

STUDIES IN  
CARBONIUM ION REARRANGEMENTS.

THESIS

presented to the University of Glasgow

for the degree of Ph.D.

by

Thomas Fulton Wilson McKillop

1968.

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## SUMMARY.

Neoclovene, a product from acid-catalysed rearrangement of caryophyllene, has been synthesised in such a manner as to demonstrate the probable intermediacy of a specific carbonium ion in the formation of neoclovene from caryophyllene. These experiments also provide evidence for the relative configuration of neoclovene.

Caryolan-1-ol, a second rearrangement product of caryophyllene, is found to yield at least ten products on dehydration with polyphosphoric acid. X-ray crystallography has been employed to determine the structure of one of the major products entitled pseudoclovene A and a synthesis of this olefin has been achieved. Mechanistic arguments are described to account for the formation of the known products.

Extended Hückel Calculations have been performed for two simulated carbonium ion rearrangement reactions in the bicyclo(3,3,1)nonane series to examine the relative efficiencies of a double bond and a cyclopropane ring in stabilising a carbonium ion. The results obtained do not compare favourably with the available kinetic data and the possible reasons for this apparent anomaly are discussed.

## ACKNOWLEDGEMENTS.

I should like to record my sincere gratitude to the many people who have assisted me in this work during the last three years and, in particular, to my supervisor, Dr. W. Parker for his sustained interest and helpful advice. I am also indebted to Dr. J. Martin, who supervised a considerable part of the early work, to Dr. G. Ferguson and Mr. D.M. Hawley for the major role they played in the X-ray crystallographic studies, and to Dr. B.C. Webster for his expert guidance during the theoretical investigations.

The stimulating and often critical discussion among the staff and fellow students of this department has contributed significantly to the work embodied in this thesis. In particular, I wish to thank Dr. J.S. Roberts whose expertise in caryophyllene chemistry has always been freely available and who has assisted invaluablely in the production of the thesis by typing the manuscript.

The analyses and spectra quoted throughout are the result of the careful work carried out by the technical staff in this department and I should like to acknowledge their important contribution.

These investigations were performed during the tenure of a Carnegie Scholarship (1965-67) and a Ramsey Memorial Fellowship (1967-68). I wish to express my sincere gratitude both to these bodies for their financial assistance and to Professor R.A. Raphael for his support in obtaining these awards.

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INTRODUCTION.

The study of carbonium ions has been in progress for over half a century and is still proceeding with a vigour unparalleled in almost any other field of organic chemistry. The extent to which these studies have shaped modern concepts is probably beyond the realisation of most chemists. Early Valence Theory required a major overhaul with the discovery that carbon formed trivalent species, and since that time a significant number of mechanistic concepts have stemmed from the detailed examination of carbonium ion reactions. The structure elucidation of a large number of natural products and many syntheses have been fraught with difficulty, as a result of unforeseen carbonium ion rearrangements; while, on the otherhand, utilisation of similar carbonium ion rearrangements have produced some elegant syntheses and been integral in demonstrating gross structures as well as fine stereochemical points in natural product chemistry. More recently a wide variety of spectroscopic and physical techniques have been brought to bear on the difficult problems associated with such transient species, and there is current interest among theoretical chemists in the application of their sophisticated calculations to this fascinating category of intermediates. Although the literature on the subject undergoes apparent exponential growth from year to year and is accompanied by increasing subtlety of argument, this thesis is an attempt to contribute in some small way to

several problems thought to involve carbonium ions.

The name "carbonium ion" was first used by Baeyer<sup>1</sup>, alluding to the supposed relationship of these carbon species to the other "onium" ions (eg. ammonium, phosphonium, oxonium etc.). However, apart from the fact that they all carry a positive charge, the name is misleading, since all the other "onium" ions increase their normal valency by one, while the carbonium ion has a valency of three, instead of the normal carbon valency of four. In the modern literature one meets an almost interminable list of definitions for a carbonium ion, but for our purposes it may simply be regarded as the species,  $R_3C^+$ , in which the central carbon atom has six electrons in its valence shell and formally carries a unit positive charge. In the parlance of accepted Valence Theory, the three bonds associated with the central carbon atom will preferentially utilise  $sp^2$  hybrid orbitals, causing the cation to be planar unless other energy considerations such as imposed strain outweigh the benefits of  $sp^2$  hybridisation.

The first example of ionisation of an organic molecule leading to a carbonium ion was reported by Walden<sup>2</sup> in 1902, closely followed by the studies of Gomberg<sup>3</sup> in the same year. These investigators measured the conductivity of a variety of solutes in liquid sulphur dioxide, and found that, when triarylmethyl halides were used, the conductivity of the solution increased markedly, indicative of the formation of ions. There ensued several fairly detailed



examinations on series of such compounds with different solvents, the main emphasis of this work being on the calculation of dissociation constants. A number of other techniques such as cryoscopy, dielectric polarisation studies and rather primitive spectrophotometric examination were applied at an early date to the investigation of these "stabilised" ions, and a summary of these may be found elsewhere<sup>4</sup>. The stability of some carbonium ions was placed beyond question, chiefly as the result of the incisive researches carried out by Hantzsch<sup>5</sup>, who prepared the coloured, solid, perchlorate salt  $\text{Ph}_3\text{C}.\text{ClO}_4$ , and showed that the conductivity and other physical properties were of the same order as that of a normal inorganic salt. Modern studies on the carbonium ions from triarylmethane derivatives in fact remarkably resemble the pioneering work outlined above, and have fully confirmed the early conclusions, as well as provided chemistry with many intriguing reactions such as intermolecular hydride transfers<sup>6</sup>.

As distinct from stable carbonium ions, Meerwein and Van Emster<sup>7</sup>, in 1922, first proposed the critical role these ions might play as intermediates in the rearrangement of camphene hydrochloride to isobornyl chloride. This work was taken up, notably by Whitmore and co-workers<sup>8</sup>, who investigated the rearrangements of neopentyl halides, and invoked carbonium ions in their arguments by implication without actually describing the intermediates as cationic. It fell to Ingold<sup>9</sup> to explicitly propound the "Ionisation Hypothesis" and,

in so doing, lay the foundation of a large area of physical-organic chemistry, as well as a system of mechanistic classification<sup>10</sup>. In the light of the much earlier and generally accepted work on triarylmethyl carbonium ions, it is really surprising that organic chemists were so loathe to accept the ionisation postulate, especially since the vital role played by the solvent in assisting charge separation and stabilising the resultant ions had been emphasised on numerous occasions<sup>11</sup>. Without doubt the majority of work done since this period has involved the investigation of carbonium ions as postulated reaction intermediates rather than as stable ions in solution. Within the former category, one may subdivide the developments further into two classes:- a) carbonium ions in rearrangements, particularly of natural products, and b) the physical investigation of the actual intermediates.

Meerwein's proposal of a cationic reaction intermediate was made with reference to a terpenoid rearrangement, and, since that time, natural product chemistry has benefitted enormously from the physical-organic chemist's scrupulous examination and discussion of the fundamental problems involved. This insight into the mechanistic subtleties has permitted the formulation of meaningful generalisations concerning stereochemical relationships and reaction rates. On the other hand, natural product chemistry has provided a wealth of novel carbonium ion reactions worthy of further investigation. The vital role played by carbonium ions in the rearrangements of carbohydrates,

terpenes, alkaloids, peptides, and steroids has been reviewed extensively elsewhere<sup>12</sup>. Another fascinating problem for the organic chemist has been the biogenesis of these naturally occurring compounds and once again many key intermediates are believed to be carbonium ion in character<sup>13</sup>, especially notable in this sense being the acid-catalysed cyclisations, which yield terpenes and steroids<sup>14,15,16</sup>. One class of compounds, viz. the sesquiterpenes, provides a plethora of structural variety, and the contortions undergone by these molecules are often so complex as to be almost mystical. Caryophyllene, one of the most acrobatic of sesquiterpenes, and the rearrangements of the hydrocarbon and some of its derivatives is the subject of the first part of this thesis, in which the emphasis is largely on the more classical approaches of synthesis and structure elucidation.

The application of kinetic techniques, combined with the growing appreciation of stereochemical implications, led to a revolution in thought concerning the mechanism of carbonium ion formation and the subsequent reactions of the species. In the recent literature, arguments rage on subjects like bond participation in the ionisation step, the stereochemical requirements for group migration, ion-pairs, internal return phenomena, the strain energy involved in hybridisation changes, and the exact nature of the transition state. To some extent the result of the increased activity in the field has been the controversy over non-classical carbonium ions, but, rather than proving an impasse, this issue has been the stimulus for extensive research

the results of which are of great value to the development of science irrespective of their primary objective. No attempt is going to be made to survey the field, or even to outline the arguments involved, since justice could not be done to them in the short space available, and, in any case, they have been the subject of several reviews<sup>17</sup>. Although approximate molecular orbital calculations were performed as early as 1953<sup>18</sup> (excluding, of course, the even earlier simple Hückel calculations on carbonium ions in  $\pi$ -electron systems), there has been a recent increase in the popularity of such an approach, chiefly due to the efforts of Hoffmann<sup>19</sup>. The second section of this thesis comprises of an investigation into the use of molecular orbital calculations in studying the problem of cyclopropyl and double-bond participation, during the solvolysis of (3,3,1) bicyclic compounds.

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CHAPTER 1.HISTORICAL BACKGROUND.

"Nature hath framed strange fellows in her time."

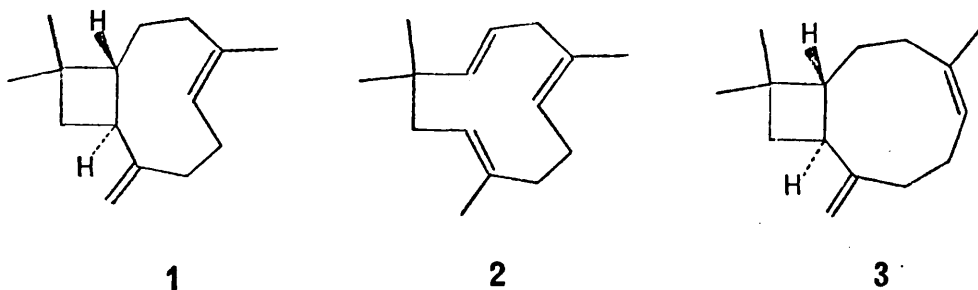
W. Shakespeare, "The Merchant of Venice."

Since its first isolation in 1834<sup>1</sup>, caryophyllene (1), which is the main hydrocarbon constituent in oil of cloves (from Eugenia caryophyllata), has been the subject of intense and prolonged investigation. Yet it was only in 1951 that Barton<sup>2</sup> proposed the, now unanimously, accepted structure (1) and only in 1963 that the first total synthesis of the diene was achieved<sup>3</sup>. That much active research is still proceeding in this area of chemistry is a tribute to Nature's architectural genius in producing such an intriguing molecule.

At first sight, caryophyllene appears to be a deceptively simple molecule, causing one to wonder at the difficulty experienced by early workers in trying to establish its structure and to synthesise the molecule. However, a brief perusal of the literature reveals the two principal obstacles encountered in this work. The first was the question of purity, and, since caryophyllene was only obtainable from natural sources, it was always accompanied by other hydrocarbons such as



humulene (2) and isocaryophyllene (3). (In the early literature the

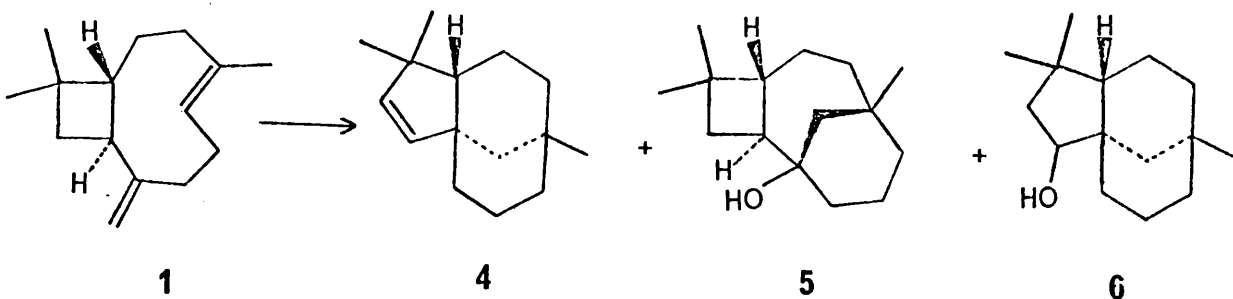


names  $\alpha$ -caryophyllene,  $\beta$ -caryophyllene and  $\gamma$ -caryophyllene were ascribed to humulene, caryophyllene and isocaryophyllene respectively, but the use of these names has been discontinued with the structure elucidation of the terpenes.). Even after these compounds were recognised and reasonably pure samples of caryophyllene were obtained, the task was still a formidable one, since it was found that caryophyllene and a number of its derivatives underwent complex molecular rearrangements under a wide variety of conditions. Often these rearrangements complicated the attempts at classical structure elucidation, sometimes positively misleading early investigators, but Barton, seeing their utility, identified some rearrangement products, and was able to reconstruct the jig-saw, so establishing the structure of caryophyllene.

