

SOME RING-OPENING REACTIONS OF
CYCLOPROPYL DERIVATIVES

by

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ABSTRACT

The introduction to the Thesis is concerned with metal-ammonia reductions of acetylcyclopropanes. By studying the preferred direction of ring-opening of acetylcyclopropanes substituted in the 2-position of the cyclopropane ring it has been shown that both steric and electronic factors are important in deciding the products of rearrangement.

The Discussion section is divided into ten parts. In the first part, the reduction of 1-acetyl-2,2-dimethylcyclopropane with lithium in liquid ammonia was studied and both qualitative and quantitative explanations for the relationship between the ratio of rearranged products and the concentration of the reducing metal are presented.

The second part investigates the observation that some recovered starting material is always present in the reduction products of acetylcyclopropanes. By the use of deuterium labelling this was attributed partially to the formation of the enolate ion of the acetylcyclopropane in the reduction solution and partially to the presence of an anion formed by reaction between the acetylcyclopropane and ammonia; both ions regenerate the starting ketone on addition of a proton source.

In the third section 1-acetyl-2-phenylcyclopropane and the corresponding p-dimethylamino-derivative were reduced to obtain information on the electronic character of the transition state at the moment of bond-cleavage of the cyclopropane ring, but due to analytical difficulties no definite conclusions could be drawn.

The reduction of benzoylcyclopropane to the corresponding hydrocarbon, benzylcyclopropane, is reported in the fourth part of the Discussion and an explanation is presented for the reluctance of the cyclopropane ring to rearrange in this case.

The reduction of acetylcyclopropanes is generally accepted to be overall a 2-electron process although the possibility of a 1-electron reduction process occurring has been reported. In the fifth section, titrations of lithium in liquid ammonia with various acetylcyclopropanes, performed to distinguish between these two processes, showed that reduction does in fact occur predominantly via a 2-electron process and also that at low lithium concentrations, radical rearrangement of the cyclopropyl ring occurs followed by dimerisation of the intermediate.

The lithium in ethylamine reduction of acetylcyclopropane and the reduction of 1-acetyl-2,2-dimethylcyclopropane in hexamethylphosphoramide are described in parts six and seven respectively.

Since lithium in liquid ammonia reduction of acetylcyclopropanes is known to occur via a carbanion intermediate under normal reduction conditions the attempted rearrangement of trans-2-methylcyclopropylmethylamine via an authentic carbanion intermediate was undertaken using the Nickon-Sinz reaction (part 8). However, the rearranged products were characteristic of a radical, rather than carbanion, ring-opening.

The lithium-ammonia reduction of trans-1-acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane is

described in part 9. It was found that charge stabilisation of the intermediate carbanion species via delocalisation through an allylic intermediate produces exclusive ring-opening via C₁-C₃ bond-cleavage. The attempted radical-induced rearrangements of this ketone were thwarted by a competing thermal rearrangement.

The conformational analysis of some cyclohexanoxide ions in solution using ¹³C nmr spectroscopy is described in part 10.

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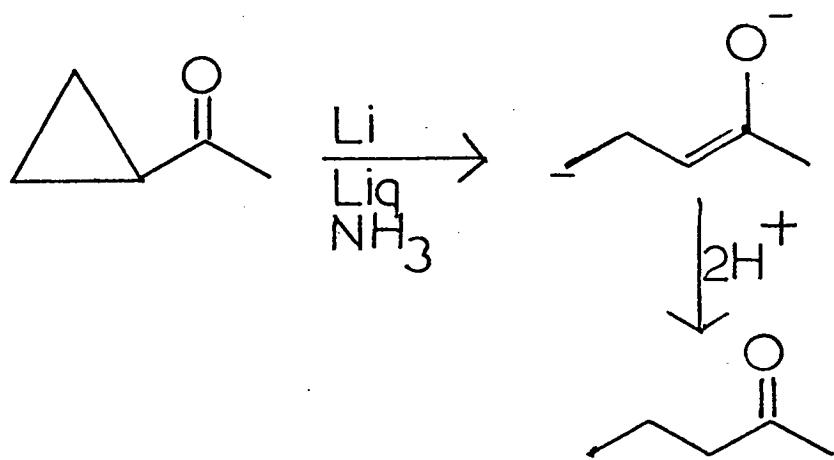


Figure 1

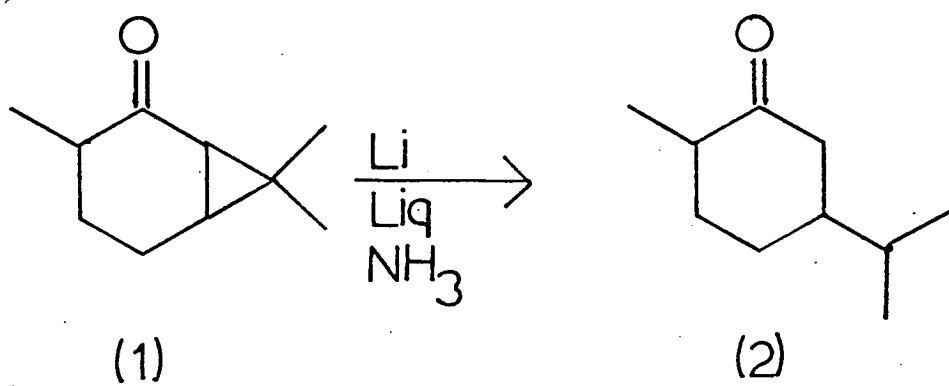


Figure 2

INTRODUCTION

Reductive Ring-Opening of Conjugated Cyclopropyl Ketones.

The reduction of organic compounds with metals in liquid ammonia is a well established and documented technique.¹ Alkylation² and deuteration³ experiments in the lithium/liquid ammonia reduction of enones have shown that the β carbon atom behaves as a carbanion during reduction. When conjugated cyclopropyl ketones are reduced with metals in liquid ammonia⁴ they undergo reductive cleavage of the cyclopropane ring via a mechanism generally considered⁵ to be similar to that for enones and thus the carbanionic character of the β carbon could influence the mechanism of ring opening (Fig. 1). However, it has been shown^{5,6} that the selective bond-cleavage of the cyclopropane ring which occurs is dependent on steric as well as electronic factors. For instance, when the cyclopropyl grouping is contained in a bicyclic system e.g. bicyclo[n,1,0]alkan-2-one, the stereochemistry of the starting material appears to determine the steric course of the ring-opening. In these systems the geometry is fixed and examination of molecular models indicates that the cyclopropyl bond which cleaves is the one which has the greater orbital overlap with the adjacent carbonyl π system. The reductive cleavage of (+)-carone (1) with lithium in liquid ammonia⁵ to give only (-)-carvomenthone (2) illustrates the high selectivity of the process (Fig. 2). None of the product derived from the thermodynamically more stable secondary carbanion was observed. Similarly,

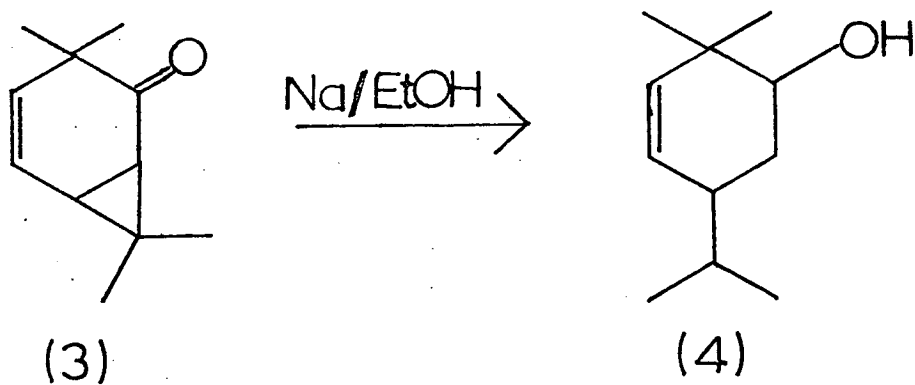
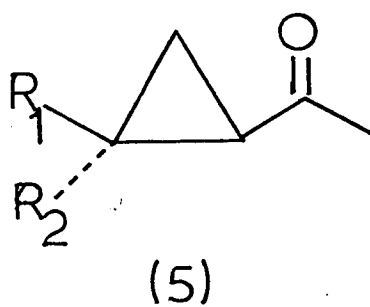


Figure 3



(R₁R₂ = H, Me; Me, H; or Me, Me.)

in the reduction of 3-methylcar-4-en-2-one (3) with sodium in ethanol⁶ only product (4), resulting from C₁-C₇ bond-cleavage, is found even though C₁-C₆ bond-cleavage would give rise to a more energetically stable allylic intermediate (Fig. 3). In order to study the electronic effects in the reduction of cyclopropyl ketones uncomplicated by these steric effects, reductive cleavage of acyclic conjugated ketones of the type (5) have been studied. This system is free from conformational restraints and the acetyl carbonyl can rotate freely over both bonds of the cyclopropane ring. Thus, evaluation of the importance of electronic factors in deciding the direction of ring opening should be possible.

Reductive cleavage of conjugated cyclopropyl ketones is overall a 2 electron process, and cleavage of the cyclopropyl ring could occur in two possible ways involving two different electronic species, namely (a) a radical anion, or (b) a dianion. It is known that the stability of radicals increases with increasing substitution in the order $\text{CH}_3\cdot < \text{RCH}_2\cdot < \text{R}_2\text{CH}\cdot < \text{R}_3\text{C}\cdot$ and, conversely, that the stability of a carbanion decreases with increasing substitution, i.e. $\text{CH}_3^- > \text{RCH}_2^- > \text{RCH}^- > \text{R}_3\text{C}^-$ (R = alkyl). Thus, by suitably substituting the cyclopropane ring and considering the different stabilities of primary, secondary, and tertiary radicals and carbanions it should be possible to deduce whether the rearrangement occurs through a radical species, formed by the addition of 1 electron to the carbonyl group, or through a carbanion species, generated by the addition of 2 electrons to the carbonyl group (Fig.4).

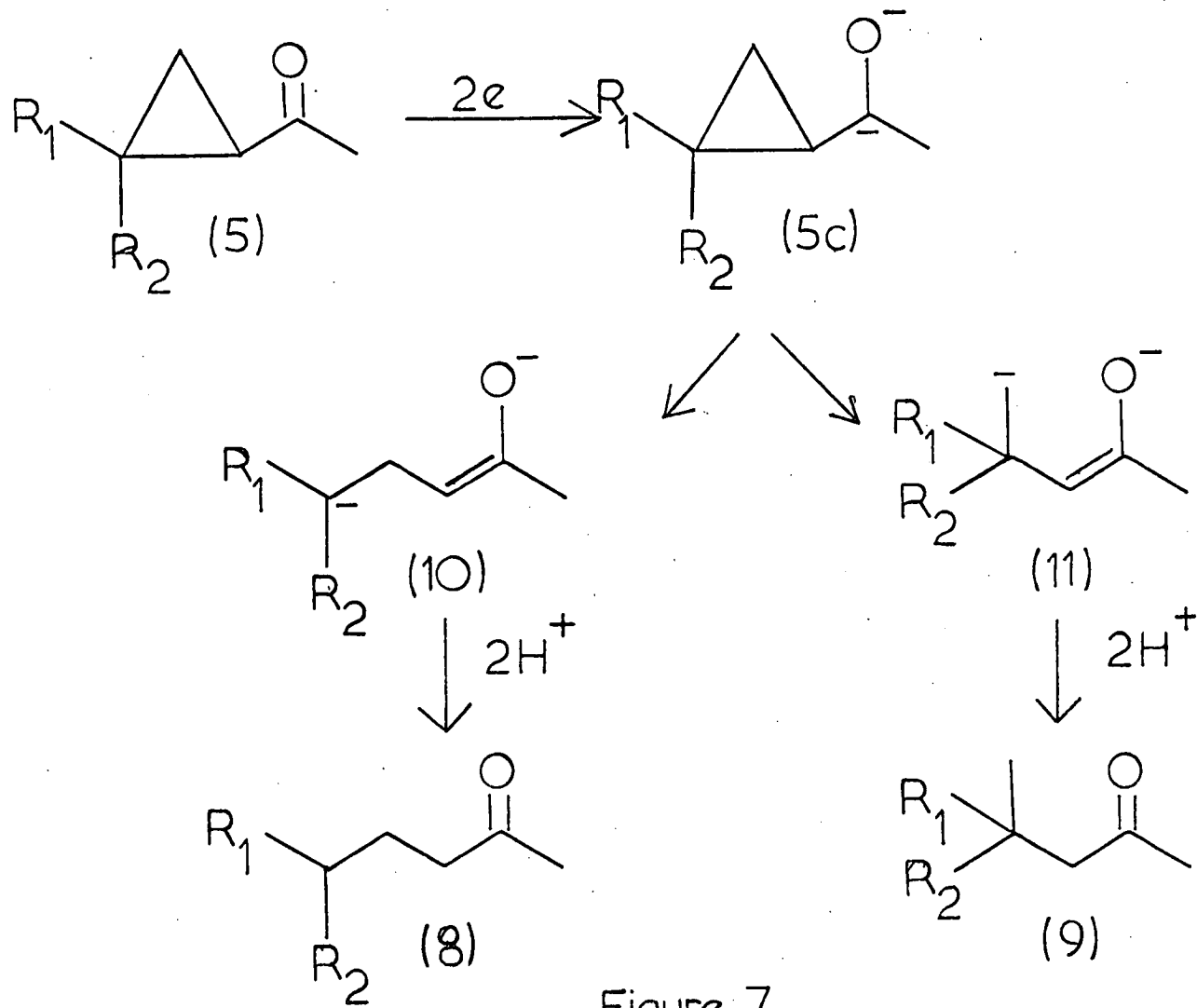


Figure 7

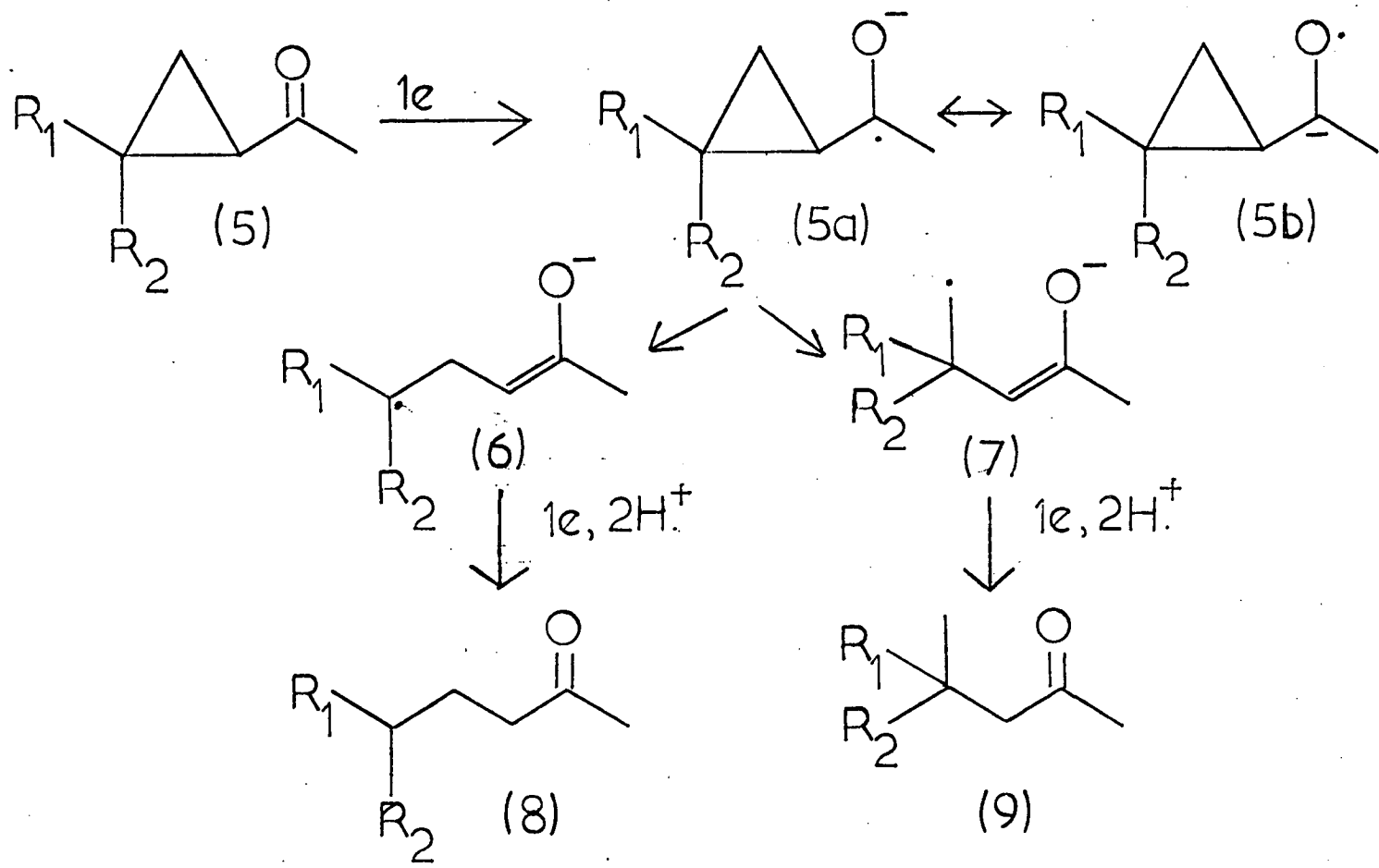


Figure 6

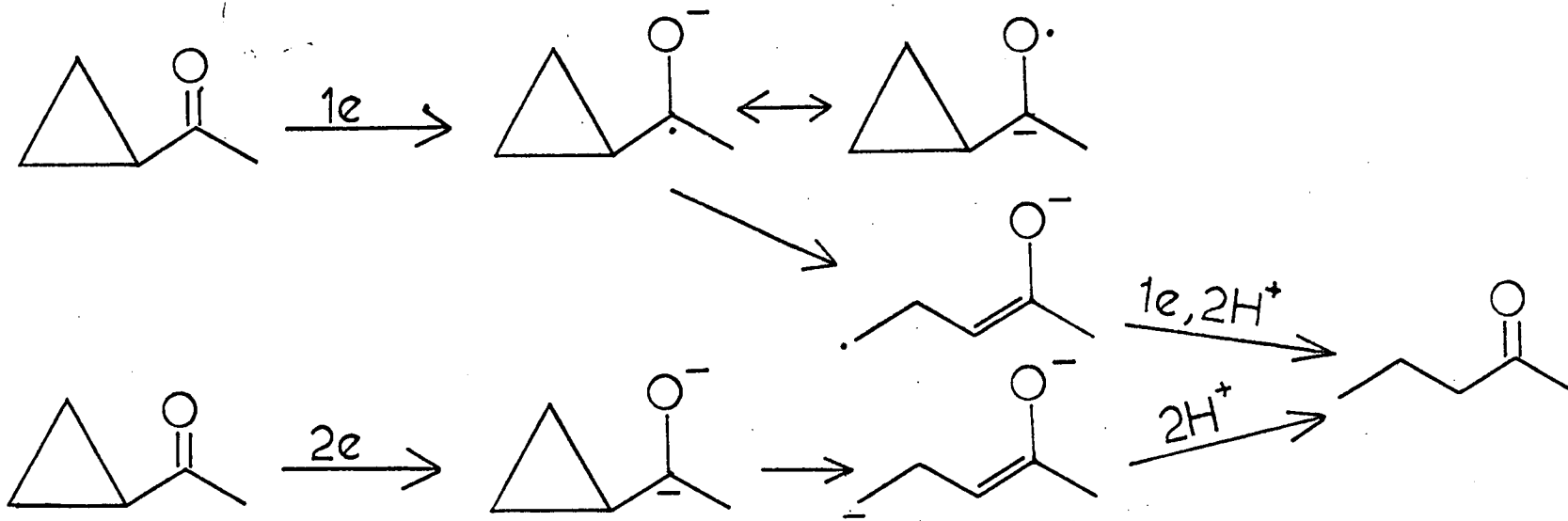


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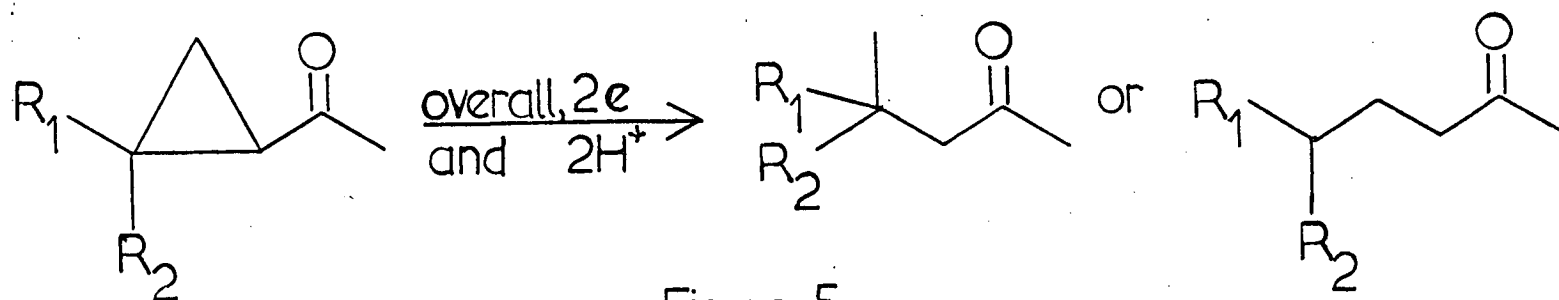


Figure 5

For cyclopropyl ketones of the type (5) ring-opening can occur in two ways depending on which bond of the ring, C_1-C_2 or C_1-C_3 , is broken (Fig. 5). For a radical anion process, from ketone (5) two possible intermediate species (6) and (7) are envisaged, leading to products (8) and (9) respectively (Fig. 6). Assuming that the carbonyl π system can overlap equally well with both bonds of the cyclopropane ring and that the energy of the transition state reflects the energy of the intermediate species being formed, we would expect compound (8) to be the predominant product from consideration of the thermo-dynamic stabilities of the intermediate species, since a tertiary or secondary free radical (6) is more stable than a primary free radical (7). (It is unlikely that species (5b) undergoes ring-opening as radical anions are known to preferentially accommodate the negative charge on the oxygen atom⁹).

Similarly, two intermediate anionic species (10) and (11), leading to the same products (8) and (9), are predicted for ketone (5) involved in a dianion process (Fig. 7). By a similar argument to that forwarded for the radical anion process we would expect product (9) to predominate in the reduction mixture from consideration of carbanion stabilities (primary carbanion more stable than secondary or tertiary carbanions). Thus, by examination of the open-chain products it should be possible to decide whether a radical anion or carbanion intermediate species controlled the direction of ring-opening.

For the above premise we assume that, providing only electronic effects are operative, the direction of ring-

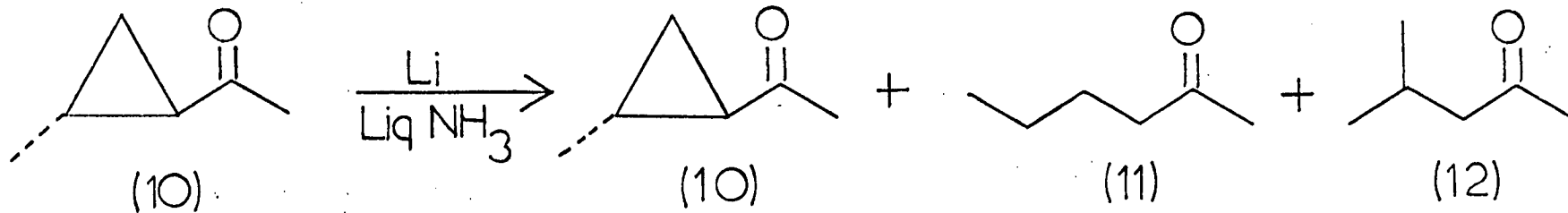


Figure 8

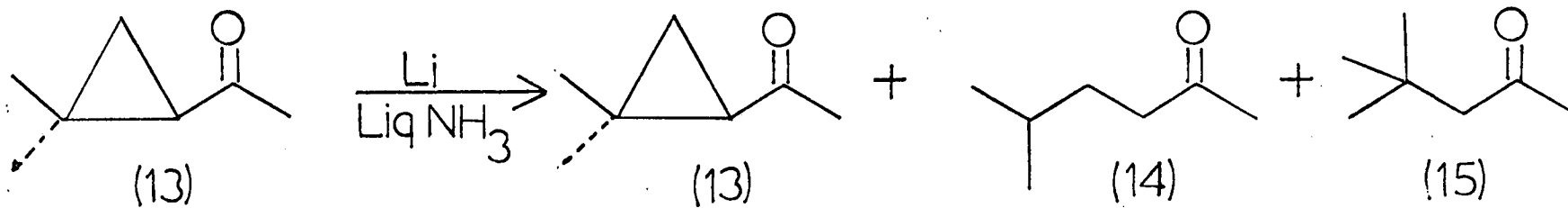


Figure 9

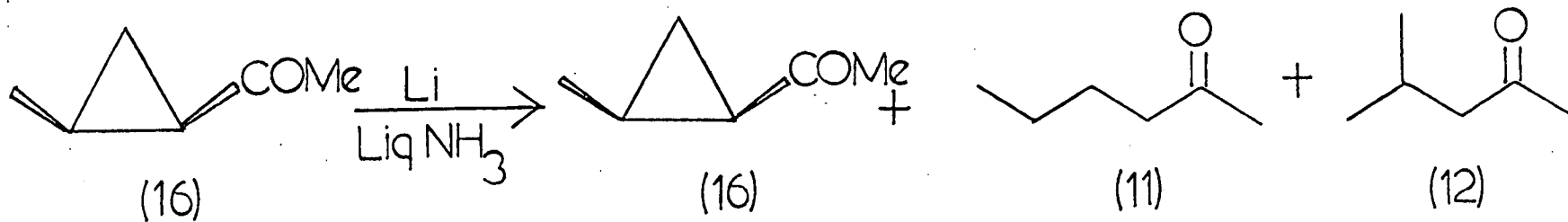


Figure 10

opening is related to the type and stability of the intermediate species. This assumption has been substantiated for authentic radical,⁷ and carbanion⁸ rearrangements.

In a study carried out by I.R. Hall¹⁰ on the reduction of the ketones, trans-1-acetyl-2-methylcyclopropane (10), 1-acetyl-2,2-dimethylcyclopropane (13), and cis-1-acetyl-2-methylcyclopropane (16) with lithium in liquid ammonia it was shown that for ketones (13) and (16) steric, as well as electronic, factors influenced the direction of ring-opening of the cyclopropane ring. Similar observations for the same systems have been reported by Dauben and Wolf¹¹ and by Fraisse-Jullien and Frejaville.¹²

Hall¹⁰ found that reduction of trans-1-acetyl-2-methylcyclopropane (10) gave, after oxidation of any resulting alcohols, the starting ketone (10), hexan-2-one (11), and 4-methylpentan-2-one (12) (Fig. 8). The main product of rearrangement was ketone (12), and the ratio of (11)/(12) varied from 0.0518 to 0.0431 consistent with a carbanionic type ring opening. For the same reduction Dauben and Wolf¹¹ obtained ratios of (11)/(12) of 0.068 and 0.027. Fraisse-Jullien and Frejaville¹² however, observed only one product, ketone (12), in the reduction of (10). An authentic radical ring-opening¹⁰ of ketone (10) and of the corresponding alcohol, trans-1-(2-methylcyclopropyl)ethanol, gave ratios of (11)/(12) of 4.5 for the ketone and 3.0 for the alcohol. These radical ring-opening results are as expected from consideration of the relative thermodynamic stabilities of the intermediates involved in

the ring-opening; that is, bond cleavage favours the more stable secondary open-chain radical. By previous arguments and by comparison with the authentic free radical reaction, we conclude the lithium/liquid ammonia reduction of ketone (10) to occur predominantly via the more stable primary carbanion.

In the reduction of 1-acetyl-2,2-dimethylcyclopropane (13) the three expected products were obtained on oxidation of the corresponding alcohols: starting ketone (13), 5-methylhexan-2-one (14), and 4,4-dimethylpentan-2-one (15) (Fig. 9). The main product of rearrangement was ketone (14) and the ratio of (14)/(15) varied from 2.05 to 4.50 - predominantly in the opposite direction to the ratio values obtained for the reduction of ketone (10). Dauben and Wolf¹¹ observed the same three products from the reduction of ketone (13) and found (14) to be the favoured product and also that the ratio of (14)/(15) ranged from 2.5-3.4. Fraisse-Jullien and Frejaville¹² also obtained ring-opening results quantitatively in agreement with those of Hall (Ratio 14/15 = 1.5). Authentic radical ring-opening of (13) and of the corresponding alcohol, 1-(2,2-dimethylcyclopropyl)ethanol, gave ratios of (14)/(15) of 41 for the ketone and 21 for the alcohol as would be expected from consideration of the relative thermodynamic stabilities of the intermediate radical species (tertiary radical more stable than primary radical).

The reduction of cis-1-acetyl-2-methylcyclopropane (16) also provided ratios of the rearranged products which were predominantly in the opposite direction to the values

obtained for ketone (10). Hall found that the reduction of ketone (16) gave three products: starting ketone (16), hexan-2-one (11), and 4-methylpentan-2-one (12) (Fig. 10). Ketone (11) was the favoured product of rearrangement and the ratio of (11)/(12) varied from 6.3-9.0. A similar reduction of (16) by Dauben and Wolf¹¹ gave the same three products; the ratio of (11)/(12) was found to be 13 and 22 for two reductions. Authentic free-radical rearrangement of the ketone (16) and of the corresponding alcohol, cis-1-(2-methylcyclopropyl)ethanol, gave a ratio of (11)/(12) of 8.7 for the ketone and 8.3 for the alcohol. The French workers¹² did not study the cis-ketone (16).

The anomaly in the ratio of rearranged products for the reduction of ketone (13) and (16) to the product ratio obtained for the reduction of ketone (10) suggested that factors other than electronic were determining the direction of ring-opening of ketones (13) and (16) rather than the mechanism changing to a radical type process (product ratios for ketones (13) and (16) were lower than the values obtained for authentic radical ring-opening). An explanation of these apparently contradictory results was found on examination of molecular models whereby it was observed that steric interactions existed between the cis-2-methyl substituent and the acetyl group in both ketone (13) and (16) such that free rotation of the acetyl group about the cyclopropane-carbonyl bond was hindered and one of the ring bonds, C₁-C₂, experienced an increased overlap with the carbonyl π system. Thus, for ketones (13) and (16) a steric element is in competition with electronic factors in deciding the ultimate

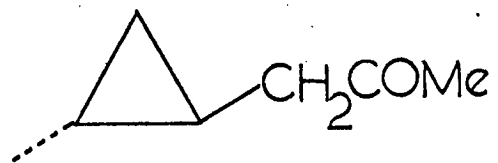
direction of ring-opening. The reduction results can therefore be explained as follows: for trans-1-acetyl-2-methylcyclopropane (10), where there is no steric effect, the favoured product of rearrangement (12) is decided solely by the relative thermodynamic stabilities of the intermediates generated. Considering previous arguments and knowing that the 4-methylpentan-2-one is the favoured ring-opened product, we therefore conclude the rearrangement to occur via a carbanion intermediate. For ketones (13) and (16), however, the tendency to form the thermodynamically most stable intermediate is outweighed by a steric effect giving the observed inversion in the ratio of rearranged products.

It was noted that the ratio of rearranged products for ketone (13) ranged from 2.05-4.5, whereas for ketone (16) the ratio varied from 6.3-9.0 even although the cis-methyl steric effect should be of similar magnitude for both ketones. This difference in values was attributed to the tendency to form a primary rather than a tertiary carbanion in ketone (13), being stronger than the tendency to form a primary rather than a secondary carbanion in (16). Assuming that the steric effect is the same for both ketones, the stronger primary-tertiary carbanion electronic effect in ketone (13) will oppose the steric influence to a greater extent than will the weaker primary-secondary carbanion electronic effect of ketone (16). Thus, as has been found experimentally, the ratio of products from the ring-opening of ketone (13) should be nearer to the value predicted on electronic grounds than the ratio of products from ketone (16). A similar competition between steric and electronic factors

has also been reported for the reductive cleavage of methyl-substituted phenylcyclopropanes.¹³

The free-radical rearrangements of ketones (10), (13) and (16) can also be explained by considering both steric factors, and the relative thermodynamic stabilities of tertiary, secondary, and primary free-radicals. The ratios of the rearranged products from radical ring-opening of ketones (10), (13), and (16) show that ring-opening is predominantly in the direction favouring the more stable radical intermediate in all cases. It was noted that the ratio of products for ketone (16) (11/12 = 8.7) was greater than for ketone (10) (11/12 = 4.5). This was attributed to a cis-methyl steric effect in ketone (16) acting in conjunction with the greater tendency to ring-open via a secondary, rather than a primary, free radical. In the trans-ketone (10), no such steric contribution is present, and ring-opening is decided solely by the competition between the thermodynamic stability of a secondary as opposed to a primary radical intermediate. The high value of the rearranged product ratio for ketone (13) (14/15 = 41) is due to a similar cis-methyl steric contribution to ketone (16) being present, reinforcing the highly favourable tendency to ring-open via a tertiary rather than a primary free-radical.

Attempted authentic carbanion rearrangements of compounds containing a methylene group α - to the cyclopropane ring on treatment with base were unsuccessful.¹⁰ For example, treatment of trans-1-(2-methylcyclopropyl)-



(17)

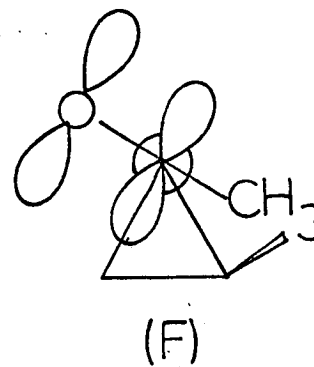
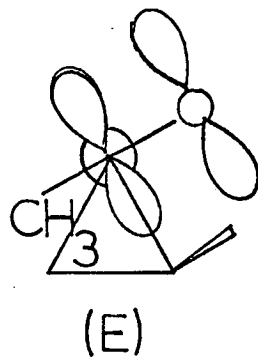
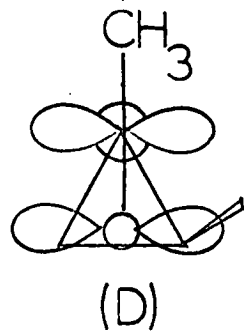
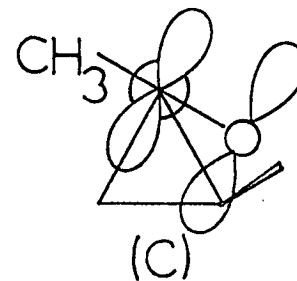
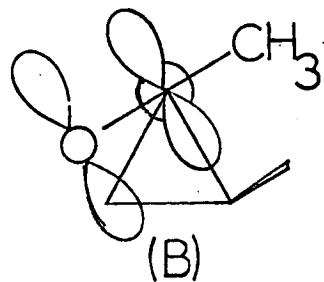
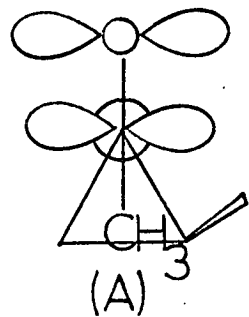


Figure 11

propan-2-one (17) with various basic conditions effected no detectable ring-opening. Since the lack of ring-opening of cyclopropylmethyl carbanions stabilised in some way, e.g. by a carbonyl or by a phenyl group,¹⁴ is well documented it was perhaps not surprising that rearrangement through a cyclopropylmethyl carbanion was unsuccessful.

Dauben and Wolf¹⁵ have explained the differences in the direction of bond cleavage between ketones (13), (16), and ketone (10) by considering the possible conformational isomers of the ketones involved in the reduction. For an acetylcyclopropane with a cis-2-methyl substituent six gauche conformers can be drawn: A, B, C, D, E, and F (Fig.11). Since the ring-opening reduction seemed to be a highly stereospecific process the 'bisected' conformers A and D were ignored; they were considered to be unimportant to the transition state at the time of ring-opening. Conformers C and F will be of higher energy than B and E owing to steric interactions and thus, either the ground state cisoid conformer B or the transoid conformer E could give rise to C₁-C₂ bond cleavage. However, it is known from nmr evidence¹⁶ that the cisoid conformer predominates in the ground state conformational population of acetylcyclopropanes. Dauben and Wolf¹⁵ showed that the transition state conformational population resembled that of the ground state by showing that the intermediate enolate ions (trapped as their enol acetates and examined by nmr) from the lithium/liquid ammonia reductions of ketones (10), (13), and (16) were predominantly in the trans form and, consequently, were derived from a cisoid conformation at the time of ring-

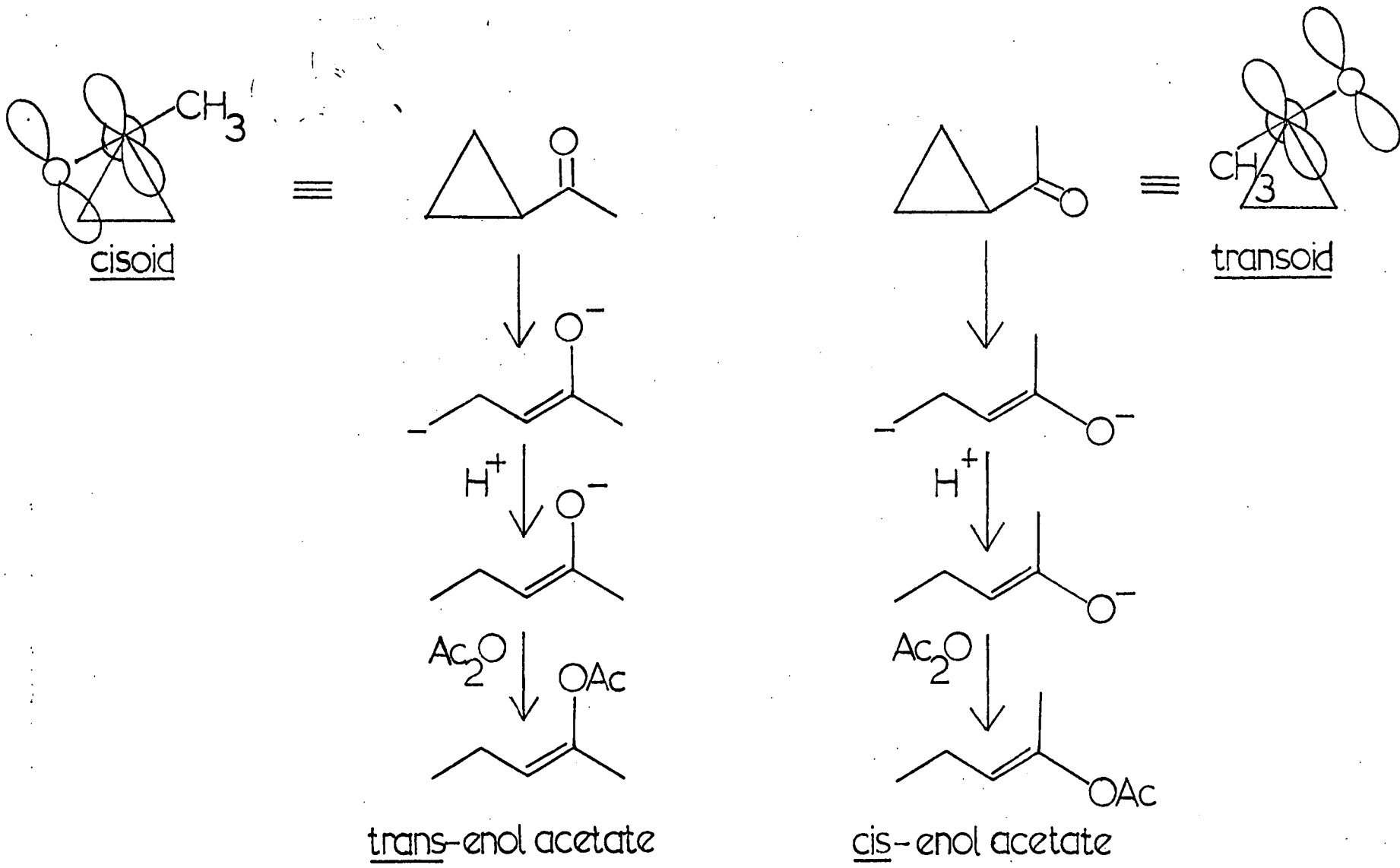


Figure 12

opening (Fig. 12).

