimethylpentan-2-one (4.1g, 62%) b.p. 80-85°/30mm (lit.[291] 54°/3.3mm). G.l.c. (column A, 120°) showed the ketone to be homogeneous.

The foregoing ketone (1.5g) was added to a stirred solution of sodium hypobromite (prepared from bromine (2.3ml), and sodium hydroxide (4.8g) in water (20ml)) at 0° and the mixture then stirred at room temperature for 24h. The excess of sodium hypobromite was then destroyed by the addition of sodium metabisulphite and the mixture extracted with

ether. The aqueous solution was then accidified with 2N sulphuric acid and extracted with ether. The dried ether solution was evaporated and the residual oil distilled to afford 3,3,4-trimethylpentanoic acid (1.2g, 79%) b.p. 105-107°/10mm (lit.[292] 105-108°/10mm). The acid was shown to be pure by g.l.c. analysis (column A, 145°) of the ethyl ester prepared by treatment of the foregoing acid with an ethereal solution of diazoethane.

Reduction of the foregoing acid (8.2g) with lithium aluminium hydride in ether in the usual way afforded 3,3,4-trimethylpentan-1-ol 7.5g, 98%) b.p. 82-85°/15mm (lit.[292] 78-82°/10mm). The alcohol (3.0g) was oxidised[269] with chromic acid and pyridine in methylene chloride to afford 3,3,5-trimethylpentanal (2.0g, 67%).

Using the procedure described for the preparation of 2,2,3,3-tetramethylmethylenecyclobutane (153) the crude aldehyde (2.0g) was converted into the required olefin (0.9g, 44%). A sample of the olefin purified by preparative g.l.c. (column B, 80°, N_2 40ml min^{-1}) had n_D^{15} 1.4304 (lit.[293] n_D^{20} 1.4251) n.m.r. ($CDCl_3$) δ 0.8 (6H, s, CH_3), 0.85 (6H, d, J=7Hz, CH_3), 1.35 (1H, m, CH), 1.95 (2H, br d, CH_2), 4.85 - 5.15 (2H, m, $=CH_2$) 5.3 - 6.3 (1H, m, =CH).

2-Ethylcyclopentene (259)

The Grignard coupling of ethyl magnesium iodide with 2-chlorocyclopentene was conducted according to the procedure described by Crane, Boord and Henne[294] to afford 2-ethylcyclopentene, b.p. 100-104°, n_D^{18} 1.4351 (lit.[294] 98.1°, n_D^{20} 1.4321).

Cycloheptene (261)

The reduction of cycloheptatriene with sodium in ammonia as previously described[295] gave cycloheptene, b.p. 114-116° (lit.[295] 113.5-114.5°). G.l.c. (column I, 50°) showed the olefin to be of >90% purity.

CHAPTER 11

The Generation of α-Oxygen Substituted Cyclopropylcarbinyl Radicals.

E.p.r. spectroscopy

A Varian E9 e.p.r. spectrometer, with 100KHz modulation and an X-band Klystron, was used in conjunction with a mixing chamber which allowed the mixing of two reactants *ca.* 0.02sec before the solution entered the sample cavity of the spectrometer.

For the generation of hydroxyl radicals the two solutions which were mixed in the flow cell contained respectively; (a) 12.5% (w/v) titanium(111) chloride solution (12.5ml l^{-1}), concentrated sulphuric acid (2ml l^{-1}) and the substrate (*ca.* 4ml l^{-1}), and (b) 30% hydrogen peroxide (1.7ml l^{-1}).

For the generation of carbon dioxide radical anion the solutions contained; (a) sodium formate (30g l^{-1}) disodium ethylenediaminetetra-acetic acid (9g l^{-1}), 12.5% (w/v) titanium(111) chloride (12.5ml l^{-1}) and the substrate (*ca.* 4ml l^{-1}), and (b) sodium formate (30g l^{-1}) and 30% hydrogen peroxide (1.7ml l^{-1}).

Hyperfine coupling constants were measured to within ± 1 G and *g*-factors to within ± 0.0001. The instrument was calibrated by adding aqueous solution of Fremy's salt to one of the reactant solutions.

The details of the spectra recorded are given in chapter 7.

1-*Methylnortricyclen*-3-*ol* (274)

The sequence of reactions described by Paasivirta[296] was used to convert norborn-5-en-2-one[297] into the required alcohol, b.p. 82-83°/8mm (lit.[296] 75-77°/8mm). G.l.c. (column I, 150°) showed the alcohol to be a mixture of the *syn*- and *anti*-isomers in the ratio 1:5.