After close scrutiny of the molecular structure, this facility for rearrangement is readily understood in the light of modern ideas on conformational analysis and ring strain. The first striking feature

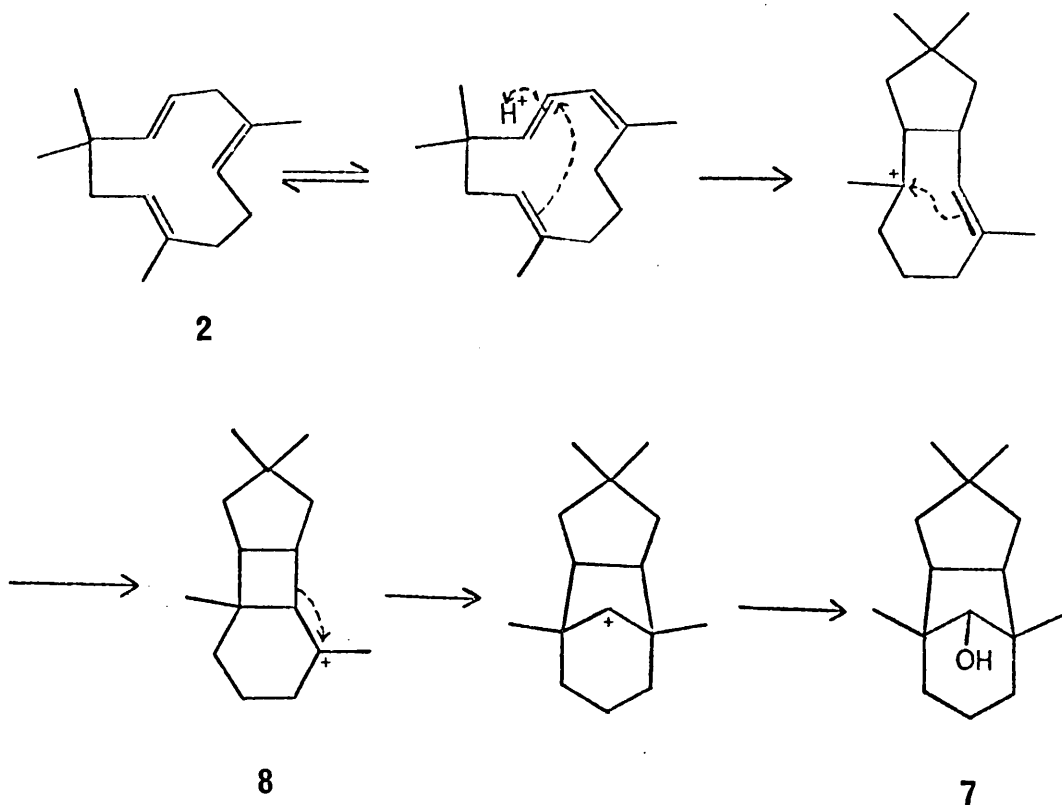
of caryophyllene is the presence of a highly strained, four-membered ring trans fused to the equally uncommon, nine-membered ring in a (7,2,0) bicyclic system. As well as this, one has a 1,5 disposition of exo-endo double bonds in the nine-membered ring, with the endo olefinic bond having the less favourable trans geometry. On studying molecular models, it becomes apparent that the combination of these features still allows a fair degree of conformational mobility in the nine-membered ring, so that the two double bonds can approach fairly close to one another, thereby leading to transannular cyclisations. Some examples of these transannular rearrangements will now be described.

The original work of Asahina and Tsukamoto<sup>4</sup>, in which caryophyllene (1) was treated with concentrated sulphuric acid in ether, seemed to show that three products were formed, which have since been identified as clovene (4), caryolan-1-ol\* (5) and a second alcohol,  $\alpha$ -caryophyllene alcohol, ascribed the structure (6).



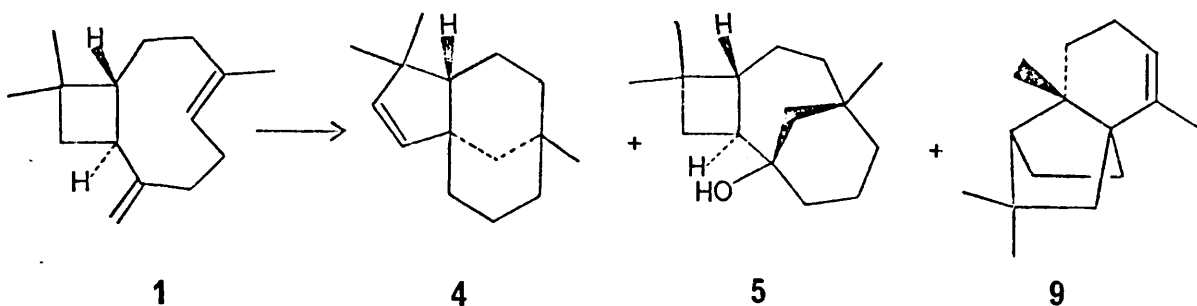
\* Often named  $\beta$ -caryophyllene alcohol in the early literature.

It is now known that the structure (6) is incorrect for  $\alpha$ -caryophyllene alcohol, and that this compound is not a product in the cyclisation of pure caryophyllene, resulting instead from the acid-catalysed cyclisation of the humulene (2), present as a contaminant in most commercial samples of caryophyllene<sup>5</sup>. The correct structure (7) for  $\alpha$ -caryophyllene alcohol has been established both by X-ray crystallography and by chemical degradation<sup>6</sup>, while Corey<sup>7</sup> has synthesised it by a novel route, which also helped to demonstrate the probable intermediacy of the carbonium ion (8) in the proposed mechanism of formation  $[(2) \rightarrow (8) \rightarrow (7)]$ .



The other significant contribution to the clarification of this caryophyllene rearrangement has been the discovery that, as well as clovene (4), a number of other hydrocarbons are formed, one of which, viz. neoclovene (9), has been identified as a major constituent of the hydrocarbon fraction<sup>8</sup>. Thus a more correct summary of knowledge concerning the acid-catalysed rearrangement of caryophyllene (1) is that it yields clovene (4), caryolan-1-ol (5), neoclovene (9) and small amounts of other hydrocarbons.

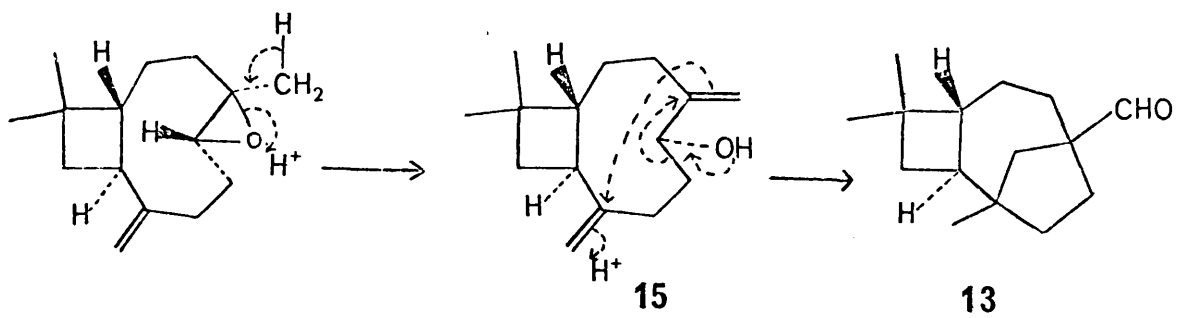
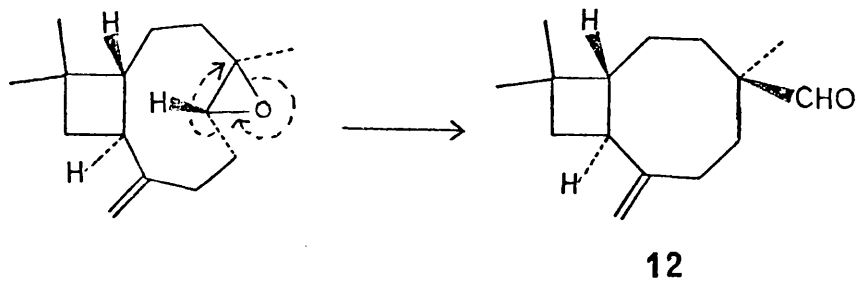
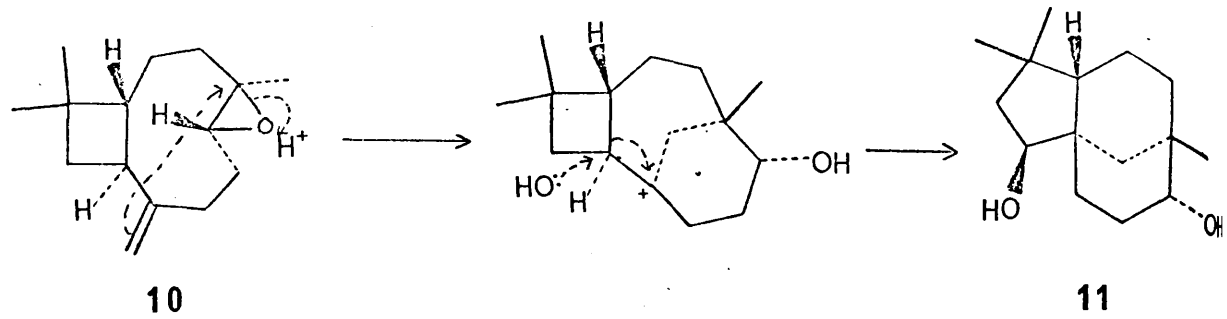
i.e.



+ small amounts of other hydrocarbons.

A more detailed examination of the mechanistic implications of this reaction will be described later, but, to enable this to be placed in proper perspective, several other rearrangements of the caryophyllene skeleton must first be mentioned.

Acid Catalysed Rearrangements Of Caryophyllene Epoxide.

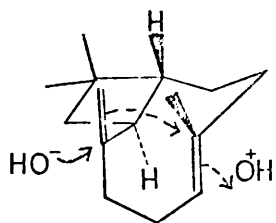


+ **(14)** of undetermined structure.

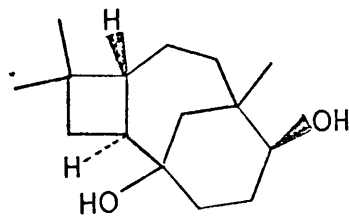
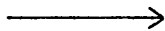
**Fig. 1**

Warnhoff has recently<sup>9</sup> re-examined the early studies on caryophyllene monoepoxide (10) which was found to cyclise under acidic conditions. Barton<sup>10</sup> had previously isolated the clovan-2 $\beta$ ,9 $\alpha$ -diol (11) from this reaction, but, in addition, Warnhoff was able to separate three carbonyl compounds (12, 13 and 14) as their 2,4-dinitrophenylhydrazones. The structures of two of these have been determined from spectroscopic examination and their relationships to known compounds. Warnhoff's suggested mechanisms are shown opposite.

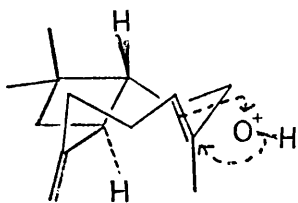
It is interesting to note that Nigam and Levi<sup>11</sup> have also observed the rearrangement of caryophyllene epoxide to the aldehyde (12) during the gas chromatography of the epoxide on an acidic support, and they were able to show that this did not take place when a basic support material was employed. The feasibility of the dienol (15) as the probable intermediate in the formation of the aldehyde (13) is enhanced by Warnhoff's work, in which he showed that simple column chromatography of caryophyllene epoxide on neutral alumina gave 80% conversion to the dienol and subsequent reaction of this product in acid conditions yields (13). Although there are two possible cyclisations, either above or below the nine-membered ring, only one product is obtained, and, while there is no final proof of the matter as yet, it is reasoned by analogy to other cyclisations that the bridge is up, i.e. cis to the C-5 hydrogen.