In the reduction of 1-acetyl-2,2-dimethylcyclopropane (13), Hall¹⁰ found that the ratio of products (14)/(15) increased with an increase in the concentration of the lithium metal used. A plot of the ratio (14)/(15) against the lithium concentration gave a straight line up to concentrations of 1.7 moles litre⁻¹ (correlation coefficient 0.9994 for 9 points) of slope 0.981 litres mole⁻¹ and an intercept at (14)/(15) = 2.03. (No distinct variation in the ratio of products for ketones (10) and (16) were found under these conditions). This was attributed to a salt effect operating in the reduction as the results could be approximately reproduced by using a fixed concentration of lithium metal and adding varying concentrations of lithium ions (in the form of lithium iodide). The ratio varied with the total molarity of lithium ion present although the weight of lithium metal was constant. In the reduction of the same ketone (13) with varying concentrations of lithium metal, Dauben and Wolf¹¹ found that the ratio of rearranged products varied randomly from 2.5 to 3.4 with an increase in metal concentration.

Hall performed some reductions of ketone (13) in the presence of a cation sufficiently large to prevent ion-pairing with the intermediate anion by adding tetra-ethylammonium chloride to solutions of metals (Na, Ba, Li) in liquid ammonia. When lithium or barium were used as the reducing metal, the metal cations were precipitated as the insoluble metal chloride leaving only tetra-ethylammonium cations in

solution. With lithium and barium the ratio of (14)/(15) dropped by comparison with the ratios obtained using lithium and barium alone. With sodium, the ratio was approximately the same as that found using sodium alone, possibly because sodium chloride is soluble in liquid ammonia (4.0g/100g NH_3 ¹⁷) and thus sodium ions were still present to exert a salt effect.

In further liquid ammonia reductions of ketone (13) with metals Li, Na, and Ba, undertaken to investigate if any correlation existed between the ratio of product ketones obtained and the size of the reducing metal, Hall¹⁰ found only a small variation in the ratio of rearranged ketones. Dauben and Wolf reported similar results in reductions of ketone (13) with metals Li, Ca, K, Na, and Mg. The reason for the lack of variation in the ratio with increasing metal size was attributed by both groups^{10,11} to be due to the fact that the lithium ion, being the metal with the smallest atomic size, is already large enough to fix the preferred cisoid conformation in both the ground and transition states.

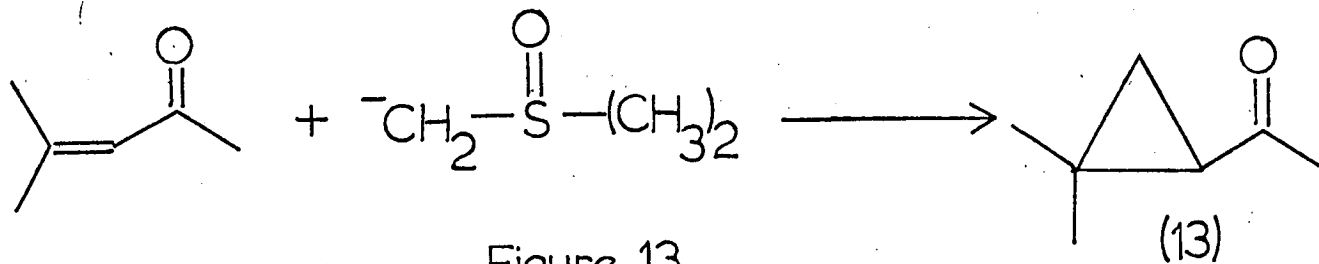


Figure 13

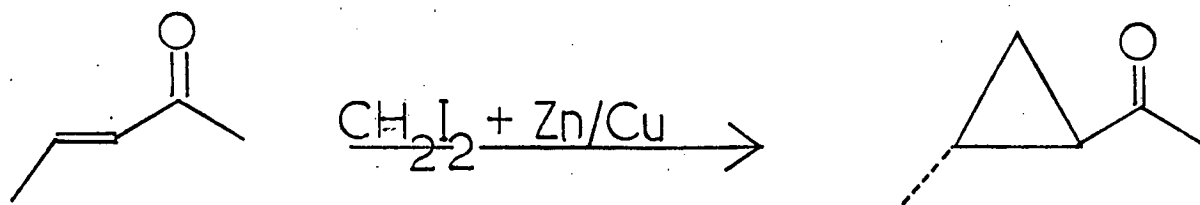


Figure 14

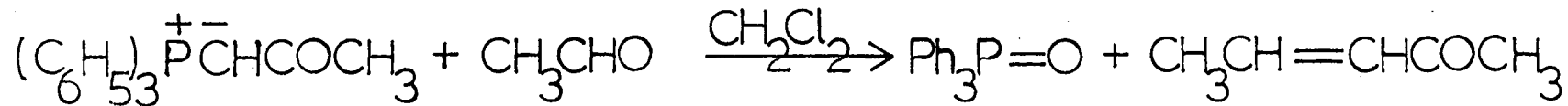


Figure 15

DISCUSSION

Reduction of Substituted Acetylcyclopropanes with Lithium in Liquid Ammonia

Preparation of ketones used in this section:

A. 1-Acetyl-2,2-dimethylcyclopropane (13). - This compound (13) was prepared by the method of Corey-Chaykowsky¹⁹ from mesityl oxide as directed by Roberts *et al.*,²⁰ by the attack of the anion of trimethyloxosulphonium iodide¹⁸ in a Michael type addition to the enone (Fig. 13).

B. trans-1-Acetyl-2,2-methylcyclopropane (10). - Since it was reported²¹ that α,β -unsaturated alcohols gave better yields than α,β -unsaturated ketones in the Simmons-Smith reaction,²² the first route to ketone (10) was through oxidation of the corresponding alcohol obtained from the Simmons-Smith reaction on trans-pent-3-en-2-ol.²³ Using the Simmons-Smith reaction as modified by Perraud and Arnaud,²⁴ trans-pent-3-en-2-ol was treated with the organo-zinc compound formed in situ from methylene iodide and zinc-copper couple.²⁵ The reaction product, which was shown to contain mainly the required cyclic alcohol by comparative v.p.c. with an authentic sample of the alcohol (Hall¹⁰) was not purified at this stage, but was immediately oxidised with 6N chromic acid. However, oxidation of the alcohol was inefficient and even after three successive treatments with chromic acid, conversion to the ketone was incomplete. Preparation of ketone (10) was therefore attempted using the modified Simmons-Smith reaction on the ketone, trans-pent-3-en-2-one, which was itself prepared using the Wittig reaction

of acetylmethylenetriphenylphosphorane and acetaldehyde in methylene chloride (Fig. 15). The product obtained on fractional distillation was trans-pent-3-en-2-one (5.4g, b.p., 120-121^o; lit.,²⁷ b.p., 124^o) which contained 5.6% impurity by v.p.c. analysis. The spectral data was in agreement with that reported.^{27a}

Three different Simmons-Smith reactions on trans-pent-3-en-2-one were attempted using the conditions described in the Experimental section (p. 72). Two of these reactions gave products containing methylene iodide as the major component; the remainder consisted of unreacted starting ketone and a complex mixture of unidentified components. Attempts to remove methylene iodide from the product mixture were unsuccessful. In a third reaction, 99.999% zinc was used in the preparation of the zinc-copper couple and the reaction was followed by v.p.c. until all the starting material had reacted (20 hours). This gave the required cyclic ketone (10) containing less than 2% impurity but in only 10% yield. Therefore, the Simmons-Smith approach as a preparative method was abandoned.

trans-1-Acetyl-2-methylcyclopropane (10) was prepared by the reaction of dimethylsulphoxonium methylide in dimethylsulphoxide on trans-pent-3-en-2-one as described for ketone (13). The purified product (41% yield) contained less than 1% impurity by v.p.c. analysis.

Reduction of 1-Acetyl-2,2-dimethylcyclopropane with Lithium/Liquid Ammonia

Hall¹⁰ had found that in the reduction of 1-acetyl-2,2-dimethylcyclopropane (13) with lithium in liquid ammonia the ratio of rearranged products (14)/(15) increased with an increase in the concentration of the reducing metal. For a number of reductions of ketone (13) a plot of the ratio (14)/(15) against the molarity of lithium metal used in the reduction was linear up to a lithium concentration of 1.7 moles litres⁻¹ and had a slope of 0.981 litres moles⁻¹ and an intercept of 2.03. However, Dauben and Wolf,¹¹ in their reductions of ketone (13) did not observe any relation between the ratio of rearranged products and the molarity of lithium, but found instead that the product ratio varied randomly with the concentration of metal used.

In an attempt to clarify the discrepancy between the ring-opening results of Hall and Dauben and Wolf a series of reductions of ketone (13) were carried out using a reduction method identical to that used by Hall¹⁰ whereby the ketone (13) was added dropwise to a homogeneous solution of lithium in liquid ammonia. After the reduction had stirred for 2 hours, solid ammonium chloride was carefully added to the blue solution to destroy the excess of lithium, neutralise the lithium amide formed, and hydrolyse the organo-lithium enolate. The product was then extracted with ether, dried (MgSO₄), and any alcohols routinely converted to the corresponding ketones with 6N chromic acid before being analysed by v.p.c.

In four of the reductions performed, decane was added as an internal v.p.c. standard at the start of the reaction. Comparison of the ratio of starting ketone (13): decane before reaction to the ratio of total products: decane after reaction (v.p.c. peak integration) showed a preferential loss of the standard. Hall¹⁰ found that there was little or no alteration in the respective ratios before and after reduction. However, it was reported by Dauben and Wolf¹¹ that when cyclo-octane was added as an internal v.p.c. standard for reductions of ketone (13) there was a preferential loss of standard; no explanation for this loss was offered. Since both Hall, and Dauben and Wolf, showed that the ratio of rearranged products (14)/(15) was independent of the percentage conversion to product ketones the loss of standard was not considered detrimental to the investigation of the relationship between the ketone product ratio (14)/(15) and the molarity of lithium.

The results in Table (1) confirm the findings of Hall,¹⁰ and clearly indicate that the ratio of rearranged products (14)/(15) increases in direct proportion to the molarity of lithium used in the reduction. After oxidation of any alcohols present, the three expected ketones from the reduction were obtained, namely, starting ketone (13), 5-methylhexan-2-one (14), and 4,4-dimethylpentan-2-one (15) (see Fig. 9, p. 4). Ketone (14) was the favoured product of rearrangement and the ratio of (14)/(15) varied directly from 2.41 to 3.74 with an increase in lithium molarity from 0.28 to 2.29 moles litres⁻¹. For the same reduction Hall found the product ratio to vary directly from 2.17 to

3.75 for an increase in lithium molarity of 0.13–2.54 moles litres⁻¹. A plot of the ketone ratio (14)/(15) against the molarity of the lithium solution gave a straight line with a slope of 0.682 litres moles⁻¹ and an intercept of 2.315. These results were qualitatively in agreement with those found by Hall (slope 0.981 lm⁻¹; intercept 2.03) although the remarkable correlation coefficient (0.994) was not realised in our case. However, better agreement with Hall's values was obtained with a repeat of the least means square calculation excluding the final point ([Li⁺] = 2.289 ml⁻¹). This gave a straight line with a slope of 0.863 lm⁻¹ and an intercept of 2.12 (Graph 1).

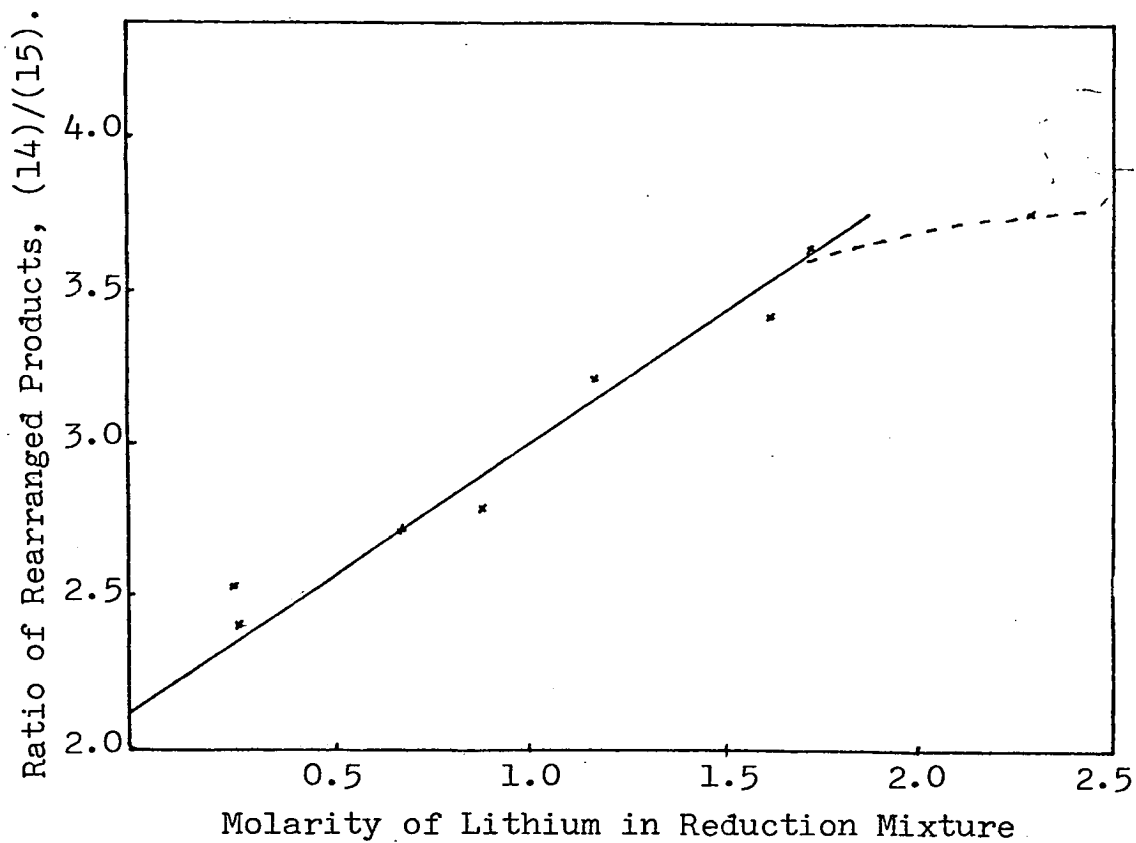
A possible explanation for the difference between our results and those of Dauben and Wolf¹¹ might be found in the experimental procedures. In our method of reduction, the reducing solution was stirred for 30 minutes prior to the addition of the cyclopropyl ketone to ensure a completely homogeneous solution of lithium in liquid ammonia. Hence, knowledge of the exact lithium ion concentration in solution at the start of the reduction was possible. Dauben and co-workers^{5,11} appear to add the ketone to the reducing solution directly after the addition of lithium to the liquid ammonia. In this situation reduction of the ketone initially occurs in a solution of varying molarity. Only after complete dissolution of the lithium has been effected are the reducing conditions similar to those in our reductions. The fact that at the end of the reductions, Dauben and Wolf¹¹ allowed the ammonia to evaporate before addition of the ammonium chloride, whereas in our case the

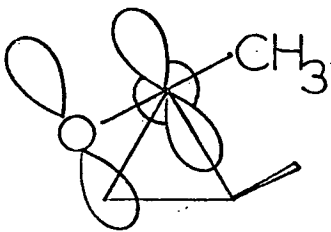
proton source was added prior to evaporation of the solvent, should have little or no effect on the rearranged product ratios since by then reduction/rearrangement of the ketone (13) is complete.

The observation that the ratio of rearranged ketones (14/15 = 2.41 - 3.74) for the reduction of ketone (13) was predominantly in the opposite direction to values found for the reduction of ketone (10) (11/12 = 0.0431 - 0.0435), suggesting that the preferred product of rearrangement was that derived from the apparently thermodynamically less stable tertiary carbanion intermediate, is in fact due to the presence of a steric effect between the cis-2-methyl group of ketone (13) and the acetyl group such that the C₁-C₂ cyclopropane bond has a better overlap with the carbonyl π system (see Introduction p. 6). Thus, when a cis-2-methyl substituent is present in the ketone a steric effect outweighs the tendency to ring-open towards the thermodynamically more stable intermediate (viz. primary carbanion from C₁-C₃ bond cleavage).

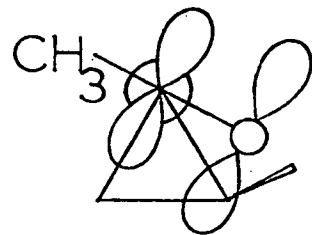
The straight line part of Graph 1 indicated that the competition between the two possible routes of bond-cleavage was directly dependent upon the concentration of lithium ions and that the bond-cleavage was a highly stereoselective process. To consider possible explanations for this selective ring-opening it is necessary to consider the various possible conformers of ketone (13). For an acetylcyclopropane incorporating a cis-2-methyl substituent, 6 gauche conformers are possible, A, B, C, D, E, and F. (See Fig. 11 in Introduction, p. 9). As has been explained previously

Graph 1. Ratio of rearranged products, (14)/(15), from the reduction of 1-acetyl-2,2-dimethylcyclopropane with lithium in liquid ammonia plotted against molarity of lithium in the reduction mixture.





(B)



(C)

Figure 16

the bisected conformers A and D are expected to contribute little to the transition state geometry of the cyclopropane ring at the time of ring-opening since bond-cleavage has been shown to be a highly selective process.^{10,11,12} Dauben and Wolf¹⁵ have shown that the transition state conformational population in the reductions of acetylcyclopropanes is predominantly cisoid at the moment of ring-opening and therefore, in order to explain the highly stereoselective bond-cleavage of ketone (13), we must consider the cisoid, gauche conformers B and C to be representative of the transition state and hence determine the direction of ring-rearrangement. Conformer B will give rise to C₁-C₂ bond-cleavage whereas conformer C will favour C₁-C₃ ring-opening, and the ratio of rearranged ketones (14)/(15) will depend on the relative importance of these two conformers at the time of ring-opening (Fig. 16). From an examination of molecular models it is apparent that as a result of steric interactions between the cis-2-methyl substituent and the acetyl group conformer B will predominate in the transition state population distribution of B and C and will therefore give rise to preferential C₁-C₂ bond-cleavage.

In the presence of lithium ions, ion-pairing occurs with the oxygen anion which increases the effective size of the latter. Thus, an increase in lithium ion concentration will increase the contribution of conformer B to the transition state conformational distribution at the expense of conformer C and consequently, the number of molecules experiencing ring-opening by C₁-C₂ bond-cleavage will be increased. This approximation can therefore qualitatively

explain the relationship between the ratio of rearranged products (14)/(15) and the molarity of lithium which is depicted graphically as a straight line.

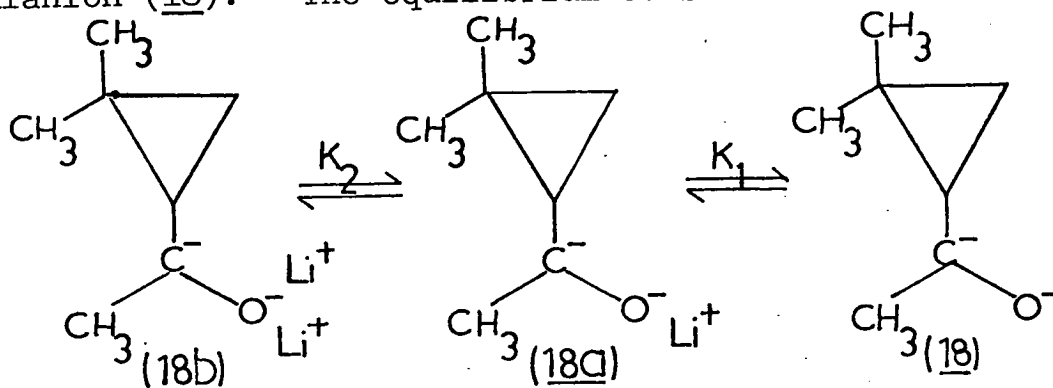
The fact that there is a slight levelling-off in this graph (Graph 1) at high concentrations of lithium can possibly be explained by consideration of the steric forces present in the molecule at the time of ring-opening. It is apparent from Fig. 16 that as the effective size of the oxygen anion increases with an increase in lithium molarity, a critical lithium concentration will be reached beyond which the oxygen-anion size will be so large as to stop inter-conversion of B and C and hence fix the transition state population distribution of the two conformers. At this critical point of maximum ring-opening via C_1-C_2 bond-cleavage we might expect the ratio of products (14)/(15) to show little increase with an increase in lithium concentration. This is observed as a levelling-off in the relevant graph above a lithium molarity of 1.72 ml^{-1} . Hall found a similar levelling-off in the graph of product ratio:lithium molarity above a lithium concentration of $1.7 \text{ moles litres}^{-1}$.

The intercept value of 2.129 implies that at zero lithium molarity the tendency of ketone (13) to be reduced by C_1-C_2 bond-cleavage is 2.129 times greater than the tendency to reduce by C_1-C_3 bond-cleavage.

So far, the correlation between the ratio of rearranged products and lithium molarity has been considered only on a qualitative basis. This variation can also be explained on a quantitative basis. The straight line part of Graph 1 suggests that reduction of ketone (13) is a highly stereo-

selective process. Hall showed that the competition between the two possible routes of bond-cleavage must be directly dependent on the concentration of lithium ions, since virtually the same curve was obtained using lithium metal plus lithium iodide as was obtained using lithium metal alone. This can, however, be rationalised by assuming that the anion formed in the reduction process forms ion-pairs with lithium.

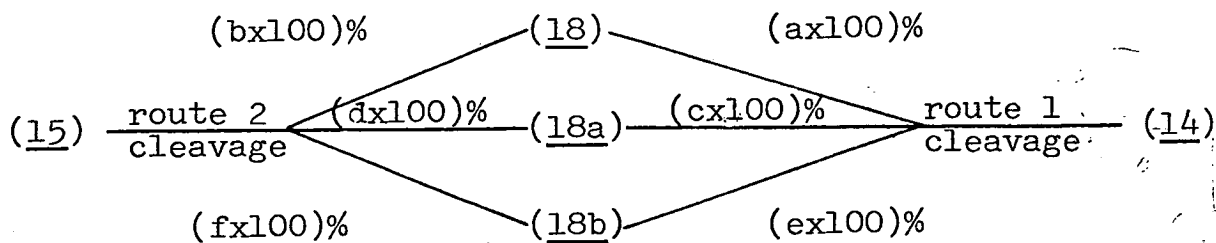
If it is assumed that the anionic species is formed by the addition of two electrons to the carbonyl group before the bond-cleavage step, two possible ion-paired species (18a) and (18b) can be envisaged (Fig. 18). There will be an equilibrium between the ion-pair (18a) and the ion-triplet (18b), and also between the ion-pair (18a) and a free dianion (18). The equilibrium constant between the free



dianion (18) and the ion-pair (18a) is assumed to be K_1 , and between the ion-pair (18a) and the ion-triplet (18b), K_2 . Product (14) arises from cleavage of the C₁-C₂ cyclopropane bond (route 1 cleavage) and product (15) from cleavage of the C₁-C₃ cyclopropane bond (route 2 cleavage).

We assume that when the dianion (18) undergoes rearrangement, a fraction a follows route 1 cleavage and a fraction b follows route 2 rearrangement. Similarly, when

the ion-pair (18a) undergoes rearrangement, fractions c and d follow routes 1 and 2 cleavage respectively, and when the ion-triplet (18b) rearranges, fractions e and f follow routes 1 and 2 cleavage respectively. The relative rates of rearrangement of (18), (18a), and (18b) are k_1 , k_2 , and k_3 , respectively. It then follows that the observed ratio



of (14)/(15) is equal to:

$$\frac{\frac{a}{a+b} \cdot k_1 [(\underline{18})] + \frac{c}{c+d} \cdot k_2 [(\underline{18a})] + \frac{e}{e+f} \cdot k_3 [(\underline{18b})]}{\frac{b}{a+b} \cdot k_1 [(\underline{18})] + \frac{d}{c+d} \cdot k_2 [(\underline{18a})] + \frac{f}{e+f} \cdot k_3 [(\underline{18b})]}$$

Since $(a+b) = 1$, $(c+d) = 1$, and $(e+f) = 1$, this ratio is equal to:

$$\frac{ak_1 [(\underline{18})] + ck_2 [(\underline{18a})] + ek_3 [(\underline{18b})]}{bk_1 [(\underline{18})] + dk_2 [(\underline{18a})] + fk_3 [(\underline{18b})]}$$

$$K_1 = \frac{[(\underline{18})][\text{Li}^+]}{[(\underline{18a})]}, \quad \text{and} \quad K_2 = \frac{[(\underline{18a})][\text{Li}^+]}{[(\underline{18b})]}$$

\therefore Ratio of (14)/(15) =

$$\begin{aligned}
 & \frac{ak_1 K_1 [(\underline{18a})]/[\text{Li}^+] + ck_2 [(\underline{18a})] + ek_3 [(\underline{18a})][\text{Li}^+]/K_2}{bk_1 K_1 [(\underline{18a})]/[\text{Li}^+] + dk_2 [(\underline{18a})] + fk_3 [(\underline{18a})][\text{Li}^+]/K_2} \\
 & = \frac{ak_1 K_1 K_2 + ck_2 K_2 [\text{Li}^+] + ek_3 [\text{Li}^+]^2}{bk_1 K_1 K_2 + dk_2 K_2 [\text{Li}^+] + fk_3 [\text{Li}^+]^2}
 \end{aligned}$$

For $[\text{Li}^+]$ large,

$$\text{Ratio} = \frac{ck_2 K_2 + ek_3 [\text{Li}]}{dk_2 K_2 + fk_3 [\text{Li}]}$$

The straight line obtained by plotting the ratio of (14)/(15) against molarity of lithium has been shown to have a gradient of 0.863 l m^{-1} , and zero intercept of 2.12. Therefore at extrapolated zero concentration of lithium

$$2.12 = \frac{ck_2K_2}{dk_2K_2} = \frac{c}{d}$$

$$\therefore c = 0.68 \text{ and } d = 0.32 \text{ (since } (c+d) = 1).$$

It is apparent from molecular models, that steric interaction between the carbonyl group and a cis-2-methyl substituent on the ring would cause route 1 cleavage of the C_1-C_2 cyclopropane bond to be favoured. It is also obvious from the models that increasing the effective bulk of the oxygen anion by ion-pair formation would also cause route 1 cleavage of the C_1-C_2 bond to be favoured. Hence we would expect that the ratio $\frac{a}{b} < \frac{c}{d} < \frac{e}{f}$.

Assuming that $e \sim 1$, and $f \sim 0$, since the steric effect of two lithium atoms in the ion triplet (18b) should make route 2 cleavage much less favourable than in the rearrangement of the ion pair (18a), the gradient,

$$0.863 \sim \frac{ek_3}{dk_2K_2}$$

$$\therefore \frac{k_3}{k_2K_2} \sim 0.863 \times 0.32.$$

The variation of the product ratio with molarity of lithium used for the reduction of ketone (13) can be rationalised by the above theory.

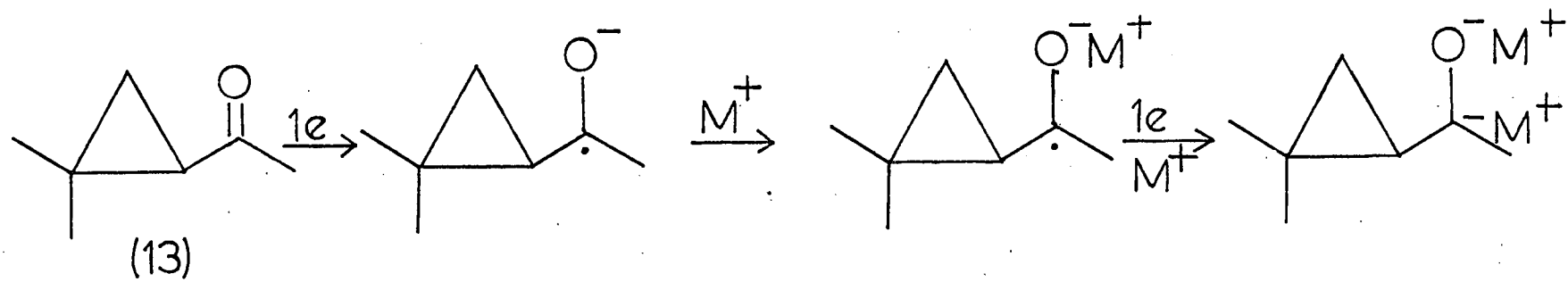


Figure 19

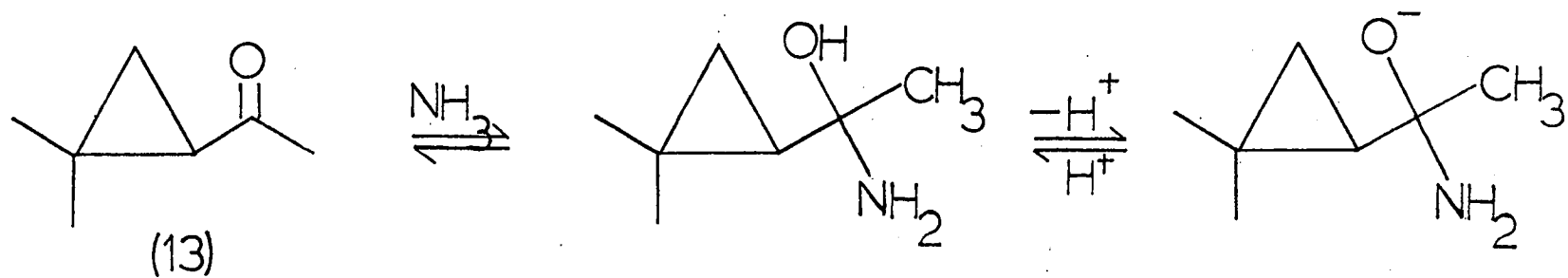


Figure 20

Investigation of Possible Reasons for the Recovered Starting Ketone Observed in Lithium/Liquid Ammonia Reductions of Acetylcyclopropanes

From Table (1) it is apparent that the percentage of recovered starting ketone (13) increases with an increase in the molarity of lithium used, from 2.5% at $[\text{Li}^+] = 0.286 \text{ ml}^{-1}$ to 16.3% at 2.289 ml^{-1} . This suggested that as the concentration of lithium increased the metal ions were, in some way, preventing ring-opening. One explanation for this phenomenon could be complexation between the lithium ions and the intermediate anions which would become more dominant as the metal concentration increased thus reducing the activity of these intermediate anions (Fig. 19). Murphy and Sullivan²⁹ have considered the possibility of a similar complexation in the metal/ammonia reduction of camphor using an excess of reducing metal.

Another possibility could be the formation of an anion by reaction of the ketone with ammonia (Fig. 20). This would be stable during the reduction and would, on addition of a proton source, regenerate ketone (13). Hall, Bartels and Engman³⁰ have stated the likely existence of a similar anion in the lithium/liquid ammonia reduction of benzaldehyde to toluene.

The third, and most likely explanation for the recovery of starting ketone (13), is the formation of an intermediate cyclopropyl enolate ion (21) which remains inactive in the reducing solution until treated with a proton source thus regenerating the starting ketone. The question remains as to what species present in the reduction solution

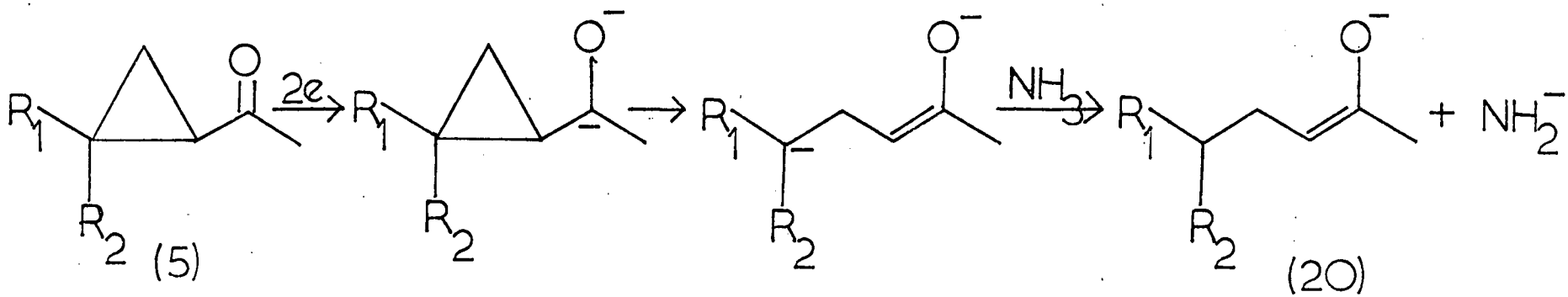


Figure 21

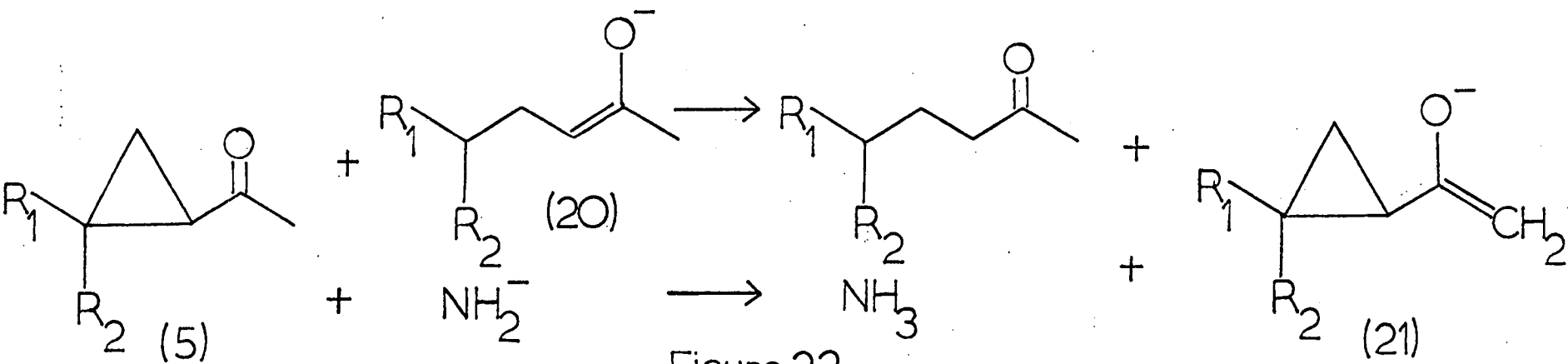


Figure 22

is sufficiently basic to abstract a proton from the acetyl methyl group of the cyclopropyl ketone.

The reduction of conjugated acetylcyclopropanes (5) can be viewed as being an overall 2 electron process which gives a carbanion-enolate intermediate. This intermediate is then sufficiently basic ($pK_a > 50$) to abstract a proton from ammonia ($pK_a 34$) to form an enolate ion (20) and the amide ion, NH_2^- (Fig. 21). It is thought that either the rearranged enolate (20) or the amide ion can then abstract a proton from the starting ketone to give an unreactive enolate ion, (21) (Fig. 22). To investigate the possibility of such an ion (21) being responsible for the recovered starting material in the reduction of 1-acetyl-2,2-dimethylcyclopropane (13) the trideuterio-methylketone (Prepared by treating ketone (13) with a solution of sodium methoxide in $[^2H_1]$ methanol; the nmr spectrum of the isolated product showed that 99% of 3 replaceable acetyl protons had been exchanged along with the 1-H cyclopropyl ring proton.) was reduced with lithium in liquid ammonia. Firm proof of the intermediacy of such an ion (21) in the reduction solution would be obtained if all the molecules in the recovered starting ketone each experienced mono-deuterium exchange.

The reduction product was shown by v.p.c. to be a mixture of the starting ketone (13), 4,4-dimethylpentan-2-one (15), 5-methylhexan-2-one (14), and their corresponding alcohols. (Chromic acid oxidation of the alcohol products to the corresponding ketones was not undertaken before v.p.c. analysis as a precaution against any deuterium

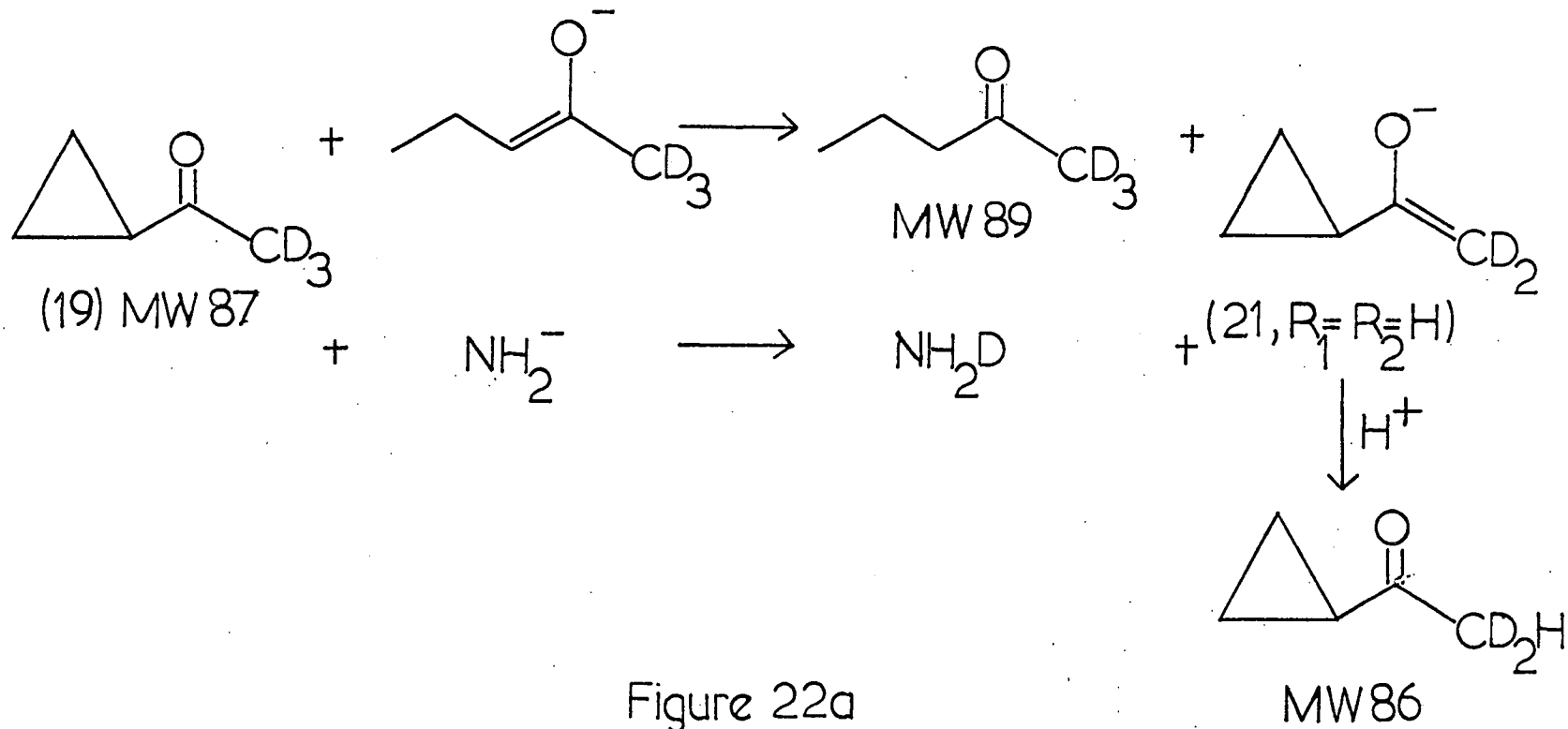


Figure 22a

exchange occurring during the oxidation reaction).

Ms/v.p.c. analysis of the recovered ketone (13) showed that only partial monodeuterium exchange had taken place (m/e 115 increased from 11.8 \rightarrow 16.7%). This would seem to question the presence of an intermediate enolate ion (21; $R_1=R_2=Me$) contrary to the findings of Hall¹⁰ who found on comparison of the mass spectra of the ketone, 5,5,5-tri-deuterio-acetylcyclopropane, before and after reduction, that the deuterium distribution had changed from 96% d_3 , 4% d_2 to 9% d_3 , 91% d_2 .