1-*Methylnortricyclen*-3-*one* (273)

Using the general procedure described by Brown, Garg and Liu[298] the foregoing alcohol (6.2g) in ether (25ml) was treated with 6N chromic acid (50ml) at 0° to afford the required ketone, b.p. 98-100°/25mm (lit.[296] 75°/16mm). G.l.c. showed the ketone to be of >98% purity.

Photoreduction of 1-*methylnortricyclen*-3-*one* (273)

The photoreduction of the ketone (273) was conducted according to the procedure described by Dauben and co-workers[49]. The product mixture was analysed by g.l.c.-mass spectrometry (column C, 160°, N_2 75ml min^{-1}). The results are summarised on p. 121.

Reduction of 1-*methylnortricyclen*-3-*one* (273) *with tri*-n-*butylstannane*

The reduction was conducted according to the procedure of Godet and Pereyre[59]. A mixture of the ketone (273) (110mg) and tri-*n*-butylstannane (520mg) was irradiated at 25° for 24h. The product was then treated with methanol and the products (96%) analysed by g.l.c.

(column I, 150°). The relative yield of products obtained from the reduction are indicated in scheme 34 (see p. 122).

Reaction of 1-*methylnortricyclen*-3-*ol* (274) *with di*-t-*butyl peroxide*

A mixture of the alcohol (274) (150mg) and di-*t*-butyl peroxide (28mg) was heated[58] in a sealed tube 24h at 140°. The ampoule was then cooled, opened and the products were analysed by g.l.c. (column I, 150°). The recovery of material was greater than 95%. The relative yields of products indicated in scheme 35 (see p. 122) represent the average obtained from four experiments.

Reduction of 1-*methylnortricyclen*-3-*one* (273) *with lithium in ammonia*

Lithium (110mg) was added to anhydrous liquid ammonia (50ml; dried by distillation from sodium) and the resulting blue solution was stirred for 30min to ensure complete dissolution of the metal. The ketone (600mg) was then added slowly to the solution. Stirring was continued for 2h and then the mixture was quenched by the careful addition of an excess of solid ammonium chloride. Ether (50ml) was added before the ammonia was allowed to evaporate. After adding water the ether layer was separated and the aqueous layer was extracted with ether. The combined extracts were dried and evaporated. G.l.c. analysis (column I, 150°) showed the product to be a mixture of 4-methylnorborn-5-en-2-one (277) (60%) and the unchanged ketone (40%).

Product identification

The products of the above-mentioned reactions were identified by comparison of their g.l.c. retention times (column I, 150°) with those of authentic samples. A mixture of *endo*- and *exo*-, 5- and 6-methylnorborn-5-en-2-one was available[300] from the hydroboration-oxidation[299] of 5-methylnorbornene. In addition a mixture of the *exo*-compounds was available from the hydrogenation[301] of *exo*-tricyclo[3.2.1.$0^{2,4}$]octan-6-one. The assignment of the 5- and 6-methyl compounds was made on the basis of available g.l.c. data[300,301]. 4-Methylnorborn-5-en-2-one (277) was obtained as the minor product (5%) from the preparation of 1-methylnorborn-5-en-2-one[302]. In addition a sample, m.p. 110°-111° (Found: C, 77.8; H, 10.1. Calc for $C_8H_{12}O$ C, 77.4; H, 9.7%), of the ketone (277) of >98% purity was isolated from the product of the lithium-ammonia reduction of the ketone (273).

3-Chloro-1-methylnortricyclene (283) *and* (284)

Using the procedure described for the attempted preparation of *exo*-7-(1'-chloroethyl)bicyclo[4.1.0]heptane (79), 1-methylnortricyclen-3-ol (2.0g) was converted into the required chloride (2.1g, 91%). G.l.c. (column J, 105°) showed the product to be a mixture of the *syn*- and *anti*-isomers in the ratio 2:1. The *syn*- and *anti*-isomers were separated by preparative g.l.c. (column B, 150°, N_2 70ml min^{-1}). The *syn*-isomer had n_D^{26} 1.4840 (Found: C, 67.2; H, 7.7; Cl, 24.8. $C_8H_{11}Cl$ requires C, 67.4; H, 7.8; Cl, 24.9%), n.m.r. ($CDCl_3$) δ 1.0 - 1.45 (5H, complex), 1.3 (3H, s, CH_3), 1.8 - 2.1 (2H, complex), 3.85 (1H, br s, CHCl). The *anti*-isomer had n_D^{26} 1.4828, n.m.r. ($CDCl_3$) δ 1.1 - 1.4 (4H, complex) 1.15 (3H, s, CH_3) 1.5 - 2.2 (3H, complex), 3.9 (1H, br s, CHCl).