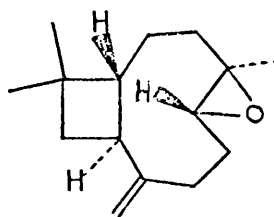
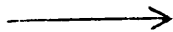
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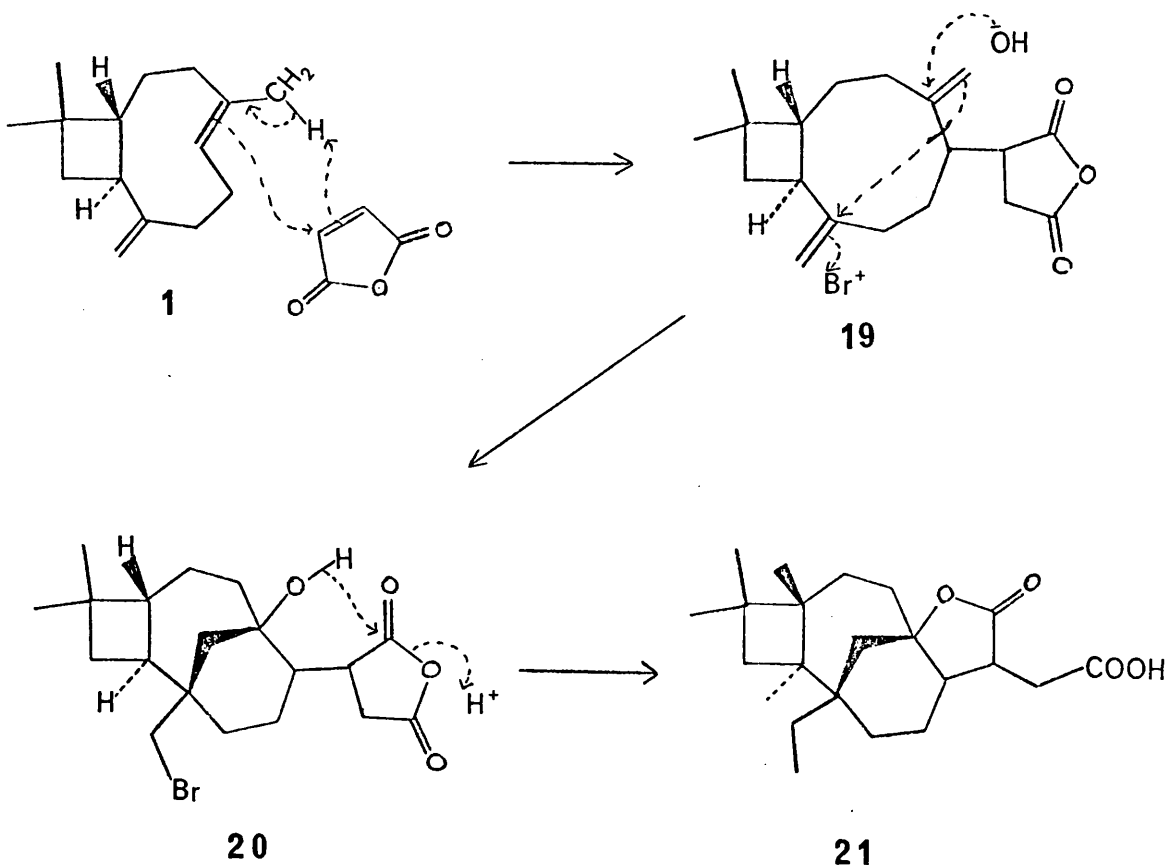
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Fig. 2

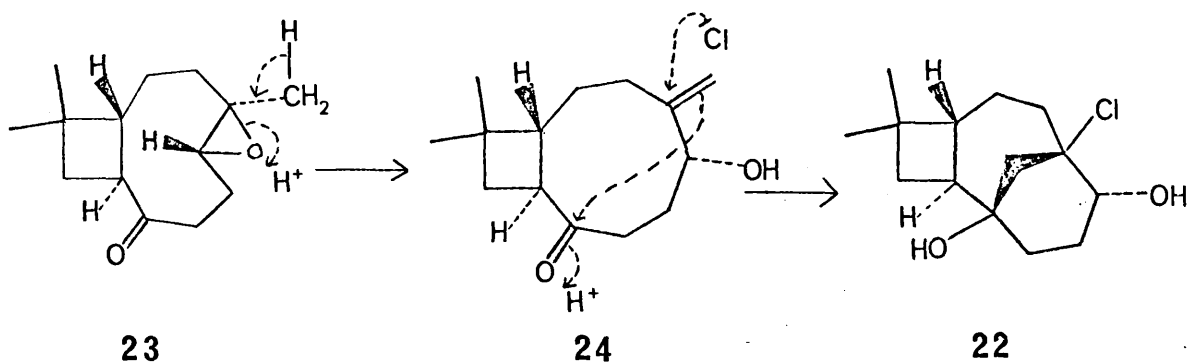
At first sight, it may seem surprising that the diol (16) has not been observed as a product from the rearrangement of caryophyllene epoxide, particularly since Barton<sup>12</sup> has demonstrated that it is a by-product in the preparation of the epoxide. Rationalisation of this diol formation assumes electrophilic attack by  $\text{OH}^+$ , followed by rearrangement in a process similar to protonation of the epoxide. The explanation of the absence of diol (16) in the products from rearrangement of caryophyllene epoxide may lie in the fact that electrophilic attack can occur on the endocyclic double bond while the molecule is in two conformations (17) and (18). The conformer with the exomethylene and methyl groups  $\beta$  is suitably aligned to undergo transannular cyclisation yielding diol (16), in which it is predicted that the secondary hydroxyl must be  $\beta$ , whereas  $\text{OH}^+$  attack on conformer (18) seems to lead to the stable caryophyllene epoxide. As yet the epimeric epoxide from conformer (17) has not been isolated, lending credence to the belief that attack from this side leads to diol (16). Opening of caryophyllene epoxide would then have the wrong geometry to permit formation of diol (16).



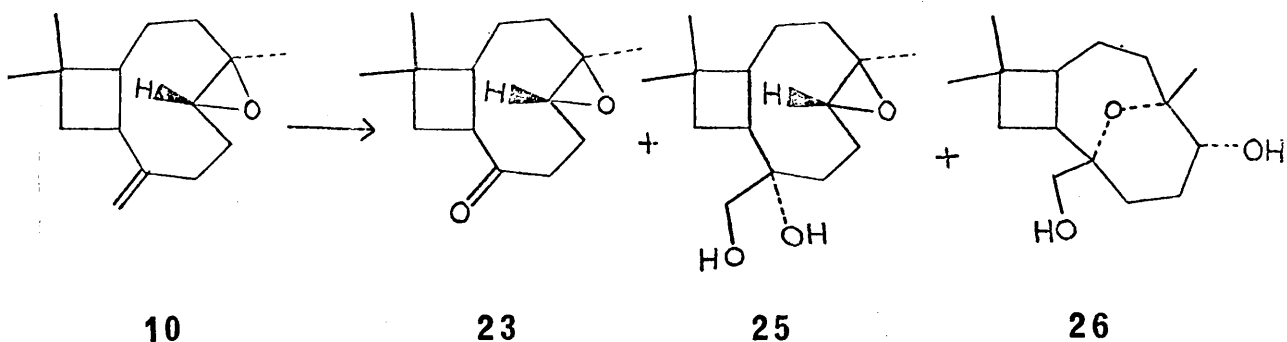
Cyclisations of the type (10)  $\rightarrow$  (15)  $\rightarrow$  (13) are not unusual in caryophyllene chemistry. On treatment with maleic anhydride caryophyllene forms the 1:1 adduct (19), and Nickon<sup>13</sup> has observed many cyclisations analogous to that of the epoxide involving the two exomethylene double bonds. An example of this occurs when the adduct is treated with N-bromosuccinimide in aqueous dioxane, the first formed bromo-hydroxy-anhydride (20) rearranging to the lactone (21).



A further example is found in Sutherland's work<sup>14</sup> on the chlorohydrin (22) formed from caryophyllene epoxy-ketone (23), first prepared by Treibs<sup>15</sup>. In a manner exactly analogous to that for caryophyllene epoxide, the oxirane ring opens to form the corresponding hydroxy-olefin (24) which cyclises picking up HCl as indicated. In this case the stereochemistry of the bridge in the (4,3,1) bicyclo system was conclusively shown to be  $\beta$ .



Perhaps one of the most unusual cyclisations undergone by a caryophyllene derivative is manifest in a by-product during the cleavage of the exomethylene group in caryophyllene epoxide (10) to give Treibs' epoxy-ketone (23). As well as the epoxy-ketone, two diols are formed, whose structures have been determined by Warnhoff<sup>16</sup>.

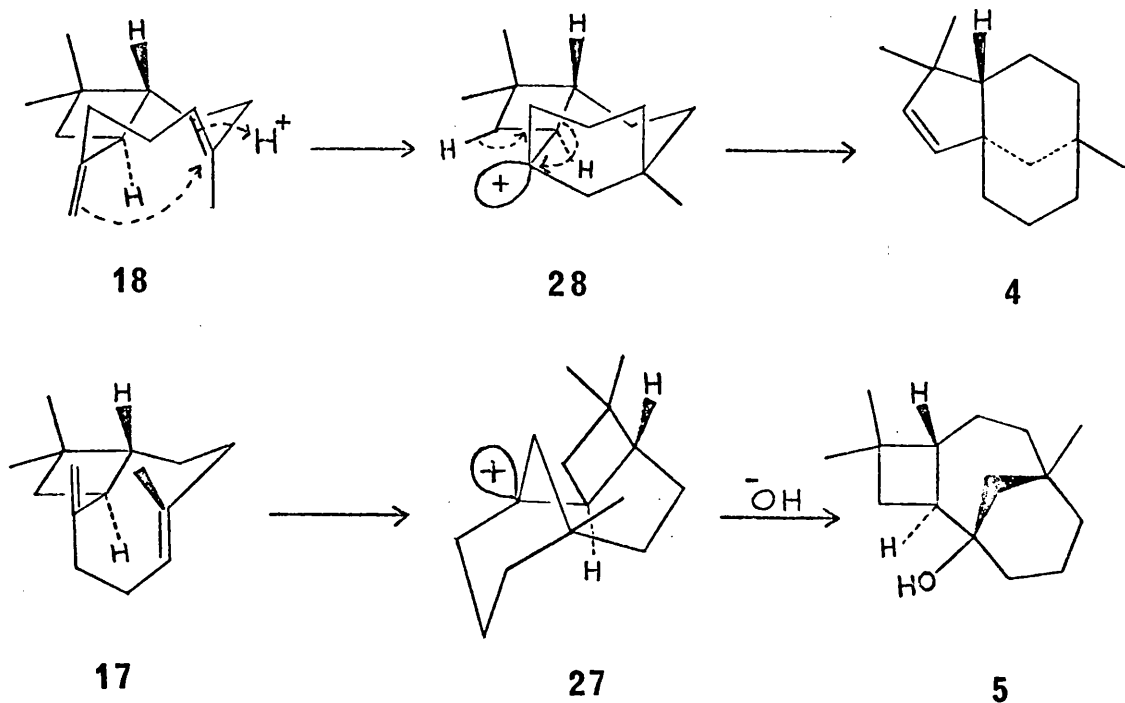


The first diol (25) is simply derived from attack by the oxidising agent (potassium permanganate or osmium tetroxide) on the  $\alpha$ -face of the double bond, but this can react further, the tertiary hydroxyl group participating in the opening of the oxirane ring to give the second diol (26) with an  $\alpha$ -oxygen bridge stereochemistry.

This brief summary of some typical skeleton rearrangements encountered in caryophyllene chemistry is a convenient background against which the mechanistic implications of the acid-catalysed rearrangements of caryophyllene itself can be considered.

Barton<sup>17</sup> rationalised the formation of clovene (4) and caryolan-1-ol (5) by considering that protonation occurred at the trisubstituted double bond preferentially, followed by transannular cyclisation from the exocyclic double bond to the more stable tertiary carbonium ion. With characteristic insight, he also realised that, if protonation could occur when caryophyllene was in two different conformations, then clovene (4) and caryolan-1-ol (5)

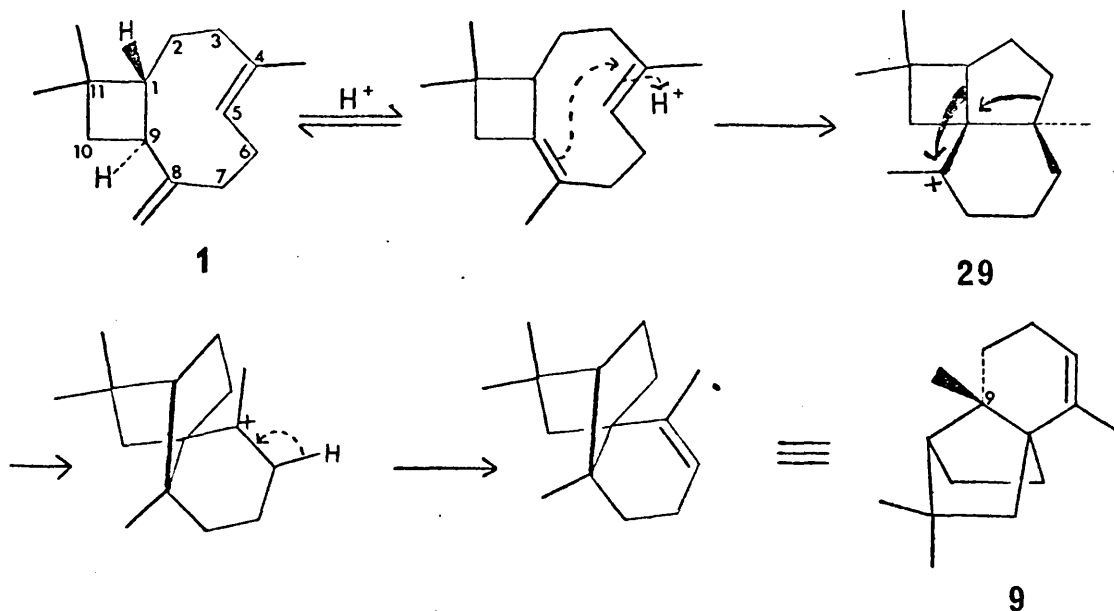
would have different bridge stereochemistries. Examination of the bridgehead carbonium ions so formed, viz. (27) and (28), shows that the  $C_2-C_5$  bond in (28) is suitably aligned to migrate to the back side of the bridgehead and, if migration is followed by loss of a proton, clovene (4) results.