In order to simplify analysis of the reduction product mixture and to examine the latter result the remainder of the deuteration experiments were performed on acetylcyclopropane (19) itself. From arguments expressed previously we would expect reduction of ketone (19) to occur as depicted in Fig. 22a and thus any deuterium exchange occurring in the reduction could be easily estimated by ms/v.p.c. (The tri-deuteriated product was prepared by treatment of ketone (19) with sodium methoxide/ $[^2H_1]$ methanol as described for ketone (13). Mass spectral analysis of the product indicated that the total deuterium exchange was 96% of three replaceable hydrogens).

The reduction product of ketone (19) was shown by ms/v.p.c. to be a mixture of pentan-2-one (m/e 89), acetylcyclopropane (m/e 87), and pentan-2-ol (m/e 91, weak). As shown in Table (2), only partial mono-deuterium exchange, similar to that observed in the reduction of ketone (13), had again taken place (m/e 86 increased from 24.6 \rightarrow 31.8%).

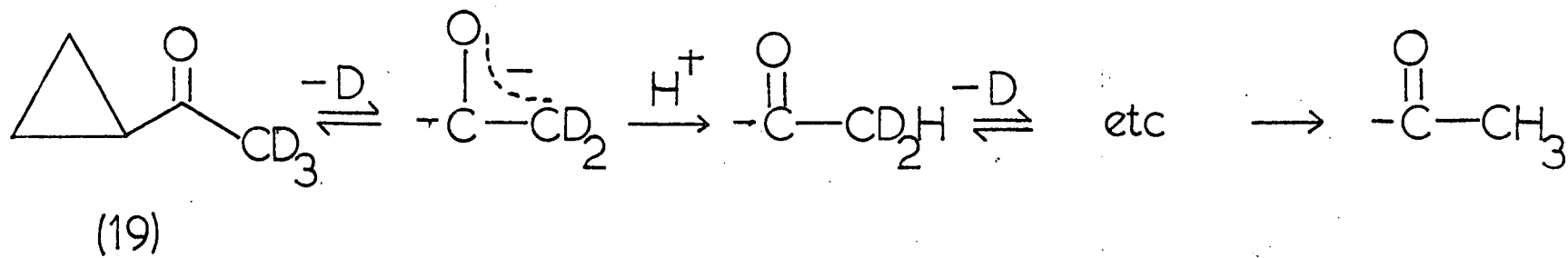


Figure 23

A possible reason for this small percentage of mono-deuterium exchange observed might be insufficient reaction time. In order to investigate this possibility a 6h reduction was performed on ketone (19), the results of which are shown in Table (2). The ratio of m/e 86/87 increased from 0.328 to 0.63 which indicates a slight increase in the percentage of mono-deuterium exchanged product compared to the increase observed in the two hour reduction, but proves that insufficient reaction time was not, in itself, responsible for incomplete mono-deuterium exchange. The results from these two reductions suggest that some deuterium exchange occurs via an enolate ion but that the amount of enolate ion present at any one time is not sufficient to account for all the recovered starting ketone. Apart from incomplete mono-deuterium exchange in the recovered starting ketone the results also show that a form of deuterium "scrambling" occurs in each reduction to give a recovered product ketone (19) composed of molecules with varying percentages of d_0 , d_1 , d_2 , and d_3 atoms. The extent of this "scrambling" appears to increase with an increase in the reaction time. For example, the number of molecules which experienced complete deuterium exchange increased from 10.8 to 27.1% on increasing the reaction time from 2 to 6 hours. This deuterium 'scrambling' suggests that a repetitive exchange process occurs during the reduction (Fig. 23). This same phenomenon was found to be present in the rearranged deuteriated ketone, pentan-2-one, as is shown in Table (4). Again, the extent of exchange increases with an increase in the reaction time.

Since it was at first thought that the deuterium 'scrambling' could occur during the reaction work up procedure a 'control' reaction was undertaken on the deuteriated acetylcyclopropane (19) in liquid ammonia in the absence of lithium metal. After stirring for 2 hours, ammonium chloride was cautiously added to the colourless solution and the product was extracted with ether in the usual manner. Ms/v.p.c. analysis showed that the ratio of m/e 86/87 for the recovered ketone was identical to that of the starting ketone which eliminates the possibility of the deuterium 'scrambling' occurring during work-up. The possibility of repetitive exchange being due to the manner of addition of ammonium chloride at the end of the reduction was also eliminated by reducing the deuteriated ketone (19) with lithium in liquid ammonia and then adding excess ammonium chloride in one large portion. Ms/v.p.c. analysis of the recovered ketone (19), (Table 3), showed that repetitive deuterium exchange was again obtained with similar proportions of mono-, di-, and tri-deuterio-exchanged species to those obtained in the first reduction (2h) of the ketone in which the ammonium chloride was cautiously added to the reduction solution (Table 2). It cannot, therefore, be said that the work up procedure has any effect on the distribution of deuterium labelled molecules in the recovered product ketone.

In the latter 'control' reduction it was noted that the percentage of total products isolated as alcohols, pentan-2-ol and 1-cyclopropylethanol, was reduced to 5% from a value of 60% when the proton source was added slowly to the reduction solution. This substantiates the concept

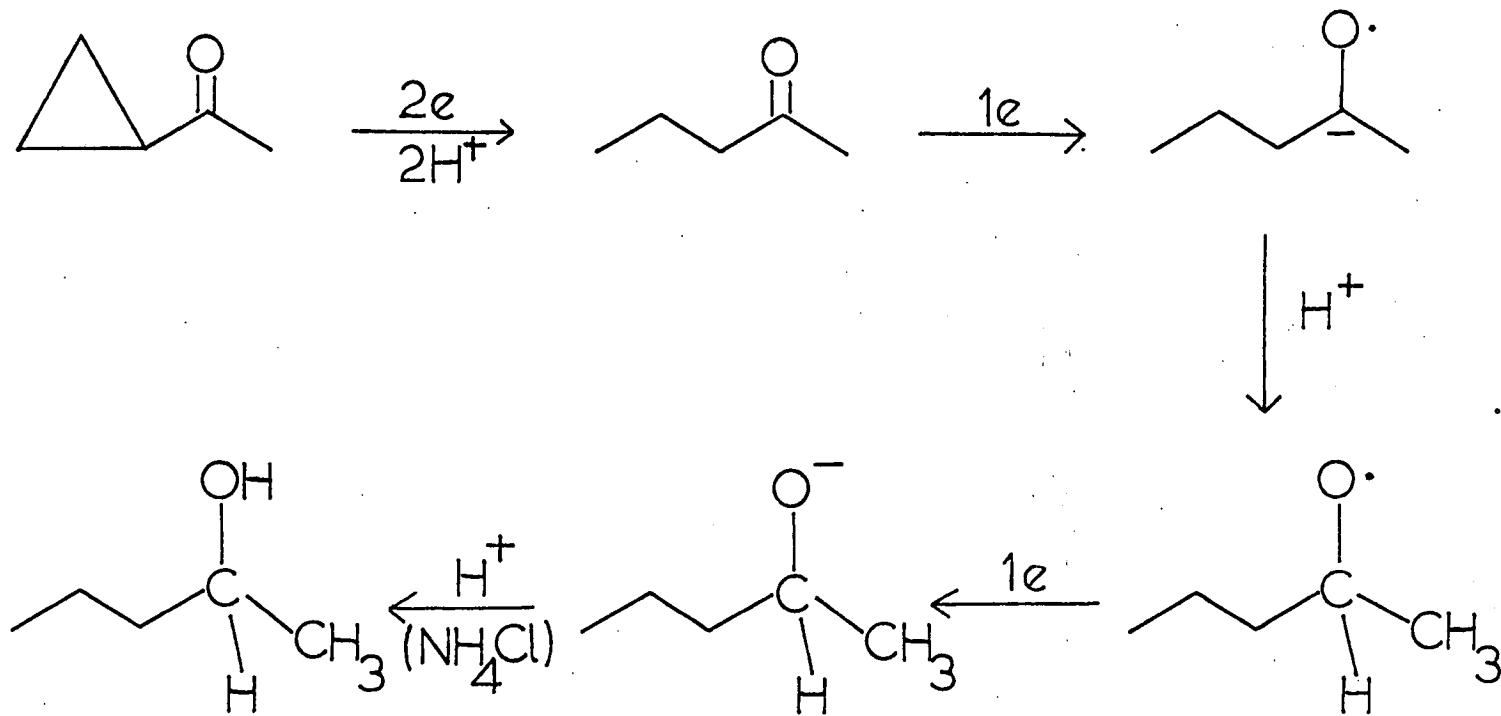


Figure 24

that alcohol formation in the reduction of acetylcyclopropanes occurs in the work up via protonation of the product enolates to produce the free ketones which, in the presence of excess electrons, are further reduced to the alcohols (Fig. 24).

Since the reductions of the deuterium-labelled ketones (13) and (19) did not conclusively prove the existence of an enolate ion (21), though suggesting that such a species was present by virtue of the deuterium 'scrambling' found, two further reductions of the deuteriated ketone (13) were carried out - (a) in the absence of a proton source (i.e. normal reduction), and (b) in the presence of ethanol. The premise to this work was that the presence of a proton source should reduce the percentage of recovered starting ketone obtained as it inhibits the formation of a stable intermediate enolate ion and hence increases the ring-opening probability of the ketone. On chromic acid oxidation of the products from both reductions, v.p.c. analysis showed that the percentage of recovered starting ketone (13) had dropped from 13.3 to 3.4% on incorporation of ethanol in the reduction. This indicates conclusively that an enolate ion is present as an intermediate in the reduction. It was also noted that the ratio of rearranged products (14)/(15) decreased from 2.98 to 1.8 in the presence of ethanol. From Graph 1 (p.18) this effect is equivalent to a decrease in the concentration of lithium in the reduction solution. This is possibly due to solvation of lithium ions by ethanol which reduces ion-pairing between metal cations and the

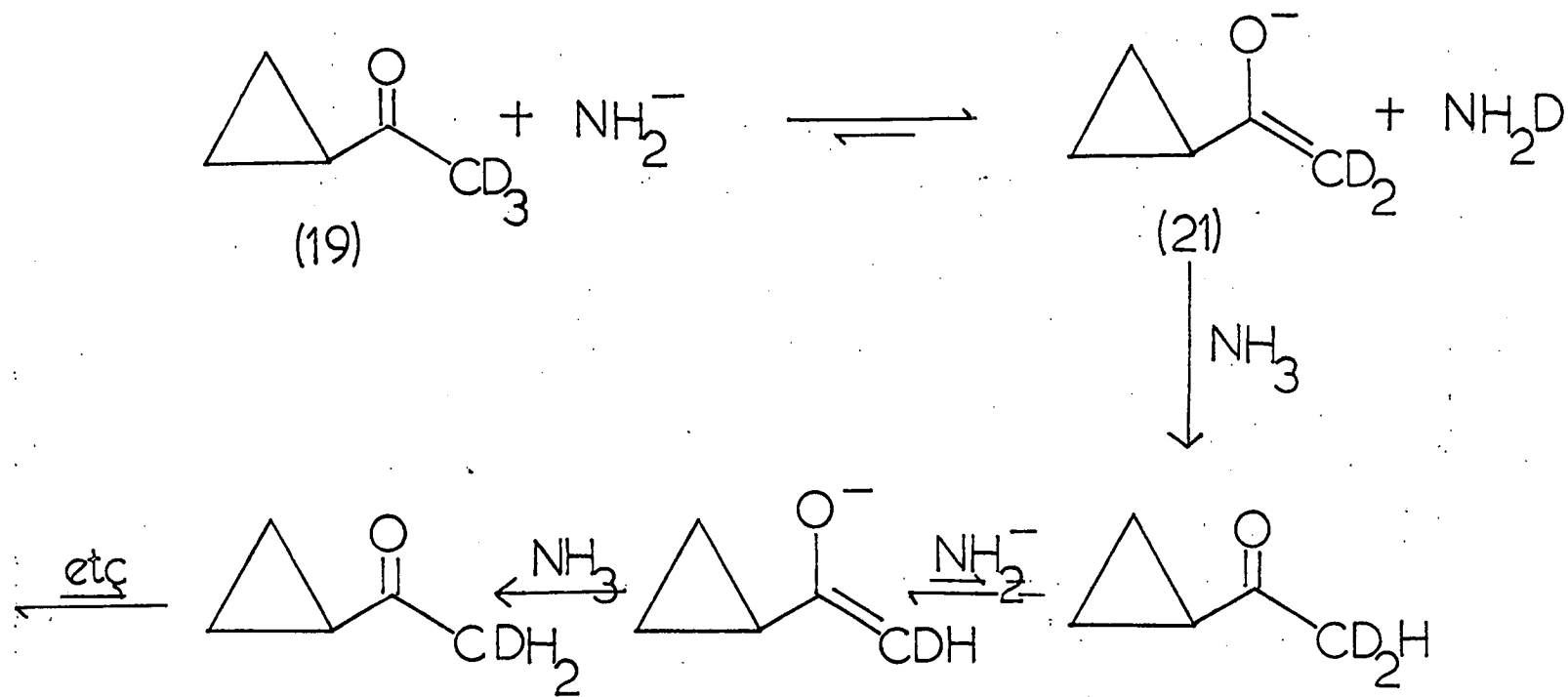
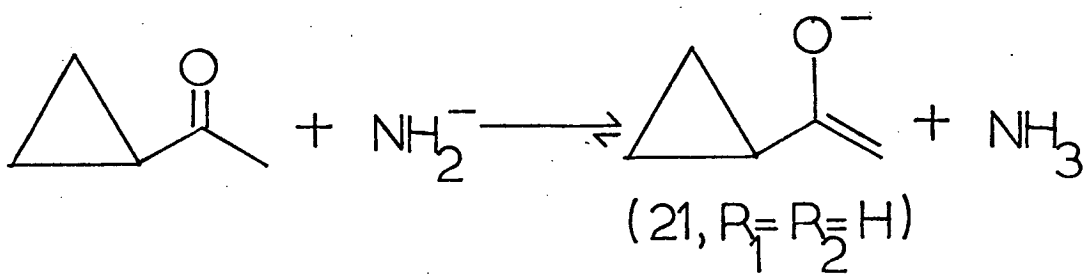


Figure 24a



Equation 1

anions in solution.

The last two experiments prove the existence of an intermediate enolate ion which is responsible, on addition of a proton source, for the regeneration of starting ketone. However, the question still remains as to how this ion is formed and also, how it participates in a mechanism involving repetitive deuterium exchange. Two species, namely, the amide ion (NH_2^-) and the rearranged enolate ion (20) were considered to be sufficiently basic to abstract a proton from the starting ketone (19) to form the intermediate enolate ion (21) (see Fig. 22). If we consider the amide ion to be the proton abstracting base then, for Equation 1, the difference in pK_a values is 12 units in favour of the equilibrium lying to the R.H.S. The deuterium 'scrambling' could be explained by a mechanism of this sort; whereby repetitive exchange of deuterium could take place by interconverting (19) and (21). To investigate this possibility the deuteriated acetylcyclopropane (19) was treated with a 5% potassium amide/ammonia solution.³² After stirring for 2 hours the product was isolated and analysed by ms/v.p.c. From the chosen experimental conditions we would expect 5% of the molecules to undergo deuterium exchange in the absence of a reversible proton abstraction. However, from the results obtained (Table 5) it is obvious that all the molecules are subject to exchange, proving that although the equilibrium shown in Equation 1 lies predominantly to the R.H.S (> 99%), equilibration, via proton abstraction from ammonia by the enolate ion (21), does occur in the manner

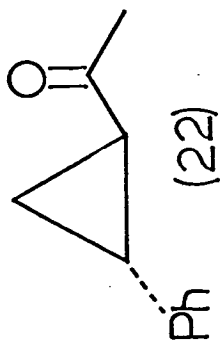
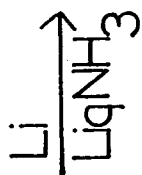
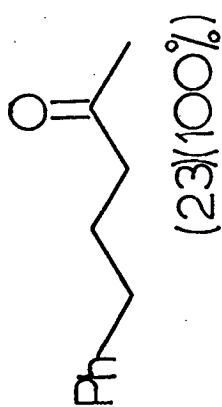
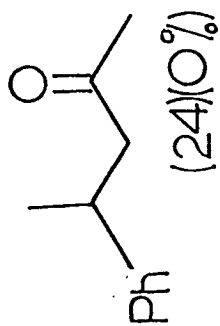


Figure 25

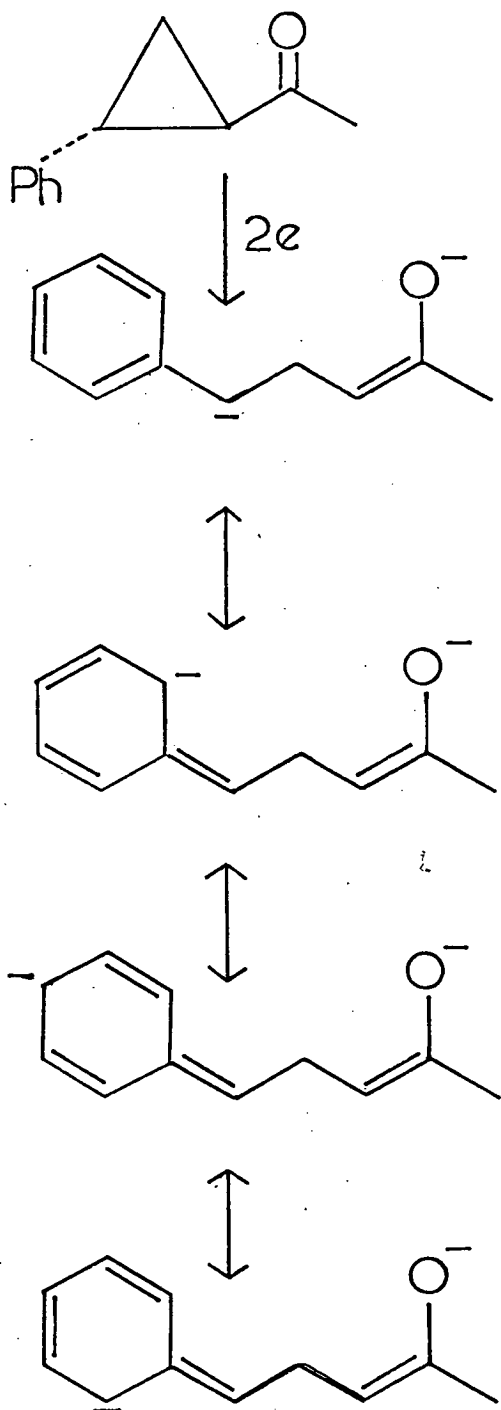


Figure 26

shown (Fig. 24a) to give the deuterium 'scrambled' product mixture.

Reduction of 1-Acetyl-2-phenylcyclopropane with Lithium in Liquid Ammonia.

In the lithium/liquid ammonia reduction of trans-1-acetyl-2-methylcyclopropane it was found, by both Hall¹⁰ and Dauben and Wolf,¹¹ that the ketonic products of rearrangement were hexan-2-one (11) and 4-methylpentan-2-one (12) and, since ketone (12) was the major product (11/12 ~ 0.047), the reduction mechanism of sterically unhindered acetylcyclopropanes was concluded to involve an anionic intermediate. Similar reductions of the same ketone (10) by Jullien and Frejaville¹² found ketone (12) to be the only rearranged product; no evidence of the ketone (11) resulting from C₁-C₂ bond-cleavage was found. The same workers¹² also reported that reduction of trans-1-acetyl-2-phenylcyclopropane (22) yielded only one product, namely, 5-phenylpentan-2-one (23); the rearranged ketone, 4-phenylpentan-2-one (24), resulting from C₁-C₃ bond-cleavage was not observed (Fig. 25). The direction of ring-opening in the case of ketone (22) is the direct opposite of that obtained for the reduction of ketone (10) although, from molecular models, ketone (22) should, like ketone (10), be free from any steric interactions between the acetyl carbonyl group and the trans-2-ring substituent. The anomalous ring-opening pattern shown by ketone (22) was explained by considering the possible resonance forms of the aromatic

ring which help to delocalise the carbanionic charge and thus stabilise the secondary carbanion sufficiently to favour production of the linear rearranged ketone (Fig.26). In this case the competition is between the stability of a phenyl carbanion and a primary carbanion whereas for ketone (10) the competition is between secondary and primary carbanion stabilities.

It was proposed to reduce ketone (22) and examine the reduction product mixture for the presence of ketone (24), resulting from C₁-C₃ bond-cleavage of the ring. It was also hoped that by suitably substituting the benzene ring some information on the electronic character of the transition state would be obtained viz. application of the Hammett equation:

$$\text{Log } k/k_0 = \rho\sigma$$

where k/k_0 is the ratio of the two products formed from the two possible bond cleavages; ρ is the reaction constant and σ the substituent constant.

The premise to this study was that for a carbanion ring-opening of the cyclopropane ring we would expect an increase in the electron density on passing to the transition state and therefore expect a positive value of ρ . By substituting the benzene ring in the *p*-position with an electron donating group e.g. dimethylamino (*p*-Me₂N; $\sigma = -0.60$),³³ we would expect destabilisation of the transition state and thus a tendency to ring-open away from the aryl group by C₁-C₃ bond cleavage. However, if ring-opening of ketone (22) occurs via a radical species then we would expect the ρ value for

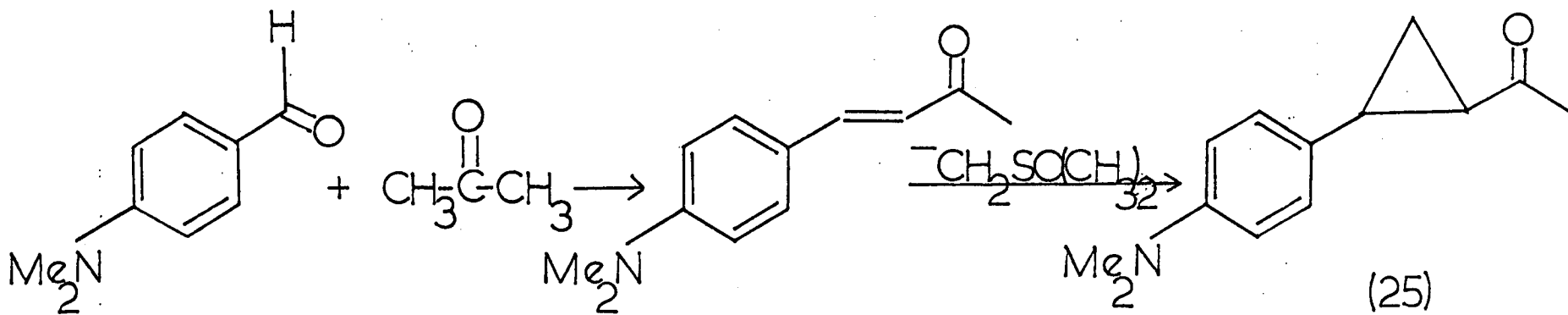


Figure 27

the reduction to be negative on consideration of the radical reactions quoted in the literature³³ which almost invariably have negative values of ρ . In this case, substitution of the aromatic ring by the electron donating p -Me₂N would further stabilise the transition state in favour of exclusive ring-opening towards the aryl group. (It is assumed that the unsubstituted bond-cleavage (C₁-C₃) rate is constant irrespective of the substituent placed on the benzene ring). Thus an examination of the rearranged product(s) from the reduction of ketone (22) and ketone (25), 1-acetyl-2- p -dimethylaminophenylcyclopropane, may distinguish between a radical and a carbanion intermediate in the ring-opening of ketone (22).

The trans-1-acetyl-2-phenylcyclopropane (22) was prepared from 4-phenylbut-3-en-2-one using trimethyloxosulphonium methylide.¹⁹ trans-1-Acetyl-2- p -dimethylaminophenylcyclopropane (25) was prepared by using the same method on 4- p -dimethylaminophenylbut-3-en-2-one, prepared from the condensation reaction of p -dimethylaminobenzaldehyde with acetone (Fig. 27). Since v.p.c. analysis of the product (25) was unsuccessful on an extensive range of columns, analysis of the reduction product had to be undertaken by nmr spectra examination.

In the reduction of ketone (22), v.p.c. analysis of the oxidised product revealed only one major component (~ 98%) identified as 5-phenylpentan-2-one (23) by comparative v.p.c., and several small products (~ 2%). None of these corresponded to the alternative rearranged ketone, 4-phenylpentan-2-one (24). (An authentic sample of ketone (24) was

prepared by the 'abnormal' ~~GAINARD~~ addition of methyl magnesium iodide to 4-phenylbut-3-en-2-one³⁵). It seems, therefore, that ring-opening of ketone (22) occurs exclusively (~ 100%) to give the phenyl stabilised intermediate, as was found by the French workers.¹²

Reduction of 1-acetyl-2-p-dimethylaminophenylcyclopropane (25) gave a product mixture which, like the starting material (25), was not analysable by v.p.c. A nmr spectrum of the final oxidised product showed that the major component (94%) was 5-p-dimethylaminophenylpentan-2-one. No absorptions were observed which corresponded to the tertiary 4-H proton of the alternative product, 4-p-dimethylaminophenylpentan-2-one. However, it was estimated that for concentrations of the latter ketone of less than 10%, the 4-H multiplet absorption would be barely visible in the nmr spectrum. Thus, accurate estimation of the ratio of rearranged products was severely limited by the method of analysis.

The results, however, indicate that even with a strong electron donating substituent on the phenyl group, cyclopropane ring-opening is overwhelmingly towards the aryl substituent. In view of the analytical limitations it was not possible to draw any firm conclusions as to the electronic nature of the transition state at the moment of ring-opening.

Reduction of Benzoylcyclopropane with Lithium in Liquid Ammonia

Benzoylcyclopropane (26) was reduced with lithium in liquid ammonia to establish if any reductive ring-opening to butyrophenone (28) occurred. The reduction process was

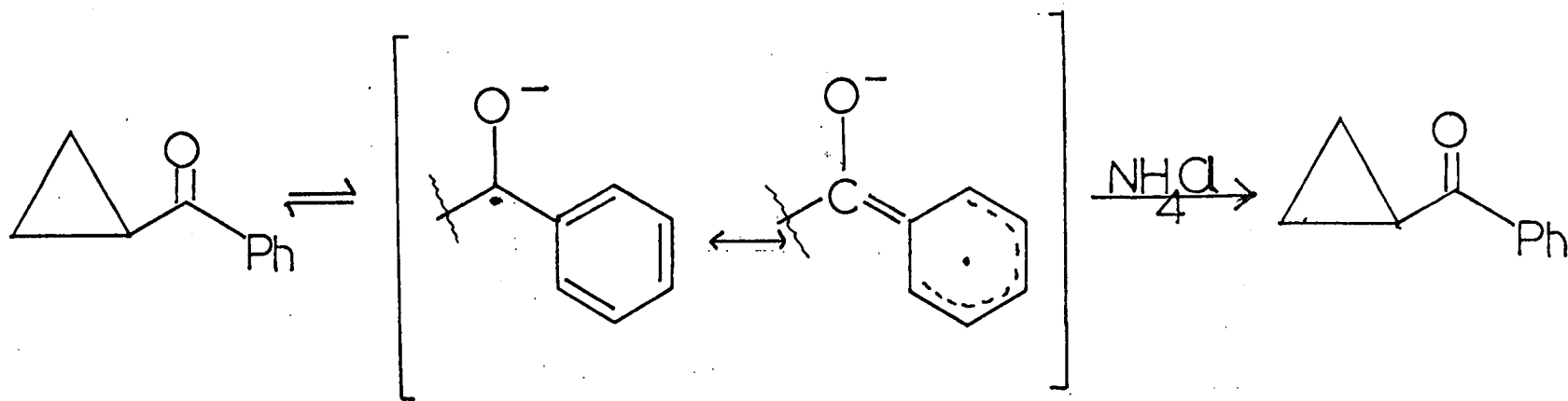


Figure 29

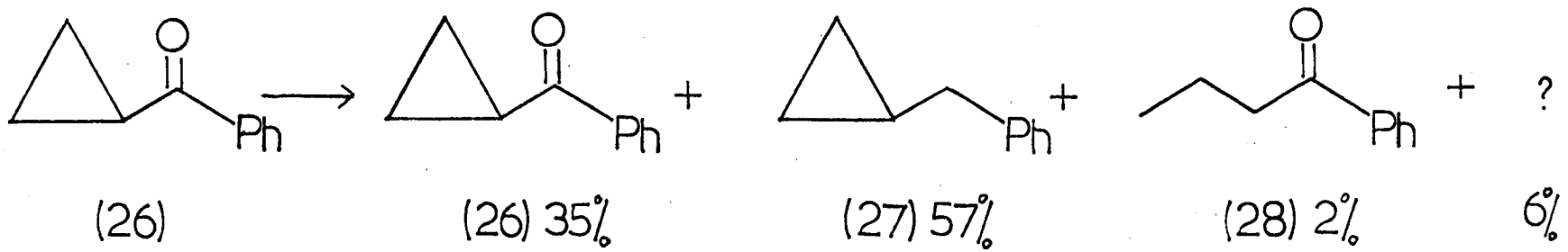


Figure 28

exactly as described for the reductions of ketones (10), (13) and (16). V.p.c. analysis of the oxidised product showed it to be a mixture of 4 components, A(6%), B(35%), c(2%) and D(57%). Preparative v.p.c. separated the two major components, B and D, which were identified from their spectral properties (ir, nmr, ms) as the starting ketone (26) and benzylcyclopropane (27), respectively. Component C(2%) was identified as the ring-opened ketone, butyrophenone (28), by comparison of its v.p.c. retention time with that of an authentic sample of (28). Component A(6%) was not identified. Thus, reduction of (26) gives only 2% rearranged product and is preferentially reduced to the hydrocarbon, benzylcyclopropane (Fig. 28).

The very low percentage of ring-opened product obtained was attributed to charge delocalisation of the intermediate radical or anion species. This would therefore reduce the tendency for cyclopropyl ring-opening and would also regenerate the starting ketone on addition of a proton source (Fig. 29). However, the question remained as to how benzylcyclopropane, in such a high yield, was formed in the reduction process. Hall and co-workers³⁶ have shown that aromatic ketones are reduced to aromatic hydrocarbons by anhydrous lithium/liquid ammonia solutions, followed by an ammonium chloride quench. The reduction was shown to be a two step process; the first (slow) is the conversion of the aromatic ketone to a benzyl alkoxide in lithium/ammonia. The second step (fast) is initiated by the added proton source (NH_4Cl) generating the benzyl alcohol, which in turn is reduced to the aromatic

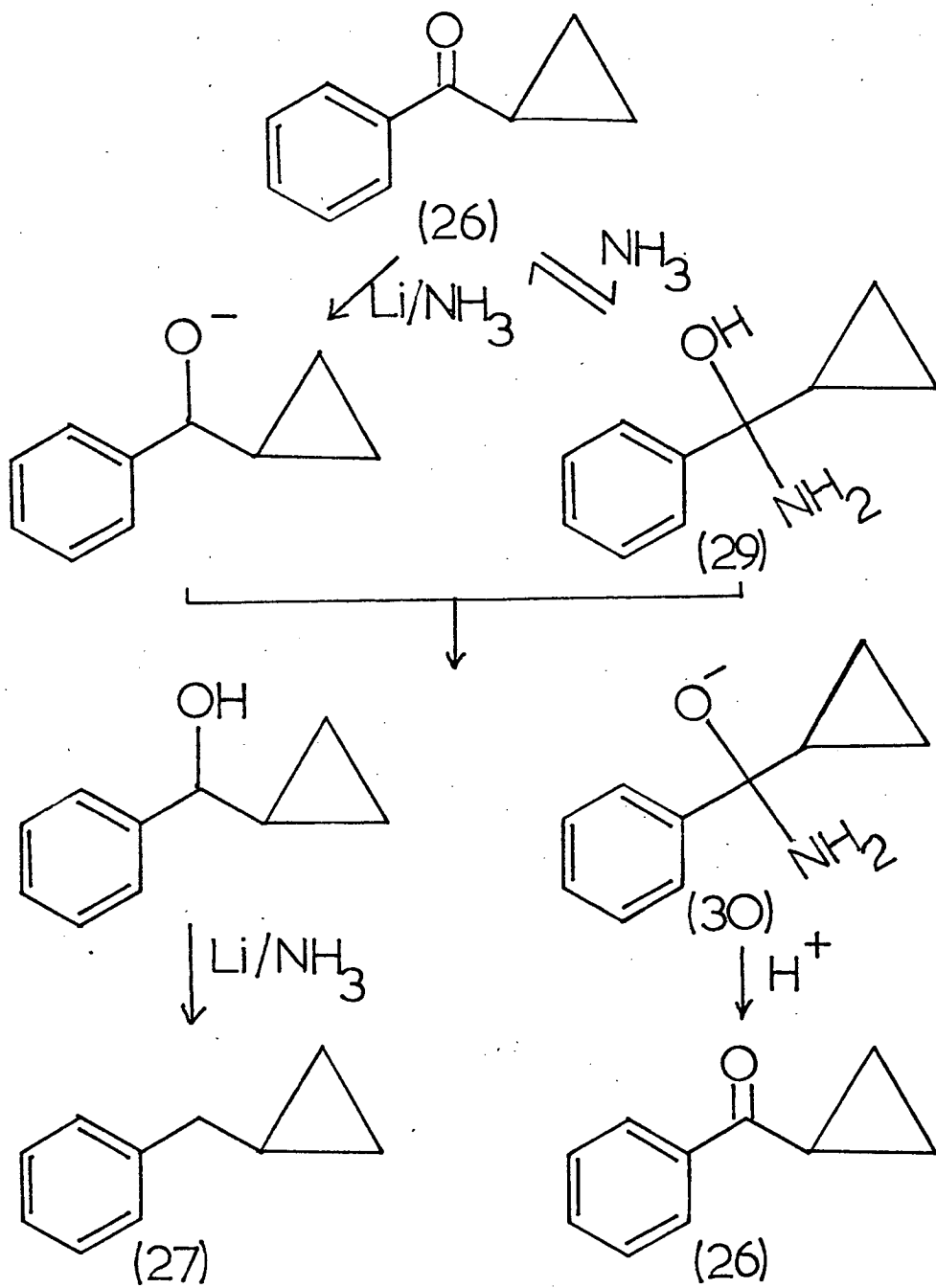
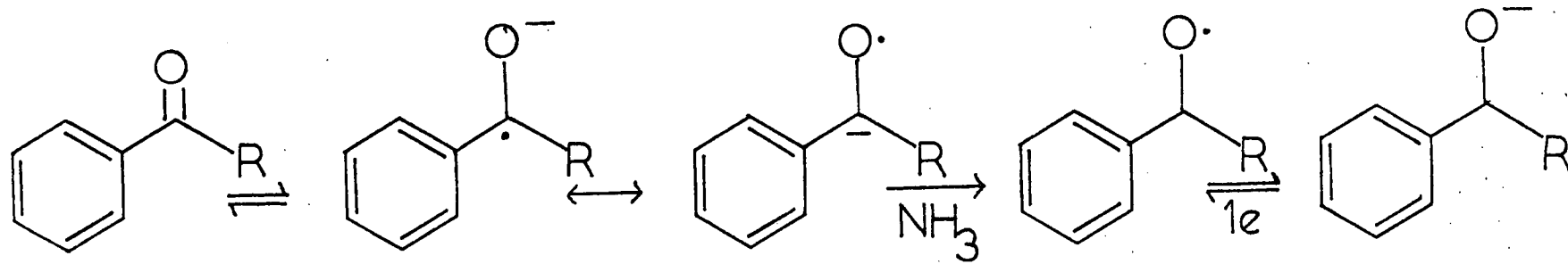
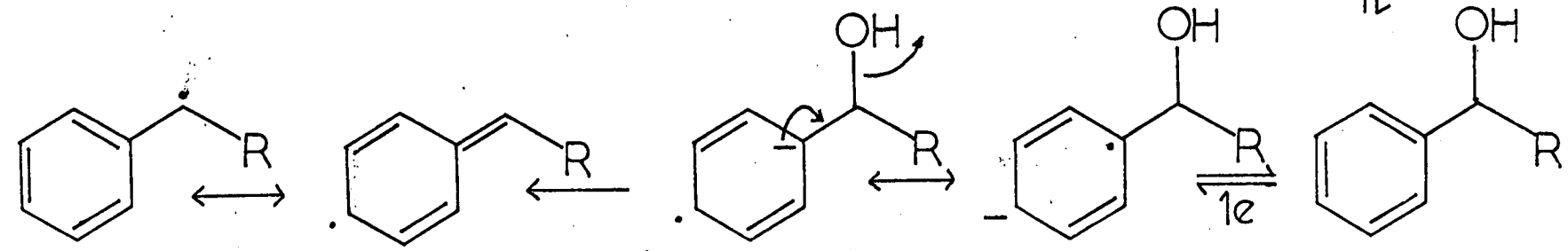


Figure 31



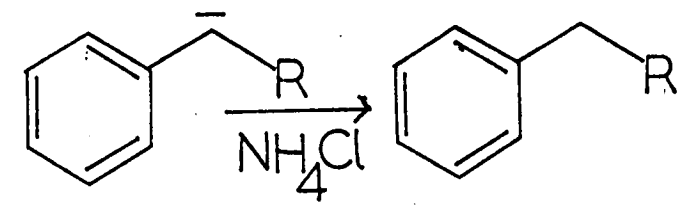
(26, R=cyclopropane)

1st Sequence.



$\uparrow 1e^-$

2nd Sequence.



(27)

Figure 30

hydrocarbon before all the excess lithium is destroyed. It is likely that a similar mechanistic sequence is in operation in the reduction of ketone (26) (see Fig. 30). This mechanism incorporates the accepted reduction mechanisms of ketones to alcohols³⁷ and benzyl alcohols to aromatic hydrocarbons.^{1a}

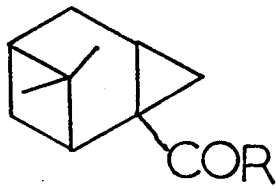
It was suggested earlier that the presence of recovered starting ketone in the reduction mixture of ketone (26) was due to charge delocalisation inhibiting reductive cleavage of the cyclopropane ring (Fig. 29). An alternative explanation involves the hydrobenzamide (29) as a proton source in the reduction. In this rationalisation, ketone (26) is quickly reduced to the alkoxide, protonated by the hydrobenzamide (29), and then is reduced further to the aromatic hydrocarbon (Fig. 31). The anion (30) will resist reduction until ammonium chloride is added, regenerating the starting ketone (26). The reaction scheme outlined in Fig. 31 can therefore explain the presence of both ketone (26) and hydrocarbon (27) in the reduction product of ketone (26). Hall and co-workers³⁰ state that a similar type mechanism is present in the lithium/ammonia reduction of benzaldehydes to toluenes. They found, using sodium benzoate as a quenching agent, that a 1:1 mixture of toluene and benzaldehyde was formed, whereas with an ammonium chloride quench toluene was found to be the main product (~ 90%). This suggested that an equilibrium exists in liquid ammonia between the free aldehyde and the corresponding hydrobenzamide, such that a certain percentage of the aldehyde (~ 50%) is

reduced to the hydrocarbon in the reduction solution. The remaining percentage hydrocarbon observed in the product mixture was generated on the addition of ammonium chloride and suggests therefore, that the latter must be added for complete reduction of the carbonyl to the hydrocarbon.

Since reduction of ketone (26) which involved an ammonium chloride quench gave only 57% hydrocarbon product a further reduction of (26) was performed which involved a sodium benzoate quench followed by the usual isolating procedure. V.p.c. analysis of the oxidised product gave the same four components A, B, C, D, as observed in previous reductions. The yield of benzylcyclopropane (27) decreased from 57% to 26% using the benzoate quench as expected, since the latter destroys excess reducing agent and therefore removes Sequence 2 (Fig. 30) as a means of generating the hydrocarbon.

It is interesting to note that the mechanism outlined in Fig. 31 incorporates the formation of alcohols as a result of the reaction between the benzyl alkoxide and the hydrobenzamide (29). It is feasible that a similar method of alcohol formation exists in the reduction of acetylcyclopropanes (10, 13, 16, 19 etc.) which could partially contribute to the percentage of alcohols observed in the reduction mixture, i.e., a certain percentage of the alcohol product could be formed "internally" in the reduction solution and not exclusively in the work up procedure as depicted in Fig. 24.