Reduction of syn- *and* anti-3-*chloro*-1-*methylnortricyclene* (283) *and* (284) *with tri*-n-*butylstannane*

The reduction was carried out using the general procedure described on p. 186 with the modification that hexane was used as the solvent. Samples of 1-methylnortricyclene (286), 4-methylnorbornene (288), and 5-methylnorbornene (290) required for product identification was available from the Wolff-Kishner reduction at the corresponding ketones as previously described[296,302]. The relative and absolute yields of products obtained from the reduction have been summarised in table 20.

Reduction of cyclopropyl methyl ketone with lithium in ammonia

Using the apparatus described by Fieser[230] lithium (90mg) was slowly added to a solution of cyclopropyl methyl ketone (1.0g) in dry ammonia (50ml) during 2.5h. After the addition the mixture was worked up in the usual way to afford a mixture (0.8g) of butan-2-one (40%), decan-2,9-dione[58] (∿ 10%) and unchanged ketone (50%) (g.l.c. column K, 150°).

Reduction of cyclopropyl methyl ketone with lithium in ammonia in the presence of isobutylene

The foregoing procedure was used with the modification that isobutylene (*ca.* 8.0g) was employed as a co-solvent. After the usual work up the unchanged cyclopropyl methyl ketone and butan-2-one were removed by distillation and the residue was analysed by g.l.c.-mass spectrometry (column C, 120°, N_2 50ml min^{-1}). The results are discussed on p. 133.

APPENDIX

Enthalpy of Reaction Calculation.

Enthalpy of reaction calculation

(i) *Enthalpy data for the cyclobutylcarbinyl radicals*

Experimental data for the cyclobutylcarbinyl radicals are not available and enthalpies of formation have only been reported for a few of the parent hydrocarbons[199,200]. The enthalpies were therefore calculated in each case directly from group additivity rules[136,198,201]. A typical group additivity calculation is as follows:

To estimate ΔH_f^o(1-methylcyclobutylcarbinyl radical):

$$\Delta H_f^o = \Delta H_f^o[\dot{C}\text{-}(C)(H)_2] + \Delta H_f^o[C\text{-}(\dot{C})(C)_3]$$
$$+ \Delta H_f^o[C\text{-}(C)(H)_3] + 3\Delta H_f^o[C\text{-}(C)_2(H)_2]$$
$$+ \text{ring correction.}$$
$$= 35.82 + 1.5 - 10.08 - 16.85 + 26.2$$
$$= 38.59 \text{ kcal mol}^{-1}$$

(ii) *Enthalpy data for the olefinic radicals*

Enthalpy of formation data for the majority of the parent olefins is available[197,198] and these data have been used together with a correction term based on the group additivity rules[201] (formally equivalent to the C-H bond dissociation energy) to calculate the heats of formation of the olefinic radicals*. An example of a calculated enthalpy is shown below:

To estimate ΔH_f^o(4-methylpent-4-enyl radical):

$$\Delta H_f^o = \Delta H_f^o(\text{2-methylpent-1-ene}) - \Delta H_f^o[\text{C-(C)(H)}_3] - \Delta H_f^o[\text{C-(C)}_2\text{(H)}_2] + \Delta H_f^o[\dot{\text{C}}\text{-(C)(H)}_2] + \Delta H_f^o[\text{C-}(\dot{\text{C}})\text{(C)(H)}_2]$$

$$= -14.89 + 10.08 + 4.95 + 35.82 - 4.95$$

$$= 31.71 \text{ kcal mol}^{-1}$$

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* A similar value (± 0.5 kcal mol^{-1}) may be obtained through the direct use of the group additivity rules.

Table 35

Enthalpy of formation data[a].

Cyclobutylcarbinyl radical	ΔH_f^o	Olefinic radical	ΔH_f^o
(208)	45.3 (45.3)[b]	(210)	10.6
(212)	36.8 (36.1)[b]	(214)	33.0
-	-	(216)	33.4
(218)	27.3	(220)	25.9
(222)	38.6	(224)	31.7
(226)	30.6	(228)	27.5
(230)	38.2	(232)	32.5
(236)	39.2	(234)	34.1
(238)	31.6	(240)	24.2
(244)	25.9	(246)	15.9

[a] The enthalpies of reaction calculated on the basis of these parameters are given in table 18 (see p. 97).

[b] Value based on the known heat of formation of the parent hydrocarbon[199,200].

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