It may very well be the case that an intermediate sulphate is formed, which, being a good leaving group, is readily displaced as the  $C_2-C_5$  bond migrates in trans anti-parallel fashion. The geometry of conformer (17), however, leads to a carbonium ion (27) in which neither the  $C_2-C_5$  bond nor any other in the four-membered ring is

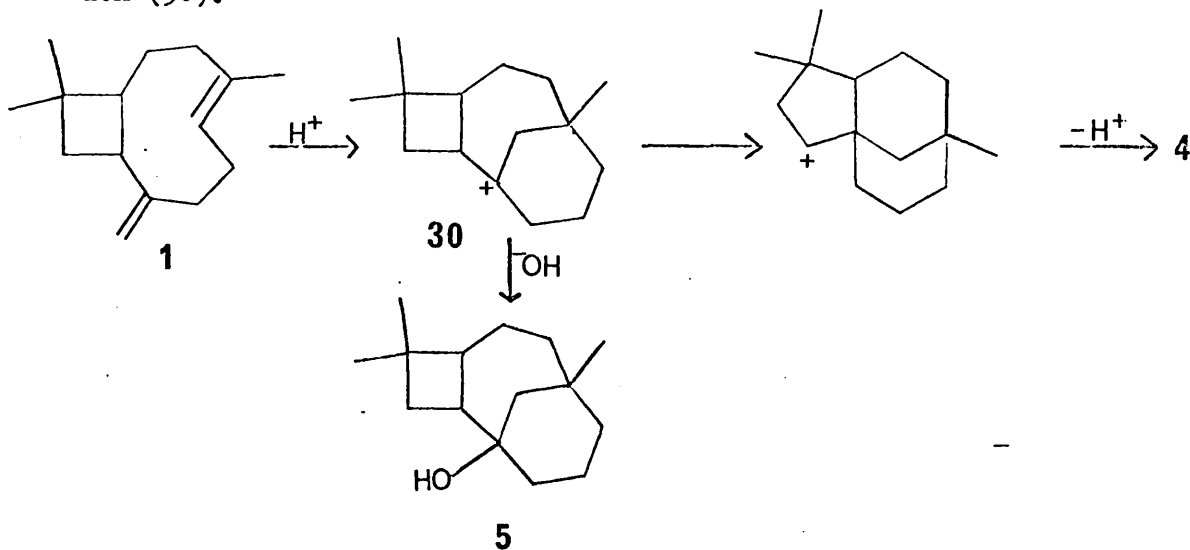
suitably oriented to migrate thereby relieving strain. Hence this carbonium ion presumably picks up a sulphate group which is hydrolysed on work-up to give caryolan-1-ol. These arguments presented by Barton and his co-workers were well received and certainly seemed to explain the known facts, as well as predict several other points about structure and stereochemistry, all of which have been fully justified. How then can the structure of neoclovene (9) and its mode of formation be fitted into Barton's mechanistic framework?

The answer is that it cannot. Parker, Raphaël and Roberts<sup>8</sup> have proposed a mechanism for the formation of neoclovene, which goes through the interesting, intermediate carbonium ion (29), formed by closure between the positions 5 and 9 in caryophyllene, subsequent to a postulated double bond isomerisation. Wagner-Meerwein shifts and deprotonation as shown might yield neoclovene.



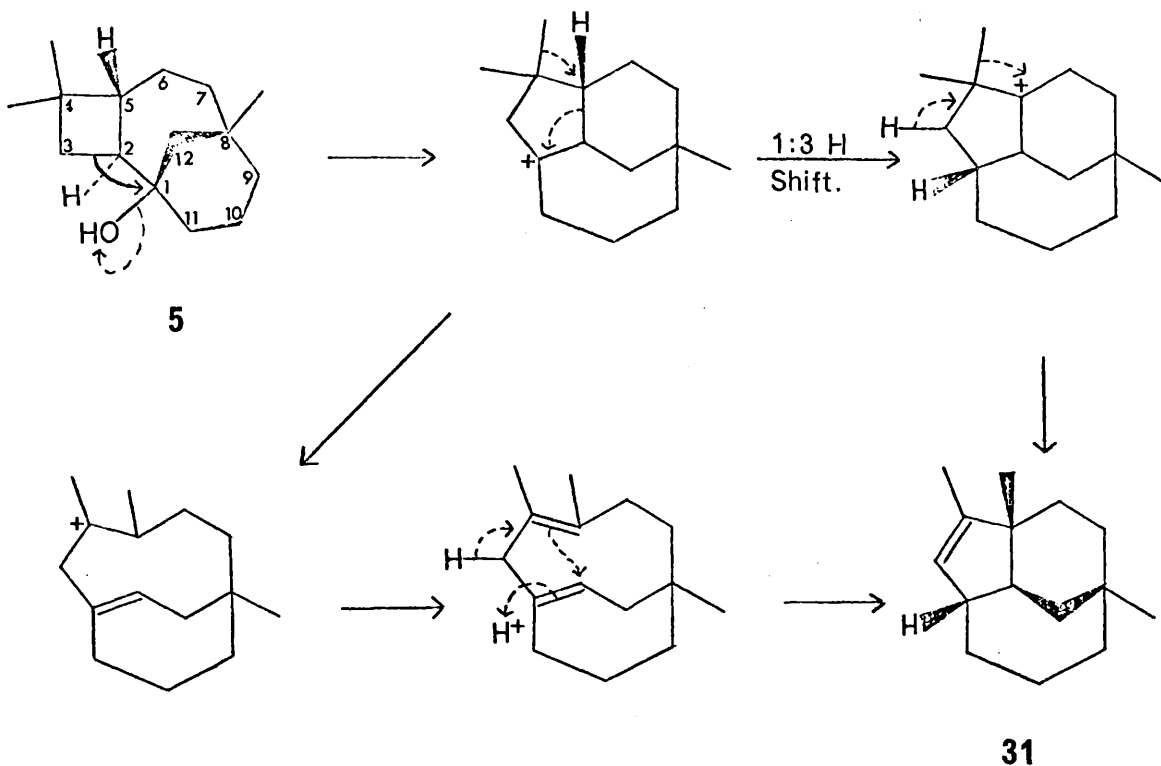
Although the gross structure of neoclovene had been determined, the relative configuration of the methyl group at C<sub>9</sub> to the gem-dimethyl group had not been established. The first part of this work discusses a synthesis of neoclovene, which answers the question of the relative configuration and also provides some support for the proposed mechanism.

Before Barton had rationalised the mode of cyclisation of caryophyllene, the subtle stereochemical points in the mechanism were not appreciated, and hence many workers had tried to demonstrate that caryolan-1-ol (5) was convertible to clovene (4) via the carbonium ion (30).

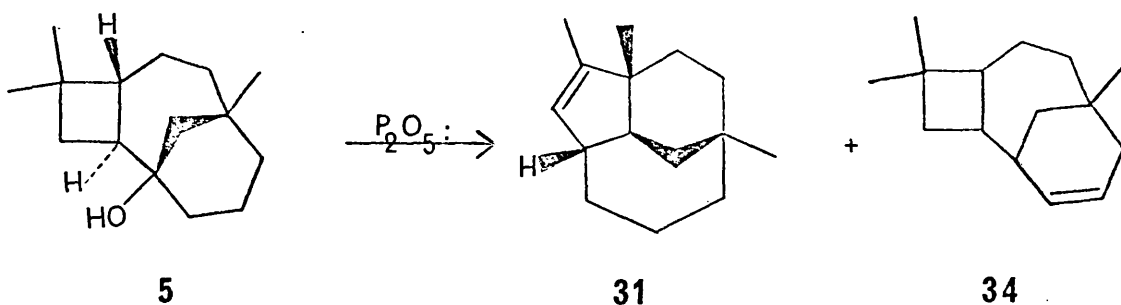
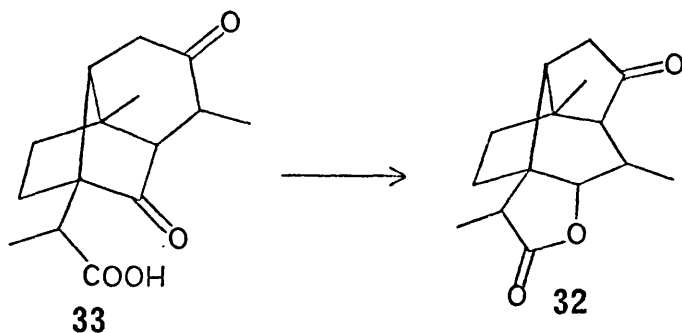


Wallach and Walker<sup>18</sup> obtained an oil, which they believed to be clovene (4) from treatment of caryolan-1-ol with phosphoric oxide, but the product was shown to be inhomogeneous by later investigators<sup>19</sup>.

Instead of merely clovene, it was demonstrated that careful distillation gave clovene together with a higher boiling hydrocarbon given the name of isoclovene (31). Clunie and Robertson<sup>20</sup> made the hydrobromide of this olefin, and have conclusively shown that it has the structure (31) by X-ray analysis. The rearrangement of caryolan-1-ol to isoclovene represents an unusual problem in carbonium ion mechanism. Barton<sup>21</sup> suggests two possible mechanisms both of these involving initial migration of the C<sub>2</sub>-C<sub>3</sub> bond.



If this were the correct mechanism, then it is a rare example of an "interchange rearrangement", of which the earliest example is that reported by Woodward<sup>22</sup> in the formation of parasantonide (32) from santonic acid (33). However there are distinct differences since the latter case is not thought to involve carbonium ions and a much higher temperature is used.



The other hydrocarbon fraction from the dehydration of caryolan-1-ol, originally believed to be clovene, was re-examined by Lutz and Reid<sup>23</sup>, who showed that, despite very close similarities in some physical properties, this material differed from authentic clovene in its optical rotation, infra-red spectrum and chemical behaviour. On rather tenuous evidence they suggested that this new hydrocarbon, which they called pseudoclovene, might have the structure (34).

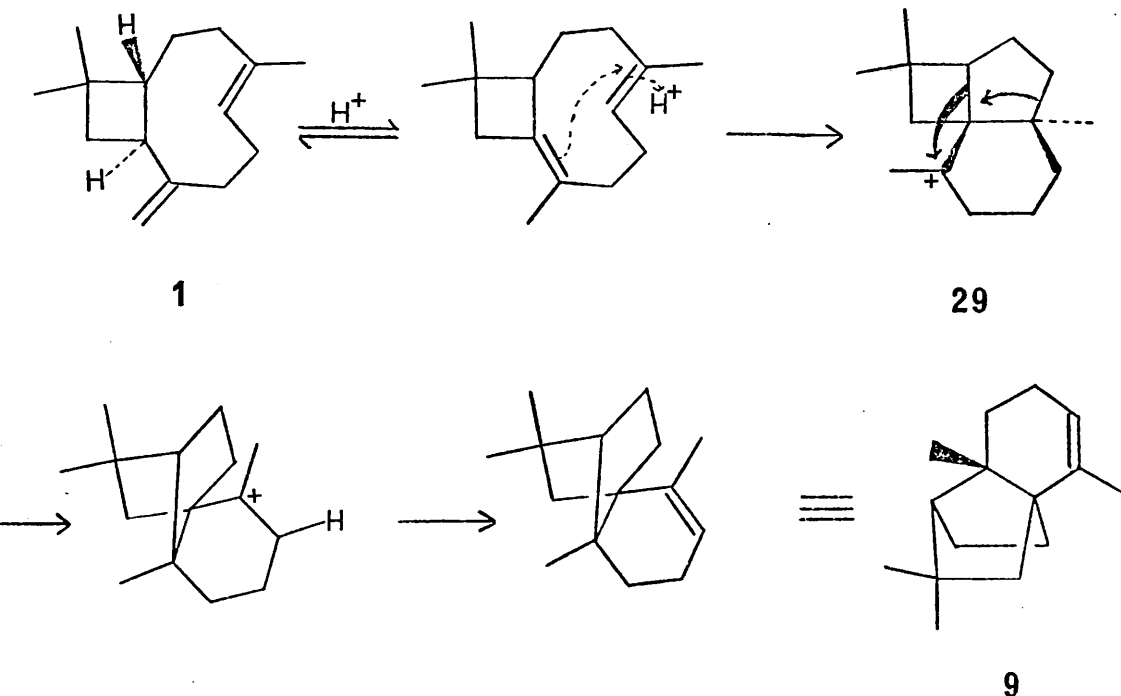


It was decided to study this dehydration reaction in more detail, since it promised to provide some mechanistic questions of fundamental importance in carbonium ion chemistry ; further, it was felt, almost intuitively, that the proposed structure for pseudoclovene was incorrect. The results of these investigations together with the novel synthesis of neoclovene are described in the following sections.

CHAPTER 2.THE SYNTHESIS OF NEOCLOVENE.

Until fairly recently, synthesis has been regarded as the final proof of a structure assignment, but two factors have changed this outlook. Firstly, it has been demonstrated that synthesis, no matter how apparently unambiguous, does not by itself constitute a fool-proof method of structure determination, as is seen in the well-known attempted synthesis of patchouli alcohol<sup>24,25</sup>. Perhaps even more significantly, there is now seldom any need for synthesis as proof of structure, since either X-ray crystallography or modern, spectroscopic techniques, coupled with mild specific degradative reactions, generally provide an unambiguous structure determination. While synthetic work is still of immense value as an academic exercise in creative thinking, and will always be an incentive to the discovery of new and valuable reactions, there is a growing tendency for synthesis to be tackled only if it is coupled with other objectives. Hence it was decided that, rather than undertake a classical synthesis of neoclovene, some approaches to which have recently been reported by Loewenthal<sup>26</sup>, it would be more interesting to elaborate caryophyllene to one of the proposed carbonium ion intermediates in the mechanism leading to neoclovene, and examine its behaviour.