In conclusion, it appears that the small amount of cyclopropyl ring opening observed in the reduction of ketone



(A)

(26) is due to the presence of an alternative reaction pathway which preferentially reduces the ketone to the hydrocarbon. The reluctance for benzoylcyclopropanes to ring-open has also been demonstrated by El-Gaied and Bessiere Chretien³⁸ who found that for the lithium-liquid ammonia reductions of cyclopropyl ketones of the type (A) when R=Phenyl, only the epimeric alcohols were obtained. No cyclopropyl ring-opening was observed.

Titration of Lithium-Liquid Ammonia Solutions with Acetylcyclopropanes

In titrations of lithium-liquid ammonia solutions with various ketones Hall¹⁰ found that for acyclic enolisable ketones such as 5-methylhexan-2-one that the mole ratio of lithium to ketone was unity. However, in the titrations of acetylcyclopropanes with lithium/liquid ammonia he consistently found that the mole ratio of lithium used to ketone was also very nearly unity, and not 2:1 as expected from the generally accepted view that reduction of these ketones is overall a 2 electron process. One suggested reason for this was that not all the ketone had been reduced in the titration since some molecules can form an unreactive enolate ion (21; Fig. 22) which does not use up any lithium and regenerates the starting ketone on addition of a proton source. Therefore, if the ratio of rearranged product: starting ketone was unity and the reduction process requires two electrons the overall mole ratio of lithium used:ketone...

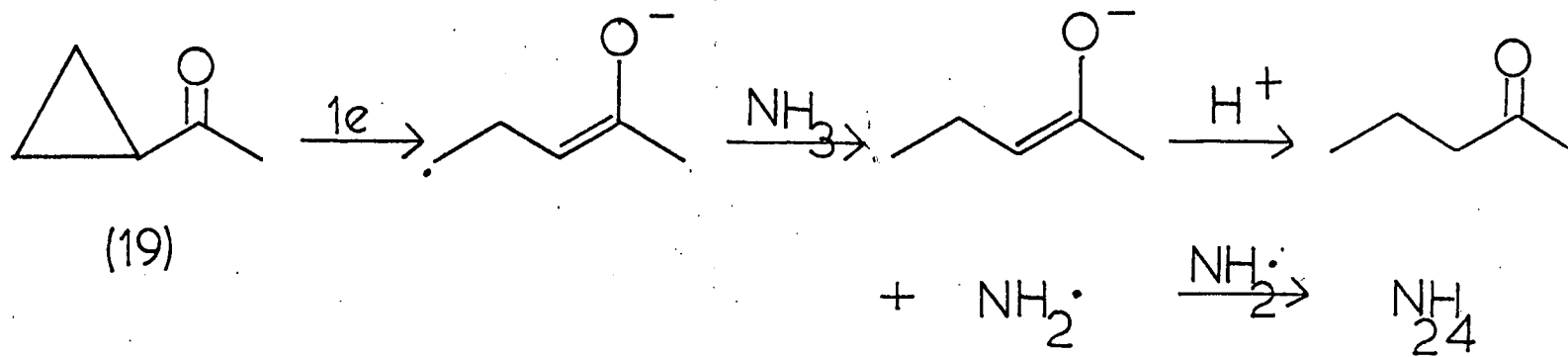
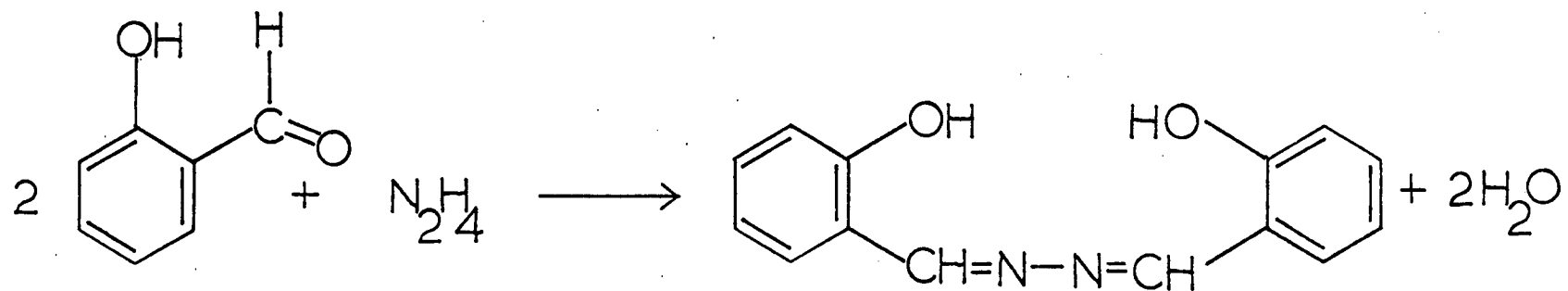


Figure 32



Salazaine

Figure 33

will be unity. However, for ketones (10), (13), and (19) the ratio of rearranged products:starting ketone was found to vary from 0.4 to 4, although the ratio of lithium:ketone was always virtually unity. A ratio 4 (i.e. 80% rearranged product) could not have been produced solely by a 2 electron reduction process and thus Hall's results suggested that reduction was possibly occurring by a 1 electron process (Fig. 32).

Evidence for the occurrence of this scheme would be realised by the detection of hydrazine in the reduction solution. It was tested for by treating the product from the titration of acetylcyclopropane with lithium-liquid ammonia with o-hydroxybenzaldehyde/acetic acid solution³⁹ in the hope of forming the condensation product, o-hydroxybenzaldehydeazine (Salazine)(Fig. 33). This test has been reported³⁹ to be sensitive to 1 microgramme of hydrazine in 1 ml of solution.

A number of titrations were performed by adding the ketone (19) dropwise, by syringe, to a stirred solution of lithium in liquid ammonia until the blue colour was just discharged. The number of moles of ketone required to neutralise the reducing solution was calculated in each case. This was followed by the addition of water (5 ml) and then, after evaporation of the ammonia, a sample of this aqueous solution was treated with one drop of the test solution of o-hydroxybenzaldehyde/acetic acid.

In the first titration of ketone (19), the addition of 1 drop of the test solution to 1 drop of the aqueous

product gave a slight precipitate after 15 mins. Consequently, 5 ml of the test solution were added to the remainder of the aqueous titration product and the resulting solution was extracted with ether. Removal of the solvent gave a white solid (m.p. 240-241^o) which was not the expected condensation product, salazine (m.p. 215^o).³⁹ The possibility that this solid had been formed by the condensation of ketone (19) with benzaldehyde was eliminated since a control reaction, which involved the addition of ketone (19) to a sample of the test solution, yielded no precipitate. This solid was not observed in any subsequent titrations and was not identified.

In two further reductions of ketone (19) no precipitate was observed in the aqueous solution on addition of the hydrazine test solution. Isolation of the product gave an oil which was shown (v.p.c.) to be a mixture of salicylaldehyde and an unknown compound. The nmr spectrum of the latter showed a distinctive triplet (δ 2.1) and singlet (δ 2.0) with an integral ratio of 2:3 and the ir spectrum indicated a carbonyl group, ν_{\max} 1710cm⁻¹. These spectral properties suggested that the unknown compound might be the dimeric ketone, decane-2,9-dione, formed from two C₅ radical species. To examine this possibility a further titration of (19) was performed which involved the addition of acetic acid only to the aqueous titration solution in order to eliminate benzaldehyde contamination of the product, and also to assess the possibility of the unknown being formed in the absence of the aldehyde. Isolation of the titration product as before

gave an oil which was shown by v.p.c. (Apiezon L, 45° ; 140°) to be a mixture of starting ketone (19), pentan-2-one, and the same unknown. This component was positively identified as decane-2,9-dione (31), by comparison of its spectra (ir, nmr, ms) with those of an authentic sample of the dione. A final titration of ketone (19) was carried out which involved only the addition of water in the work up procedure to exclude the possibility of dimer formation being due to the presence of acetic acid. Isolation of the product gave decane-2,9-dione. A rationalisation of the formation of (31) will be given later (p. 45).

Preparation of an authentic sample decane-2,9-dione was achieved by treating ~~the~~ 1,8-dicarbonylchloride⁴³ with a solution of dimethylcadmium in benzene.⁴⁴ Isolation of the product gave a white solid (m.p. $60-61^{\circ}$, lit., m.p. 62° ⁴⁵) which was identified (ir, nmr, ms) as pure decane-2,9-dione (31). (Several unsuccessful attempts to prepare the dione (31) are dealt with in the Experimental section, p.87).

From the titrations of ketone (19) with lithium in liquid ammonia (Table 6) it is apparent that the complete reduction of (19) requires the participation of almost two equivalents of lithium ions for each equivalent of the ketone present in solution. This is in keeping with a 2 electron reduction. Only in the third reduction (entry 3, Table 6) did the ratio of lithium:ketone tend towards unity as is required by a 1 electron reduction process. However, even this reduction, which we might expect to produce the most hydrazine (if reduction is via a 1 electron process),

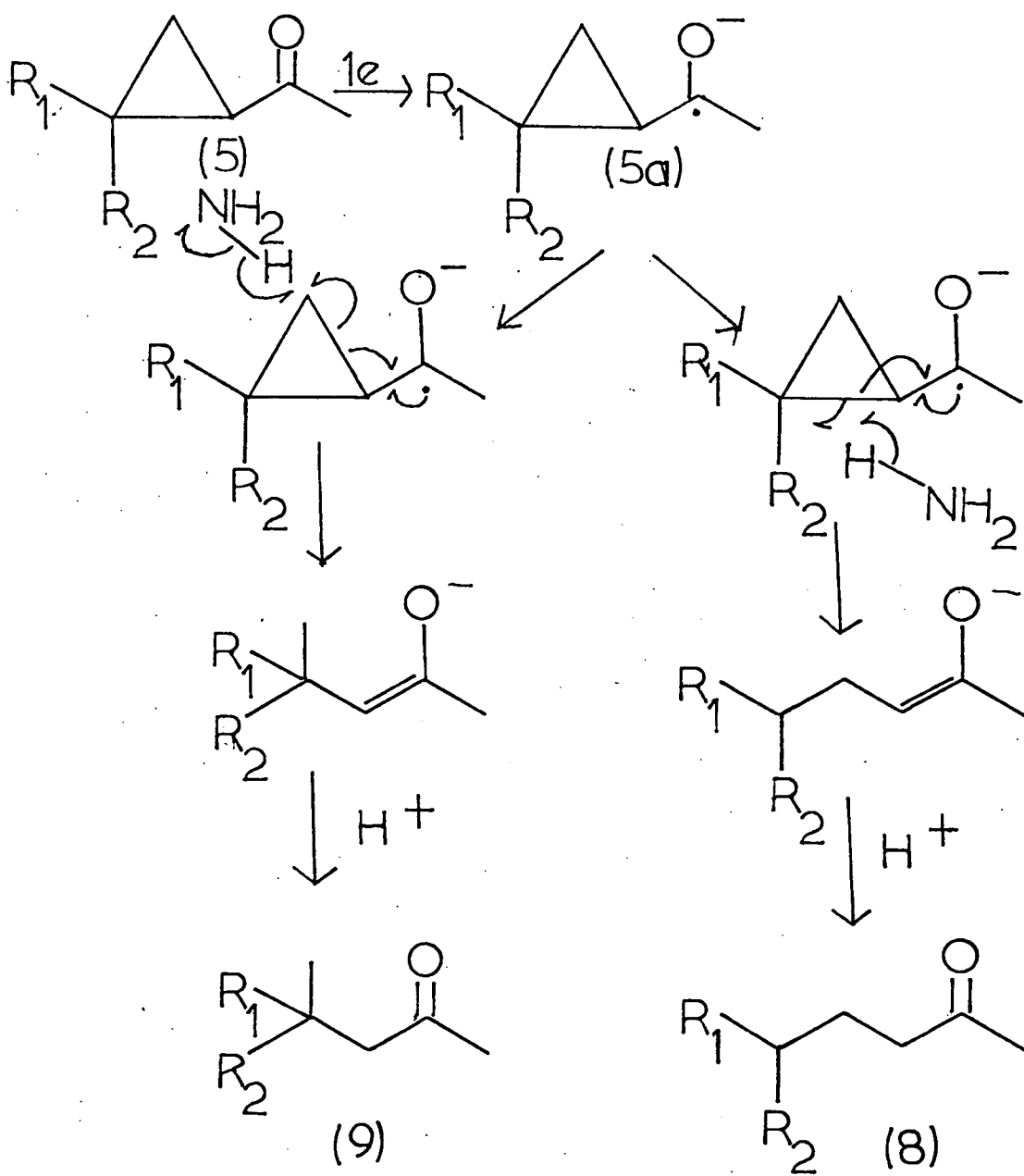


Figure 34

did not give any precipitate with the hydrazine solution. In conclusion, the indication from the titration results is that reduction of acetylcyclopropanes is, as generally accepted, via an overall 2 electron process. This conclusion is contrary to Hall's observations from corresponding titrations. No adequate explanation can be forwarded at present for his observation that the ratio of rearranged products/starting ketone varied so greatly whilst the ratio of lithium/ketone remained unity except, perhaps, that he experienced loss of product; no decane standard was used in his titrations.

In all the lithium/liquid ammonia reductions of substituted acetylcyclopropanes by Hall¹⁰ and in the present work it has been assumed that rearrangement and protonation were separate steps, and that discrete reaction intermediates, in the form of radical anions (5a, 5b), or carbanions (5c), were involved in the reduction process. However, it is possible that rearrangement and addition of hydrogen can occur concomitantly so that the observed reduction products need not be those expected on the grounds of radical or carbanion stability alone (Fig. 34). However, the fact that no hydrazine was observed in the titrations would suggest, at least for a radical type ring-opening, that concomitant rearrangement and hydrogen abstraction is unlikely. The results do not however, disprove the possibility of such a process occurring via an anionic ring-opening after the addition of 2 electrons to the carbonyl.

The isolation of decane-2,9-dione from the titration reactions strongly indicates that some cyclopropyl ring-

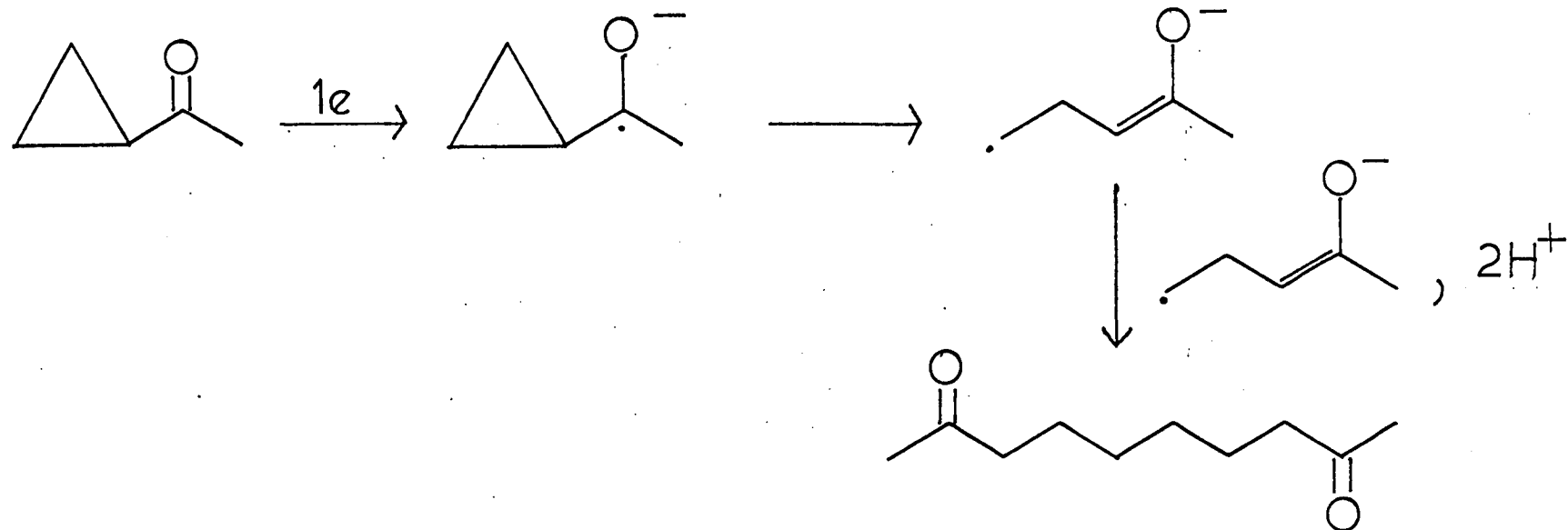
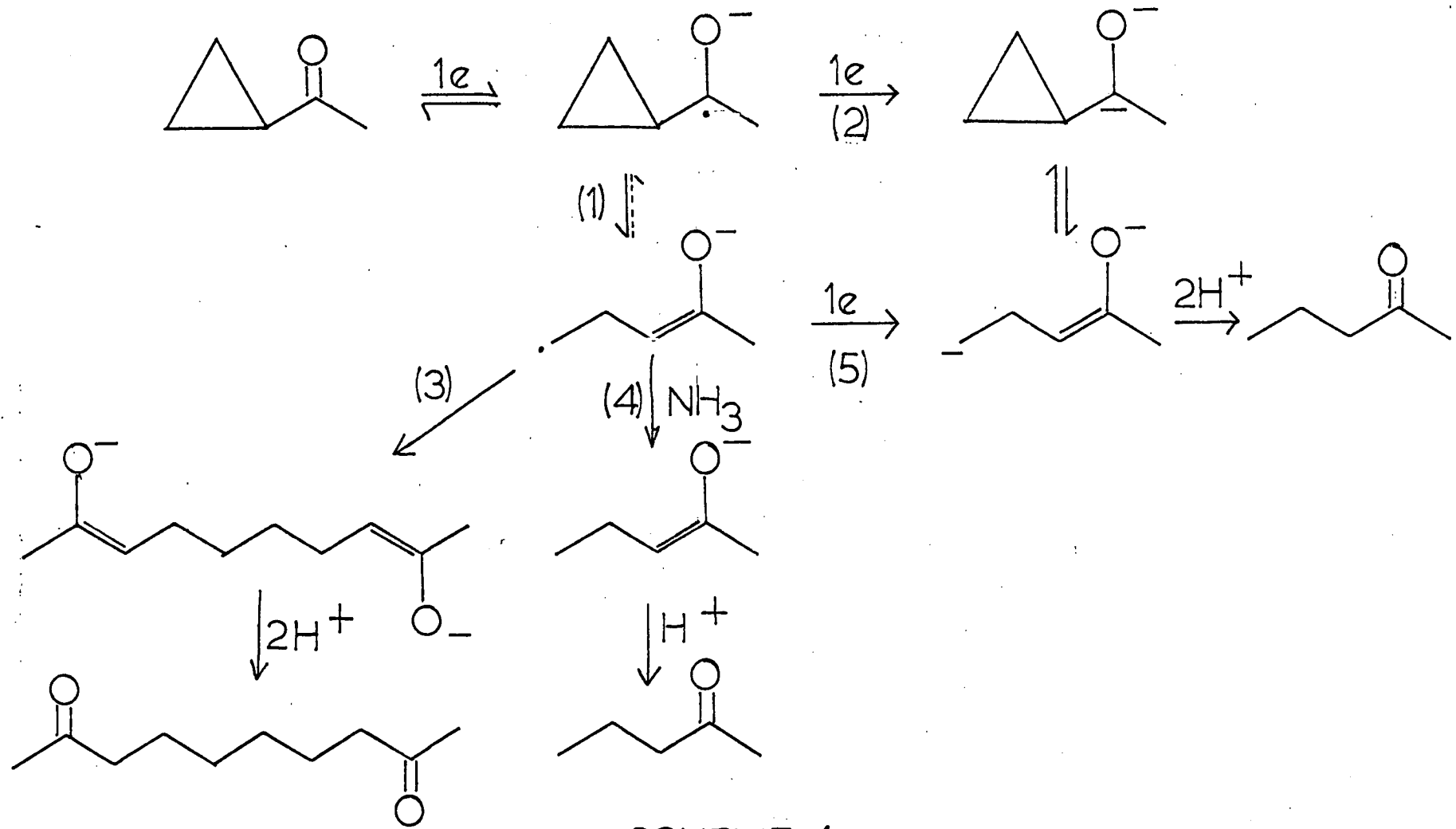


Figure 35

opening is occurring via a radical intermediate to give a radical-enolate species which dimerises (Fig. 35). The possibility of this dimerisation mechanism also being present in titrations of ketone (13) and (10) was investigated.

A titration of 1-acetyl-2,2-dimethylcyclopropane (13) with lithium in liquid ammonia was undertaken by the same procedure described for ketone (19). No precipitate was obtained on addition of 1 drop of the hydrazine test solution to a drop of the aqueous extract from the reaction solution. The products were isolated as an oil which contained (v.p.c., Apiezon L, 165°) a mixture of ketones (13), (14), and (15) (total = 95%), and three minor components which constituted 5% of the total product mixture. Each of these three minor peaks gave molecular ions with mass greater than 200 (exact measurement of the a.m.u. was not possible due to poor resolution of the mass spectrum above 180 a.m.u). This suggests that the high molecular weight components are the three possible dimeric products formed by (a) dimerisation of two species formed from C₁-C₂ bond cleavage, (b) dimerisation of two species formed from C₁-C₃ bond cleavage, and (c) cross-dimerisation.

In the titration of 1-acetyl-2-methylcyclopropane (10), no precipitate of salazine was observed on addition of the hydrazine test solution to the aqueous extract. Isolation of the products gave an oil which showed two peaks on ms/v.p.c. analysis. The major peak (70%) was a mixture of ketones (10), (11), and (12). The ir and nmr spectra of the oil were



SCHEME 1

similar to those of decane-2,9-dione (after allowing for the more volatile components (10), (11), (12)) and its mass spectrum showed a molecular ion at 141 a.m.u. which probably corresponded to the cation formed by loss of an acetyl radical ($\text{CH}_3\text{COCH}_2\cdot$) from the dimeric ketone (MW = 198). The ratio of rearranged ketones (11)/(12) was found to be 0.088 which was quantitatively in agreement with the value found by Hall (0.045). This indicates that even under these conditions, viz. no excess lithium, ring-opening to the rearranged ketones involves an intermediate anionic species.

However, the titration experiments on ketones (19), (13), and (10) show that ring-opening of the cyclopropane ring via a radical type mechanism is a significant reduction pathway. For ketone (19) this leads to around 40% dimeric product in the reduction mixture. For ketones (10) and (13) dimerisation is reduced to $\sim 30\%$ and $\sim 5\%$ respectively as would be expected from consideration of a steric factor i.e. the possibility of the rearranged radical-enolate from ketone (13) dimerising should be less than that for the same species from ketone (10) due to the steric inhibiting effect of the two methyl groups.

Considering the titration results along with the 'normal' lithium-liquid ammonia reduction results of the substituted acetylcyclopropanes it appears that the concentration of lithium ions in solution is a major influence on the direction and mode of opening of these ketones. From these considerations Scheme 1 is postulated. The first step is the

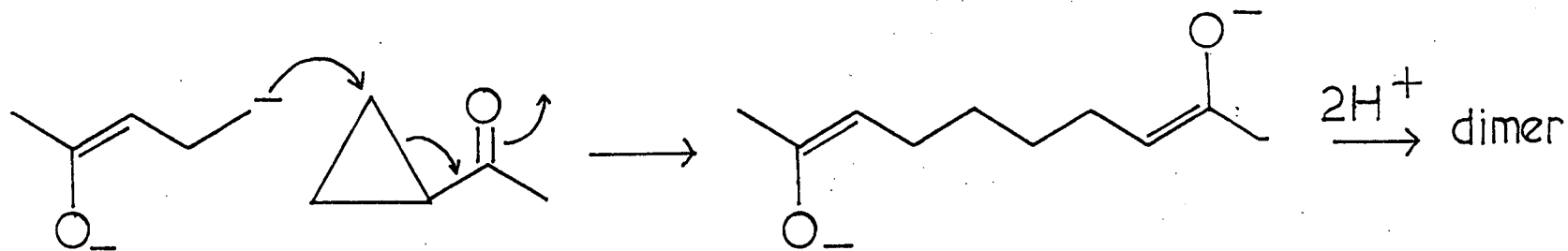
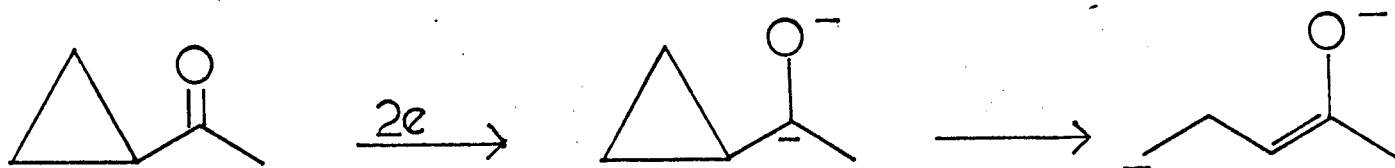


Figure 35a

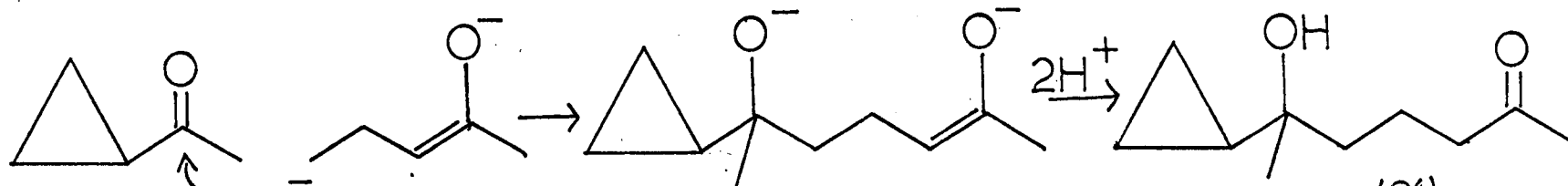


Figure 35b

(31a)

reversible uptake of an electron by the ketone to form the anion-radical. At low concentrations of lithium, e.g. the titration experiments, ring-opening of the radical-anion occurs (Step 1) to give the radical enolate. This species can be consumed in three possible ways, by Steps (3), (4) (5). We would expect that a radical-enolate with no bulky substituents on the C₅ carbon could easily dimerise at low lithium concentrations as is found for ketones (10) and (19).

The fact that no hydrazine was detected in the titration reactions removes the likelihood of Step 4 being present.

As the concentration of lithium is increased we can envisage Step 2, giving the dianion, being increasingly important. By the same token, the radical-enolate from Step 1 will have an increased tendency to pick up a second electron, Step 5, (and consequently reduce the probability of dimerisation) to give the carbanion-enolate. To explain the competition between C₁-C₂ and C₁-C₃ bond cleavage in ketones (10), (13), and (16), this carbanion-enolate must then equilibrate with the cyclopropyl dianion which can ring-open by an anionic mechanism to give the rearranged ketone products.

In summary; at low concentrations of lithium metal we expect reduction via Steps 1 and 3 to be significant, but as the concentration of lithium metal increases we expect Steps 2, 1 and 5 to be the predominant routes.

It is feasible that the dimeric product, decane-2,9-dione, could have been formed by the attack of a carbanion-enolate species on a molecule of the starting ketone as indicated in Fig. 35a. However, it is far more likely that

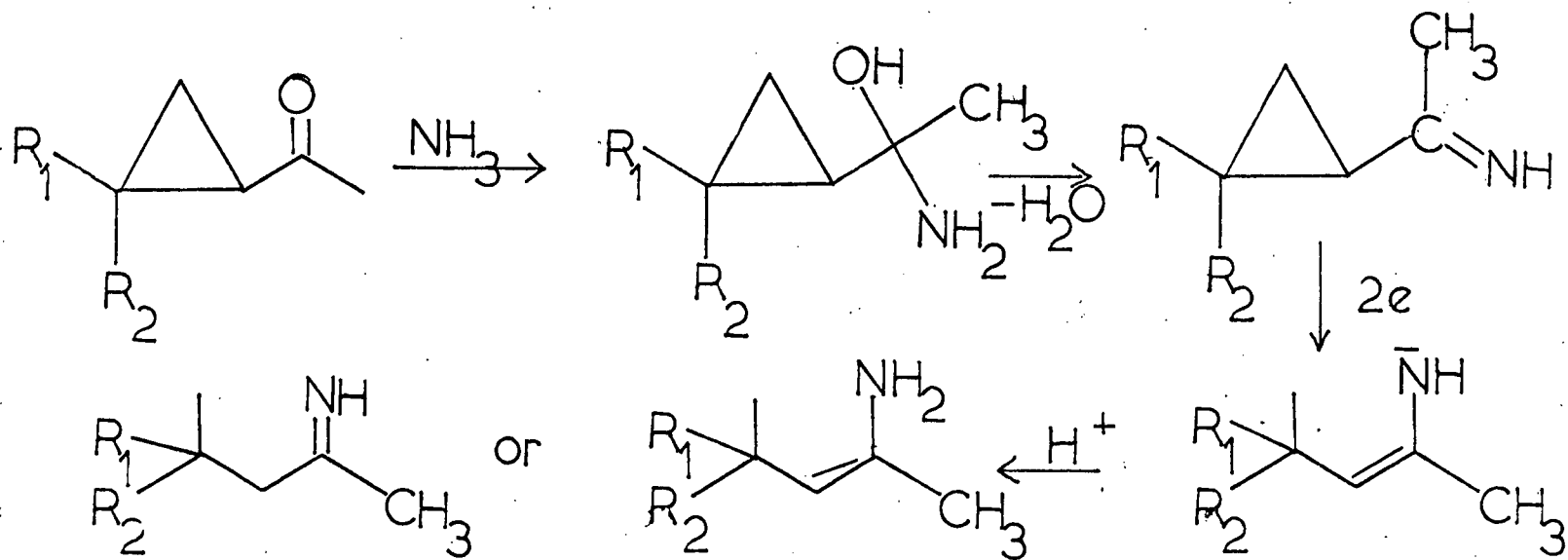


Figure 36

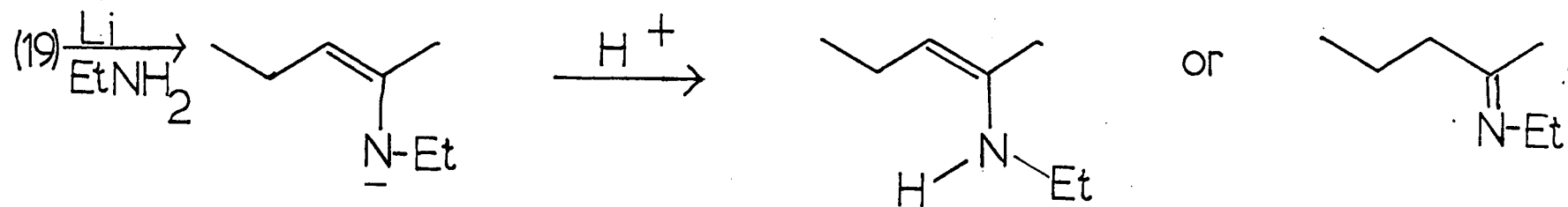


Figure 36a

this species would abstract a proton from ammonia to give the corresponding enolate ion (see Fig. 21). It is also likely that any attack of this carbanion-enolate species on the starting ketone would preferentially occur at the carbonyl group to give a cyclopropyl-enolate intermediate (Fig. 35b) rather than the dimeric precursor postulated in Fig. 35a. No trace of the saturated cyclopropyl compound (31d) was observed in the titration reactions which indicates that the sequence Fig. 35a does not occur.

Reduction of Acetylcyclopropane with Lithium in Ethylamine

Although no nitrogen containing products were ever isolated or identified in the reductions of acetylcyclopropanes in liquid ammonia they could possibly be formed as outlined in Fig. 36. To investigate this possibility, acetylcyclopropane was reduced in lithium/ethylamine and the products were analysed for either of the nitrogen compounds postulated in Fig. 36a. The reduction of ketone (19) was performed in a similar manner to the lithium/liquid ammonia reductions. The isolated product was shown to be a mixture of acetylcyclopropane (81%) and pentan-2-one (19%). A sodium fusion test for nitrogen on the product mixture was negative indicating that no nitrogen containing compounds were present.

Reduction of 1-Acetyl-2,2-dimethylcyclopropane with Metals in Hexamethylphosphoramide (HMPA).

Reduction of ketone (13) was carried out by adding the ketone dropwise, by syringe, to a homogeneous solution of the metal in HMPA.⁴⁶ After stirring at room temperature, the excess of metal was destroyed by adding methanol and the mixture was partitioned between water and pentane. The crude product was then oxidised (chromic acid) and examined by v.p.c. Three reductions of ketone (13) with lithium in HMPA were performed, two of which were given different reaction times, and the third incorporated a proton source in the reduction solution (Table 7, entries 1, 2, 3 respectively).

The three expected products namely, ketones (13), (14) and (15) were obtained and ketone (14) was found to be the major product in each reduction. From the Table the ratio of rearranged products, (14)/(15) was 1.3 (average). These are smaller than the values found for corresponding reductions of ketone (13) in liquid ammonia and appear to be independent of the reaction time. The incorporation of a proton source in the reduction mixture (entry 3) however, increased both the ratio of (14)/(15) and the percentage of ring-opening to values similar to those found in lithium/liquid ammonia reductions.

Reduction of ketone (13) with a solution of sodium/HMPA/t-butanol (entry 4) gave similar results to the third lithium/HMPA reduction.

In conclusion, it appears that reduction of ketone (13) with metal/HMPA solutions occurs by a similar mechanism to

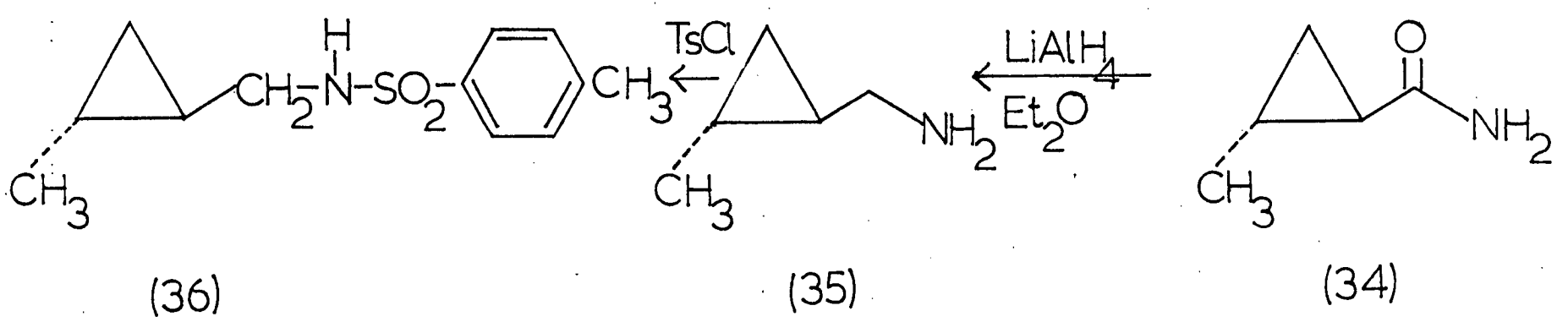
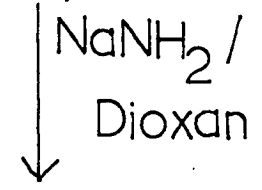
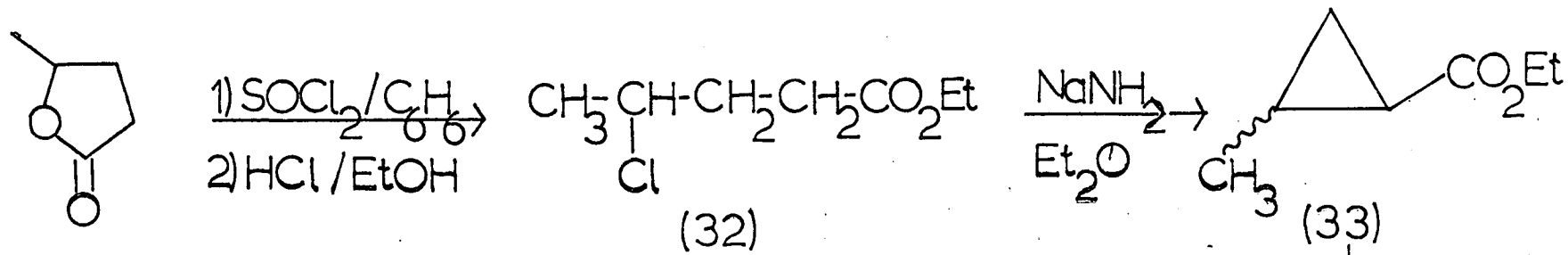


Figure 37

reductions of the ketone in metal/liquid ammonia solutions. From the ratio of products (14)/(15), rearrangement of the cyclopropane ring involves an anion intermediate.

Ring-Opening of Substituted Cyclopropanes via a Carbanion Intermediate.

Since the lithium/ammonia reduction of acetylcyclopropanes has been shown to proceed via a mechanism involving a carbanion intermediate, it was of interest to synthesise trans-2-methylcyclopropylmethylamine (35) and attempt to generate a carbanion on the carbon α to the cyclopropane ring, via the Nickon-Sinz reaction,⁵⁶ in order to study the preferred direction, if any, of ring-opening. Cram and Bradshaw⁵⁷ have reported that this reaction⁵⁶ proceeds via a carbanionic mechanism. Preparation of the amine (35) was undertaken as outlined in Fig. 37.

Ethyl 4-chloropentanoate (32), obtained in 67% yield from tetrahydro-5-methyl-2-furanone, was shown (v.p.c.) to contain 4% impurity in the form of the unreacted lactone. In the presence of a large excess of thionyl chloride this reaction gave a product mixture composed of the chloro-ester (32) (75%) and diethyl sulphite (25%) formed from the reaction between ethanol and the thionyl chloride.

Treatment of the chloro-ester (32) with an equimolar amount of sodium amide in ether⁵⁰ gave ethyl cis-/trans-2-methylcyclopropylcarboxylate (33) (cis:trans \cong 1:4) in 64% yield, containing less than 1% impurity by v.p.c. In a similar reaction, the chloro-ester (32) with a two-fold excess of sodium amide in ether gave a crystalline product

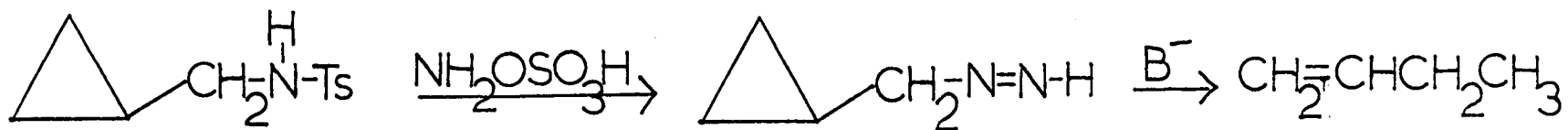
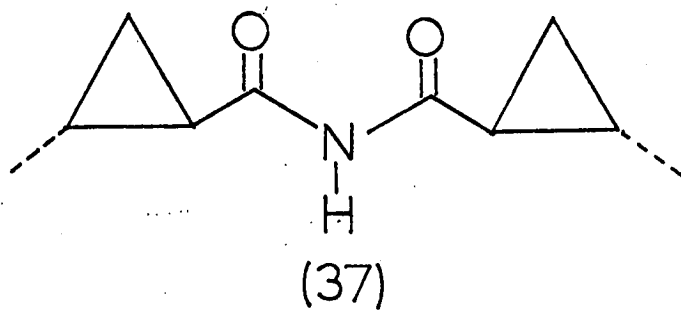


Figure 37a

(m.p. 162-164°) which was identified (ir, nmr, ms) as trans-2-methylcyclopropyl imide (37). The production of this compound was not due to the presence of excess sodium amide since treatment of the chloro-ester (32) with a three-fold excess of sodium amide gave only the cyclic ester (33).

trans-2-Methylcyclopropylcarboxamide (34) was prepared by treating a cis/trans mixture of the cyclic ester (33) with a suspension of sodium amide in boiling dioxan. Recrystallisation of the crude product (ex pentane/methylene chloride) gave the pure trans-amide (m.p. 109-110°) in 20% yield. Reaction of the ester (33) with a solution of methanolic ammonia gave (34) in only 3% yield.

Attempts to prepare the trans-2-methylcyclopropylmethylamine (35) by reacting the amide (34) with diborane⁵³ gave only unreacted starting material (34). However, reduction of the amide with lithium aluminium hydride in ether⁵⁴ gave the amine, which was not isolated at this stage, but was immediately treated with toluene-p-sulphonyl chloride in pyridine. Isolation of the product gave a crystalline solid (m.p. 40-41°) which was identified (ir, nmr, ms, chemical analysis) as pure N-(trans-2-methylcyclopropylmethyl)toluene-p-sulphonamide (36).