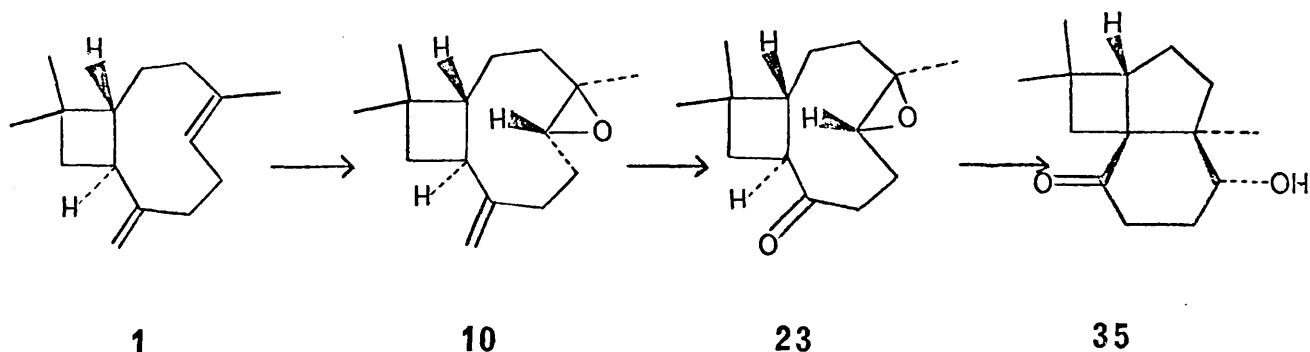
The postulated mode of formation of neoclovene (9) from caryophyllene (1) was via the carbonium ion (29) and it was this species which constituted the synthetic goal of this work.



The principal reason for choosing this intermediate is that it is structurally vastly different from caryophyllene and neoclovene, so that, if it is converted in good yield to neoclovene, then considerable weight is lent to the proposal of its intermediacy. It also proves to be a very convenient choice, since the carbon skeleton represented in (29) is well-known in caryophyllene chemistry.

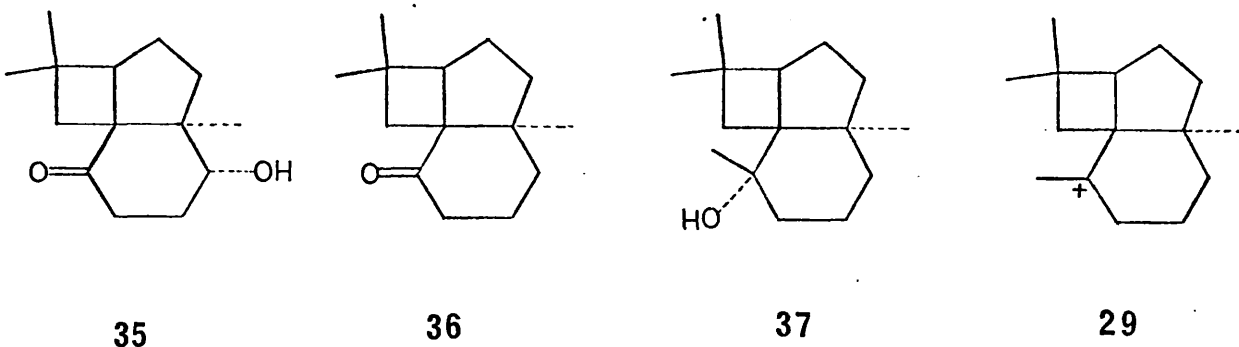
As already mentioned, Treibs had epoxidised the trisubstituted double bond in caryophyllene to give caryophyllene epoxide (10),

which on oxidation gave the epoxy-ketone (23). On treatment with potassium hydroxide in methanol a very efficient isomerisation takes place to give the hydroxy-ketone (35)<sup>2</sup>, a key compound in Barton's work on the structure elucidation of caryophyllene. The stereochemistry shown has been determined by Horeau and Sutherland<sup>27</sup> using a modification of Prelog's "asymmetric synthesis" method<sup>28</sup>.



Since, during the postulated cyclisation of caryophyllene to the carbonium ion (29), closure occurs between the identical atoms to those in (23)  $\rightarrow$  (35), it is reasonable to suppose that carbonium ion (29) will have the same stereochemistry as (35). In fact this is the only likely stereochemistry, since any other necessarily involves either a trans fused four and five membered ring system, or a trans indane skeleton, which, in this case, with the rigidity imposed by the four membered ring, seems impossible. Clearly then Barton's ketol (35) is an obvious precursor for carbonium ion (29). In principle all that is required is the removal of the hydroxyl group to give the ketone (36), followed by some methylation procedure yielding the tertiary alcohol

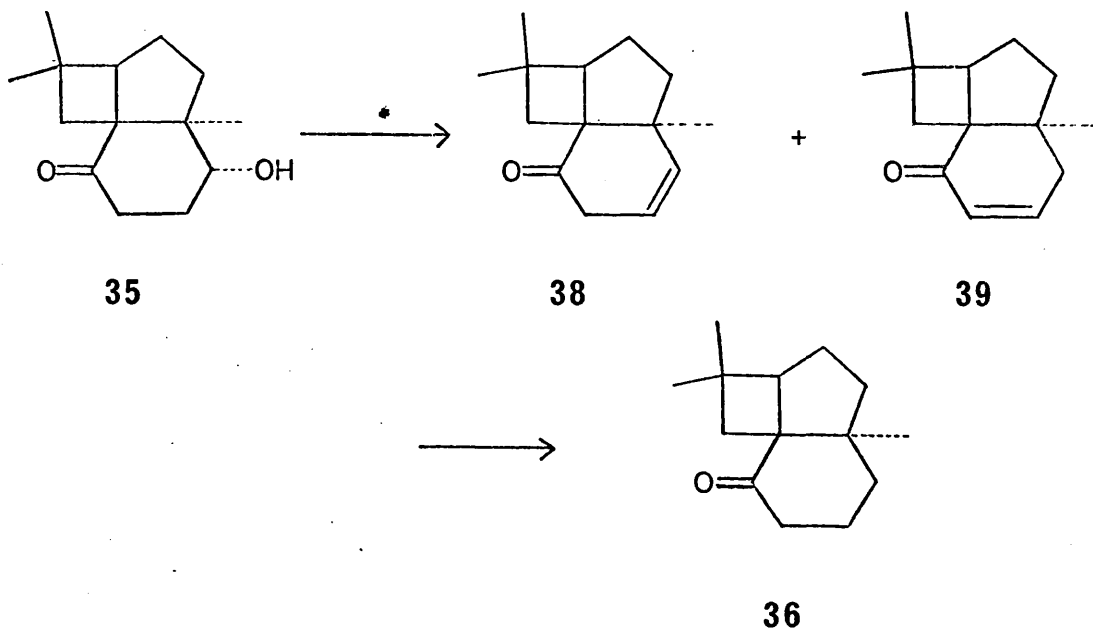
(37), which on acid treatment should readily furnish the desired carbonium ion. Although initial difficulties were encountered this has been successfully effected. The removal of the innocuous-looking hydroxyl group proved more difficult than anticipated and shows the importance of considering carefully the stereochemistry of the system.



Initially the ketol (35) was made exactly as described in the literature<sup>2,15</sup>, but, in our hands, the yields of caryophyllene epoxide (10) and epoxy-ketone (23) were lower than those reported. It was found that the epoxidation of caryophyllene could be carried out very efficiently (>90%) using the commercially available *m*-chloroperbenzoic acid<sup>29</sup>. While potassium permanganate in acetone treatment did give the epoxy-ketone (23), the reaction was messy and only about 30% of pure material could readily be extracted. This may very well be attributed to poor technique on our part, since Warnhoff<sup>16</sup> has reported that they could obtain 60% yields using potassium permanganate, which bears out the earlier work by Treibs. On small scale, ozonolysis of the

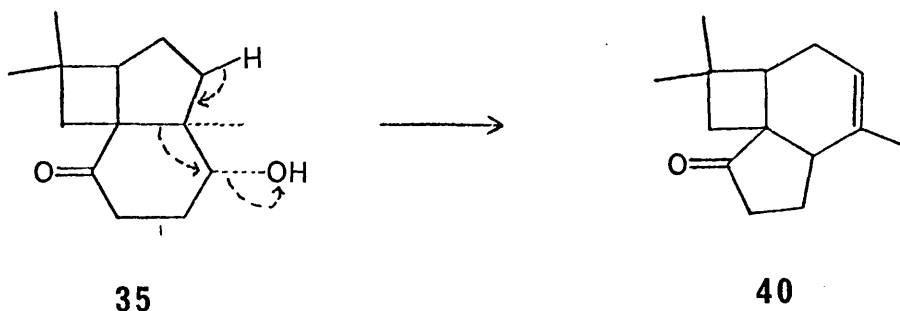
exomethylene group appeared very promising, but, when repeated on a larger scale, direct distillation of the crude products resulted only in polymeric substances. The most consistent method of achieving >60% yields of Treibs' epoxy-ketone was found to be osmium tetroxide-sodium metaperiodate cleavage in aqueous dioxane<sup>30</sup>. At first sodium bisulphite was used during the work-up to destroy any excess osmium tetroxide<sup>31</sup> but latterly hydrogen sulphide gas was found to be more convenient. Isomerisation of the epoxy-ketone (23) to the ketol (35) was efficiently effected by methanolic potassium hydroxide as described by Barton<sup>2</sup>.

The most obvious method of removing the hydroxyl group in the ketol is by dehydration, and then catalytic reduction of the keto-olefin (38) so formed will give rise to the saturated ketone (36).



In attempts to achieve this purpose, phosphorus oxychloride and thionyl chloride were both used under a variety of conditions, but in every case a complex mixture of at least five compounds resulted. Combined gas chromatography-mass spectroscopy showed that two of these compounds contained chlorine and from the parent ion ( $m/e$  240) and isotope distribution it was seen that these would correspond to the chlorides derived from replacement of the hydroxyl group by chlorine. It is noteworthy that phosphorus oxychloride and thionyl chloride in benzene gave predominantly different chloro compounds, as might be expected, since the latter is known to effect chloride formation with retention<sup>32</sup> while the former usually gives inversion in the product. The crude products were also examined by ultraviolet spectroscopy, and a fairly strong absorption at 233  $\mu$  was observed, which might be attributed to the conjugated enone (39). At a later point, when a mixture of (38) and (39) were obtained free from other impurities, it was shown that two of the olefins formed in minor amounts by the above dehydration techniques corresponded in GC/MS behaviour to these olefins. It should also be noted that the stereochemistry of (35) places the central bond of the indane skeleton exactly trans-antiparallel to the hydroxyl group, hence it is probably not very surprising that a complex mixture results on dehydration, since rearrangement would be fairly facile and might yield an olefin of the type (40). Although almost certainly some of the desired products were obtained, for synthetic purposes

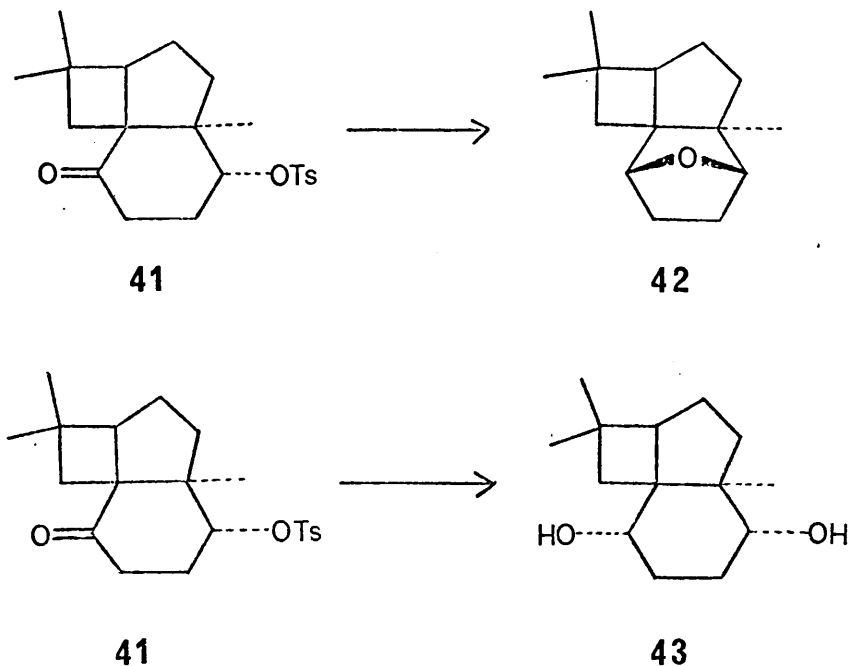
such an approach was deemed unsatisfactory, and no further investigations were conducted to unravel the mixture and confirm the suspicions outlined above.