Bumgardner, Martin and Freeman⁵⁸ have reported the successful treatment of N-cyclopropylmethyl toluene-p-sulphonamide with hydroxylamine-O-sulphonic acid and base to give an intermediate which rearranges, through a carbanion species, to give but-1-ene (Fig. 37a). However, Hall¹⁰ found that a similar reaction between N-1-(trans-2-methylcyclopropyl)ethyl toluene-p-sulphonamide and the sulphonic acid

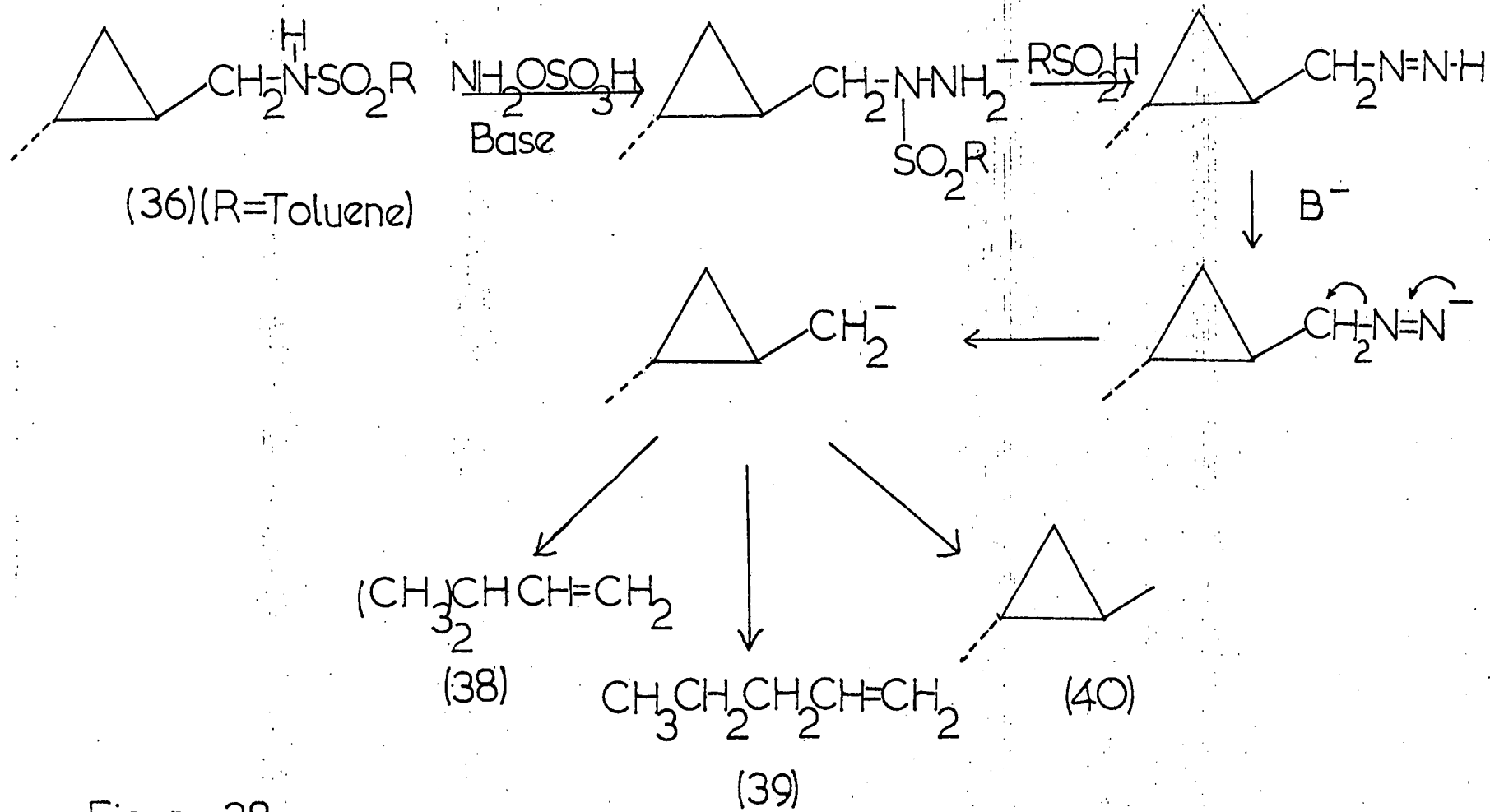


Figure 38

gave no detectable ring-opening.

The proposed reaction of N-(trans-2-methylcyclopropylmethyl)toluene-p-sulphonamide (36) with hydroxylamine-O-sulphonic acid can be formulated as shown in Fig. 38. The generated carbanion could ring-open to give 3-methylbut-1-ene (38) by C_1-C_3 bond-cleavage, pent-1-ene (39) by C_1-C_2 cleavage, or alternatively, it could pick up a proton to give trans-1,2-dimethylcyclopropane (40).

The Nickon-Sinz reaction was first carried out on cyclohexyl toluene-p-sulphonamide since the latter was more readily available than compound (36). Analysis (v.p.c.) of the ethanolic fraction distilling at 80-85° showed that successful reductive deamination to cyclohexane had occurred.

The reaction was then performed on the amine derivative (36) as described in the Experimental (p.100). After the complete addition of hydroxylamine-O-sulphonic acid to the solution of (36) in sodium hydroxide/ethanol in each reaction, the mixture was heated until 10 ml of solvent had distilled into ice-cold carbon tetrachloride. The products were analysed by v.p.c. using both gas and direct injection. A large number of peaks were observed in the v.p.c. trace in addition to the three expected products, (38), (39), (40). It was initially thought that some of these peaks might be due to products formed by rearrangement of the two expected olefins (38), (39) and/or 1,2-dimethylcyclopropane (40) e.g. 2-methylbut-2-ene, 2-methylbut-1-ene, cis/trans-pent-2-ene. However, this possibility was eliminated by comparative v.p.c. since none of the peaks corresponded to those of

authentic samples of the possible rearranged products. It was subsequently shown by 'control' reactions, which involved adding hydroxylamine-O-sulphonic acid to N-methyl toluene-p-sulphonamide and to the ethanol/base solution in the absence of (36) that all the 'extra' peaks could be attributed to the solvents (EtOH, CCl₄) and/or to products derived from ethanol and the toluene-p-sulphonamide fragment in the presence of hydroxylamine-O-sulphonic acid.

The results of a number of Nickon-Sinz reactions using varying base concentrations and conditions are summarised in Table 8. Pent-1-ene was found to be the favoured product of rearrangement in all but one (1a) of the reactions employing aqueous basic conditions. This suggests that ring-opening does not occur via a carbanion intermediate as expected from the chosen reaction conditions but by a radical rearrangement. Cram and Bradshaw⁵⁷ have observed that in the reactions of the intermediate diazene species formed by the application of the Nickon-Sinz and related procedures to optically active systems, in all solvent systems except pure water, there is a threshold base concentration above which rearranged products are obtained solely via a carbanionic intermediate. Thus for runs 4(a) and 4(b) (Table 8) employing non-aqueous conditions we might expect 3-methylbut-1-ene (38), from a carbanionic ring-opening, to be the major product. However, even under these conditions olefin (38) is found to constitute only ~ 75% of the cleavage products, the remainder being pent-1-ene (39). This indicates that some non-carbanionic ring-opening pathway is occurring which competes with the carbanionic route.



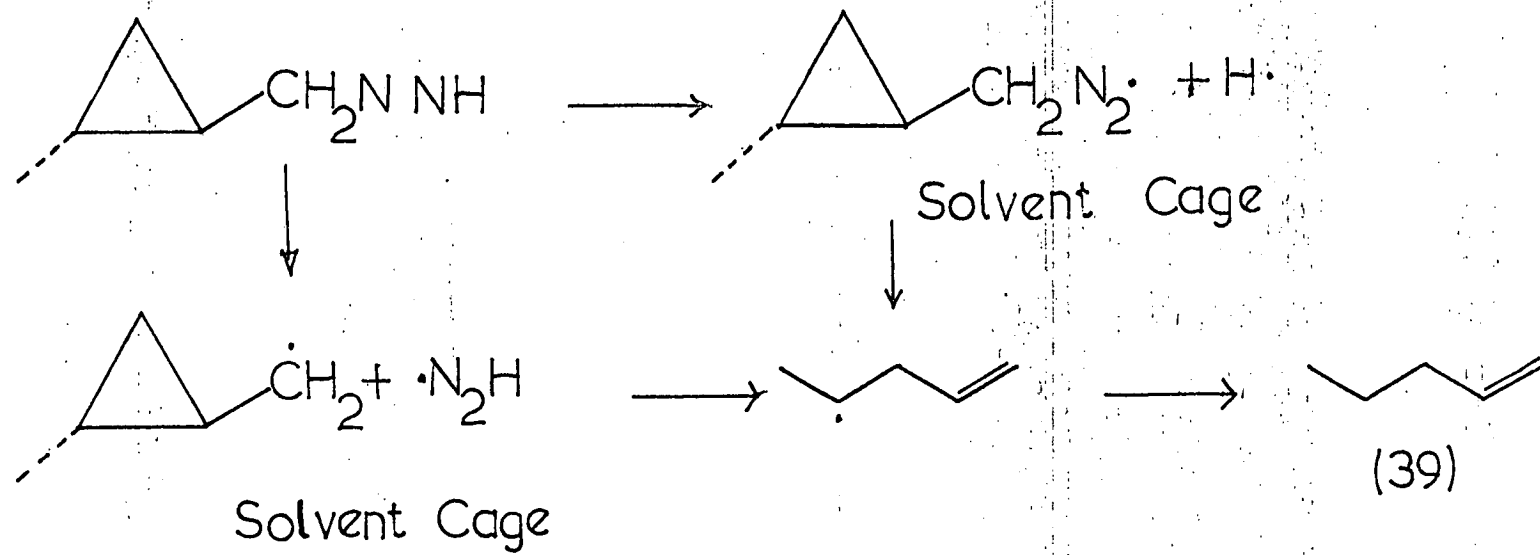


Figure 39

Reaction 1(a) seems to contradict the findings of reactions 1(b), (c), (d), 2(a), (b), (c) and 3(a), (b) in that 3-methylbut-1-ene (38) is the major product. One possible explanation is that this happened to be the first reaction undertaken and involved extensive manipulation whilst optimum conditions for analysing the product on the vacuum line were being sought. This could result in preferential loss of pent-1-ene (39) relative to 3-methylbut-1-ene (38). It is also noted from runs 1(b), (c) and (d) that the manner of introduction of the sulphonic acid (37) to the reaction has no effect on the rearranged product ratio although with run 1(b), where the acid was present in the reaction vessel as an ethanolic solution, the yield of products was reduced. The third possible product from the Nickon-Sinz reaction, 1,2-dimethylcyclopropane (40) was observed only in runs 1(a), (b), (d) which used a sensitive vacuum line system for analysis of the products. Compound (40) constituted only 4% (average) of the total product mixture.

The results in Table 8 suggest that the Nickon-Sinz reaction involves a non-base-catalysed process which could occur by either of two processes. The first involves a homolytic cleavage of either the carbon-nitrogen or the nitrogen-hydrogen bond of the intermediate alkyldiazene followed by disproportionation of the radical pair formed within the solvent cage (Fig. 39). The 'solvent-cage' concept is strongly implicated since no dimeric products were found in the Nickon-Sinz reactions.

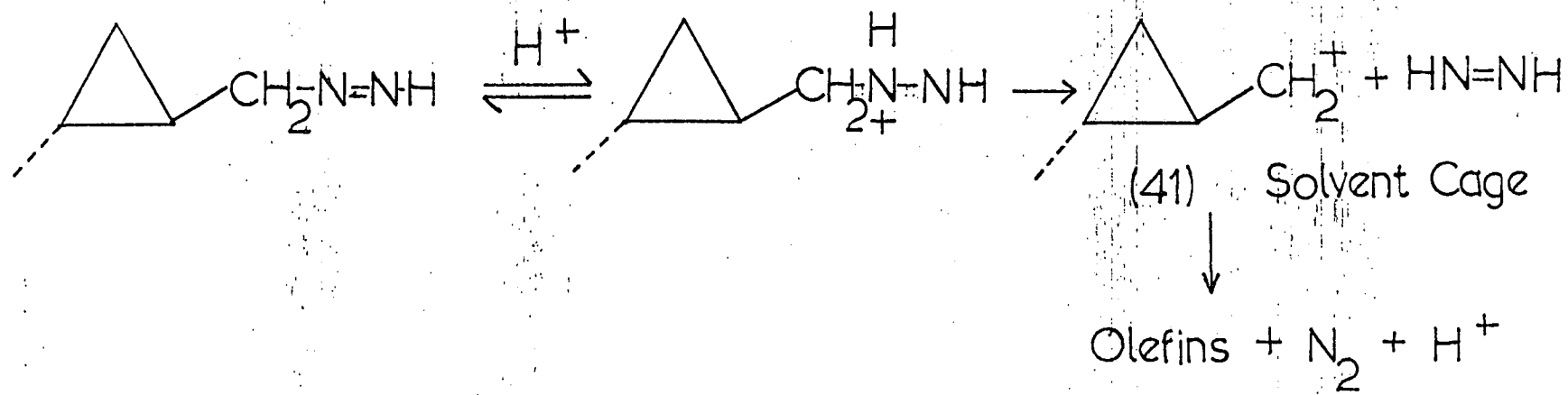


Figure 40

The second possible mechanism is acid-catalysed, and involves initial formation of the cation (41) and diazene (Fig. 40). This mechanism was considered unlikely since Cram⁵⁷ could not detect the presence of diazene in any corresponding non-base catalysed rearrangements of 2-phenylbut-2-yl diazene.

It is known^{60,61} that hydroxylamine-O-sulphonic acid in the presence of aqueous or methanolic alkali yields diazene which is capable of hydrogenating olefinic double bonds. This could occur in our system, with the result that the ratio of olefinic products observed need not be a true indication of the actual ratio formed in the ring-opening. To investigate the relative rates of hydrogenation of (38) and (39) by diazene an approximately equimolar mixture of the olefins was treated with an excess of anthracene-9,10-di-imine (prepared from the reaction of diethyl anthracene-9,10-dicarboxylate⁶² and methanolic sodium hydroxide) in hot ethanol⁶³ (60°). V.p.c. analysis of the product solution showed it to be a mixture of 2-methylbutane (36.8%), 3-methylbut-1-ene (9.7%), pent-1-ene (7.9%) and pentane (41.8%). The relative rates of hydrogenation of (38) and (39) were then calculated from the equation:⁶⁴

$$\frac{k_1}{k_2} = \frac{\text{Log}[A]/[A_0]}{\text{Log}[B]/[B_0]}$$

where $[A]/[A_0]$ and $[B]/[B_0]$ are the fractions of pent-1-ene (39) and 3-methylbut-1-ene (38) remaining at the end of the reaction, and k_1 and k_2 are the rate constants for hydrogenation of (39) and (38) respectively. Therefore,

Path c:

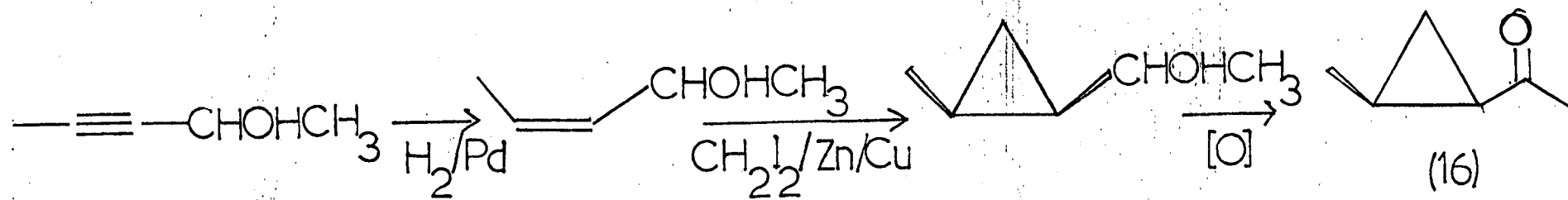


Figure 41

Path a:

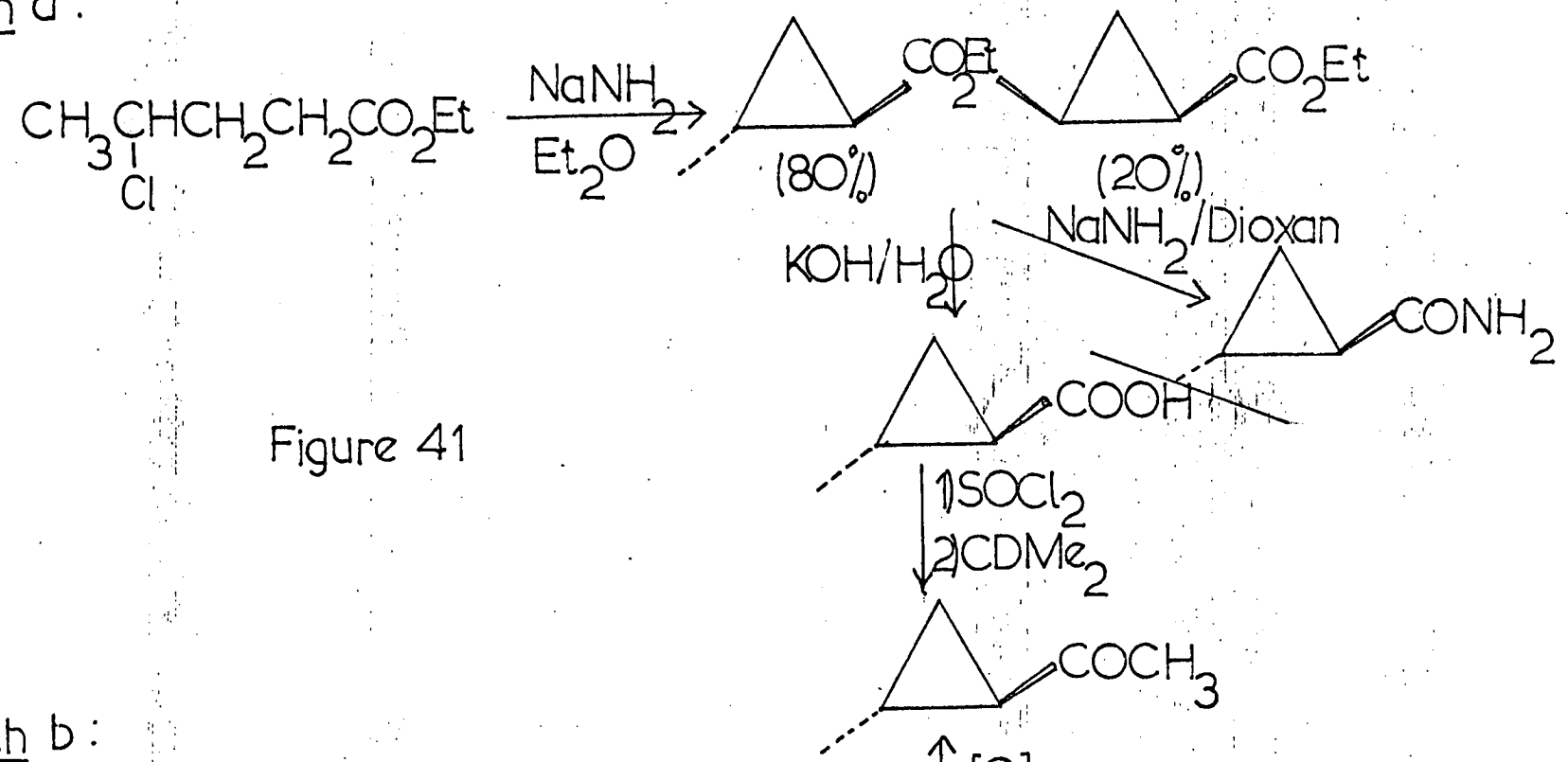
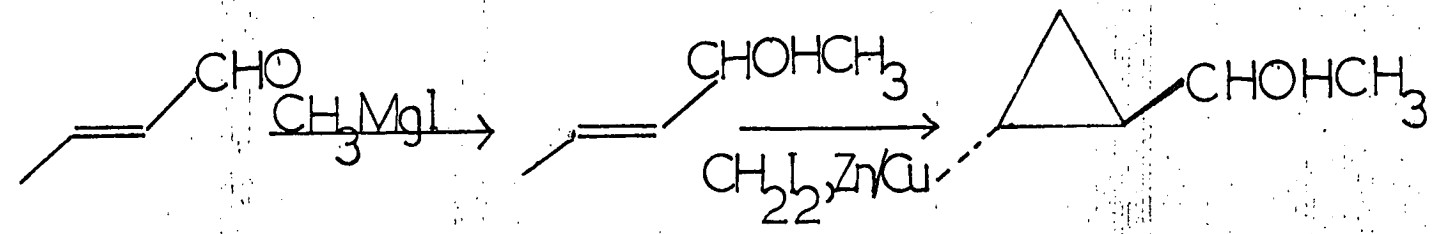


Figure 41

Path b:



$$\frac{k_1}{k_2} = \frac{\text{Log } 7.9/49.7}{\text{Log } 9.7/46.5}$$

$$= \underline{1.173}$$

As expected, pent-1-ene is hydrogenated faster than the branched isomer, 3-methylbut-1-ene. This result shows that if hydrogenation by diazene occurs in the reaction environment of a Nickon-Sinz reaction then the ratio of (39)/(38) observed will be slightly lower than that actually formed.

In the synthesis of trans-2-methylcyclopropylcarboxamide (34) it was assumed that, after recrystallisation of the crude product obtained from the action of sodamide/dioxan on compound (33), only the trans-isomer (m.p. 110°) was obtained. This assumption was based on the identity of the ir spectrum and the melting point with the literature values.⁶⁵ However, if the literature assignments had been inadvertently attributed to the trans-isomer whereas in fact they describe the cis-isomer, then the Nickon-Sinz reaction results would be those derived from ring-opening of cis-2-methylcyclopropylcarboxamide and consistent with a carbanionic mechanism with a steric effect due to the cis-2-methyl group. This possibility was eliminated since the ir spectrum of trans-1-acetyl-2-methylcyclopropane (10) prepared from two different synthetic routes,^{66,10} path (a) and path (b) (Fig. 41), path (a) using the same cyclised precursor as in the synthesis of (34), were found to be identical and significantly different from that of the cis-1-acetyl-2-methylcyclopropane (16)(prepared via path (c)). It therefore appears that the

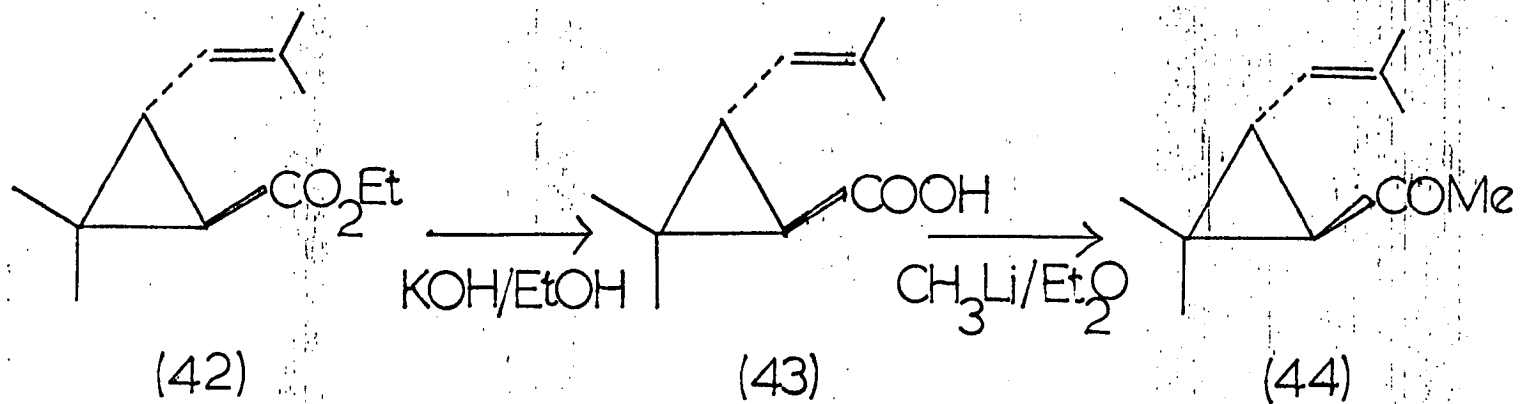


Figure 42

literature assignments are correct, and that the Nickon-Sinz reaction results were due to a radical type ring-opening of the trans-2-methylcyclopropylmethyl intermediate species.

Reduction of trans-1-Acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl) cyclopropane with Lithium in Liquid Ammonia

It has been mentioned earlier (see Introduction p. 2) that the reduction of 3-methylcyclopropanone (3) with sodium in ethanol⁶ gave exclusive ring-opening via C₁-C₇ bond-cleavage; none of the product arising from the more stable intermediate formed by C₁-C₆ bond-cleavage was observed. It was proposed to reduce a similar type of system, trans-1-acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane (44), in which unlike (3), the carbonyl group is free to overlap with both cyclopropane bonds, in order to estimate the effect, if any, of the 2-methylpropenyl group on the direction of ring-opening of the ketone. Preparation of the acetylcyclopropane (44) was undertaken as outlined in Fig. 42.

Pure trans-ester (42) (ethyl chrysanthemate) was prepared from a mixture of the cis/trans-esters (35% cis:65% trans) by refluxing the isomer mixture with ethanolic sodium ethoxide⁶⁷ for 7 days. Several unsuccessful attempts to isolate the pure trans-ester from a mixture of the trans- and the cis-esters by employing physical techniques are described in the Experimental (p./04). One attempted separation was based on a kinetic approach. This involved saponification of the ester mixture (35% cis:65% trans) with 0.65 equivalents of base, sufficient to saponify the trans-isomer only. It was thought that it would be more difficult

for the cis-ester to pass from an already crowded sp^2 ground state to an even more crowded sp^3 transition state than it would for the trans-ester under the same reaction conditions. However, nmr spectral analysis of the hydrolysed product showed that the percentage of trans-isomer had increased from 65% to only 79% and that the cis-isomer constituted the remaining 21%. A repeat of the hydrolysis which involved stirring the basic mixture for 3 days at a lower temperature (25°) reduced the percentage of cis-isomer to 18%.

The pure trans-ester (42) was then saponified (KOH) to the corresponding acid (43) which was shown to contain less than 2% impurity (v.p.c., nmr).

Treatment of the acid (43) with a slight excess (0.5) of lithium methyl in ether gave a product mixture containing two components, which, after separation by dry-column chromatography, were identified as the required acetylcyclopropane (44) (81%) and 2-trans-[2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl]propan-2-ol (19%). In a further reaction in which an approximately equimolar amount of lithium methyl was used the percentage of tertiary alcohol was reduced to 7.5%.

Attempted preparation of the acetylcyclopropane (44) by treating the trans-ester (42) with an excess of lithium methyl gave mainly (~70%) unreacted starting material and a mixture of several components, which from the ir spectrum were shown to be mainly alcohols. Using a method described by Corey and Chaykowsky,⁷¹ another attempted preparation involved reacting the trans-ester (42) with a solution of

methylsulphinylicarbanion ($\text{CH}_3\text{SOCH}_2^-$) in tetrahydrofuran. A product mixture was obtained which was shown (ir) to contain the required β -ketosulphoxide and also an alcoholic component. (In the first attempt, this reaction gave products containing unreacted starting ester and the corresponding acid (43); the presence of the latter was attributed to wet solvents). On reducing this product mixture with aluminium amalgam at 65° for 80 minutes, and in a later attempt, at 0° for 10 minutes, an oil was obtained which was a mixture of six components by v.p.c. The components were not identified.

The lithium/liquid ammonia reduction of trans-1-acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane was carried out as described for ketones (13), (19) etc. It was anticipated that identification of the reduced products would be easier if the olefins were first hydrogenated. Before this approach could be effected it was essential to be able to hydrogenate the unchanged starting ketone without reducing the cyclopropane ring. However, treatment of a sample of ketone (44) with potassium azo-dicarboxylate and acetic acid gave unreacted starting material while attempted catalytic hydrogenation using Platinum/ethanol and Platinum/cyclohexane gave unreacted starting material with one (Pt/EtOH reaction) or more unidentified components. An attempted catalytic hydrogenation of the oxidised product from a lithium/ammonia reduction of ketone (44) gave unreacted starting material and an unknown component which did not correspond to any of the expected reduction products. In view of the

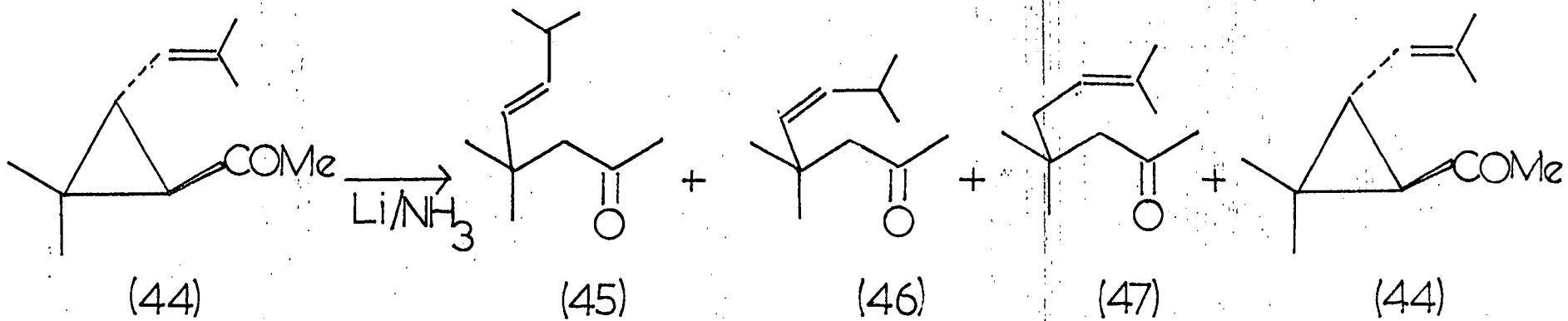


Figure 43

unsatisfactory nature of this approach it was proposed to analyse the reduction product after the oxidation stage without hydrogenation.

After oxidation of any alcohols present, the reduction product mixture was shown to contain (v.p.c.) four components which were identified (ir, nmr, v.p.c.) as trans-4,4,7-trimethyloct-5-en-2-one (45; 48%), cis-4,4,7-trimethyloct-5-en-2-one (46; 22%), 4,4,7-trimethyloct-6-en-2-one (47; 16.1%), and starting ketone (44; 13.9%) (Fig. 43). From these results it is seen that ring-opening of the ketone (44) occurs exclusively via C₁-C₃ bond cleavage towards the 2-methylpropenyl group which is in the opposite direction to the ring-cleavage of ketone (13) (C₁-C₂ bond-cleavage). It seems that charge stabilisation of an intermediate secondary carbanion by delocalisation through an allylic intermediate completely outweighs any steric effect forcing ring-opening by C₁-C₂ bond-cleavage (see Introduction p. 6). In the case of 3-methylcar-4-en-2-one (3) it appears that the steric orbital overlap considerations control the direction of ring-opening and that they are sufficiently strong to outweigh any electronic effects operating, e.g. the tendency to form a delocalised allylic intermediate.

Radical Rearrangement of Ketone (44).

It was also of interest to study the radical cleavage of ketone (44). On heating ketone (44) with butan-2-ol and di-t-butylperoxide for 48 hours at 140° a product was obtained which was shown (v.p.c.) to be a mixture of ketones (45), (46), (47) (total = 4.5%), starting ketone (44) (5.5%), and a

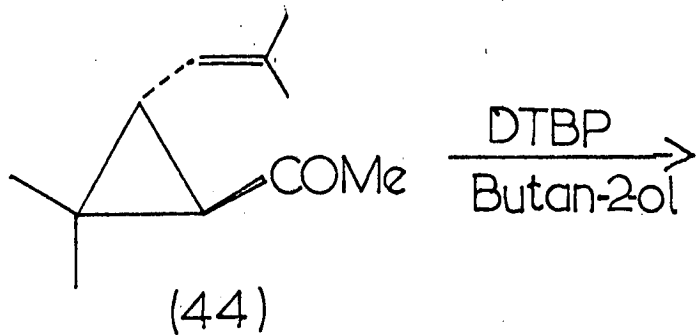


Figure 44

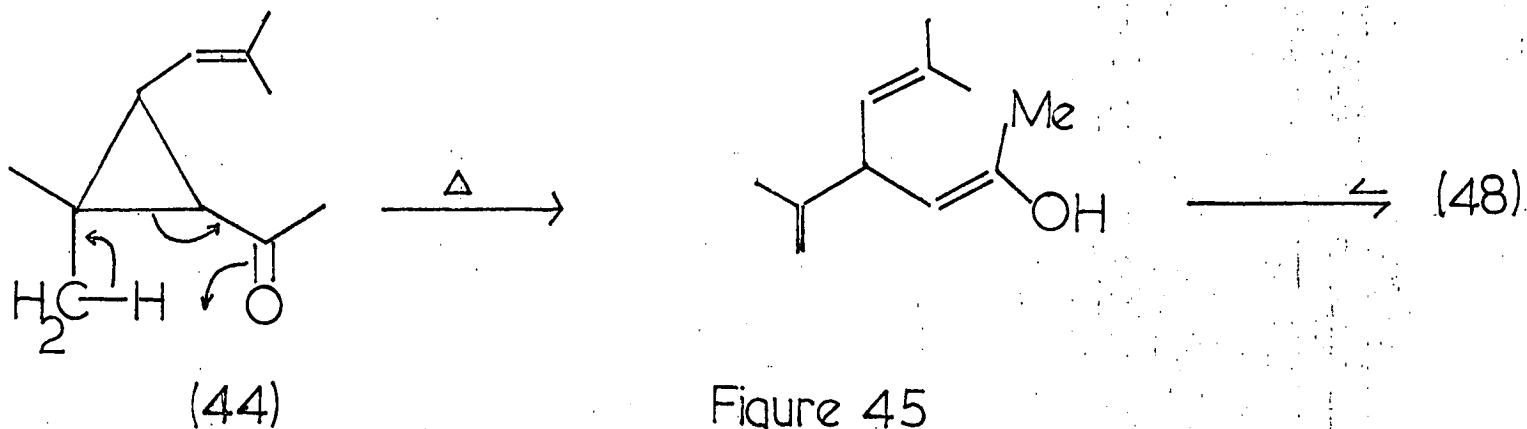


Figure 45

fifth component which was identified (ir, nmr, mass spectrum) as 6-methyl-4-(prop-1-en-2-yl)hept-5-en-2-one (48)(90%) (Fig. 44). The results of a number of reactions employing different reaction times are summarised in Table 9. Ketone (48) is the main product of rearrangement and its percentage increases with the reaction time.

A similar series of reactions on the corresponding alcohol, 1-[trans-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl]ethanol (prepared by lithium aluminium hydride reduction of ketone (44)), resulted in the formation of a polymeric product in each case.

The fact that the product (48) appears to be formed by proton abstraction, suggested that it was in fact formed by thermal rearrangement of ketone (44) via the 'Ene' reaction (Fig. 45). This was proved to be correct by heating ketone (44) and butan-2-ol in the absence of peroxide; the product was a mixture of ketones (44) and (48). 1-Acetyl-2,2-dimethylcyclopropane (13) was also found to undergo concerted ring-opening and 1,5 hydrogen shift to 5-methylhexen-2-one (as was reported by Roberts et al.²⁰) under the same reaction conditions.

The only products derived from a radical rearrangement (5%) all involve C₁-C₃ bond-cleavage and appear to be formed in the first 10 hours of reaction. An authentic radical ring-opening of ketone (13) was found¹⁰ to ring-open predominantly via C₁-C₂ bond-cleavage to give a ratio of (14)/(15) of 41 (see Introduction p. 5). It appears, therefore, that for ketone (44) charge stabilisation of an intermediate

secondary radical (formed by C_1-C_3 bond cleavage) by delocalisation through an allylic intermediate outweighs the two effects (i.e. a steric effect and the tendency to form a more stable tertiary, rather than secondary radical intermediate) favouring ring-opening by C_1-C_2 bond-cleavage in ketone (13).

NMR Spectroscopic Analysis of some Alkali Metal Cyclohexanoxide Salts.

In the reduction of 1-acetyl-2,2-dimethylcyclopropane (13) with lithium in liquid ammonia it was found that the ratio of rearranged products (14/15) increased with an increase in the concentration of lithium metal used. This relationship was qualitatively explained by considering the possibility of ion-pairing between the oxygen anion and metal cations in the two relevant transition state gauche conformers, B and C (see Discussion p. 19). In order to study possible changes in the size of an oxygen anion on ion-pairing, and its effect upon conformational equilibria we decided to investigate the conformational behaviour of salts of substituted cyclohexanols by nmr spectroscopy using the method of Eliel.⁸⁶ This involves the use of locked cis- and trans-4-t-butylcyclohexyl derivatives where it is assumed that the chemical shift of the equatorial proton resonance of the cis-4-t-butyl^{cyclo}hexyl derivative is accurately representative of the proton chemical shift in the axial mono-substituted cyclohexane. Likewise, the chemical shift of the axial proton in the trans-4-t-butylcyclohexyl derivative

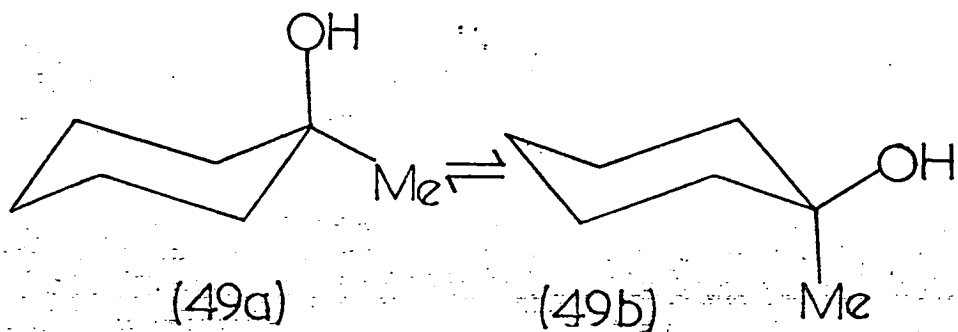


Figure 46

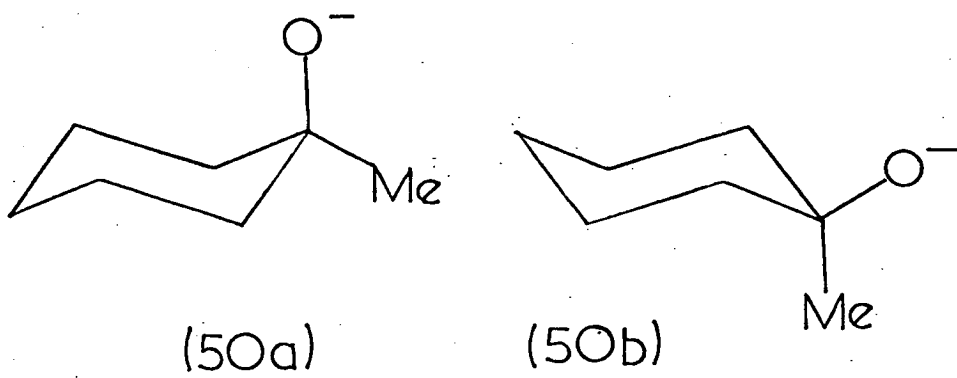


Figure 47

is taken as representative of the proton chemical shift in the equatorial mono-substituted derivative.