It was felt that the complications resulting from probable skeletal rearrangement could be avoided and the hydroxyl group removed by hydrogenolysis of the keto-tosylate (41). The tosylate was readily formed from the ketol by treatment with tosyl chloride in pyridine at 0°C. Stevenson<sup>33</sup>, who was working on the same problem in these laboratories, reported the formation of a small amount of ketone,  $\gamma_{\text{max.}}(\text{nujol}) = 1745 \text{ cm}^{-1}$  during this tosylation reaction. This by-product may be the result of a small amount of rearrangement similar to that suggested by the dehydration studies and certainly the carbonyl absorption in the infra-red would fit a ketone such as (40). As yet however, this work is unconfirmed. Treatment of the keto-tosylate (41) with lithium aluminium hydride in refluxing anhydrous ether for 36 hours gave a colourless oil, which showed two spots on thin-layer chromatography. The two compounds were readily



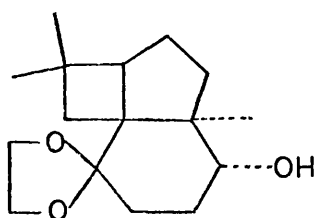
separated by column chromatography and examined spectroscopically. The less polar compound, a low melting solid (31-32°C), showed no  $\gamma_{\text{O-H}}$  or  $\gamma_{\text{C=O}}$  in the infra-red spectrum, but did have C-O stretching at 1010 and 1030  $\text{cm}^{-1}$  together with some very sharp fine structure. The NMR spectrum showed two highly asymmetric absorptions at 5.75  $\tau$  (1H) and 6.05  $\tau$  (1H). This data indicated an ether and so the structure (42) was postulated. Analysis and mass spectroscopy confirmed the molecular formula. The second product showed strong  $\gamma_{\text{O-H}}$  around 3400  $\text{cm}^{-1}$  and  $\gamma_{\text{C-O}}$  between 1000 and 1100  $\text{cm}^{-1}$ , but very little else. Analysis gave the molecular formula  $\text{C}_{14}\text{H}_{24}\text{O}_2$ , and from the m.p. and optical rotation this compound is taken to be identical to the diol (43) obtained by Barton<sup>12</sup> on treatment of the ketol (35) with sodium in n-propyl alcohol.



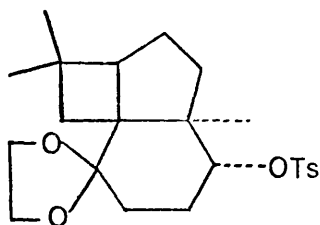
Again the historian becomes a prophet in reverse, for it is simple, in retrospect, to see that in this system, hydride attack from the  $\alpha$ -face on the ketone orients the developing oxy-anion for participation in eliminating the tosylate group to give the oxo bicyclo(2,2,1) ring structure (42). Attack on the  $\beta$ -face cannot readily lead to transannular reaction, and so one might have expected normal hydrogenolysis of the tosylate to occur. Surprisingly, this was not the case and it appears that S-O bond cleavage is preferred to C-O cleavage in this compound. While this is not without precedent<sup>34</sup>, it is much less common, and it was felt that the carbonyl group in ketol (35) should be prevented from participating in the hydrogenolysis before a final judgment on this synthetic approach could be made.

The carbonyl group was protected as the ethylene ketal, but some difficulty was encountered in effecting this at first, since ketalisation did not occur at all in ethylene glycol and boron trifluoride etherate, and only to a small extent when refluxed in benzene with *p*-toluenesulphonic acid as catalyst. The method of choice proved to be that reported by Jaques<sup>35</sup>, in which the ketone is heated to 150°C with *p*-toluenesulphonic acid, ethylene glycol and ethyl orthoformate, the ethanol formed being distilled off into a receiver. After chromatography a yield of hydroxy-ketal (44), greater than 70%, could be attained. The tosylate derivative (45) of the hydroxyl group was then made in the normal manner and, since a solid material showing the correct infra-red spectrum was obtained, this was treated with

lithium aluminium hydride in ether. The sole product was identical in infra-red spectrum and on thin-layer chromatography with starting hydroxy-ketal (44). Further, on warming with 4*N* hydrochloric acid for ten minutes, a reasonable yield of pure ketol (35) was obtained. Thus, in this example it is quite apparent that normal tosylate hydrogenolysis does not proceed in the normal manner, cleavage of the S-O bond being totally preferred to the more usual C-O bond cleavage.



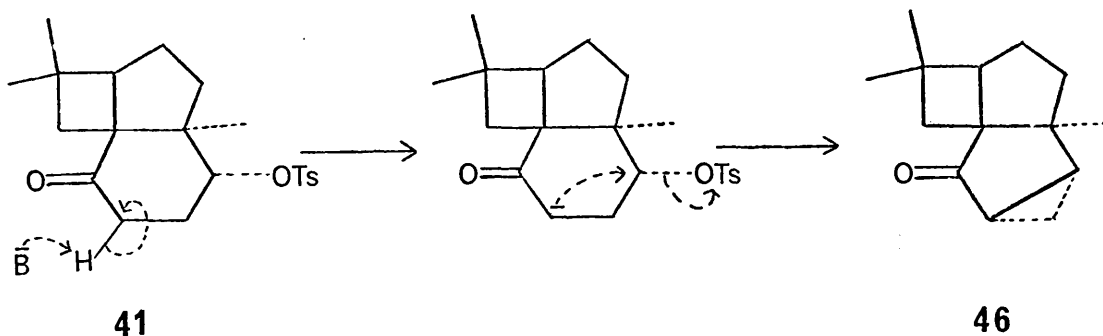
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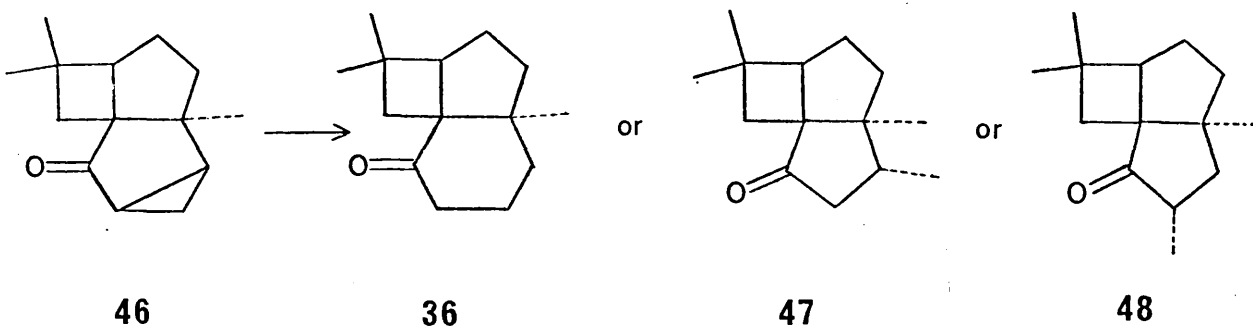
During this time, Stevenson<sup>33</sup> had been attempting to remove the hydroxyl group by two other methods. The first of these was pyrolysis, but, since the acetate of Barton's ketol did not show any tendency to undergo pyrolytic elimination even at a temperature of 450°C, this had been temporarily abandoned. The other approach was to try to effect elimination of the tosyl group by means of strong base. From the reaction of the keto-tosylate (41) with 10% sodium ethoxide in ethanol beautiful, white, plate-like crystals separated. Extraction gave a 75% yield of a highly crystalline ketone of m.p. 66-67°C.

The infra-red spectrum showed no hydroxyl absorption, nor any sign of a tosylate group, but what was more puzzling, the product did not appear to be an olefin. It was soon realised that the strong base had generated an anion adjacent to the keto group and that this anion had participated in tosylate elimination to yield the novel cyclopropyl ketone (46). NMR, mass spectroscopy and analysis confirmed this.

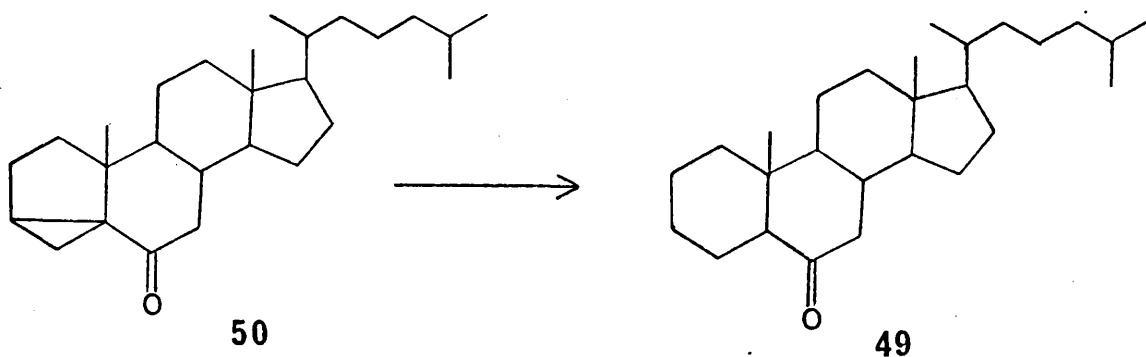


Since the hydroxyl group had been removed in high yield, it was anticipated that this compound might be of great value in the synthesis, if the cyclopropane ring could be cleaved in the correct manner. Shortage of time did not permit Stevenson to carry out this work, and so the problem was taken up in the course of this study.

For our purposes the best method of cleavage would clearly be catalytic reduction, since this would lead directly to the desired ketone (36), provided hydrogenolysis took place to give the cyclohexane in preference to either possible methylcyclopentane, i.e. (47) or (48).



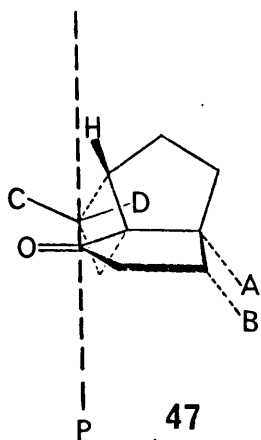
There are analogies in the literature for such cleavage of cyclopropyl ketones under catalytic hydrogenation conditions, the classic example in this sense being the work on *i*-cholestanes. Windaus and Dalmer achieved an almost quantitative yield of the steroidal ketone (49) from the *i*-cholestanone (50) by reduction using palladium charcoal in acetic acid<sup>36,37</sup>.



Using these conditions on the cyclopropyl ketone (46), hydrogenation proceeded slowly, stopping after the uptake of one equivalent of hydrogen. The product was shown to be pure by GIC and from the infrared spectrum which showed  $\nu_{C=O}$  at  $1725\text{ cm}^{-1}$ , it was suspected that a cyclopentanone had been formed, since, in all the other cyclohexanone compounds in this series, the ketone absorption was below  $1700\text{ cm}^{-1}$ . The NMR spectrum confirmed this suspicion, there being four methyl signals, of which one was a doublet at  $9.03\tau$  and the other three were the expected tertiary methyls. There were still two possibilities for this compound, viz. (47) or (48). A further examination of the literature<sup>38</sup> indicated that cleavage was most likely between the carbon activated by the ketone group and the carbon bearing the least number of substituents. This guiding principle would predict that the product should be the  $\beta$ -methyl cyclopentanone\* (47). Evidence in support of structure (47) was obtained from NMR solvent shift studies.

\* In this context  $\beta$  refers to the position and not to the stereochemistry. From the solvent shift data and the mechanism of formation, the methyl group is taken to be  $\alpha$  in stereochemistry.

The empirical rule<sup>39,40</sup>, most commonly used in correlating solvent shifts may be stated as follows. If a plane (P) is drawn through the carbon atom of the carbonyl group and at right angles to the C-O bond, then protons in the environment of P show distinct changes in chemical shift on alteration of solvent. The magnitude and sign of these changes critically depend on the stereorelationship between P and the proton being considered. Hence, if one defines  $\Delta\tau = \tau_{\text{benzene}} - \tau_{\text{CDCl}_3}$ , then protons on that side of P nearest the oxygen atom show negative  $\Delta\tau$  values, the effect being small when very close to P, increasing to a maximum at about  $3 \overset{\circ}{\text{A}}$ , and then dying off almost immediately. Protons on the other side of P show positive  $\Delta\tau$ 's which also increase as one moves away from P to a maximum and then disappear.



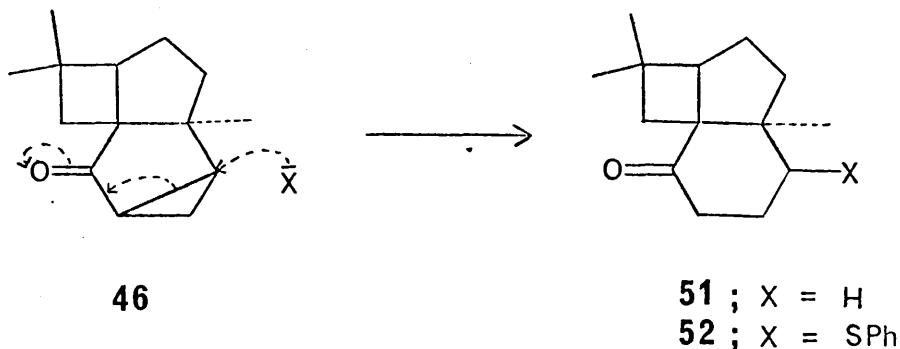
Methyl Group	$\tau_{\text{benzene}}$	$\tau_{\text{CDCl}_3}$	$\Delta\tau$
A (singlet)	9.46	9.21	+0.25
B (doublet)	9.30	9.03	+0.27
C (singlet)	8.70	8.83	-0.13
D (singlet)	9.21	9.09	+0.12

Consideration of the data in the table together with a molecular model lends a good deal of support to the proposal that the compound formed by cyclopropane opening is the  $\beta$ -methyl cyclopentanone. Assuming that the methyl groups are properly assigned in both solvents, then it can be seen that the shifts for the two methyl groups on the cyclopentane ring are almost the same, which would require two  $\beta$ -methyl groups to be cis to one another. (An  $\alpha$ -methyl group would only give a shift of approximately  $0.1\tau$ ). The gem-dimethyl group in the four-membered ring is bisected by the plane (P), so that one methyl group suffers a downfield shift of almost the same magnitude as the other undergoes in the upfield direction. It must be stated here that no deuteration studies were carried out to check the correctness of the methyl assignments, and hence, while structure (47) is a reasonable proposal from the evidence available, it cannot be assumed final. Deuteration of the various methyl groups would have been an almost impossible task, and, since it is clear that the cyclohexanone (36) was not formed in the hydrogenolysis, there remained no interest in the compound as a synthetic intermediate.