One of the systems investigated was 1-methylcyclohexanol (49) in which the two conformational isomers (49a) and (49b) are in equilibrium with each other through inversion of the cyclohexane ring (Fig. 46). For this system, i.e. a 1,1-disubstituted cyclohexane in which the substituents are different but of similar size, the preferred conformation will be the one in which the group with the largest A value,⁸³ the methyl group, ($\Delta G^{\circ} = -1.7 \text{ KCalmole}^{-1}$; ΔG° for OH = $-0.6 \text{ KCalmole}^{-1}$) is equatorial. This is indeed found to be the case as reported by Uebel and Goodwin⁸⁵ who investigated the conformational equilibrium of 1-methylcyclohexanol (49) by nmr spectroscopy using the chemical shift of the hydroxyl protons as a conformational probe. Using chemical shift data obtained from cis- and trans-4-t-butyl-1-methylcyclohexanol a ΔG of $-0.35 \text{ KCalmole}^{-1}$ was calculated for the equilibrium Fig. 46 in dimethylsulphoxide at 35° , indicating a slight preference for the equatorial methyl, axial OH conformer (49a). This value was considerably smaller than the value of $-1.1 \text{ KCalmole}^{-1}$ expected assuming additivity of the conformational energies of the methyl group ($\Delta G^{\circ} = -1.7 \text{ KCalmole}^{-1}$) and the hydroxyl group ($\Delta G^{\circ} = -0.6 \text{ KCalmole}^{-1}$). This deviation from the additivity relationship tends to be the rule for 1,1-disubstituted cyclohexanes.⁸³

The premise to our work on (49) was that by converting the alcohol into a salt, ion-pairing would be likely to occur

between the alkoxide ion and the cation. Different cations in a given solvent of low dielectric constant (ϵ) would form ion-pairs of different sizes and consequently the bulk of the oxygen function would vary. As the effective size of the oxygen anion increases so also would the energy difference between the anion in the equatorial and axial positions, resulting in the axial conformer (50a) being significantly less stable than the equatorial conformer (50b) (Fig. 47). We might expect, therefore, the conformational equilibrium constant of the alkoxide ion to be a function of the cation present.

We might also expect the equilibrium constant to be a function of the dielectric constant (ϵ) of the solvent used i.e. for solvents of low ϵ , ion-pairing would be substantial and the oxygen anion would preferentially occupy the equatorial position (50b) so as to minimise non-bonded interactions between the ion-pair and the two syn-axial hydrogens. For solvents of high ϵ , little ion-pairing of the alkoxide ion would occur and conformer (50a), with the oxygen anion in the axial position, as for the pure alcohol, would be preferred.

In our investigation of compound (49) it was proposed to examine the relationship between the conformational equilibrium and (a) the cation used, and (b) the solvent dielectric constant (ϵ) by ^{13}C nmr spectroscopy using the methyl carbon absorption as a probe. (Proton nmr analysis of this molecule was found⁷⁸ to be inadequate since the C_1 -methyl proton absorption in the equatorial and the axial positions were not sufficiently well separated). Since

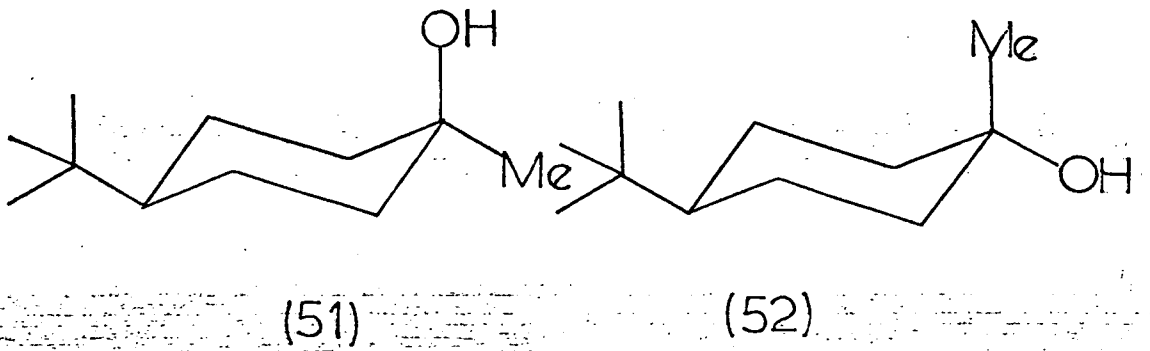


Figure 48

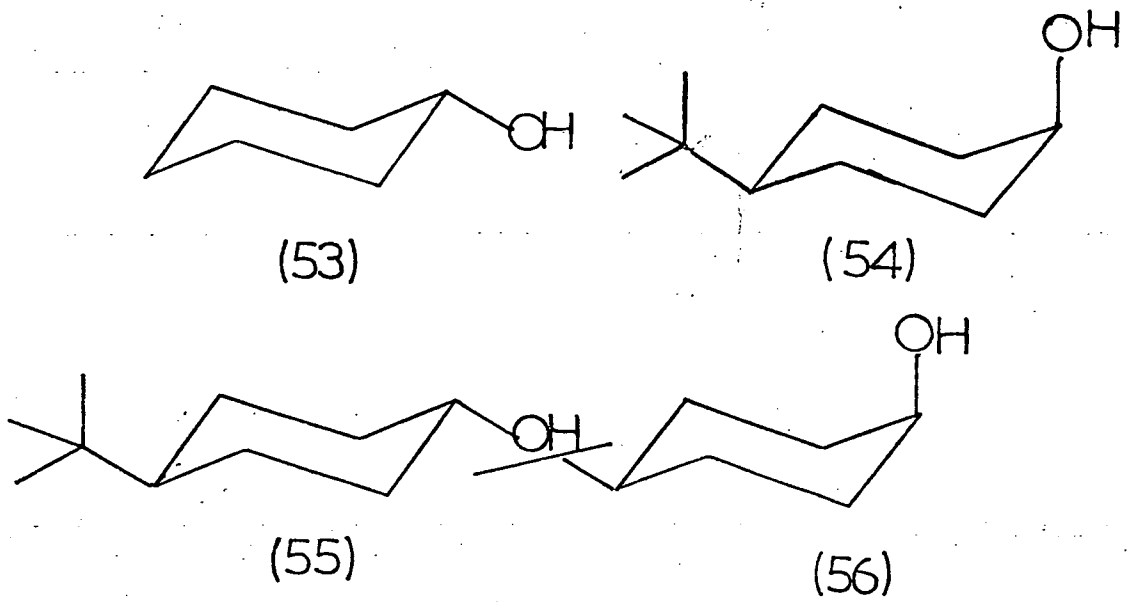


Figure 49

at room temperature, interconversion of the two conformers of compound (49) is at a rate very much faster than the rate of the nuclear transition being examined, a weighted average of the axial and equatorial chemical shifts is obtained. The location of this peak is thus a measure of the proportion of conformers in the equilibrium. As models for comparison, the spectra of the conformationally fixed cis-(51) and trans-4-t-butyl-1-methylcyclohexanol (52) were run under the same conditions (Fig. 48). Assuming that the 4-t-butyl group does not affect the chemical shift in any other way than by biasing the molecule in favour of one conformation, these model compounds should reflect the chemical or spectroscopic properties of the two conformers of the mono-substituted cyclohexanol. This method of analysis has been applied to a large number of substituents⁸⁶ but its validity has been questioned^{83,87} since it has been found that the t-butyl group does affect the geometry of the ring and hence the chemical shifts of the ring carbon atoms.

From the ^{13}C spectra of compounds (49), (51), and (52) it was found that the C_1 carbon was the only atom which could definitely be assigned to a specific peak in all three spectra; all others were only tentatively assigned (Table 10). From the position of this peak in compounds (49), (51), and (52) it was calculated that the equilibrium constant (K) for the equilibrium Fig. 46 was 1.5 ± 0.354 and that the hydroxyl group preferentially occupied the axial position ($60\% \pm 9\%$) in agreement with the literature.^{81,85} However, the large error limits involved and the proximity of the C_1 absorptions

of (49), (51), and (52) to each other rendered this molecule (49) to be an unsatisfactory system for analysis. In view of this, the monosubstituted secondary alcohol, cis-4-methylcyclohexanol (56), and the cis- (54) and the trans-4-t-butylcyclohexanol (55) (Fig. 49) were investigated with the intention of using the $^{13}\text{C}_1$ absorption as a probe. It was also proposed to study the secondary alcohol, cyclohexanol (53), for comparison.

Pure trans-4-t-butylcyclohexanol (55) was separated from a mixture of the cis- and the trans-alcohol (1g; 20% cis:80% trans) by dry column chromatography. However, since the percentage yield of pure cis-alcohol (54) obtained from this separation was low (0.5%) preparation of the latter was approached by an alternative route. This involved catalytic hydrogenation of the corresponding ketone, 4-t-butylcyclohexanone over platinum/glacial acetic acid/hydrogen chloride as described by Eliel.⁸⁰ The isolated product was then refluxed with methanolic sodium methoxide to convert the acetate to the alcohol. This gave a solid containing (v.p.c.) the cis-alcohol (54) (90%; Lit.,⁸⁰ 80%), trans-alcohol (55) (4%) and the starting ketone.

cis-4-methylcyclohexanol (56) was similarly prepared by catalytic (Pt/^{Ac}OH/HCl) hydrogenation of the corresponding ketone, 4-methylcyclohexanone. The product obtained was a mixture (v.p.c.) of cis- and trans-4-methylcyclohexanol (cis:trans \equiv 4:1) which were separated by dry column chromatography. The ^{13}C spectral assignments of (54), (55), and (56) are listed in Table 11.

After the best conditions had been found for converting alcohols to their lithium salts using cyclohexanol itself, the lithium salts of (55) and (56) were prepared by adding an equimolar quantity of butyl lithium in deuteriobenzene to a mixture of the alcohols (equimolar cis-4-methylcyclohexanol:cis/trans-4-t-butylcyclohexanol) in deuteriobenzene under a nitrogen atmosphere using a titration technique. The titration was followed by the addition of samples of the salt solution to a solution of triphenylmethane in dimethoxyethane and the end-point was indicated by a permanent red colouration. The solution of the salts prepared in this manner was then examined by ^{13}C nmr.

The chemical shifts (relative to T.M.S.) of the C_1 absorptions in the spectrum of the anions of cis-4-methylcyclohexanol (56), cis-4-t-butylcyclohexanol (54) and trans-4-t-butylcyclohexanol (55) were readily assigned from the relative intensities of the peaks and the known ratio of the components. They appeared at 67.0, 68.1, and 74.4 ppm respectively. (No other carbon absorptions were assigned to specific peaks in the spectrum). It was noted that the C_1 absorption of all three anions were downfield relative to the absorption in the corresponding alcohols, the least affected being cis-4-methylcyclohexanol (66.4 \rightarrow 67.0 ppm). It was also noted that the C_1 absorption of this anion (67.0 ppm) fell outside the corresponding values for the anions of (54) and (55) (68.1 and 74.4 ppm. respectively). This is probably due to the inherent limitations of the Eliel⁸⁶ method of conformational

analysis mentioned earlier. However, the results give a strong indication that in benzene (ϵ 2.26) the oxygen anion in the salt of (56) exclusively occupies the

axial position. *It appears in this instance that the lithium cation is not sufficiently large to change the conformation of the molecule.*

The solubility of the lithium salts was found to be very limited in dioxan (ϵ 2.2), carbon tetrachloride (ϵ 2.24), and dimethylsulphoxide (ϵ 49).

EXPERIMENTAL

The infra-red spectra were recorded on a Unicam SP200 and Perkin Elmer 237 Spectrophotometers; the suffixes to the infra-red bands quoted are abbreviated weak (w), medium (m), strong (s), and broad (b).

^1H Nuclear Magnetic Resonance spectra were run on a Perkin Elmer R.10 spectrometer (60 MHz) at 33° , an E.M-360 (60 MHz) at 33° or a Varian Associates H.A.100 Spectrometer (100 MHz) at 28° . Samples were run as solutions (5-10%) in carbon tetrachloride, deuteriochloroform or deuteriobenzene with tetramethylsilane as the internal reference, or as solutions (5-10%) with benzene as solvent and internal reference, using the δ value of 7.27 for the benzene absorption to convert chemical shifts to the δ scale. In the tabulation of nmr data the following abbreviations are used: singlet (s), doublet (d), doublet of doublets (d of d), triplet (t), quartet (q) and multiplet (m).

^{13}C Nuclear Magnetic Resonance spectra were run on a Varian XL 100 [12" wide-gap magnet] operating in the pulse and Fourier transform mode. Several hundred transients were accumulated in a 620 L (16K) computer before Fourier transformation to give the frequency-intensity spectrum. Samples were run as solutions in benzene with deuteriobenzene as internal reference and deuteriobenzene or trimethylsilane as lock.

Analysis figures were obtained using a Perkin Elmer 240 elemental analyser.

Mass spectra were run on an A.E.I. M.S. 902 double

focussing instrument, or on an A.E.I. M.S.20 single focussing, low resolution mass spectrometer, which was coupled to a Pye Unicam-104 gas chromatograph through a silicone membrane separator. The glass columns used in the latter were packed with either 5% Polyethylene glycol on Chromosorb G (7 ft x .2 in), 1% S.E.30 on Chromosorb G (7 ft x .2 in), 5% Carbowax on Chromosorb G (7 ft x .2 in), or 10% Apiezon L on Chromosorb G (7 ft x .2 in). The carrier gas was Helium (40ml/min).

Melting points are uncorrected.

Analytical v.p.c. was carried out on a Perkin-Elmer F.11 instrument, equipped with a flame ionisation detector using (a) a 50 m. stainless-steel capillary column coated with either Apiezon L or Carbowax, and (b) a 5 m. packed column with bis-methoxyethyl adipate or bis-methoxyethyl adipate + di-2-ethylhexyl sebacate as the stationary phase. Integration of peaks on v.p.c. traces was achieved using a Kent Chromalog III Digital Integrator.

Preparative v.p.c. was performed on a Wilkins Instrument and Research Inc. Aerograph Autoprep Instrument, model A.700 using either 15% Carbowax 20 M on Chromosorb S (10 ft x .375 in) or 30% S.E.30 on Chromosorb W (20 ft x .375 in) as the column packing. The carrier gas was helium (200 ml/min) and the injector, detector and collector temperatures were 120^o, 150^o and 120^o respectively.

Preparation of Trimethylsulphoxonium Iodide¹⁸ - Dimethylsulphoxide (120g, 1.54 moles) and methyl iodide (510g, 3.6 moles) were mixed in a 500 ml round-bottomed flask and left to stand for 14 days.

The solid reaction product was filtered off and the dark yellow crystals recrystallised from water. The recrystallised product was finally washed with aqueous sodium thiosulphate solution (2 x 15 ml) and chloroform (2 x 15 ml) to give white crystals.

Preparation of 1-Acetyl-2,2-dimethylcyclopropane¹⁹ - Pure, dry trimethylsulphoxonium iodide (40g, 0.182 mole) was added, with stirring, to dimethylsulphoxide in a 500 ml round-bottomed flask. A nitrogen atmosphere was maintained while sodium hydride (4.2g, 0.175 mole) was added slowly, the temperature being kept below 40° with an ice bath. Mesityl oxide (16.7g, 0.17 mole, 19.6 ml) was then added slowly over a period of 15 mins, and again the ice-bath was used to moderate the temperature of the stirred mixture. The stirring was continued for 3 hours and the reaction mixture was then allowed to stand at room temperature for 60 hours. On pouring onto ice (150g) two layers formed. Pentane (50 ml) was added and, after separation, the aqueous layer was extracted with pentane (2 x 100 ml). The combined organic layers were washed with water (3 x 100 ml), brine (1 x 100 ml), and finally dried (MgSO₄).

The pentane was removed by rotary evaporation and vacuum distillation of the residue gave a product (7.92g,

42%), b.p. 58-59°/50 mm whose spectral data (ir and nmr) was in agreement with that reported,¹⁸ and whose v.p.c. retention time (Apiezon L, 85° and Carbowax 60°) was identical to that of an authentic sample of 1-acetyl-2,2-dimethylcyclopropane.¹⁰

Preparation of 1-(trans-2-Methylcyclopropyl)ethanol. - The Simmons-Smith²² procedure as modified by Perraud and Arnaud²⁴ was employed using trans-pent-3-en-2-ol.²³ A mixture of trans-pent-3-en-2-ol (15g, 0.175 mole), anhydrous ether (200 ml), and zinc-copper couple²⁵ (22.68g, 0.35 mole) under nitrogen was heated to reflux with vigorous stirring, and methylene iodide (93.5g, 0.35 mole) was added slowly. The reaction mixture was refluxed for 3.5 hours and then hydrolysed with saturated aqueous ammonium chloride solution (30 ml). The solid residue was filtered off, crushed, and then washed with ether (4 x 50 ml). The combined filtrates were dried (MgSO₄) and concentrated. Vacuum distillation of the residue yielded two fractions (b.p. 57-60°/67 mm and 64-66°/65 mm) which were shown by v.p.c. (Apiezon L, 70°) to contain mainly the required product by comparison with an authentic sample of 1-(trans-2-methylcyclopropyl)ethanol. Further purification was not undertaken at this stage but both fractions were combined and oxidation to the corresponding ketone attempted.

Attempted Preparation of trans-1-Acetyl-2-methylcyclopropane.

- Both fractions obtained from the Simmons-Smith reaction on

trans-pent-3-en-2-ol were dissolved in ether (10 ml) and treated, dropwise, with cooling, with 6N chromic acid (3 ml). After stirring for 3.5 hours v.p.c. examination (Apiezon L, 70°) indicated that some unchanged alcohol remained. After the addition of a further 2.0 ml of chromic acid the reaction mixture was stirred for 3 hours. Examination by v.p.c. again showed the presence of unreacted alcohol.

Preparation of trans-Pent-3-en-2-one.²⁶ - A solution of triphenylphosphine (225g) and freshly distilled chloroacetone (73.1g) in chloroform (650 ml) was refluxed for 45 minutes. The solvent was then removed by rotary evaporation and the unchanged starting material removed by washing with a chloroform/ether mixture (200 ml, 1:10 vol/vol). The product acetyltriphenylphosphonium chloride was filtered off and dried. The yield was 235g; m.p. 235-237° (lit.,⁷⁵ m.p. 234-237°).

Acetyltriphenylphosphonium chloride (235g) was shaken with an excess of 12% aqueous sodium carbonate for 12.5 hrs and the acetylmethylenetriphenylphosphorane formed was filtered off and dried. The yield was 205g; m.p. 195-197° (lit.,⁷⁵ m.p. 199-202°).

Acetylmethylenetriphenylphosphorane (50g) in methylene chloride (125 ml) was treated with freshly distilled acetaldehyde (15g) in methylene chloride (30 ml) and the mixture was refluxed for 6 hrs. After a further 15 hrs at 20° the solvent was distilled off through a 50 cm column packed with Fenske helices and the residue diluted

with pentane (125 ml). The precipitated triphenylphosphine oxide was filtered off and washed, until colourless, with pentane. The organic filtrates were combined and the solvent was distilled off through the fractionation column.

Distillation of the residue through a 25 cm Vigreux column yielded trans-pent-3-en-2-one (5.4g, b.p. 120-121^o, lit.,²⁷ b.p. 124^o), which contained 5.6% impurity (v.p.c., Apiezon L, 65^o). The ir spectral data was in agreement with that reported.^{27a}

Preparation of trans-1-Acetyl-2-methylcyclopropane. -

Method A. The Simmons-Smith procedure, as modified by Perraud and Arnaud, was employed on trans-pent-3-en-2-one. The procedure used was identical to that for trans-pent-3-en-2-ol (page 70).

A mixture of trans-pent-3-en-2-one (2g, .028 mole), anhydrous ether (40 ml), and zinc-copper couple (3.24g, .051 mole) under nitrogen was heated to reflux with stirring, and methylene iodide (13.4g, .05 mole) added slowly. The reaction mixture was refluxed for 3.5 hrs and then hydrolysed with saturated, aqueous ammonium chloride solution. The solid residue was filtered off, crushed, and washed with ether (4 x 10 ml). The combined filtrates were dried (MgSO₄) and concentrated. Final distillation of the residue yielded two fractions, b.p. 58-62^o and 65-66^o respectively, which were both shown to contain (v.p.c., Apiezon L, 65^o) methylene iodide (~45%). Isolation of the other component was effected by preparative v.p.c. (30% S.E.30, 100^o). This gave material which contained <1%

impurity and was identified (ir, nmr, v.p.c.) as unreacted pent-3-en-2-one.

The Simmons-Smith reaction was repeated on a further quantity of pent-3-en-2-one (20.83g) and the reaction mixture refluxed under nitrogen for 12 hrs. Final distillation of the residue yielded a product which was shown to contain approximately 40% methylene iodide. The removal of this impurity was attempted using (a) aqueous silver nitrate solution,⁷⁶ (b) tri-methylamine,⁷⁷ and (c) 5% hydrochloric acid solution, but was unsuccessful.

In a final attempt to prepare the trans-1-acetyl-2-methylcyclopropane by Simmons-Smith reaction on the ketone (3.75g) it was found that by using 99.99% pure zinc powder in the preparation of the couple and following the reaction by v.p.c. (Apiezon L, 65°) until all the starting ketone had reacted (20 hrs), the final product (~10% yield) was the required cyclic ketone containing less than 2% impurity (v.p.c., Apiezon L, 65°). The spectra (ir and nmr) of the product were in agreement with those reported for trans-1-acetyl-2-methylcyclopropane.²⁰

Preparation of trans-1-Acetyl-2-methylcyclopropane. -

Method B. The method described in the literature²⁰ involving the reaction of trimethylsulphoxonium iodide with α,β unsaturated ketones was used.

A mixture of sodium hydride (0.66g, 0.025 mole) and powdered trimethylsulphoxonium iodide¹⁸ (5.5g, 0.025 mole) was stirred under nitrogen whilst dimethylsulphoxide (36.25 ml) was added slowly to it, ensuring that the

temperature was kept below 40° (ice-bath). trans-Pent-3-en-2-one (2.1g, 0.025 mole) was added dropwise over a period of 10 minutes; the mixture was stirred at 20° for 3 hours, and then left to stand for 12 hours. The reaction mixture was poured onto ice (50g) and pentane (20 ml) was added. After separation, the aqueous layer was extracted with pentane (2 x 30 ml) and the organic extracts were combined, washed with water (2 x 10 ml), saturated sodium chloride solution (2 x 10 ml), and finally dried (MgSO_4). The pentane was distilled off at atmospheric pressure and vacuum distillation of the residue yielded a product, b.p. $34^{\circ}/13$ mm.

The nmr and ir spectra indicated a mixture of products, the major component being the desired trans-1-acetyl-2-methylcyclopropane. Preparative v.p.c. (Se 30, 85°) gave trans-1-acetyl-2-methylcyclopropane (41% yield) which contained less than 1% impurity (v.p.c., Apiezon L, 65%).

Reduction of 1-Acetyl-2,2-dimethylcyclopropane with Lithium in Liquid Ammonia. - Lithium (.1g, .014 mole) was added to anhydrous liquid ammonia (50 ml)(dried by passing through calcium oxide) contained in a vessel fitted with a Dry-Ice condenser and protected from atmospheric moisture by a drying tube filled with calcium oxide. The resulting blue solution was stirred for 30 minutes to ensure complete dissolution of the lithium and a mixture of 1-acetyl-2,2-dimethylcyclopropane and decane (.25g, Ratio ketone:decane $\approx 3.49:1$), was added, dropwise, to it. Stirring was continued for 2 hours, and then the reduction mixture was

decomposed by the careful addition of aqueous ammonium chloride solution. Ether (25 ml) was added and the ammonia was allowed to evaporate. Water (25 ml) was added, the ether layer was separated, and the aqueous layer extracted with ether (2 x 25 ml). The combined organic extracts were washed with dilute hydrochloric acid (2 x 15 ml), sodium bicarbonate solution (2 x 15 ml), and dried (MgSO_4). After concentrating to about 2 ml, the product solution was analysed by v.p.c. (Apiezon L, 65°); 6 components and decane were indicated. These were identified as 1-acetyl-2,2-dimethylcyclopropane, 4,4-dimethylpentan-2-one, 5-methylhexan-2-one and their corresponding alcohols by comparative v.p.c. (Apiezon L, 65°). The reduction product mixture in ether (5 ml), was oxidised with 6N chromic acid. V.p.c. analysis (Apiezon L, 65°) of the oxidised product showed it to be a mixture of decane and three components. These were identified as 1-acetyl-2,2-dimethyl cyclopropane, 4,4-dimethylpentan-2-one, and 5-methylhexan-2-one by comparative v.p.c. (Apiezon L, 65°). Peak integration on several v.p.c. analysis of this product gave the product distribution. Table (1) shows the results of several reductions using the conditions described above. The ratio of starting material to decane before each reduction was 3.49:1.

Deuteration of 1-Acetyl-2,2-dimethylcyclopropane. - The ketone (4.48g, 0.04 mole) was added to a solution of sodium (0.12g) in [$^2\text{H}_1$]-methanol, the reaction mixture was refluxed for 15 hours and was then poured into water- d_2 (20 ml). The

aqueous solution was extracted with ether (3 x 5 ml) and the combined organic extracts were dried (MgSO_4) and concentrated. The nmr spectrum of the product showed that 99% of three replaceable acetyl protons had been exchanged along with one cyclopropyl proton (1-H).

Deuteration of Acetylcyclopropane. - Acetylcyclopropane (0.84g, .01 mole) was deuterated using the same procedure as above. The mass spectrum indicated that the total deuterium exchange was 96% of three replaceable hydrogens.

Reduction of Deuteriated 1-Acetyl-2,2-dimethylcyclopropane with Lithium in Liquid Ammonia. - The deuteriated ketone (0.22g) was added to a solution of lithium (0.5g) in liquid ammonia (50ml) in the usual manner. The solution was stirred for 2 hours and an excess of solid ammonium chloride was added, followed by anhydrous ether (25 ml). After the ammonia had evaporated, water (15 ml) was added, and the layers separated. The ether layer was dried and concentrated (2 ml). The reduction product was shown by v.p.c. (Carbowax 50⁰) to be a mixture containing the starting ketone, 4,4-dimethylpentan-2-one, 5-methylhexan-2-one, and their corresponding alcohols. MS20/v.p.c. (5% Carbowax) analysis showed that the ratio m/e 115:m/e116 of the starting ketone before and after reaction had changed from 0.134 to 0.20

Reduction of Deuteriated Acetylcyclopropane with Lithium in Liquid Ammonia. - The deuteriated acetylcyclopropane (0.25g) was added to a solution of lithium (0.4g) in liquid ammonia (50 ml) and the reduction was carried out in the usual manner. MS20/v.p.c. (5% Carbowax 60^o) analysis of the product resolved three components with parent ions A. m/e 89, B. m/e 87, C. m/e 91, which were identified as pentan-2-one, acetylcyclopropane, and pentan-2-ol respectively. (The mass spectrum "cracking" pattern of C was identical to that reported³¹). The percentage of ²H₁ exchange which had occurred in the reduction was calculated (see Table 2).

The reduction was repeated using the same quantities of starting materials, but the stirring was continued for 6 hours. MS20/v.p.c. (5% Carbowax, 65^o) analysis showed the product to be a mixture of pentan-2-one (28%, m/e 89), acetylcyclopropane (9%, m/e 87), pentan-2-ol (58%, m/e 91 (w), 73) and 1-cyclopropylethanol (5%, m/e 89 (w), 74). (The compounds were identified by comparative v.p.c. (5% Carbowax, 65^o). An authentic sample of 1-cyclopropylethanol was prepared by reducing acetylcyclopropane with lithium aluminiumhydride). The percentage of ²H₁ exchange was again calculated (see Table 3).

Reduction of Acetylcyclopropane with Lithium in Ethylamine. - Lithium (0.14g) was added to anhydrous ethylamine (50 ml) and the resulting blue solution was stirred for 30 minutes to ensure complete dissolution of the lithium. Acetylcyclo-

propane (0.25g) was added dropwise, and the reaction mixture was stirred for 2 hours. The reduction mixture was decomposed with an excess of solid ammonium chloride (added in one portion), ether was added and the ethylamine was allowed to evaporate. Water (25 ml) was added and the ether layer was separated and washed with dilute hydrochloric acid (2 x 15 ml) and aqueous sodium bicarbonate solution (2 x 15 ml). After drying (MgSO_4) and concentrating, an oil was obtained which was a mixture of acetylcyclopropane (81%) and pentan-2-one (19%) (v.p.c., Apiezon L, 50°). The absence of nitrogen in the product mixture was indicated by a sodium fusion test. The ir spectrum of the product was identical to the superimposed ir spectra of acetylcyclopropane and pentan-2-one.

Reduction of 1-Acetyl-2,2-dimethylcyclopropane with Lithium in Liquid Ammonia, in (a) the Absence, and (b) the Presence of a Proton Source.

(a) Without a proton source. - 1-Acetyl-2,2-dimethylcyclopropane (0.25g) was reduced in a solution of lithium (0.4g) in liquid ammonia (50 ml) for 2.5 hours. Solid ammonium chloride and ether (30 ml) were added and the ammonia was allowed to evaporate. Water (25 ml) was added and the ether layer was separated, dried (MgSO_4), and concentrated to ~2 ml and was then oxidised with 6N chromic acid. V.p.c. analysis (Apiezon L, 65°) showed the product to be a mixture of the starting ketone (13.3%), 5-methylhexan-2-one (63.2%) (14), 4,4-dimethylpentan-2-one (21.2%) (15), and an unidentified component (2.3%). The ratio of (14):(15) was

2.98:1.

(b) With a proton source. - Lithium (0.4g, 0.057 mole) was added to anhydrous liquid ammonia (50 ml) and the solution was stirred for 30 minutes. Ethanol (3.3 ml, 2.62g, 0.057 mole) was then added to the solution, followed by 1-acetyl-2,2-dimethylcyclopropane, and the reaction mixture was stirred for 2.5 hours. The product was isolated in the manner described above. V.p.c. analysis (Apiezon L, 65°) showed the product to be a mixture of the starting ketone (3.4%), 5-methylhexan-2-one (59.7%) (14), 4,4-dimethylpentan-2-one (33.3%) (15), and an unidentified component (2.6%). The ratio of (14):(15) was 1.8:1.

Reaction of Deuteriated Acetylcyclopropane with Potassium Amide in Liquid Ammonia. - The deuteriated ketone (0.25g)

was added dropwise to a 5% solution of potassium amide in liquid ammonia³² (from 0.5g potassium in 50 ml ammonia) and the reaction mixture was stirred for 2 hours. Solid ammonium chloride and ether (25 ml) were added to the reduction solution and the product was isolated as in previous reductions. After oxidising with 8N chromic acid the product was examined by v.p.c. (5% Carbowax, 65°) and the percentage of $^2\text{H}_1$ exchange in the recovered starting ketone was estimated (see Table 5).

*Preparation of 1-Acetyl-2-phenylcyclopropane (22). - A mixture of sodium hydride (2.4g, 0.1 mole) and powdered trimethylsulphoxonium iodide (22g, 0.1 mole) was stirred

under nitrogen whilst dimethylsulphoxide (100 mls) was added slowly to it, ensuring that the temperature was kept below 40° (ice-bath). 4-Phenyl-but-3-en-2-one (15g, 0.1 mole) in dimethylsulphoxide (10 mls) was added dropwise to the solution and the reaction mixture was stirred for 3 hours and then left to stand at 20° for 24 hours. The reaction mixture was poured onto ice (120g) and the product was extracted with pentane (4 x 25 ml). The organic extracts were washed with water (2 x 10 ml), saturated sodium chloride solution (2 x 10 ml) and were finally dried (MgSO_4). After concentrating, vacuum distillation of the residue gave a fraction, b.p. $124-128^{\circ}/11$ mm (11g, 70%; lit., b.p.³⁴ $118^{\circ}/2$ mm), which was a mixture of 3 components by v.p.c. (Apiezon L, 150°). Purification by preparative v.p.c. (Diethylene glycol succinate, 150°) gave the desired product containing less than 2% impurity. (V.p.c., Apiezon L, 150°). ν_{max} (film) 1690 cm^{-1} ; $\delta(\text{CCl}_4)$ 1.22 (m, 1-H, 3-H), 1.55 (m, 1H, 3-H₁), 2.12 (m, 4H, CH_2CO , cyclopropyl H), 2.38 (m, 1H, cyclopropyl H), 7.10 (m, 5H, aromatic).

*Preparation of 1-Acetyl-2-p-dimethylaminophenylcyclopropane (25). - The experimental procedure was as described above. 4-p-Dimethylaminophenylbut-3-en-2-one (19.4g, 0.1 mole; prepared from the reaction of p-dimethylaminobenzaldehyde with acetone in the presence of base) in dimethylsulphoxide (10 mls) was added dropwise to a solution of sodium hydride (2.4g, 0.1 mole), trimethylsulphoxonium iodide (22g, 0.1 mole), and dimethylsulphoxide (90 ml) and the reaction mixture was

stirred at 20° for 18 hours. The solution was poured onto ice (150g) and the product was extracted with ether (4 x 25 ml). The organic extract was washed with water (2 x 20 ml), dried (MgSO₄), and concentrated. Vacuum distillation of the residue gave a fraction (8.8g, 43%), b.p. 198-202°/15 mm, which was shown to be the desired product (25). ν_{\max} (film) 1670 cm⁻¹; δ (CCl₄) 1.02-1.30 (m, 1H, 3-H), 1.30-1.68 (m, 1H, 3-H), 1.83-2.10 (m, 1H, cyclopropyl), 2.14 (s, 3H, CH₃.CO), 2.20-2.45 (m, 1H, cyclopropyl), 2.82 (s, 6H, Me₂N), 6.5, 6.84 (two d, 4H, aromatic).

V.p.c. analysis of ketone (25) was unsuccessful on an extensive range of columns, e.g. Polyethylene glycol, Silicon elastomer, Apiezon L, Polyethylene glycol Succinate, Carbowax, and Tritolyl phosphate.

*Reduction of 1-Acetyl-2-phenylcyclopropane with Lithium in Liquid Ammonia. - The ketone (0.01g, 0.0006 mole) in ether (1 ml) was added dropwise, with stirring, to lithium (0.16g, 0.023 mole) in anhydrous liquid ammonia (50 mls) and the reaction solution was stirred for 2 hours. Solid ammonium chloride and ether (25 ml) were added and the ammonia was allowed to evaporate. Water (25 mls) was added and the separated ether layer was washed with sodium chloride solution (1 x 10 ml) and dried (MgSO₄). The ether was removed by rotary evaporation and the residue (~2 ml volume) was oxidised with 8N chromic acid. The isolated product was shown to be 5-phenylpentan-2-one (>98%) by comparative v.p.c. (Apiezon L, 150°). The v.p.c. retention time of authentic

4-phenylpentan-2-one (prepared from the 'abnormal' Michael addition of methylmagnesium iodide to 4-phenylbut-3-en-2-one³⁵) did not correspond to any of the minor bands constituting the remaining 2% of the reaction product.

*Reduction of 1-Acetyl-2-p-dimethylaminophenylcyclopropane with Lithium in Liquid Ammonia. - The reduction was carried out on the ketone (0.595g, 0.0029 mole) as described above. The nmr spectrum of the final oxidised product showed that the major component was 5-p-dimethylaminophenylpentan-2-one (~94%). There were no peaks characteristic of 4-p-dimethylaminophenylpentan-2-one (an authentic sample was prepared as directed in the lit.³⁵).

* Experiments performed in conjunction with J. Dingwall (4th Year Undergraduate Research Project 1971).

Reduction of Benzoylcyclopropane with Lithium in Liquid Ammonia. - Benzoylcyclopropane (0.25g, 0.017 mole) was added dropwise to a solution of lithium (0.3g) in anhydrous liquid ammonia (50 ml) and the reaction mixture was stirred for 2 hours. Solid ammonium chloride and ether (25 ml) were added to the reduction solution and the product was isolated as in previous reductions. The product was then oxidised with 8N chromic acid. V.p.c. analysis (Apiezon L, 175^o) of the product showed it to be a mixture of four components; retention times (minutes) - A. 6.6 (5.4%), B. 7.0 (35.1%), C. 9.5 (1.9%), D. 11.0 (57.5%). Preparative

scale v.p.c. (Se 30, 120°) resolved the two major components, D and B; they were identified from their spectral properties (ir, nmr, mass spectrum) as benzylcyclopropane and benzoylcyclopropane respectively. Component D. - $\delta(\text{CCl}_4)$ 0.42-0.6 (m, 4H, 2-H₂, 3-H₂), 0.84-1.08 (m, 1H, 1-H), 2.51 (d, 2H, Ph-CH₂, J_{1-H,CH₂} 7Hz), 7.13 (s, 5H, aromatic). Irradiation of the multiplet δ 1.0 collapsed the doublet δ 2.51 to a singlet; Mass spectrum m/e 132. Component C (1.9%) was identified by comparative v.p.c. (Apiezon L, 175°) as butyrophenone. Component A was not identified.

The reduction was repeated using the same quantities of starting materials. (The ammonia was dried by passing through freshly fired calcium oxide). V.p.c. analysis (Apiezon L, 175°) of the final oxidised product showed a mixture containing the same four components; A(4.6%), B(36.2%), C(1.7%) and D(57.5%).

In a further reduction an excess of solid sodium benzoate was added to the stirred reduction solution (after 2 hours) followed by solid ammonium chloride and ether (25 ml). V.p.c. analysis (Apiezon L, 175°) of the final oxidised product showed a mixture of components A, B, C, D and benzoic acid (53%). The percentages of A, B, C, and D were 7%, 54%, 11%, 28% respectively.

Titration of Lithium in Liquid Ammonia. A. With acetyl-
cyclopropane. -

Titration A. - Lithium (0.0698g, 9.97m.moles) was dissolved in anhydrous liquid ammonia (10 ml) and acetylcyclopropane was added dropwise by syringe injection until the blue colour of the stirred solution was just discharged. The weight of ketone required was 0.563g (6.70 m.moles). Water (5 ml) was cautiously added to the reaction solution and the ammonia was allowed to evaporate. A 'test' solution of o-hydroxybenzaldehyde (5g) in aqueous acetic acid (5 ml; 50%) was added to the titrated solution - no precipitate was apparent - and the mixture was extracted with ether (3 x 10 ml). After drying (MgSO_4), the ether was removed to give an oil which crystallised to a white solid (m.p. 239-240°, from ethanol). This m.p. was 25° above that of o-hydroxybenzalazine (Salazine, lit., m.p. 214°³⁹) and the compound was not identified.

Titration B,C. - In two further reductions, 10.14 m.moles (0.071g) and 20.05 m.moles (0.14g) of lithium in liquid ammonia (10 ml) required 6.4 m.moles (0.516g) and 16.2 m.moles (1.365g) of acetylcyclopropane respectively to discharge the blue colour of the liquid ammonia solution. The titrated solutions were treated with water (5 ml) and the "test" solution (5 ml), and the products were isolated as above. After drying (MgSO_4), the two ether extracts were concentrated to oils. Both residues were shown by v.p.c. (Carbowax 50°, Apiezon L 140°) to be a mixture of o-hydroxybenzaldehyde and an unknown whose long retention time (26

mins on Apiezon L, 140°) suggested a high molecular weight component. The nmr spectrum (CCl_4) of both residues showed a distinctive triplet $\delta 2.10$ and a singlet $\delta \sim 2.06$ in the integral ratio of 2:3. The ir spectrum showed a carbonyl absorption, $\nu_{\text{max}} 1705 \text{ cm}^{-1}$. (see D below).

Titration D. - Using the above procedure (titration A), 10.2 m.moles (0.072g) of lithium in liquid ammonia (10 ml) required 6.54 m.moles (0.547g) of the acetylcyclopropane. The titrated solution was treated with water and acetic acid only, and the product was isolated by extraction with ether as directed above. After drying (MgSO_4), the ether extract was concentrated to an oil which was shown by v.p.c. (Apiezon L, 45° ; Apiezon L, 140°) to be a mixture of pentan-2-one, acetylcyclopropane, and the unknown component. The latter was identified as decane-2,9-dione from its mass spectrum and by comparison of its ir and nmr spectra with those of an authentic sample of the dione (see p. 89 for preparation of the dione). ν_{max} (film) 1705 cm^{-1} ; $\delta(\text{CDCl}_3)$ 0.67-2.0 (m, 8H, aliphatic), 2.14 (s, 6H, $\text{CH}_3 \cdot \text{CO}$), 2.44 (t, 4H, $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2$); mass spectrum P, 170, 152, 113, 71, 58, 43.

Titration E. - In a final reduction, 10.55 m.moles (0.0739g) of lithium in liquid ammonia (10 ml) required 6.66 m.moles (0.557g) of the ketone for neutralisation. The titrated solution was treated with water only, and the product was extracted and isolated as directed above. The final product was an oil which was identified (ir, nmr; v.p.c., Apiezon L, 140°) as decane-2,9-dione.

B. With 1-Acetyl-2,2-dimethylcyclopropane. - Using the procedure described in A (titration A), 9.2 m.moles (0.0644g) of lithium in liquid ammonia (10 ml) required 7.72 m.moles (0.812g) of the ketone to discharge the blue colour of the liquid ammonia solution. Water (5 ml) was added to the titrated solution and the product was extracted with ether (3 x 10 ml). From v.p.c. analysis (Apiezon L, 65°), the dried extract (MgSO₄) was a mixture of (13), the starting ketone (54%) (14), 5-methylhexan-2-one (39%), and (15), 4,4-dimethylpentan-2-one (7%). (Ratio 14:15 = 5.5:1). Removal of the ether by rotary evaporation gave an oil which contained four components (A). (95%, starting ketone + rearranged ketones) and 3 small components (5%) by MS 20/v.p.c. (Apiezon L, 165°). The three minor components each gave a mass spectrum with parent ions of mass > 200. (Poor resolution of the spectrum above 180 a.m.u. rendered exact counting impossible). ν_{\max} (film) 3500, 1678 cm⁻¹; The nmr spectrum of the product was poorly resolved with no distinctive peaks.

C. With trans-1-Acetyl-2-methylcyclopropane. - Using the procedure described in A (titration A), 4.4 m.moles (0.0308g) of lithium in liquid ammonia required 2.8 m.moles (0.2803g) of the ketone for neutralisation. Water (5 ml) was added and the aqueous solution was extracted with ether (3 x 10 ml), dried (MgSO₄), and concentrated to an oil (0.0856g). MS 20/v.p.c. analysis of the product resolved two components, one of which, (A), (1.7 minutes, 70%) was identified as a mixture of starting and rearranged ketones. The other component, (B), (14 minutes, 30%) gave a mass spectrum, P141,

123, 85, 82, 58, 55, 43; ν_{\max} (film) 1710 cm^{-1} . The nmr spectrum (CDCl_3) of the product was similar, but not identical, to that of decane-2,9-dione. (% products (by weight) - (A), 74%, (B), 26%).

In a further reduction, 2.34 m.moles (0.0164g) of lithium in liquid ammonia required 1.34 m.moles (0.1338g) of the ketone for neutralisation. Water (5 ml) was added and the product was extracted with ether (3 x 10 ml) and the combined organic extracts dried (MgSO_4). V.p.c. analysis (5% Carbowax, 75°) of the extract resolved 3 components; (10), starting ketone (72.8%), (12), 4-methylpentan-2-one (25%), and (11), hexan-2-one (2.2%). The ratio of (11):(12) was 0.088:1.

Attempted Preparation of Decane-2,9-dione. -

Method 1. - An excess (x .5) of lithiummethyl in anhydrous ether (70 ml) was added dropwise, with stirring, to a solution of octane-1,8-dicarboxylic acid (1.74g, 0.01 mole) in ether (40 ml) and the reaction mixture was stirred for 15 minutes under nitrogen. The excess lithiummethyl was destroyed with aqueous ammonium chloride solution. The ether layer was separated and washed with aqueous ammonium chloride (2 x 15 ml), water (2 x 15 ml) and was then dried (MgSO_4) and concentrated to an oil. MS20/v.p.c. analysis (10% Apiezon L, 160°) of the residue showed it to be a mixture of four components; A(9%, m/e 160), B(47%, m/e 170), C(16%, m/e 171), and D(28%, m/e 169). (Product B is most likely the desired dione). Separation of the components by preparative v.p.c. (Se 30, 165°) was unsuccessful.

Method 2. - The procedure involved the reaction of acetylcyclopropane with sodium in tetrahydrofuran.⁴¹

Sodium (0.175g, 0.0076 moles) was added to acetylcyclopropane (0.42g, 5 m.moles) in tetrahydrofuran (6 ml) and the solution was stirred at 0° (ice/salt bath) for 3.5 hours. Water (30 ml) was added and the solution was extracted with ether (3 x 16 ml). The ether extracts were then washed with water (2 x 10 ml), dried (MgSO₄), and concentrated to an oil, which was shown to contain several components by v.p.c. (Apiezon L, 50°, 150°). A sample of the residue was dissolved in ether (2 ml) and oxidised with 8N chromic acid. The ir spectrum of the oxidised product was similar to the diketone product obtained from lithium in liquid ammonia titrations with acetylcyclopropane. The nmr spectrum indicated an impure product.

Method 3. - The procedure involved the reaction of acetylcyclopropane with sodium amalgam in ether.⁴²

A 1% sodium amalgam was prepared by adding sodium (0.46g) pieces, on the end of a pointed glass rod, to mercury (46g). Acetylcyclopropane (0.84g) in ether (30 ml) was cautiously added to the amalgam at 0° and the reaction mixture was then shaken at 20° for 3 hours. The ether solvent was removed and the residue was washed with more ether (2 x 10 ml). The combined organic extracts were dried (MgSO₄) and concentrated to an oil (0.08g). The nmr and ir spectra were too weak and diffuse to merit investigation.

Preparation of 1,8-Dicarbonyl chloride.⁴³ - Octane 1,8-dicarboxylic acid (8.7g, 0.05 moles) was treated with an excess of thionyl chloride (18g, 0.15 moles) and the reaction mixture was stirred at 40° for 3 hours. The excess of thionyl chloride was removed by distillation at atmospheric pressure and the residue was vacuum distilled to give a fraction, b.p. 102-103°/.1mm, which was shown to be the pure di-acid chloride. ν_{\max} (film) 1790(s)(b), 1470(m), 1410(m), 1345(w), 1255(w), 1145(m), 1198(m), 1000(s), 950(s), 930(m), 820(m); $\delta(\text{CCl}_4)$ 1.0-2.1 (m, 8H, aliphatic), 2.88 (t, 4H, $\text{CH}_2 \cdot \text{CO}$).

Preparation of Decane-2,9-Dione. - The di-acid chloride (2.11g, 0.01 mole) in benzene was added dropwise, with stirring, to a solution of dimethylcadmium⁴⁴ (0.1 mole) in benzene (25 ml) and the reaction mixture was refluxed for 45 minutes under nitrogen. The solution was then poured into ice/sulphuric acid and the layers separated. The aqueous layer was extracted with benzene (2 x 50 ml) and the combined organic extracts were then washed with water (2 x 30 ml), saturated sodium carbonate solution (until alkaline), water (2 x 30 ml), saturated aqueous sodium chloride solution, and finally dried (MgSO_4). The benzene was removed by rotary evaporation to give a white solid (m.p. 60-61°, ex pentane; lit., m.p. 62°, ex pet-ether (40-60°)⁴⁵) which was identified as decane-2,9-dione containing less than 2% impurity by v.p.c. (Apiezon L, 150°; 10% Apiezon L, 165°). $\nu_{\max}(\text{CCl}_4)$ 2890(s), 2810(m), 1710(s), 1465(w), 1415(m), 1358(m), 1160(m), 1090(w), 1025(w), 690(w);

$\delta(\text{CDCl}_3)$ 1.0-2.0 (m, 8H, aliphatic), 2.15 (s, 6H, $\text{CH}_3\cdot\text{CO}$), 2.43 (t, 4H, 3-H₂, 8-H₂); Mass spectrum P, 170, 152, 113, 71, 58, 43.

The preparation was first attempted using an excess (x 5) of dimethylcadmium prepared from the reaction between methylmagnesiumiodide (rather than the bromide) and cadmium dichloride. In this case the main reaction product was the di-tertiary alcohol.

Reduction of 1-Acetyl-2,2-dimethylcyclopropane with Lithium in Hexamethylphosphoramide. - A solution of lithium (0.179g, 0.026 moles) in pure hexamethylphosphoramide⁴¹ (10 ml) was stirred at 0° for 1 hour under nitrogen. The ketone (0.25g, 0.022 moles) was then added dropwise to the blue solution and the reaction mixture was stirred at 20° for 1.25 hours. Methanol (2 ml), water (20 ml), and pentane (20 ml) were added to the product solution, and the organic layer was separated and washed with saturated sodium chloride solution (3 x 10 ml) and finally dried (MgSO_4). After concentrating, the product was analysed by v.p.c. (Apiezon L, 70°).

A number of reductions were performed incorporating slight modifications in the experimental procedure and conditions. (see Table 7).

Preparation of Ethyl 4-Chloropentanoate (32).⁴⁷ - Thionyl chloride (200g) was added to a solution of tetrahydro-5-methyl-2-furanone (γ -valerolactone; 55g) in anhydrous benzene (110 ml) and the solution was refluxed for 20 hours. On cooling, the mixture was treated with a saturated solution

of hydrogen chloride in ethanol (400 ml) and the mixture was stirred for 30 minutes. The solvents were removed by rotary evaporation and the chloro-ester (32) was isolated by distillation (60.84g, 67%, b.p. 74-76°/9 mm; lit., b.p. 78°/10 mm⁴⁷). It contained 4% of unreacted γ -valerolactone (v.p.c., Apiezon L, 80°). The product had the following spectral data: ν_{\max} (film), 1725(vs) cm^{-1} ; $\delta(\text{CCl}_4)$ 1.25 (t, 3H, $\text{CH}_3\text{-CH}_2$, $J = 7\text{Hz}$), 1.54 (d, 3H, 4- CH_3 , $J = 6\text{Hz}$), 2.0 b (m, 2H, 3- CH_2), 2.45 (t, 2H, 2- CH_2 , $J_{\alpha} = 7\text{Hz}$), 3.38 b (m, 1H, 4-H), 4.08 (q, 2H, $\text{CH}_3\text{-CH}_2$, $J = 7\text{Hz}$); Mass spectrum $P = 164$; at low eV the major peaks were at m/e 121, 119, 101, and 88.

In a further reaction of thionyl chloride with γ -valerolactone (77g) the final distillation of the residue yielded two fractions, b.p. 60-62°/10 mm and 76-78°/10 mm respectively. V.p.c. analysis (Apiezon L, 70°) showed fraction 2 to be the required chloro-ester (>98%), but fraction 1 contained only 50% of the chloro-ester. From the nmr spectrum and mass spectrum of fraction 1 it was deduced that the remaining 50% was diethyl sulphite.⁴⁸ This was verified by an accurate mass measurement of the prominent peaks in the mass spectrum at low eV; $P_{138} - \text{C}_4\text{H}_{10}\text{O}_3\text{S}$, $123 - \text{C}_3\text{H}_7\text{O}_3\text{S}$, $110 - \text{C}_2\text{H}_6\text{O}_3\text{S}$, $93 - \text{C}_2\text{H}_5\text{O}_2\text{S}$, $59 - \text{C}_3\text{H}_7\text{O}$. The maximum error for each peak was within a limit of 7 ppm.

Preparation of Ethyl (trans-2-Methylcyclopropyl)carboxylate (33).⁴⁹ - The preparation involved the reaction of ethyl 4-chloro-pentanoate (32) with sodamide⁵⁰ in ether.

Ethyl 4-chloropentanoate (60.84g, 0.37 mole) was added dropwise to an excess of sodamide (x 2) in ether over a period of 2 hours and the reaction solution was stirred under nitrogen for 80 hours. The excess of sodamide was destroyed with water and the aqueous layer was extracted with ether (2 x 50 ml). The combined organic extracts were dried (MgSO_4) and the ether removed by distillation through a 30 cm Vigreux column. Final distillation gave trans-2-methylcyclopropyl imide as a crystalline solid (m.p. 162° - 164°).

ν_{max} (nujol) 3260(m), 3170(m), 1715(s), 1548(m), 1515(m), 1420(m), 1342(m), 1224(w), 1190(s), 1170(m), 1085(w), 1050(w), 1038(w), 990(w), 890(w), 720(w) cm^{-1} ; ν_{max} (CCl_4) 3260(m), 3200(m), 3140(m), 1725(s), 1670(s), 893 cm^{-1} ;

δ (CDCl_3) 0.76 b (m, 2H, 2-H), 1.12 (d, 6H, 2-Me, $J_{\text{Me}, 2\text{-H}}$ 5 Hz), 1.30 b (m, 4H, 3-H), 2.03 (m, 2H, 1-H), 9.5 b (s, 1H, NH);

Mass spectrum: P 181, 140, 99, 82, 55, 39; Accurate mass measurement: P 181.11072 - $\text{C}_{10}\text{H}_{15}\text{NO}_2$.

The reaction was repeated on ethyl 4-chloropentanoate (8g) using a three-fold excess of sodamide in ether to determine if formation of the imide was dependent upon the presence of an excess of sodamide. Final distillation gave a fraction, b.p. 59 - $60^\circ/15$ mm, identified as ethyl (2-methylcyclopropyl)carboxylate containing less than 2% impurity (v.p.c., Apiezon L, 70°). ν_{max} (film): 1720(s), 1460(m), 1420(s), 1593(m), 1535(s), 1272(m), 1220(s), 1195(s), 1175(s), 1088(m), 1018(m), 970(w), 900(s), 875(w), 740(m) cm^{-1} ; δ (CCl_4), 0.6 (m, 2-H), 1.2 (m, $\underline{\text{CH}_3}\cdot\text{CH}_2$, 1-H, 2- CH_3 , 3- H_2), 4.0 (two q, $\text{CH}_3\cdot\underline{\text{CH}_2}$). Expansion of the

spectrum showed the multiplet at δ 1.2 to be composed of two triplets and a doublet centred δ 1.08 ($J = 5$ Hz). Simultaneous irradiation of the quartets δ 4.05 collapsed both triplets δ 1.2 into singlets. The doublet at δ 1.08 was unaffected. The ratio of trans:cis isomers of ethyl (2-methylcyclopropyl)carboxylate was $\sim 4:1$ (nmr).

A further reaction using equimolar quantities of starting materials gave the cyclic product (9.32g, 64%), b.p. $60^\circ/9$ mm, containing less than 1% impurity (v.p.c., Apiezon L, 70°).

Preparation of trans-2-methylcyclopropyl carboxamide.⁵¹ -

Method A: - A mixture of cis/trans ethyl (2-methylcyclopropyl) carboxylate (23.85g, c/t = 1/4) was added to a solution of methanolic ammonia (300 ml) and the reaction left to stand for 6 days. The solvent was removed by rotary evaporation and the residue extracted with methylene chloride. After concentration, the solid product was recrystallised from methylene chloride/pentane to give pure trans-2-methylcyclopropylcarboxamide (3.2%, m.p. $109-110^\circ$, lit., m.p.⁵² $111-112^\circ$) whose spectra (ir, nmr) were in agreement with the literature values. $\nu_{\max}(\text{CDCl}_3)$: 3530(m), 3410(m), 1668(s), 1597(s), 1450(m), 1416(m), 1385(m), 1354(m), 1097(m), 1074(w), 1012(w), 947(m), 867(m), cm^{-1} ; $\delta(\text{CDCl}_3)$ 0.58 (m, 1H, 3-H trans to $\text{CO}\cdot\text{NH}_2$), .86-1.5 br (m, 6H, 1-H, 2-H, 2-Me, 3-H cis to $\text{CO}\cdot\text{NH}_2$), 6.0 br (s, 2H, NH_2). A more exhaustive analysis of the cyclopropyl absorptions was carried out by observing the nmr spectrum of the amide in CDCl_3 (.5 ml) in the presence of tris(dipivalomethanato)-europium(III) (.003g,

.0000045 moles). $\delta(\text{CDCl}_3)$: 0.54 (m, 1H, 3-H) trans to $\text{CO}\cdot\text{NH}_2$), 0.8-1.24 (m, 5H, 2-H, 2- CH_3 , 3-H cis to $\text{CO}\cdot\text{NH}_2$), 1.24-1.54 (m, 1H, 1-H) 6.1 br. (s, 2H, $\text{CO}\cdot\text{NH}_2$). Addition of a further .003g of the europium reagent did not alter the spectrum.

Method B: - This procedure involved the reaction of ethyl (trans-2-methylcyclopropyl)carboxylate with sodamide in refluxing dioxan. Ethyl(trans-2-methylcyclopropyl) carboxylate (7.08g, .054 moles) was added dropwise to a solution of sodamide in dioxan and the reaction mixture was refluxed for 18 hours under a nitrogen atmosphere. The excess of sodamide was destroyed with water and the residue filtered off. The solvents were removed by rotary evaporation leaving an oil which was extracted with methylene chloride (30 ml). On recrystallisation from methylene chloride/pentane a white crystalline solid (1.1g, 20.2%, m.p. 111°) was obtained whose spectra (ir, nmr) were identical to those of pure trans-2-methylcyclopropylcarboxamide.

Attempted One-Stage Preparation of trans-2-Methylcyclopropylcarboxamide from Ethyl 4-Chloropentanoate.

Method A. Reaction with Sodamide/Benzene. - Ethyl 4-chloropentanoate (3.5g, .027 mole) was added dropwise to an excess of sodamide in benzene (3.4g in 75 ml) and the reaction mixture was refluxed for 24 hours under nitrogen. The excess of sodamide was destroyed with water, the residue filtered off, and the solvents were removed by distillation through a Vigreux column. The residue was extracted with methylene

chloride and recrystallised from methylene chloride/pentane to give trans-2-methylcyclopropyl carboxamide (.247g, 11.7%), b.p. 110-111^o.

The reaction was repeated with the same quantities of starting materials but with a reflux period of 72 hours. The yield of amide was found to be less than 1%.

Method B. Reaction with Sodamide/Dioxan. - Ethyl 4-chloropentanoate (3.5g, .027 mole) was added dropwise to an excess of sodamide in dioxan (3.4g in 75 ml) and the reaction mixture was refluxed for 72 hours under nitrogen. The excess of sodamide was filtered off, washed with dioxan (2 x 15 ml), and the combined organic extracts concentrated by rotary evaporation. Extraction of the residue with methylene chloride yielded no amide.

Method C. Reaction with Sodamide/Dimethylformamide (DMF). - Ethyl 4-chloropentanoate (5g, .039 mole) in DMF (10 ml) was added dropwise to excess of sodamide in DMF (3.5g in 75 ml) and the reaction mixture was refluxed for 30 hours. The final product was an oil which did not crystallise.

Attempted Preparation of trans-2-Methylcyclopropylmethylamine.

The procedure involved the reaction of trans-2-methylcyclopropylcarboxamide (34) with diborane.⁵³

Method A. - Diborane⁵³ (50% excess) was prepared by the dropwise addition, with stirring, of sodium borohydride (1.48g, 0.039 mole) in diglyme (30 ml) to borontrifluoride etherate (10 ml) in diglyme (10 ml). The generated gas was passed

into a solution of trans-2-methylcyclopropylcarboxamide (1g, 0.01 mole) in tetrahydrofuran (THF) by means of a slow stream of nitrogen and the reaction mixture was refluxed for 2 hours. Hydrochloric acid (3 ml of 6M) was added to the cooled solution and the THF was removed by distillation at atmospheric pressure. The residue was saturated with sodium hydroxide and the aqueous layer was extracted with ether (3 x 8 ml). The combined organic extracts were dried (MgSO_4) and concentrated. Distillation of the residue yielded unreacted cyclopropylcarboxamide.

Method B. - In a further attempt to prepare the amine a solution of trans-2-methylcyclopropylcarboxamide (0.218g, 0.002 mole) in THF (3 ml) was added dropwise, with stirring, to a 1M solution of diborane⁵³ in THF. The temperature of the solution was kept at 0° during addition. The colourless solution was then refluxed for 2.75 hours, cooled, and acidified (1 ml of 6M hydrochloric acid). The THF was removed by distillation, the residue was saturated with sodium hydroxide, and the aqueous layer extracted with ether (1 x 12 mls). After drying (MgSO_4) the solution was concentrated and the residue was distilled to give two fractions, one of which was a mixture of THF and ether (v.p.c., Apiezon L, 70°), and the second a mixture of THF, ether, and unreacted amide (v.p.c., Apiezon L, 70°; and ir). The ir, nmr, and mass spectra gave no indication of the desired product.

This reaction was repeated with the same quantities of starting materials but with a reflux time of 15 hours. Final distillation of the residue gave no methylamine derivative.

Preparation of trans-2-Methylcyclopropylmethylamine (35). -

The procedure involved reduction of the amide with lithium aluminium hydride.⁵⁴

trans-2-Methylcyclopropylcarboxamide (34) (0.25g, 0.0025 mole) in anhydrous ether (10 ml) was added dropwise; with stirring, to lithium aluminium hydride (0.095g, 0.0025 mole) in ether (10 ml) and the reaction mixture was refluxed for 15 hours under nitrogen. The excess of lithium aluminium hydride was destroyed with water (0.2 ml) and the precipitated solid was filtered off. Removal of the ether by distillation at atmospheric pressure gave a reddish oil. Since the ir and nmr spectra indicated the presence of unreacted amide and of ether the oil was distilled. The nmr spectrum of the fraction b.p. 92-93^o, showed that the removal of ether was incomplete but that the required amine was present (δ_{CCl_4} 1.87, (s) and $\delta_{3.12}$, (d)).

Repeated distillations to remove the ether were unsuccessful.

Preparation of N-(2-Methylpropyl)toluene-p-sulphonamide.⁵⁵ -

2-Methylprop-1-ylamine (1g, 0.0137 mole) and toluene-p-sulphonyl chloride (3g, 0.0158 mole) were dissolved in pyridine/ether (6:1, 7ml) and the mixture was refluxed for 30 minutes. The solution was poured into water (10 ml) and the aqueous layer was extracted with ether (3 x 15 ml). The organic extract was washed with sodium bicarbonate solution, dried (MgSO_4), and concentrated to an oil which crystallised. Recrystallisation from ethanol gave the pure derivative

(0.96g, 43%) m.p. 75-77°. ν_{\max} (nujol): 3252(s), 1597(w), 1330(s), 1290(m), 1260(m), 1156(s), 1094(m), 1070(m), 935(w), 850(m), 820(m), cm^{-1} ; δ (CDCl_3): 0.85 (d, 6H, Me_2CH , $J_{\text{Me}, 2\text{-H}} 6\text{Hz}$), 1.75 b (m, 1H, 2-H), 2.42 (s, 3H, aromatic Me), 2.74 (t, 2H, CH_2), 5.0 (t, 1H, NH), 7.3, 7.76 (two d, 4H, aromatic). Irradiation of the multiplet $\delta 1.7$ collapsed the triplet $\delta 2.74$ into a doublet ($J = 7$ Hz). Shaking with deuterium oxide removed the triplet $\delta 5.0$ and collapsed the triplet at $\delta 2.74$ to a doublet indicating that both the tertiary 2-H proton and the NH proton were coupled to the methylene protons ($J_{1\text{-H}, \text{NH}} 7$ Hz, $J_{1\text{-H}, 2\text{-H}} 6.5$ Hz). Irradiation of the multiplet $\delta 1.7$ after deuterium exchange collapsed the doublet $\delta 2.74$ into a singlet.

When the reaction was repeated with the same quantities of starting materials, but with an extra quantity of ether (90 ml), the yield of product was reduced to 10.2%.

Preparation of N-(trans-2-Methylcyclopropylmethyl)toluene-p-sulphonamide. - trans-2-Methylcyclopropylcarboxamide (.975g, .01 mole) in ether (5 ml) was added dropwise, with stirring, to lithium aluminium hydride in ether and the reaction mixture was refluxed for 25 hours under nitrogen. After destroying the excess of lithium aluminium hydride with water, the product was extracted with ether (3 x 15 ml). The combined organic extracts were dried (MgSO_4) and concentrated to 1.5 mls.

Toluene-p-sulphonyl chloride (3g, 0.0158 mole) in pyridine was added to the ethereal solution of the amine and the reaction mixture was refluxed for 45 minutes. The

reaction solution was poured into water (10 ml) and the aqueous layer was extracted with ether (3 x 15 ml). The organic extract was washed with dilute hydrochloric acid (1 x 15 ml), sodium bicarbonate solution (1 x 10 ml), dried (MgSO_4), and concentrated to an oil, which crystallised. Recrystallisation from petroleum-ether (60-80°) gave white crystals of the pure derivative (2.092g, 89%), m.p. 40-41°. ν_{max} (nujol) 3280(s), 1600(w), 1435(m), 1320(s) 1153(s), 1098(m) 1065(m), 902(w), 866(w), 823(m), cm^{-1} ; δ (CDCl_3 with dioxan as external lock δ 3.56) 0.20(m, 2H, cyclopropyl), 0.5 (m, 2H, cyclopropyl), 0.93 (d, 3H, 2-Me, $J_{2\text{-Me}, 2\text{-H}}^5$ Hz) 2.40 (s, 3H, aromatic Me), 2.72 (m, 2H, CH_2), 5.63 (t, 1H, NH $J_{\text{CH}_2, \text{NH}}^7$ Hz) 7.24, 7.70 (two d, 4H, aromatic); Mass spectrum P239, 210, 198, 184, 172, 155, 91; accurate mass - 239.098435 - $\text{C}_{12}\text{H}_{17}\text{NO}_2\text{S}$; analysis - (Found C, 60.4; H, 7.0, N, 6.0. $\text{C}_{12}\text{H}_{17}\text{NO}_2\text{S}$ requires C, 60.3, H, 7.1; N, 6.0%).

Reaction of Cyclohexyl toluene-p-sulphonamide with Hydroxylamine-O-sulphonic acid (Nickon-Sinz reaction)⁵⁶. - Hydroxylamine-O-sulphonic acid (10g) was added in small portions, with stirring, to the cyclohexylamine derivative (1g, .042 mole) dissolved in hot aqueous sodium hydroxide (100 ml/20%) and ethanol (30 ml). The reaction mixture was heated and the fraction (5 ml) b.p. 80-86°, was collected in an ice-cooled flask containing carbon tetrachloride (10 ml). The product solution consisted of cyclohexane, carbon tetrachloride and ethanol by comparative v.p.c. (Carbowax 40°).

Treatment of the reaction mixture with concentrated hydrochloric acid gave 0.8126g of unreacted starting material.

Reaction of N-(trans-2- Methylcyclopropylmethyl)toluene-p-sulphonamide with Hydroxylamine-O-sulphonic acid (Nickon-Sinz reaction). - The toluene-p-sulphonyl derivative (.6g, .0025 mole) was dissolved in hot aqueous sodium hydroxide (100 ml/20%) and ethanol (30 ml) and the solution was transferred to a vessel fitted with a magnetic stirrer, reflux condenser and a take-off condenser. Carbon tetrachloride (10 ml) was placed in a round-bottomed flask (25 ml) which served as the distillation receiver. Hydroxylamine-O-sulphonic acid (10g) was then added in small portions through the reflux condenser, which was kept stoppered except during the addition of the acid, and the reaction mixture was heated until ethanol (10 ml) had been distilled into the ice-cooled receiver. The receiver was immediately placed on a vacuum line (10^{-6} τ) and samples gas-injected for v.p.c. analysis (1,2-bis-Methoxyethyl adipate, 20°).

The Nickon-Sinz reaction was repeated several times on the amine derivative using varying base concentrations and conditions (see Table 8). A control reaction was performed on methylamine toluene-p-sulphonamide using 28% aqueous sodium hydroxide as the base.

In some subsequent Nickon-Sinz reactions minor modifications were made to the experimental and analytical procedures. These included:

- (a) - replacement of the receiver flask with a test-tube (15 x 1 cm) fitted with a 14 cm delivery tube passing to the bottom of the test-tube.
- (b) - introduction of a test-tube side-arm which could be inverted at will to 'internally' discharge the sulphonic acid powder into the reaction solution.
- (c) - use of ethanol as a receiving solvent.
- (d) - direct injection (syringe) of samples for v.p.c. analysis. (See Table and Discussion).

Preparation of Methylamine toluene-p-sulphonamide. - The experimental procedure was as for N-(2-methylpropylamine) toluene-p-sulphonamide. White crystals of the pure derivative were obtained (59%, m.p. 71-73^o; lit., m.p. 76^{o59}). δ (CDCl₃) 2.41 (s, 3H, aromatic Me), 2.6 (d, 3H, Me, $J_{Me,NH}$ 5 Hz), 5.0 (q, 1H, N-H, $J_{NH,Me}$ 5 Hz), 7.32, 7.76 (two d, 4H, aromatic $J_{2,3}$ 8 Hz).

Preparation of Diethyl Anthracene-9,10-dicarboxylate.⁶² - A mixture of anthracene (4.0g, .025 mole) and diethylazodicarboxylate (4.0g, .025 mole) in toluene (25 ml) was refluxed for 20 hours and then filtered hot. After cooling, the resultant solid was filtered off and dried (70%, m.p. 133-135^o; lit., m.p. 138^{o62}).

Preparation of Anthracene-9,10-di-imine.⁶³ The diester adduct (5.5g, 0.15 mole) was added to a solution of sodium hydroxide in ethanol (180 ml/2M) and the reaction mixture was stirred for 70 hours under a nitrogen atmosphere. The

solvents were removed by rotary evaporation and the yellow residue was dispersed in water and acidified with hydrochloric acid. The insoluble anthracene was filtered off, and the di-imine was precipitated from solution by basification with potassium hydroxide solution. The di-imine was filtered off and dried (2.16g, 67%). The ir spectrum was in agreement with the literature.⁶³

Di-imide Reduction of a Mixture of Pent-1-ene and 3-Methylbut-1-ene.⁶³ - An excess (x 5) of anthracene-9,10-di-imine (1.7g) was added to an ethanolic solution (10 ml) of the two olefins (Percentage ratio (38):(39) = 42.3:52.3) and the reaction mixture was heated at 60° for 14 hours. The product solution, (analysed by v.p.c.; 1,2-bis-Methoxyethyladipate, bis-methoxyethyladipate + di-2-ethylhexylsebacate, 20°), was a mixture of 3-methylbutane (36.8%), 3-methylbut-1-ene (38) (9.7%), pent-1-ene (39) (7.9%), and pentane (41.8%).

Preparation of cis/trans-2,2-Dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl-1-carboxylic acid. - Ethyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate (50g, 35% cis:65% trans) was refluxed with potassium hydroxide in ethanol (20g in 200 ml) for 2 hours. The solvent was removed by rotary evaporation and the residue was diluted with water (200 mls) and extracted with ether. The aqueous phase was then acidified with hydrochloric acid and extracted with ether (3 x 100 ml). After drying (MgSO₄) and concentrating the extract, final distillation gave a mixture of the pure

acids (33.95g, 81%), b.p. $101^{\circ}/.4$ mm. ν_{\max} (film) 2900(s), 1690(s) cm^{-1} ; $\delta(\text{CCl}_4)$ 1.0-1.4 (m, 7H, 2-Me₂, 1-H), 1.70 (s, 6H, olefinic Me), 2.0 (m, 1H, 3-H), 4.86, 5.29 (two d, 1H, olefinic H), 13.0 (s, 1H, COOH).

Separation of cis/trans-Ethyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl carboxylates.⁶⁷ - A mixture of the esters (17.2g, 0.88 mole, 35% cis:65% trans) was added to a solution of sodium (15g) in anhydrous ethanol (300 ml) and the reaction mixture was refluxed for 7 days under nitrogen. The solution was poured into ether (500 ml) and was treated with aqueous acetic acid (500 ml, 30%). The organic layer was separated and washed with sodium bicarbonate solution, and finally dried (MgSO₄). The ether was removed by rotary evaporation to give an oil which was shown (v.p.c., Apiezon L, 120° ; nmr) to be a mixture of the cis- (6%) and the trans- (94%) esters. Vacuum distillation of the oil gave trans-ethyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl-1-carboxylate (13.7g, b.p. $65-67^{\circ}/.2$ mm) which was shown to be pure (>99%) by v.p.c. (Apiezon L, 145°) and nmr. $\delta(\text{CCl}_4)$ 1.0-1.4(m, 10H, 2-Me₂, 1-H, CH₃-CH₂), 1.69 (s, 6H, olefinic Me₂), 1.90 (m, 1H, 3-H), 4.05 (q, 2H, CH₃-CH₂), 4.84 (d, 1H, olefinic H); ν_{\max} (film) 1720(s), 1240(s), 1200(s), 1164(s), 1118(s), cm^{-1} .

Attempted Separation of cis/trans-Ethyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl-1-carboxylate.

Method 1. Fractional Recrystallisation of the cis/trans Acid.⁶⁸ - A mixture of the cis/trans ethyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl carboxylic acids (33.95g, 36% cis:64% trans) was dissolved in ethyl acetate and the solution left at -78° for 18 hours. The solution was then filtered at -78° and the filtrate was concentrated to an oil. NMR of the oil showed that the trans-acid was the major isomer (90%). Successive recrystallisations from ethyl acetate did not reduce the percentage of cis-isomer below 10%.

Method 2. Thin-Layer Chromatography (T.L.C.) - No separation of the mixture of cis/trans acids was obtained by T.L.C. using a mixture of benzene/methanol/acetic acid (45:8:4) as the solvent.⁶⁹

Method 3. Saponification of the Esters - Kinetic Approach. (see Discussion). - The mixture of the ethyl esters (.5g, .025 mole, 35% cis:65% trans) was refluxed with potassium hydroxide (.084g) in ethanol (2 ml) for 2 hours. The final hydrolysis product was a mixture of the cis- and the trans-acids (21% cis:79% trans by nmr).

The reaction was repeated with the same quantities of starting materials but the reaction mixture was stirred at 20° for 3 days. The final product was a mixture of the cis- and the trans-acids (18.3% cis:81.7% trans by nmr).

Method 4. Ion-Exchange Chromatography.⁷⁰ - A solution of the cis/trans acids in ethanol/water (3:1, 400 ml) was introduced (1.0 ml/min) onto a column (12 x 1.5 cm) containing

Amberlite I.R.A. 938 ion-exchange resin in the chloride ion form. The column was eluted with a solution of 0.1N hydrochloric acid in ethanol (200 ml), and 10 ml samples were collected and analysed (nmr (CCl_4)). No separation of the cis- and trans- isomers was obtained.

The experiment was repeated using .001N hydrochloric acid/ethanol solution (150 ml) as the eluent. No separation of the acid isomers was effected.

Separation was also attempted using Amberlite I.R.A. 900 ion-exchange resin with, (a) 0.01N hydrochloric acid/ethanol solution and (b) pyridine/acetic acid (10:1) as the eluent. No separation of the isomers was obtained in either case.

Method 5. Preparative V.P.C. - Separation of the cis- and the trans- acids and esters was unsuccessful. The columns employed were:

- (a) Diethyleneglycol succinate (100° and 150°)
- (b) Silver nitrate (70°)
- (c) Apiezon L. (120° , 140°).

Attempted Preparation of trans-1-Acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane. -

Method A. - An excess (x 2) of lithium methyl⁴⁰ in ether (15 ml) was added dropwise, with stirring, to ethyl-trans-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl-1-carboxylate (1.25g) in ether (10 ml) under nitrogen. The excess of lithium methyl was destroyed with aqueous ammonium chloride solution, and the organic layer was separated,

washed with water (2 x 10 ml) and dried (MgSO_4). The ether was removed by rotary evaporation and the residue vacuum distilled to give a fraction, b.p. 43-46 $^\circ$ /.2 mm which was shown by v.p.c. (Apiezon L. 145 $^\circ$) to contain five components. The main component was unreacted ester (70%). The other four components were not identified although an alcohol was indicated by ir (ν_{max} (film) 3300 cm^{-1}).

Method B. - The procedure was as described in the literature.⁷¹

Stage 1. - Ethyl-trans-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl-1-carboxylate (1g, .5g equivalents based on 1g equivalent of methylsulphinyl carbanion) was added dropwise, with stirring, to an ice-cooled solution of methylsulphinyl carbanion (.01M) in tetrahydrofuran (2 ml) under nitrogen. The reaction mixture was stirred at 20 $^\circ$ for 30 mins.

Water (10 ml) was added, the solution was acidified with dilute hydrochloric acid and extracted with chloroform (4 x 20 ml). The organic extracts were washed with water (3 x 15 ml) and dried (MgSO_4). The solution was concentrated to an oil which was shown (ir, nmr) to be pure trans-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl-1-carboxylic acid.

The reaction was repeated on the ester (1g, .005 mole) using 4g equivalents of the methylsulphinyl carbanion. After treating the reaction mixture with water (75 ml) and dilute hydrochloric acid the solution was extracted with chloroform (4 x 50 ml). After drying, the solvent was removed to give an oil whose ir spectrum indicated that the required cyclopropyl methylsulphinyl compound had been formed

($\nu_{\max}(\text{film}) 1692 \text{ cm}^{-1}$) (by comparison with ir values of some methylsulphinyl compounds quoted in the literature⁷¹). An alcohol ($\nu_{\max} 3350 \text{ cm}^{-1}$) was also present. The nmr (CCl_4) spectrum showed the product to be a mixture.

Stage 2. - Aluminium foil strips (0.6g) were immersed in a 2% aqueous mercuric chloride solution for 15 secs., washed with absolute alcohol and ether, and then cut into pieces (1 cm x 1 cm) and allowed to fall into a flask containing the product from stage 1 (.5g) dissolved in 10% aqueous tetrahydrofuran (30 mls). The reaction mixture was heated at 65° for 80 mins. The remaining solid was filtered off, the filtrate was concentrated and then extracted with ether (3 x 15 ml). After drying, the ether was removed to give an oil which consisted of 6 products (v.p.c., Apiezon L, 120°). Identification of the products was not undertaken.

The entire procedure was repeated on the ester (1g) using 2g equivalents of the methylsulphinyl carbanion. The ir of the product was similar to that from the previous attempt except that some unreacted ester was indicated ($\nu_{\max} 1720 \text{ cm}^{-1}$). In the second stage the same quantities of starting materials were used. The reaction mixture was stirred at 0° for 10 mins and then filtered and extracted with ether (3 x 15 ml). After drying, the solvent was removed to give an oil which contained 6 products (v.p.c., Apiezon L, 120°). The ir spectrum showed the major product to be the unreacted methylsulphinyl compound and also showed a strong hydroxyl absorption ($\nu_{\max}(\text{film}) 3400 \text{ cm}^{-1}$).

Preparation of trans-1-Acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane. - An excess (x 0.5) of lithium methyl⁴⁰ in ether (30 ml) was added dropwise, with stirring, to pure trans-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl-1-carboxylic acid (lg, .0059 mole) in ether (10 ml) under nitrogen. The excess of lithium methyl was destroyed with saturated ammonium chloride solution and the ether layer separated, washed with water (2 x 20 ml), and dried (MgSO₄). Vacuum distillation of the concentrated residue gave a fraction (.84g), b.p. 46°/.5 mm, which contained two products (v.p.c., Apiezon L, 120°) in the ratio, 81%:19%. ν_{\max} (film) 3550(m), 1695(s) cm⁻¹. The two products were separated by dry column chromatography as follows: the reaction product mixture (.74g), absorbed on alumina (5g), was introduced to the top of a column (20 x 1 in) containing alumina (Activity III, coated Fluorescent Indicator (Green)). The column was eluted with benzene (250 ml) and the products located with a low wavelength ultra-violet light. The separated products were extracted with ether and the extract dried and concentrated. The major product (81%) was identified as trans-1-acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane with less than 2% impurity (v.p.c., Apiezon L, 120°). ν_{\max} (film) 2950(s), 1693(s), 1470(m), 1425(s), 1390(s), 1370(s), 1290(w), 1240(m), 1200(s), 1190(s), 1122(s), 1090(w), 1065(w), 1045(w), 970(m), 860(m), cm⁻¹; δ (C₆H₆) 1.10, 1.32 (two s, 6H, 2-Me₂), 1.58 (d, 1H, 1-H, J_{1,3} 5.5 Hz), 1.72 (d, 6H, olefinic Me₂), 1.99 (s, 3H, CH₃-CO), 2.55 (m, 1H, 3-H), 5.01 (d, 1H, olefinic H); Mass spectrum P 166, 123, 81, 43.

The other product was identified as 2-trans-[2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl]propan-2-ol with less than 1% impurity (v.p.c., Apiezon L, 120°). ν_{\max} (film) 3500(s), 1700(w), 1470(m), 1460(m), 1385(s), 1145(s), 960(w), 870(w), cm^{-1} ; $\delta(\text{CCl}_4)$ 0.98 (s, 3H, 2-Me), 1.0-1.50 (m, 12H, 1-H, 2-Me, 3-H, $(\text{CH}_3)_2\cdot\text{CHOH}$, OH), 1.68 (s, 6H, olefinic Me_2), 4.8 (d, 1H, olefinic H); Mass spectrum P 182, 164, 149, 124, 109, 59.