Alternative catalysts and solvents were employed in the hope that the direction of cleavage may have been reversed, but this was not the case. Adam's catalyst in methanol and palladium-charcoal in ethyl acetate gave back unchanged starting material, while Adam's catalyst in acetic acid gave a mixture of alcohols, which, on Jones'



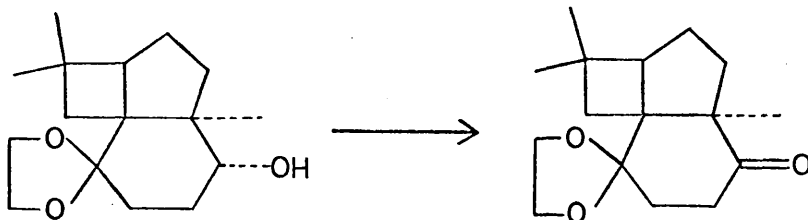
oxidation gave mostly the  $\beta$ -methylcyclopentanone (47) with less than 10% of starting ketone.



Another possible means of cleaving the cyclopropane ring which could only proceed in the desired direction, would be to make the cyclopropyl ketone undergo a type of Michael addition. As a preliminary investigation (46) was treated with lithium aluminium hydride, which would lead to compound (51) and this would presumably reduce further to the epimeric alcohols. Clearly, however, the rate of hydride reduction of the ketone group would be much faster than the reduction of the cyclopropane ring, and hence the epimeric alcohols from (46) would form first, removing all the activation for a Michael addition. In reality this is presumably what occurred since two alcohols were obtained and these could be oxidised back to starting material. A more realistic nucleophile would be the powerful thiophenolate anion, which might yield (52). It was expected that a Mozingo reaction on (52) would give the desired ketone. Although an unsuccessful, small-scale attempt was made with thiophenolate, the possibilities

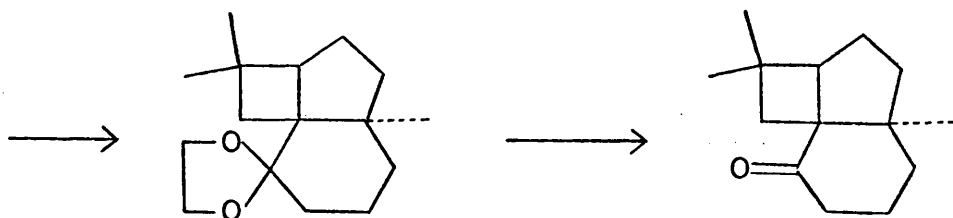
of this approach were not properly tested, since other methods being investigated at the same time were proving more successful.

The hydroxy-ketal (44), although first made with a view to tosylate hydrogenolysis, could be elaborated to the oxo-ketal (53) and a Wolff-Kishner reduction effected on the ketone group. Hydrolysis of the protecting ketal group in (54) should then yield the elusive ketone (36).



44

53



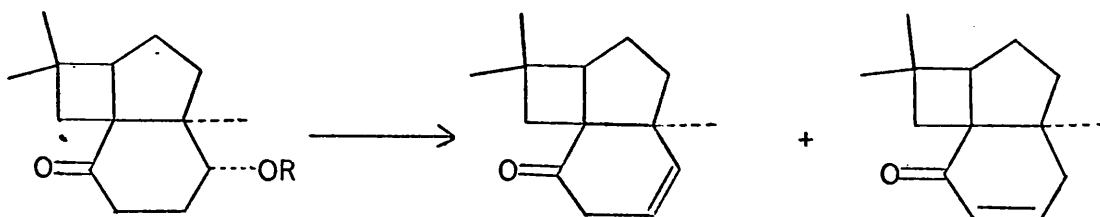
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36

Three common methods of oxidising an alcohol to the corresponding ketone were investigated. Jones' reagent was found to cause some hydrolysis of the ketal group, while Sarett oxidation<sup>41</sup>, using chromium trioxide in pyridine, was found to be slow compared to the method described by Snatzke<sup>42</sup>, in which chromium trioxide is added

to dry dimethyl formamide with a catalytic amount of concentrated sulphuric acid. This last mentioned method was found to be the most convenient yielding over 80% of purified material. Unfortunately a mixture of products resulted from the Wolff-Kishner reduction of (53), from which only 9% of the desired ketone (54) was extracted by preparative thick-layer chromatography. The other two major products were hydroxy-ketals, and, since one of these was identical to the starting hydroxy-ketal (44), the other was taken to be the epimeric alcohol from their similarity in infra-red spectra.

As already mentioned, early studies in the pyrolysis of the acetate (55) had proven most unsatisfactory, but, as a last resort, the carbonate (56) was made using redistilled ethyl chloroformate and pyridine and subjected to pyrolysis at 350°C for one hour under a nitrogen atmosphere. It was most gratifying to find that a 40% yield of olefin could readily be obtained by distillation of the crude products.



55 ; R = COMe.

56 ; R = COOEt.

38

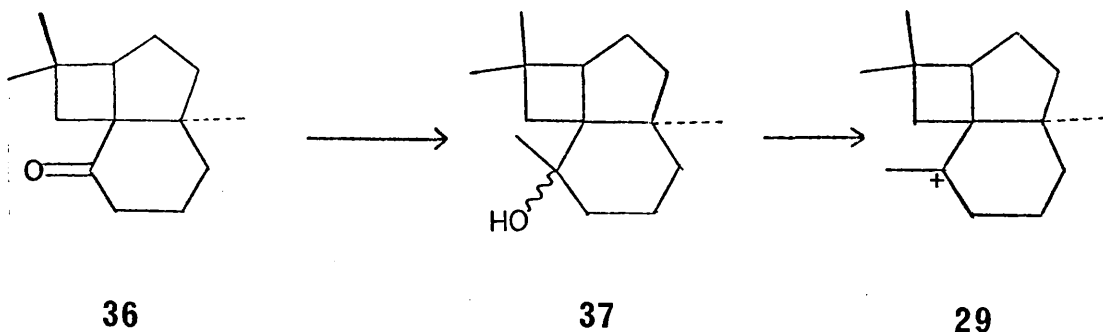
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The pyrolysis reaction invariably gave a mixture of two olefins which were shown to be the conjugated and non-conjugated enones (38) and (39) by NMR, using extensive spin-decoupling of the 100 Mc./sec. spectrum. From the GIC traces, it is estimated that 24% of the mixture is the conjugated enone and 76% is the non-conjugated. Heating a small sample of the mixture with base and with acid did not cause any double bond migration, hence it is assumed that this must be the equilibrium mixture of enones. Although initially surprising, a survey of the literature shows that the equilibrium mixture in highly substituted and rigid cyclohexenones is not always in favour of the conjugated enone<sup>43</sup>.

Hydrogenation of this mixture over 10% palladium-charcoal in ethyl acetate gave a quantitative yield of a ketone (24), shown to be identical in every respect with that obtained by the Wolff-Kishner reduction of the oxo-ketal (53).

A Grignard reaction with methyl magnesium iodide was found to proceed very slowly, but after about two days a reasonable amount of tertiary alcohol (37) was obtained. Although two epimeric alcohols were expected, only one seemed to be formed from TLC and NMR examination. As yet the stereochemistry of this alcohol is undetermined, but this did not affect the next step which was the generation of the proposed intermediary cation (29) in the formation of neoclovene. It was decided that the ideal conditions, under which to examine the carbonium ion, were the concentrated sulphuric

acid in ether mixture used to cyclise caryophyllene.

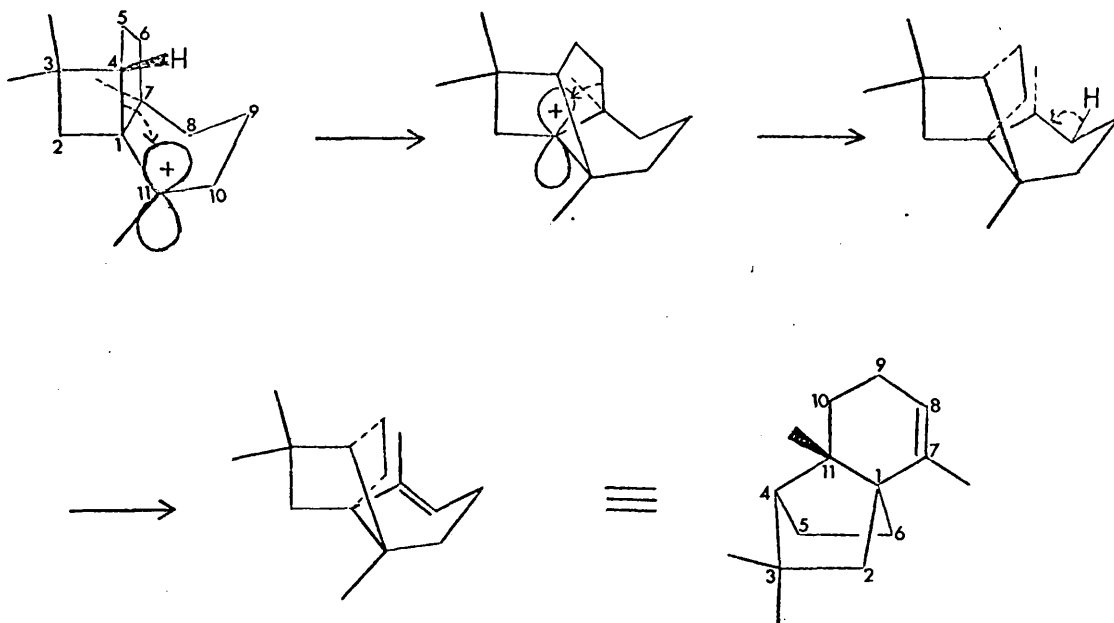


When the tertiary alcohol (37) was treated with this mixture for 30 minutes at 0°C and a further 30 minutes at ambient temperature, three products were isolated. The principal product was a hydrocarbon of molecular weight 204, which showed an identical mass spectrum to that of authentic neoclovene. This compound constituted greater than 96% of the total products. A second hydrocarbon running very close to neoclovene in the GLC and present as less than 1% of the products also had a molecular weight of 204 but a completely different mass spectral fragmentation pattern, while the last compound was unchanged starting material. This small amount of alcohol was removed from the hydrocarbons by column chromatography. Although the tiny amount of the second hydrocarbon could not be removed from the synthetic neoclovene, it did not interfere with the spectroscopic comparison of synthetic and authentic hydrocarbons. Thus the NMR and infra-red spectra were identical, and cross-injection of samples on four different GLC columns including two 50 metre capillary columns, demonstrated the

identity of the two samples. The synthetic neoclovene was also found to be optically active showing a rotation  $[\alpha]_D^{25} = -69^\circ$  ( $c = 0.40$  in  $\text{CHCl}_3$ ), which compares reasonably well with the authentic material,  $[\alpha]_D^{25} = -72^\circ$  ( $c = 1.78$  in  $\text{CHCl}_3$ ).

Having demonstrated conclusively that neoclovene (9) is formed from the tertiary alcohol (37), the implications and conclusions must now be examined in some detail. Since Corey has synthesised caryophyllene<sup>3</sup>, and this work involves the elaboration of caryophyllene to neoclovene in a specific manner, then formally one may describe the work as a synthesis of neoclovene. Much more important, however, is that considerable evidence is presented in favour of the intermediacy of carbonium ion (29) in the rearrangement of caryophyllene (1) to neoclovene (9). This is self-evident, since generation of this carbonium ion leads almost totally to neoclovene, and it is highly unlikely that, under the fairly mild conditions employed, ring opening of the carbonium ion occurs to give the protonated form of caryophyllene, which then rearranges in some other manner to give neoclovene. Two other points of interest emerge from an examination of the actual rearrangement of carbonium ion (29) to neoclovene, when recourse is made to molecular models or three-dimensional pictorial representation

as shown below.



It can be seen that the bonds which migrate during the rearrangement are cis to each other, as a result of the totally eclipsed conformation at  $C_1$  and  $C_7$ . Therefore, when the  $C_1 - C_4$  bond migrates to the carbonium ion at  $C_{11}$ , this must be followed by the cis migration of the  $C_6 - C_7$  bond, and, since the rearrangement is observed to proceed in a facile manner, this constitutes a very good exception to the trans-antiparallel rule. An alternative explanation, which has been forwarded by Cornforth<sup>44</sup> to explain the stereochemistry of the products obtained in some of his enzymatic reactions, would necessitate solvation of the carbonium ion at  $C_1$  after migration of the  $C_1 - C_4$

bond and then the C<sub>6</sub> - C<sub>7</sub> bond could displace the solvating species in a more usual trans-antiparallel manner. While this second viewpoint may conform more readily with the accepted principles of reaction mechanism, there is very little fundamental difficulty envisaged in having a cis migration, especially when the first group to migrate is quickly removed from the neighbourhood of the carbonium ion as in this case. The second feature demonstrated by the stereochemical formulae is the final configuration of the methyl group at C<sub>11</sub> with respect to the gem-dimethyl grouping at C<sub>3</sub>. This must be syn in the case of synthetic neoclovene from the carbonium ion (29), and, the optical rotation of authentic and synthetic neoclovene being similar, means that authentic neoclovene, as formed in the cyclisation of caryophyllene, must also have the methyl group syn to the gem-dimethyl group. Further evidence in support of this configuration has been obtained from optical rotatory dispersion curves on a degradation product of neoclovene<sup>45</sup>. Thus the one outstanding feature of the neoclovene structure has been accounted for and the mechanism of its formation tested satisfactorily.