A more exhaustive analysis of the nmr spectrum of the tertiary alcohol was carried out by observing the spectrum in CCl_4 (.5 ml) in the presence of tris(dipivalomethanato)-europium(III) (0.006g, .000009 mole). $\delta(\text{CCl}_4)$ 1.63 (d, 1H, 1-H, $J_{1,3}$ 6 Hz), 1.20 (s, 3H, 2-Me), 1.36 (s, 3H, 2-Me), 1.44 (s, 6H, $(\text{CH}_3)_2\text{CH}$), 1.54 (m, 1H, 3-H), 1.70 (s, 6H, olefinic Me_2), 1.88 b (s, 1H, OH), 4.87 (d, 1H, olefinic H). Addition of a further 6 mg of the shift reagent to the nmr solution resulted in the superimposing of a number of methyl absorptions.

In a further reaction of lithium methyl with the pure trans- acid (5g, .0295 mole) the percentage of methyl ketone in the product mixture was 92.5%. The remaining 7.5% was the tertiary alcohol.

Lithium/Liquid Ammonia Reduction of trans-1-Acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane (44). - Lithium (.54g, .078 moles) was added to anhydrous liquid ammonia (100 ml) in a flask fitted with a Dry-Ice condenser and the solution stirred for 20 mins to ensure complete

dissolution of the lithium. The ketone (0.3g, 0.0018 mole) was added dropwise to the stirred solution and the stirring continued for 2 hours. The reduction mixture was decomposed by the addition of solid ammonium chloride and ether (50 ml). After the ammonia had evaporated, water (30 ml) was added, and the organic layer was separated and washed with dilute hydrochloric acid (2 x 15 ml), sodium bicarbonate solution (2 x 15 ml), and finally dried (MgSO_4). After concentrating, v.p.c. examination (Apiezon L, 120°) of the residue (~2 ml volume) showed five components. Oxidation⁷² of the reduction product in pyridine (3 ml) with a chromium trioxide/pyridine complex gave a product mixture containing four components by v.p.c. examination (Carbowax 75°); retention times (minutes) - A. 6.2 (48%), B. 6.6 (22.0%), C. 8.7 (16.1%), D. 10.2 (13.9%, starting ketone). Preparative v.p.c. (Se 30, 120°) of the oxidised product mixture resolved two bands, 1 (85%) and 2 (15%). Band 1 was unresolved A and B and was identified (nmr) as a mixture of trans- and cis-4,4,7-trimethyl-oct-5-en-2-one. $\delta(\text{CCl}_4)$ 0.95 (d, 6H, 7-Me₂, $J_{7,\text{Me}}$ 6 Hz), 1.04 (s, 6H, 4-Me₂), 1.98 (s, 3H, $\text{CH}_3\cdot\text{CO}$), 2.14 (m, 1H, 7-H), 2.29 (s, 2H, 3-Hz), 5.63 (m, 2H, 5-H, 6-H). Irradiation of the multiplet δ 2.14 collapsed the multiplet at δ 5.63 into a doublet ($J_{5,6}$ 16 Hz). Irradiation of the doublet δ 0.95 collapsed the multiplet at δ 2.14 into a doublet ($J_{6,7}$ 6 Hz). Double irradiation of the doublet δ 0.95 and the multiplet δ 5.63 collapsed the multiplet δ 2.14 into a singlet.

Band 2 contained the starting ketone, D (~33%) and the

unknown component C (60%). (Components A and B constituted the remaining 7%). Component C was not isolated pure but was shown (from nmr of band 2) to be 4,4,7-trimethyloct-6-en-2-one. $\delta(\text{CCl}_4)$ 5.09 (t, 1H, 6-H), 4.92 (d, 1H, starting ketone) 2.22 (s, 2H), 2.13 (s, $\text{CH}_3\cdot\text{CO}$), 2.0 (m, $\text{CH}_3\cdot\text{CO} + \text{H}_1$) (The rest of the spectrum was due to methyl and cyclopropyl protons). Irradiation of the triplet $\delta 5.09$ collapsed the doublet contained in the multiplet at $\delta 2.0$ into a singlet. Irradiation of the multiplet $\delta 2.0$ collapsed the triplet $\delta 5.09$ into a singlet.

Di-imide Reduction of 1-Acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane (44).⁷³ - Glacial acetic acid (.06g, .001 mole) was added, with stirring, to the ketone (0.083g, .0005 mole) and potassium azo-dicarboxylate (.194g, .001 mole) in ether (9 ml) under nitrogen. After stirring for 18 hours the mixture was filtered, and the organic layer was washed with sodium bicarbonate solution (2 x 5 ml), water (2 x 5 ml) and dried (MgSO_4). Removal of the ether by rotary evaporation gave the unreacted ketone (v.p.c., Apiezon L, 120°).

The reaction was repeated using double the quantities of potassium azo-dicarboxylate (.4g) and acetic acid (.12g) and the reaction stirred for 15 hours under nitrogen. The final product was again the unreacted ketone (v.p.c., Apiezon L, 120°).

Attempted Selective Hydrogenation of 1-Acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane (44) using Platinum/Ethanol.⁷⁴ - The ketone (.02g, .00012 mole) in ethanol (2 ml) was hydrogenated over pre-reduced platinum oxide (20 mg). 4.87 ml (1.7 mole equivalents) of hydrogen were taken up. The solution was then diluted with ether and concentrated. V.p.c. analysis (Apiezon L, 120°) showed the product to contain two poorly resolved components in the approximate ratio of 86%:14%. (A trace (<1%) of the starting ketone was also present). MS20/v.p.c. (5% Carbowax, 120°) resolved 3 components, the major product (95%) having a parent ion at 168 amu. The remaining two components (3% and 2% of the total product respectively) did not give a mass-spectrum.

The hydrogenation was repeated using the same quantities of materials; 4.78 ml (1.65 mole equivalents) of hydrogen were taken up. The reaction solution was allowed to stand for 30 minutes and then diluted with ether and concentrated. V.p.c. analysis (Apiezon L, 120°) showed that the product again contained two components, the major peak (76%) was identical to that from the first hydrogenation. The minor product (24%) had a different retention time to that of the minor product in the first hydrogenation. The hydrogenation was again repeated using the same quantities of materials. The product solution was diluted with ether as soon as the uptake of hydrogen had ceased. V.p.c. analysis (Apiezon L, 120°) showed the product to be, again, a mixture of two components (87% and 13%).

Attempted Selective Hydrogenation of 1-Acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane (44) with Platinum/Cyclohexane. - The ketone (.0215g) in cyclohexane (2 ml) was hydrogenated over pre-reduced platinum oxide (20 mg). 4.52 ml (1.67 mole equivalents) of hydrogen were taken up. V.p.c. analysis (Apiezon L, 120°) of the product showed 6 components in roughly equal amounts.

Catalytic Hydrogenation of the Lithium/Liquid Ammonia Reduction Product (after oxidation). - The oxidised product (80 mg) in benzene (.5 ml) was hydrogenated over pre-reduced platinum oxide (20 mg) in ethanol (2 ml). 1.77 ml of hydrogen were taken up. The product was diluted with ether, dried (MgSO₄), and concentrated. V.p.c. analysis on Apiezon L, (120°) indicated that only one product (99%) was present but v.p.c. analysis on Carbowax (75°) showed two components, one of which (~20%) was the trans-1-acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane. The major component (~80%) was not identified.

Attempted Authentic Free-Radical Ring Opening of trans-1-Acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane. - A mixture of the ketone (44) (.182g), butan-2-ol (1.74 ml), and di-t-butylperoxide (.458g) were heated in a sealed tube at 140° for 48 hours. V.p.c. analysis (Apiezon L, 120°) of the product showed four components; retention times (minutes) - A. 10.4 (1.8%; 4,4,7-trimethyloct-5-en-2-one), B. 12.4 (90%), C. 13.4 (5.5%, starting ketone), D. 14.2

(2.7%, 4,4,7-trimethyloct-6-en-2-one). The component B (90%) was identified as 6-methyl-4-(prop-1-en-2-yl)hept-5-en-2-one from its spectral data. $\nu_{\max}(\text{CCl}_4)$ 2960(s), 1730(s), 1485(m), 1430(m), 1380(m), 1360(m), 1290(m), 1250(s), 1155(w) cm^{-1} ; $\delta(\text{CCl}_4)$ 4.84 (d, 1H, 5-H), 4.62 (t, 2H, propenyl H_2), 3.16-3.52 (m, 1H, 4-H), 2.4 (m, 2H, 3- H_2), 2.01 (s, 3H, $\text{CH}_3 \cdot \text{CO}$), 1.67 (s, 9H, 6- Me_2 + propenyl Me). (A small doublet at δ 1.13 and a multiplet at δ 0.9 were due to the small percentage (5.5%) of starting ketone present). Irradiation of the doublet δ 4.84 collapsed the multiplet at δ 3.40 into a triplet and caused "tickling" of the multiplet δ 2.40. Irradiation of the triplet δ 4.62 indicated slight coupling with the singlet δ 1.67. Irradiation of the multiplet δ 3.4 collapsed the doublet δ 5.2 into a singlet, and irradiation of the multiplet δ 2.4 collapsed the multiplet δ 3.4 into a doublet. Finally, irradiation of the singlet δ 1.67 collapsed the triplet δ 4.84 into a singlet; Mass spectrum P 166, 151, 123, 109, 55, 43 (from MS20/v.p.c., 10% Silicon, 120°).

The reaction was repeated on further samples of the ketone (0.01g) and the reaction products examined (v.p.c., Apiezon L, 120°) for different reaction times. (See Table 9 and Discussion).

Preparation of 1-[trans-2,2-Dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl]ethanol. - trans-1-Acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane (0.166g, 0.001 mole) in ether (3 ml) was added dropwise, with stirring, to lithium aluminium hydride (.076g, .002 mole) in ether (3 ml)

and the reaction mixture was refluxed for 20 hours under nitrogen. The excess of lithium aluminium hydride was destroyed with water and the product was extracted with ether. After drying, the ether was removed by rotary evaporation to give an oil (.15g, 90%) which was identified as the pure alcohol. $\nu_{\max}(\text{film})$ 3450(s), 1460(s), 1385(m), 1260(s), 1140(s), 1087(s), 1026(s), 992(m), 961(w), 885(m), 860(m), 815(s) cm^{-1} ; $\delta(\text{CCl}_4)$ 0.4-1.5 (m, 12H, $\text{CH}_3 \cdot \text{CHOH}$, 1-H, 2-Me₂, 3-H, OH), 1.6 (s, 6H, propenyl CH_3), 6.7 (m, 1H, $\text{CH}_3 \cdot \text{CH-OH}$), 5.25 (d, 1H, propenyl H).

Authentic Free-Radical Ring-Opening of 1-(trans-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl ethanol. - A mixture of the alcohol (0.042g, 0.00025 mole) and di-t-butyl peroxide (.095g) was heated in a sealed tube at 140° for 24 hours. The product was a viscous yellow oil which could not be analysed by v.p.c.

The reaction was repeated on the alcohol (0.042g) and di-t-butylperoxide (0.01g) in decane (25 ml), the latter serving as the solvent and internal standard for v.p.c. analysis. After heating at 140° for 24 hours polymerisation had again occurred.

Thermal Rearrangement ^{of} } trans-1-Acetyl-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane. - A mixture of the ketone (.172g, .001 mole) and butan-2-ol (1.4g, .00174 mole) was heated in a sealed tube at 140° for 20 hours. V.p.c. analysis (Carbowax, 75°) showed that the product contained

three components; A(41%, starting ketone), B(57.7%, 6-methyl-4-(prop-1-en-2-yl)hept-5-en-2-one) and C(1.3%, products from a radical type rearrangement).

Thermal Rearrangement of 1-Acetyl-2,2-dimethylcyclopropane. -

A mixture of the acetylcyclopropane (0.056g, .00056 mole) and butan-2-ol (.5 ml) was heated in a sealed tube at 140° for 20 hours. V.p.c. analysis (Carbowax, 50°) of the product indicated two components, one of which was the starting ketone (49%). The other component (51%) did not correspond to any of the possible products obtained from a lithium/liquid ammonia reduction of 1-acetyl-2,2-dimethylcyclopropane and was presumed to be 5-methylhex-5-en-2-one.

Separation of cis and trans-4-t-Butyl-1-methylcyclohexanol. -

cis and trans-4-t-Butyl-1-methylcyclohexanol (lg., 0.059 mole), absorbed on alumina (5g, Activity III), was introduced to the top of a column (15 x 1.5 in) containing alumina (Activity III) coated with Woelm Fluorescent Indicator (Green) and the column was developed with anhydrous benzene (250 ml). The separated isomers were located with a low wavelength ultra-violet light and were subsequently extracted with ether to give cis-4-t-butylmethylcyclohexanol (m.p. 90-92°, lit., m.p. 97-98⁰⁷⁹), containing less than 2% impurity by v.p.c., Apiezon L, 150°), and trans-4-t-butylmethylcyclohexanol (m.p. 58-59°, lit., m.p. 70⁰⁷⁹; containing 5% impurity by v.p.c., Apiezon L, 150°).

Separation of cis- and trans-4-t-Butylcyclohexanol. - A mixture of the cis- and trans-4-t-butylcyclohexanol (lg, ~20% cis:~80% trans by v.p.c., Apiezon L, 150°), absorbed on alumina (5g), was introduced onto a column (15 x 1.5 in) containing alumina (Activity III) coated with Woelm Fluorescent Indicator (Green) and the column was developed with anhydrous benzene (250 ml). The products were located with ultra-violet light, and extracted with ether as directed above to give trans-4-t-butylcyclohexanol (m.p. 78-81°, lit., m.p. 81-82°⁸¹; containing less than 2% impurity by v.p.c., Apiezon L, 150°) and cis-4-t-butylcyclohexanol (m.p. 80-81°, lit., m.p. 82.5-83.5°⁸⁰; containing less than 1% impurity by v.p.c., Apiezon L, 150°). $\delta(\text{CCl}_4; \text{trans-alcohol})$, 0.84 (s, 9H, t-butyl), 1.08 (m, 5H), 1.82 (m, 5H), 3.42 b (s, 1H, 1-H); $\delta(\text{CCl}_4; \text{cis-alcohol})$, 0.86 (s, 9H, t-butyl), 1.45 (m, 7H), 1.76 (m, 1H, 4-H), 3.94 (s, 1H, 1-H).

Separation of cis- and trans-4-Methylcyclohexanol. - A mixture of cis- and trans-4-methylcyclohexanol (lg, ~28% cis:72% trans by nmr (CCl_4)) was introduced onto an alumina column (15 x 1.5 in) as directed above and the column was developed with benzene (250 ml). After isolation with ether only 50 milligrams each of the pure cis- and trans-alcohols were obtained (Carbowax, 145°). $\delta(\text{CCl}_4; \text{trans-alcohol})$, 0.84 (d, 3H, 4-Me, $J_{4\text{H},\text{Me}}^5 \text{ Hz}$), 0.9-2.0 (m, 9H), 3.20-3.58 (m, 1H, 1-H), 4.12 (s, 1H, OH); $\delta(\text{CCl}_4; \text{cis-alcohol})$, 0.93 (d, 3H, 4-Me, $J_{4\text{H},\text{Me}}^3 \text{ Hz}$), 1.18 (s, 1H, OH), 1.23-1.8 (m, 9H), 3.87 (s, 1H, 1-H).

Preparation of cis-4-t-Butylcyclohexanol. - The method involved catalytic hydrogenation of the corresponding ketone.⁸⁰ 4-t-Butylcyclohexanone (7.65g, 0.05 mole) in glacial acetic acid (25 ml) containing hydrogen chloride (1.9g/25 ml) was reduced catalytically in the presence of platinum (0.25g) at 20° and 57 psi initial pressure for a period of 45 minutes. The catalyst was filtered off, and the filtrate was poured onto ice/water (150g/150 ml). The resulting solution was then extracted with pentane (4 x 100 ml) and the organic extract was washed with saturated aqueous sodium bicarbonate solution (3 x 150 ml) and dried (MgSO₄). After concentration the product was added to a solution of potassium hydroxide (2.5g) in water (4 ml) and methyl alcohol (18 ml), and the reaction mixture was refluxed for 6 hours. The solution was then poured into ice/water (35g/70 ml) and the precipitated solid was filtered off and was redissolved in ether (60 ml). After drying (MgSO₄) the ether was removed by rotary evaporation to give a white solid (6.4g, 85%) which was shown (v.p.c., Apiezon L, 150°) to be a mixture of cis-4-t-butylcyclohexanol (90%), trans-4-t-butylcyclohexanol (4%) and the starting ketone (6%). The pure cis-alcohol was isolated by dry column chromatography as directed above.

In a further reduction of 4-t-butylcyclohexanone, shaking the product mixture with saturated aqueous sodium bisulphite solution reduced the percentage of "impurity" (in the form of starting ketone (7%)) to 3%.

Preparation of 4-Methylcyclohexanone.⁸² - A solution of sodium dichromate dihydrate in water (375 ml)/concentrated sulphuric acid (122 ml)/acetic acid (37.5 ml) was added dropwise, with stirring, to 4-methylcyclohexanol (85.5g, 0.75 mole) in benzene (375 ml) over a period of 3 hours. The temperature of the reaction vessel was maintained at $\sim 10^{\circ}$ (ice-bath) during the addition. The reaction mixture was then stirred at 20° for 15 hours and the aqueous layer was separated, diluted with water (100 ml), and extracted with benzene (2 x 100 ml). The combined organic extracts were washed with water (2 x 100 ml), aqueous sodium bicarbonate solution (2 x 100 ml), aqueous sodium chloride solution (2 x 50 ml) and, finally, dried (MgSO_4). The benzene was removed by distillation through a 15 cm Vigreux column and the residue was vacuum distilled to give 4-methylcyclohexanone (55.5g, 66%), b.p. $58^{\circ}/15$ mm which was shown to contain less than 3% impurity by v.p.c. (Carbowax, 150°). ν_{max} (nujol) 1710(s), 1468(s), 1435(m), 1385(m), 1335(m), 1250(m), 1186(m), 1128(m), 1110(m), 960(w), 917(w), 806(w), cm^{-1} .

Preparation of cis-4-Methylcyclohexanol. - 4-Methylcyclohexanone (5.6g, 0.05 mole) in glacial acetic acid (25 ml) containing hydrogen chloride (1.9g/25 ml) was reduced catalytically in the presence of platinum (0.25g) at 25° and 57 psi for 60 minutes. The catalyst was filtered off, and the filtrate was poured onto ice/water (150g/150 ml) and the aqueous layer was extracted with pentane (4 x 100 ml).

The organic extract was washed with saturated aqueous sodium bicarbonate solution (3 x 50 ml) and, after drying (MgSO_4), was concentrated to an oil which was then refluxed with a solution of potassium hydroxide (2.5g) in water (4 ml) and methanol (18 ml). The product was poured onto ice/water (35g/70 ml) and the solution was then extracted with ether, (3 x 50 ml), dried (MgSO_4), and concentrated to an oil. Vacuum distillation of the residue gave a mixture of cis- and trans-4-methylcyclohexanol (3.1g), b.p. $64^\circ/9$ mm, which was shown to contain less than 3% impurity (in the form of starting ketone) by v.p.c. (Carbowax, 145°). The ratio of cis:trans isomers was 4:1 (nmr (CCl_4)).

The pure cis-4-methylcyclohexanol was isolated by alumina dry column chromatography as directed for the cis-4-t-butylcyclohexanol.

Attempted Preparations of the Lithium Salt of Cyclohexanol. -

Several methods were attempted. They involved reacting cyclohexanol with the following reagents:

Method 1. With Lithium in Liquid Ammonia. - Lithium (0.07g, 0.01 mole) was added to anhydrous liquid ammonia (100 ml, dried by passing through calcium oxide) contained in a vessel fitted with a Dry-Ice condenser and protected from atmospheric moisture by a drying tube filled with calcium oxide. The resulting blue solution was stirred for 30 minutes to ensure complete dissolution of the lithium, and dry cyclohexanol was then added dropwise to it (via syringe). Since the blue colour of the solution still remained on

addition of an equimolar amount of cyclohexanol (1g, 0.01 mole), more alcohol was added to just discharge the blue colour. After the evaporation of ammonia a white solid remained whose nmr spectrum (furan) indicated the presence of excess cyclohexanol.

The reaction was repeated as follows. - a solution of lithium (0.21g, 0.03 mole) in anhydrous liquid ammonia (300 ml)(prepared as directed above) was added dropwise, with stirring, to cyclohexanol (1g, 0.01 mole) in liquid ammonia (30 ml) until a permanent blue coloured solution was obtained (exact determination of the end point proved difficult as the intensity of the colour diminished on standing). After the removal of ammonia, a greyish solid was obtained whose nmr spectrum (furan) indicated the presence of hydroxyl protons.

Method 2. With Lithium Hydride in Dioxan. - Cyclohexanol (1g, 0.01 mole) was added dropwise, with stirring, to lithium hydride (1g, 0.125 mole) in anhydrous dioxan (50 ml) and the reaction mixture was refluxed for 12 hours under nitrogen. The grey solid which had precipitated out was separated from the mother liquor by centrifugation. The mother liquor was concentrated to an oil which was only very slightly soluble in both benzene and carbon tetrachloride and which gave a diffuse and unresolvable nmr spectrum in each case. The precipitate gave a complex nmr spectrum with a strong singlet $\delta 2.5$ (possibly lithium hydride).

Method 3. Lithium in Benzene. - Cyclohexanol (10g, 0.1 mole) was added dropwise, with stirring, to lithium (0.7g, 0.1g atom) in anhydrous benzene (40 ml) and the reaction mixture was refluxed for 15 hours under nitrogen. (After 2 hours, a white solid had precipitated out of the solution). The reaction solution was filtered and the filtrate was then concentrated by rotary evaporation, to a white solid. The solid was almost insoluble in furan, carbon tetrachloride and benzene. The nmr spectrum of the solid in each of these solvents showed the presence of a hydroxyl group. This was verified by the ir spectrum (ν_{\max} (nujol) 3400 cm^{-1}).

The reaction was repeated using an excess (x 2) of lithium (1.4g, 0.2g atom) and the reaction mixture was refluxed for 15 hours. The reaction solution was filtered and the filtrate was concentrated, under high vacuum, to a white solid. The latter was only slightly soluble in furan and carbon tetrachloride and its nmr spectrum in each of these solvents was so diffuse as to render exact integration impossible. The solubility of the salt in dimethylsulphoxide - d_6 and hexamethyldisiloxane was extremely low - a very weak nmr spectrum was obtained for each solvent.

An exact alkali content determination of the salt was undertaken by titrating 10 ml portions of a solution of the salt (0.53g/50ml) with standard hydrochloric acid (0.099M). The percentage alkali in solution was calculated to be 74%.

Attempted sublimation of the salt by heating for 6 hours at $160^\circ/0.05 \text{ mm}$ was unsuccessful.

Method 4. With Lithium in Dioxan. - Cyclohexanol (10g, 0.1 mole) was added dropwise, with stirring, to lithium (0.7g, 0.1g atom) in anhydrous dioxan (40 ml) and the reaction mixture was refluxed under nitrogen. The reaction was discontinued when a solid precipitated out of solution after 1 hour.

Method 5. With Lithium Methylsulphinylcarbanion in Dimethylsulphoxide. - Dry 'Analar' dimethylsulphoxide (12 ml) was added dropwise, with stirring, to lithium hydride (0.16g, 0.02 mole) and the reaction mixture was refluxed for 1.5 hours under nitrogen. A few crystals of triphenylmethane were added to the cooled methylsulphinylcarbanion solution and cyclohexanol was then added dropwise (from a syringe) to the red solution. Since the deep red colouration disappeared on the addition of 1 drop of the alcohol the reaction mixture was refluxed for a further 15 hours thus restoring the red colour. After cooling, cyclohexanol was again added to the solution. Addition was stopped when 3.5 equivalents of alcohol failed to discharge the red colouration.

Method 6. With Ethyl Lithium. - A solution of 1-bromoethane (13.08g, 0.12 mole) in dry pentane (40 cc, pre-treated with concentrated sulphuric acid) was added dropwise, with stirring to lithium (2.0g, 0.29g atom) in pentane (40 ml) and the reaction mixture was gently refluxed under nitrogen. On complete addition of the halide solution (5 hours) the reaction mixture was refluxed for a further 2 hours. The reaction solution was then diluted with benzene (70 ml), the pentane was distilled off at atmospheric pressure, and

the resulting benzene solution was siphoned and stored under nitrogen. After standing for 12 hours the clear solution was transferred to a distillation flask and 40 ml of solvent were distilled off at atmospheric pressure. Pentane (20 ml) was added to the cooled solution (ice-bath) and the small quantity of precipitated solid was filtered off under a nitrogen atmosphere. Attempted recrystallisation of the solid from benzene caused the solid to ignite. Due to this and the poor yield of ethyl lithium this method was discontinued.

Method 7. With Lithium Amalgam. - A 1% lithium amalgam was prepared by adding lithium (0.63g) in small pieces on the end of a pointed rod to mercury (63g) heated to 185°. Cyclohexanol (1g, 0.01 mole) in dioxan (20 ml) was added dropwise, with stirring, to the cooled amalgam and the reaction mixture was refluxed for 70 hours under nitrogen. The reaction mixture was filtered through celite and the filtrate was then concentrated by high vacuum rotary evaporation to an oil. Both the nmr (CCl_4) and ir(film) spectra showed the presence of a hydroxyl group.

The reaction was repeated as directed above but with benzene as the solvent. After refluxing, the reaction solution was centrifuged and the supernatant liquid was removed and concentrated to a white solid (0.1g). The ir spectrum of the solid showed that a hydroxyl group was absent. The nmr spectrum of the solid in benzene was very weak and diffuse due to its very low solubility in the solvent.

In a further reaction in benzene (to improve the yield), carried out on the same quantities of starting materials, isolation of the product gave an oily residue which contained a hydroxyl group ($\nu_{\max}(\text{film}) 3400 \text{ cm}^{-1}$).

Similar results were obtained from the reaction of the lithium amalgam with a mixture of cis- and trans-4-methylcyclohexanol.

Method 8. With Lithium Methyl. - Lithium methyl (0.01M solution)^{IN} ether (50 ml), prepared as described in Ref (40)) was added dropwise, with stirring, to a solution of cyclohexanol (1g, 0.01 mole) in dry benzene (10 ml) containing a small quantity of triphenylmethane as an indicator. During addition of the alkyl lithium a fine white solid gradually precipitated out of solution. Since no red coloured end-point was obtained on addition of an equimolar amount of lithium methyl, the solvents were removed by rotary evaporation to yield an oily residue which contained some unreacted alcohol (ir, $\nu_{\max} 3400 \text{ cm}^{-1}$).

Since it appeared that triphenylmethane did not function as an indicator for ethereal lithium methyl, the metal alkyl was prepared from lithium and methyl iodide in pentane. Addition of a small amount of triphenylmethane to this solution did not give a red colour, and the method was therefore discontinued.

Preparation of the Lithium Salt of Cyclohexanol. - Butyl lithium in benzene (10 ml/15% solution) was added dropwise from a syringe to a stirred solution of cyclohexanol (0.5g,

0.005 mole) in benzene (10 ml) under nitrogen. When an approximately equimolar quantity of the alkyl lithium solution had been added a sample of the reaction mixture was withdrawn (syringe) and injected into a solution of triphenylmethane in 1,2-dimethoxyethane (D.M.E) under nitrogen. Dropwise addition of the alkyl lithium solution was continued until a sample of the reaction solution caused a permanent red colour in the D.M.E. indicator solution. The nmr spectrum of the resulting solution showed that some butyl lithium was present. $\delta(\text{C}_6\text{H}_6)$ after 30 minutes: 0.8-2.4 (vb)(m, 1-H + impurity in butyl lithium), 3.2-4.2 (vb)(m, cyclohexane-H + butyl lithium); after 30 hours: 0.9-2.0 (b)(m, cyclohexane-H + butyl lithium), 3.23 (b)(s), 3.74 (b)(s, impurity in butyl lithium), 4.0 (b)(s, 1-H). Irradiation of the multiplet (δ 1.7) sharpened the broad singlet at δ 4.0 but did not alter the singlet at δ 3.74. Irradiation at δ 1.5, 1.2 did not alter the region δ 3.2-4.1.

Preparation of the Lithium Salt of cis- and trans-4-t-Butylcyclohexanol. - A mixture of cis- and trans-4-t-butylcyclohexanol (0.78g, 0.05 mole) in benzene (10 ml) was treated with butyl lithium in benzene as directed above. The nmr spectra of the reaction solution showed that butyl lithium was present as a slight impurity. $\delta(\text{C}_6\text{H}_6)$ after 20 minutes: 0.8-2.7(m), 3.6-4.7(m); after 90 hours: 0.8-2.7(m), 3.99(b) (s, impurity in butyl lithium), 4.24 (b)(s, axial (ax)-H), 4.58 (b) (s, equatorial (eq)-H). The ratio of equatorial: axial protons was 1:4. (The ratio of equatorial (δ 3.94): axial(δ 3.45) protons in pure cis- and trans-4-t-butylcyclo-

hexanol was 19:81%). The equatorial and axial proton absorptions in the salt have been shifted downfield by 0.79 ppm and 1.13 ppm respectively relative to their positions in the alcohol, and the chemical shift difference between the equatorial and axial proton absorptions has decreased from 0.49 ppm in the alcohol to 0.34 ppm in the lithium salt.

The reaction was repeated on a mixture of the alcohols (0.78g, 0.05 mole) in benzene (8 ml). 3.5 ml of the butyl lithium/benzene solution (2.08g in 5 ml) were required in the titration. The nmr spectrum (C_6H_6), taken after 20 minutes, was similar to that from the first reaction. After 90 minutes, $\delta(C_6H_6)$: 0.7-2.7(m), 3.94(b)(s, impurity), 4.26(b)(s, axial-H, 4.60(b)(s, equatorial-H). (Ratio of equatorial:axial protons was \sim 1:4). Water (10 ml) was added to the reaction solution and the mixture was extracted with benzene (3 x 10 ml), and the extract was dried ($MgSO_4$) and concentrated. V.p.c. analysis (Carbowax 145⁰) of the residue showed that the percentage of cis-4-t-butylcyclohexanol in the cis/trans alcohol mixture had decreased from 17% (before reaction) to 5% (after reaction).

A further reaction was carried out on cis-4-t-butylcyclohexanol [0.39g, 0.025 mole, containing some trans-alcohol and 4-t-butylcyclohexanone as impurity (4%)] in benzene (4 ml); 2.1 ml of butyl lithium/benzene solution (1.61g/5 ml) were required in the titration. After standing for 90 hours, water (20 ml) was added to the reaction and the mixture was then extracted with benzene

(3 x 10 ml). After drying (MgSO_4) and concentrating, v.p.c. analysis of the extract (Apiezon L, 145°) indicated that the product was of similar composition to the starting material ((95%) cis-4-t-butylcyclohexanol + (5%) 4-t-butylcyclohexanone and trans-alcohol). No significant increase in the percentage of trans-4-t-butylcyclohexanol was observed.

Preparation of the Lithium Salt of cis- and trans-4-Methylcyclohexanol. - A mixture of cis- and trans-4-methylcyclohexanol (0.57g, 0.05 mole) in benzene (10 ml) was treated with butyl lithium in benzene (15% solution) as directed for the 4-t-butylcyclohexanol. The nmr spectra of the product contained some butyl lithium impurity. $\delta(\text{C}_6\text{H}_6)$ after 20 minutes: 0.8-2.5(m), 3.4-4.3(b)(s); after 90 hours: 0.8-2.6(m), 3.94(s), 4.08(s). The equatorial and axial protons in the pure alcohol appeared at δ 4.28 and δ 3.98 respectively.

The reaction was repeated on cis-4-methylcyclohexanol (0.57g, 0.05 mole) in benzene (8 ml); 4.2 ml of butyl lithium/benzene solution (1.83g/5 ml) were required in the titration. The nmr spectra were observed at the same time intervals as in previous reactions. $\delta(\text{C}_6\text{H}_6)$ after 20 minutes: 0.8-2.2(m), 3.78(b)(s, impurity in butyl lithium), 4.0 (s, equatorial-H); after 90 hours: 0.8-2.6(m), 4.11(s, equatorial-H). (The singlet at δ 3.78 had disappeared). The equatorial proton of the pure cis-alcohol absorbed at δ 3.93.

Reaction of Butyl Lithium in Benzene with an Equimolar Mixture of cis-4-Methylcyclohexanol and cis- and trans-4-t-Butylcyclohexanol. - A mixture of cis- and trans-4-t-butylcyclohexanol (0.39g, 0.025 mole; ~20% cis:80%trans) and cis-4-methylcyclohexanol (0.285g, 0.025 mole) in benzene/benzene-d₆ (7:3, 10 ml) was treated with butyl lithium in benzene (3 ml, 15% solution) as previously described. When the titration was complete the reaction solution was stirred at 20° for 1 hour. The region of interest in the ¹³C nmr spectrum, observed after 24 hours and 50 hours, was poorly resolved due to appreciable background 'noise'. However, the C₁ absorption of the lithium salts of cis-4-methylcyclohexanol, cis-4-t-butylcyclohexanol and trans-4-t-butylcyclohexanol were assigned to absorptions at 64.4 ppm, 65.5 ppm and 71.9 ppm (relative to T.M.S.) respectively, by carrying out a number of reactions in which the relative concentrations of the three isomers were varied. The corresponding C₁ absorptions for the pure cyclohexanols were 66.4 ppm, 65.5 ppm and 70.8 ppm respectively (see Table 11).

TABLE 1

Reduction of 1-Acetyl-2,2-dimethylcyclopropane with Lithium
in Liquid Ammonia

Wt Li(g)	Molarity Li	%(13)	%(15)	%(14)	(14)/(15)
0.1	0.286	2.5	26.4	66.5	2.41
0.1	0.286	4.2	25.6	67.5	2.63
0.23	0.658	6.8	24.1	65.2	2.71
0.31	0.886	9.2	24.0	64.3	2.78
0.41	1.172	7.6	21.3	68.4	3.21
0.53	1.516	9.7	19.6	67.2	3.42
0.60	1.717	11.4	18.6	67.5	3.63
0.80	2.289	16.3	17.0	64.7	3.74

TABLE 2

Reduction of 1,1,1-Trideuterio-acetylcyclopropane with
Lithium in Liquid Ammonia

Molecular Ion m/e						*
	84	85	86	87	86/87	%86
% ^2H Dist ⁿ in Acetylcyclopropane						
^2H before Reduction		3.1	23.8	73.1	0.328	24.
^2H after Reduction (2 hrs)	10.8	10.8	24.9	53.5	0.450	31.
^2H after Reduction (6 hrs)	27.1	13.5	22.9	36.5	0.629	38.

* Relative to 86 α 87 only.

TABLE 3

Reduction of 1,1,1-Trideuterio-acetylcyclopropane with Lithium in Liquid Ammonia¹

Molecular Ion (m/e)	84	85	86	87	86/87	% 86
% ² H dist ⁿ in Acetylcyclopropane						
² H before Reduction		3.1	23.8	73.1	0.33	24.6
² H after Reduction(2hrs)	8.2	11.2	27.6	54.0	0.51	33.8

1. Ammonium Chloride was added in 1 portion.

TABLE 4

Deuterium Distribution in 1,1,1-Trideuterio-pentan-2-one.

Molecular Ion (m/e)	86	87	88	89	88/89	%88
% ² H dist ⁿ in Pentan-2-one						
² H before Reduction			1	99	.01	1.0
² H after Reduction(2hrs)	7.4	6.5	20.3	65.8	0.31	23.6
² H after Reduction(6hrs)	29.6	19.0	20.7	30.7	0.67	40.0

TABLE 5

Reaction of 1,1,1-Trideuterio-acetylcyclopropane with Potassium Amide in Liquid Ammonia

Molecular Ion (m/e)	84	85	86	87	86/87
% ² H dist ⁿ in Acetylcyclopropane					
% before Reduction	0	3.3	21.2	75.5	0.28
% after Reduction	36.4	36.2	19.2	8.2	2.34

TABLE 6

Titration of Acetylcyclopropane with Lithium/Liquid
Ammonia Solutions

No. of m Moles Lithium in Sol ⁿ .	No. of Moles Ketone (19) Added
9.97	6.70
10.14	6.40
20.05	16.20
10.20	6.54
10.55	6.66

TABLE 7

Reduction of 1-Acetyl-2,2-dimethylcyclopropane with Lithium in Hexamethylphosphoramide (HMPA).

Wt M(g) ^a	Wt of ketone	Solvent	Conditions	%(15)	%(13)	%(14)	(14)/ (15)	% ring- opening
0.179g Li	0.25g	10 ml HMPA	20° for 1.25 h	17.9	61.0	21.1	1.18	39
0.178g Li	0.25g	10 ml HMPA	20° for 15 h	8.9	78.4	12.7	1.44	21
0.154g Li	0.26g	10 ml HMPA + 0.5 ml <u>t</u> -butanol ^b	20° for 15 h	18.0	17.0	65.0	3.60	83
1.0g Na	0.28g	10 ml HMPA + 1.78 ml <u>t</u> -butanol ^b	20° for 0.25 h	13.8	38.7	47.5	3.46	61

a. M was the metal used (Li, Na)

b. t-butanol was used as a proton source.

TABLE 8

Nickon-Sinz Reaction on N-(trans-2-Methylcyclopropylmethyl) toluene-p-sulphonamide at Varying Base Concentrations.

Base Concentration	Ratio Pent-1-ene (39): 3-Methylbut-1-ene (38)
1. (a) 20% NaOH (CCl ₄) ^{a,b,e}	.37:1
(b) 20% NaOH (EtOH) ^{a,d,e}	1.5:1
(c) 20% NaOH (EtOH) ^{a,b,e}	1.53:1
(d) 20% NaOH (EtOH) ^{a,b,e}	1.54:1
2. (a) 28% NaOH (CCl ₄) ^{a,b,f}	8.1:1
(b) 28% NaOH (CCl ₄) ^{a,b,f}	7.4:1
(c) 28% NaOH (CCl ₄) ^{a,c,f}	19.0:1
3. (a) 10% NaOH (CCl ₄) ^{a,c,f}	19.0:1
(b) 10% NaOH (CCl ₄) ^{a,c,f}	11.5:1
4. (a) KOEt/EtOH (CCl ₄) ^{a,c,f}	0.48:1
(b) KOEt/EtOH (CCl ₄) ^{a,c,f}	0.27:1

NOTE: a. Receiving solvent; b. Sulphonic acid was added through a vertical reflux condenser; c. Sulphonic acid was added from a test-tube side arm; d. The derivative was added to an alcoholic solution of the sulphonic acid in the reaction vessel; e. Products were analysed by v.p.c. gas injection (1a,b,c) and direct injection (1d) onto an F11 Gas Chromatograph; f. products were analysed by direct injection onto an F11 Gas Chromatograph.

TABLE 9

Variation of Radical Ring-Opening Products of Ketone (44)

With Time of Reaction.

% Reaction time	A(45+46)	B(48)	C(44)	D(47)	Ratio $\frac{B}{A+D}$
10 h	1.5	4.2	91.2	3.0	.94
20 h	1.7	17.9	77.5	2.9	3.9
30 h	1.7	56.2	39.1	3.0	12.0
48 h	1.8	90.0	5.5	2.7	20.0

TABLE 10

 ^{13}C Spectral Assignments of Unsubstituted and 4-t-Butyl Substituted 1-Methylcyclohexanol

Compound	C_1	C_2	C_3	C_4	$\underline{\text{C}} \text{Me}_3$	$\text{C} \underline{\text{Me}}_3$	1-Me
1-Methylcyclohexanol (49)	129.1	156.5	172.2	169.2	-	-	165.8
<u>cis</u> -4- <u>t</u> -butyl-1-methylcyclohexanol (51)	128.5	155.6	170.0	149.0	163.6	167.9	-
<u>trans</u> -4- <u>t</u> -butyl-1-methylcyclohexanol (52)	130.0	156.5	172.1	148.6	164.1	167.7	-

TABLE 11

 ^{13}C Spectral Assignments of 4-Methyl and 4-t-Butyl Substituted Cyclohexanols (*in* C_6D_6)

Compound	C_1	C_2	C_3	C_4	$\underline{\text{C}} \text{Me}_3$	$\text{C} \underline{\text{Me}}_3$	4-Me
<u>cis</u> -4- <u>t</u> -Butylcyclohexanol	65.5	33.7	21.2	48.4	32.6	27.6	-
<u>trans</u> -4- <u>t</u> -Butylcyclohexanol	70.8	36.4	26.0	47.5	32.2	27.7	-
<u>cis</u> -4-Methylcyclohexanol	66.4	32.7	22.0	31.7	-	-	29.4

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