EXPERIMENTAL PROCEDURE.

All melting points were recorded on a Kofler block and are corrected ; boiling points are not corrected. The adsorbents used in column chromatography were commercial 'Woelm' alumina, Mallinckrodt silicic acid and 25% silver nitrate on 140-200 mesh silica gel supplied by Applied Science Laboratories Inc.. Thin (0.25 mm.) and thick (1.00 mm.) layer chromatoplates were prepared from Merck's 'Kieselgel G' and were developed with either ceric ammonium sulphate or iodine. Analytical gas chromatography was carried out on a Pye-Argon Chromatogram employing 4'x 4 mm. I.D. packed glass columns, while analytical capillary columns were used with a Perkin Elmer F. 11 gas chromatogram. Preparative gas-liquid chromatographic separations were effected on the Aerograph 'Autoprep' A-700 instrument.

Where necessary, solvents were purified and dried in the recommended manner and reagents were either distilled or recrystallised. Light petroleum refers to the fraction of b.p. 40-60°C and all organic extracts were dried over anhydrous magnesium sulphate unless otherwise stated.

Routine infra-red spectra\* were recorded on a Unicam S.P. 200 instrument and high resolution spectra were obtained using the Unicam S.P. 100 double-beam, infra-red spectrophotometer equipped with an S.P. 130 sodium chloride prism-grating double monochromator operated under vacuum. Ultraviolet absorption spectra were measured

using an automatic Unicam S.P. 800 spectrometer.

Nuclear magnetic resonance spectra<sup>‡</sup> were measured with tetramethylsilane as internal reference as solutions in deuteriochloroform. Benzene was also used during the studies on solvent shifts and the spectra obtained with this solvent are indicated in the text. In those cases in which spin decoupling was performed, a Varian 100 Mc/sec. instrument was employed, while all other spectra were recorded on a Perkin Elmer 60 Mc/sec. spectrometer. Mass spectra were routinely determined on a G.E.C.-A.E.I. M.S. 9 instrument, while volatile mixtures were normally examined by means of the L.K.B. 9000 gas-liquid chromatograph - mass spectrometer.

<sup>‡</sup> Only the major infra-red and NMR absorptions or peaks of diagnostic value are reported in the experimental sections.

EXPERIMENTAL.PURIFICATION OF CARYOPHYLLENE (1).

"Commercial" grade caryophyllene, supplied by Koch-Light, was shown by detailed GIC to contain considerable amounts of phenols (largely eugenol) and humulene (2). The following purification procedure yields greater than 99% pure caryophyllene.

Crude caryophyllene (150 gm.), dissolved in light petroleum (500 ml.), was washed several times with dil. aqueous sodium hydroxide and followed by repeated washings with water until the aqueous layer was neutral. The organic layer was then washed three times with silver nitrate solution (50%) to remove the humulene and finally with water. On drying the petroleum extract and removal of solvent, the residual, colourless oil was adsorbed on alumina (1 Kg., grade II) and eluted with light petroleum. Evaporation of the solvent and distillation afforded pure caryophyllene (1) ;  $n_D^{20} = 1.4986$  ; b.p. = 75-76°/0.14 mm. ;  $\gamma_{\text{max.}}$  (liquid film) = 3070, 1670, 1635, 890, 825 and 815  $\text{cm}^{-1}$

CARYOPHYLLENE EPOXIDE.

A solution of caryophyllene (11.00 gm., 0.054 moles) in chloroform (75 ml.) was charged into a 500 ml. conical flask fitted with a magnetic stirrer, condenser and a dropping funnel. Meta-chloro-perbenzoic acid<sup>29</sup> (11.00 gm., estimated 85% active, hence 0.0542 moles) in chloroform (120 ml.) was added over a 10 minute period keeping the

temperature at 25°C, and left stirring for 12 hours, by which time a white crystalline solid (meta-chlorobenzoic acid) had precipitated out of solution. Any excess peracid was destroyed by the slow addition of a sodium sulphite solution (10%), testing at regular intervals with starch-iodide paper. The chloroform solution was then washed with satd. sodium bicarbonate solution, brine, dried and the chloroform removed yielding an oily semi-solid mass (12.10 gm., 96% crude), distillation of which gave a small forerun of caryophyllene in addition to the desired epoxide (10) (11.00 gm., b.p. = 79-81°/0.1 mm.). Although the epoxide solidified in the receiver during distillation, this was recrystallised from ethanol at low temperature to give white crystals, m.p. 62-63°.

#### CARYOPHYLLENE EPOXY-KETONE (23).

##### a). POTASSIUM PERMANGANATE.

Solid potassium permanganate (10 gm., 0.057 moles) was added in small portions over a period of 48 hours to a stirred solution of caryophyllene epoxide (10) (4.2 gm., 0.019 moles) in acetone (50 ml.) containing water (0.5 ml.). The dark red solution was filtered through Celite 535 to remove the manganese dioxide sludge, and evaporation of the dried filtrate gave a crude red oil, which was dissolved in ether, washed with water, and dried. Removal of the ether gave a thick, yellow oil from which crystalline material was obtained by trituration with light petroleum. Recrystallisation from methanol and thorough drying

gave colourless crystals (1.3 gm., 30%), m.p. 63-64°.

b). OZONOLYSIS.

A stream of ozonised oxygen was passed through a solution of the epoxide (10) (440 mg., 0.002 moles) in ethyl acetate (4.0 ml.) and pyridine (500 mg.), cooled to -80°, until a pale blue colour persisted (ca. 2 hours). The reaction mixture was allowed to reach room temperature very slowly, treated with dil. hydrochloric acid and ether, the ethereal layer being separated, washed with sodium bicarbonate solution, brine, and dried. Evaporation of the ether gave a yellow oil (390 mg.), which was adsorbed on neutral alumina (15 gm., grade II) from petroleum ether (60-80), elution with the same solvent yielding pure epoxy-ketone (23) (280 mg., 63%). N.B. On a larger scale, attempted distillation of the crude products before chromatography resulted in polymerisation to a brown tar, which no longer contained the epoxy-ketone.

c). OSMIUM TETROXIDE / SODIUM META-PERIODATE.

Osmium tetroxide (137.5 mg., 5.4 mmoles) in ether (5 ml.) was added to a stirred solution of caryophyllene epoxide (10) (11 gm., 0.05 moles) in water (50 ml.) and peroxide-free dioxane (150 ml.). After 10 minutes, the black solution was treated with solid sodium meta-periodate (22.47 gm., 0.105 moles) in small portions over 30 minutes and then left stirring at room temperature for 12 hours. To ensure completion of the reaction more osmium tetroxide (69 mg., 2.5 mmoles) and sodium meta-periodate (5.49 gm., 0.026 moles) were

added and stirring was continued for a further period of 20 hours.

Sodium bisulphite solution (50 ml. of satd. solution) was added together with ether (150 ml.), stirred for 1 hour and then thoroughly extracted with ether. The combined extracts were washed with brine, dried and the solvent removed to give a brown semi-solid mass (9.5 gm.) which was adsorbed on neutral alumina (250 gm., grade III) from petroleum ether (60-80). Elution with this solvent gave early fractions (2 gm.) containing the epoxy-ketone (23) contaminated with starting material in addition to the pure epoxy-ketone (23) (6.6 gm., 60%), m.p. 63-64°.

An alternative work-up procedure, at least on small-scale, involving hydrogen sulphide decomposition of the osmate ester was found to give cleaner products.

#### BARTON'S KETOL (35).

The ketol (35) was prepared from caryophyllene epoxy-ketone (23) as described by Barton and Lindsey<sup>2</sup>.

#### ATTEMPTED DEHYDRATION OF BARTON'S KETOL.

##### a). PHOSPHORUS OXYCHLORIDE IN REFLUXING PYRIDINE.

Redistilled phosphorus oxychloride (0.2 ml., 2.18 mmoles) was added to an ice-cold solution of the ketol (35) (100 mg., 0.45 mmoles) in anhydrous pyridine (5 ml.) and heated under reflux for 30 minutes. The cooled reaction mixture was diluted with water, thoroughly extracted with ether and the combined extracts washed with 4  $\bar{N}$

hydrochloric acid and brine, then dried. Removal of the solvent in vacuo yielded a crude, brown oil (95 mg.), which showed at least three spots on TLC with 10% ethyl acetate/light petroleum as developing solvent, but by GLC was seen to contain five compounds. A detailed GC / MS examination of the products confirmed the presence of a mixture of olefins and chloro compounds.

b). PHOSPHORUS OXYCHLORIDE IN PYRIDINE AT ROOM TEMPERATURE.

Redistilled phosphorus oxychloride (0.1 ml., 1.09 mmoles) was added to a solution of the ketol (35) (10 mg., 0.045 mmoles) in anhydrous pyridine, and the flask was set aside at room temperature for 3 days. Identical work-up procedure to that described above yielded a similarly complex mixture of products.

c). THIONYL CHLORIDE IN REFLUXING PYRIDINE.

A solution of the ketol (35) (100 mg., 0.45 mmoles) and thionyl chloride (1 ml., 14.0 mmoles) in anhydrous pyridine (5 ml.) was refluxed under a nitrogen atmosphere for 10 minutes and then poured into ice-water. The same work-up yielded an equally complex mixture of products but in different proportions from a) and b).

d). THIONYL CHLORIDE IN REFLUXING BENZENE.

A cooled, stirred solution (0°C) of the ketol (35) (350 mg., 1.58 mmoles) in anhydrous benzene (12 ml.) was treated with redistilled thionyl chloride (2 ml., 28.0 mmoles) under a nitrogen atmosphere

and refluxing was commenced. Aliquot monitoring by TIC showed that almost all of the starting material had been consumed after 2 hours, but the principal products formed were the corresponding chlorides, which did not seem to undergo dehydrohalogenation.

#### KETO-TOSYLATE (41).

Recrystallised *p*-toluenesulphonyl chloride (476 mg., 0.25 mmoles) was added to a solution of the hydroxy-ketone (35) (500 mg., 2.25 mmoles) in anhydrous pyridine (3 ml.) and the reaction mixture was set aside at 0°C overnight. Ether and water were added and the ethereal layer was washed twice with 0.25  $\bar{N}$  hydrochloric acid, brine, dried and the solvent removed in vacuo at room temperature to give the desired tosylate (41) as a white, crystalline product (760 mg., 90%) which recrystallised from ether/light petroleum as needles, m.p. 144-146° ;  $\gamma_{\max.}$  (nujol mull) = 1690, 1600, 1185 and 1175  $\text{cm}^{-1}$

#### LITHIUM ALUMINIUM HYDRIDE REDUCTION OF KETO-TOSYLATE (41).

A solution of the above keto-tosylate (760 mg., 2.02 mmoles) in anhydrous ether (15 ml.) was heated under reflux with lithium aluminium hydride (152 mg., 4.0 mmoles) for 36 hours. Water was added dropwise to the cooled reaction mixture, until evolution of hydrogen had ceased, then the ethereal layer was filtered and the ether evaporated to give an oil (400 mg.), which was adsorbed on neutral alumina (20 gm., grade III) from light petroleum. The use of



light petroleum as eluting solvent yielded a colourless oil which crystallised on standing to give the ether (42) (320 mg., 86%) and sublimed as fine needles, m.p. 31-32°;  $[\alpha]_D^{25} = -36^\circ$  (c = 1.825);  $\gamma_{\max.}$  (molten film) = 1465, 1445, 1380, 1370, 1030, 1010, 950 and 900  $\text{cm}^{-1}$ ;  $\tau = 5.75$  (multiplet, 1H), 6.05 (multiplet, 1H), 8.8 (singlet, 3H), 9.09 (singlet, 3H) and 9.18 (singlet, 3H). (Found : C, 81.28 ; H, 10.75% ;  $\text{C}_{14}\text{H}_{22}\text{O}$  requires C, 81.50 ; H, 10.75%).

Further elution with 10% ether/light petroleum gave the diol (43) which crystallised from chloroform/light petroleum as small prisms, m.p. 160-161° (50 mg., 12%);  $[\alpha]_D^{25} = -72^\circ$  (c = 0.535);  $\gamma_{\max.}$  (nujol mull) = 3400, 1110, 1070, 1045, 1020 and 990  $\text{cm}^{-1}$ . (Found : C, 74.95 ; H, 10.78% ;  $\text{C}_{14}\text{H}_{24}\text{O}_2$  requires C, 74.91 ; H, 10.93%).

#### HYDROXY-KETAL (44).

##### a). ETHYLENE GLYCOL AS SOLVENT.

Freshly distilled boron trifluoride etherate (2 ml.) was added to a solution of the ketol (35) (100 mg., 0.45 mmoles) in ethylene glycol (20 ml.) and the mixture set aside for 2 days at room temperature. Normal work-up using chloroform and water gave only unreacted starting material.

b). P-TOLUENESULPHONIC ACID AS CATALYST.

A solution of the ketol (80 mg., 0.36 mmoles), ethylene glycol (300mg, 4.84 mmoles) and p-toluenesulphonic acid (50 mg., 0.263 mmoles) in anhydrous benzene (15 ml.) was refluxed under a Soxhlet thimble containing calcium hydride for 16 hours. The cooled reaction mixture was diluted with water and extracted with ether, the combined ethereal extracts being washed repeatedly with brine and dried. Evaporation of solvent furnished a semi-solid oil (65 mg.), which was shown by TIC to contain a considerable amount of starting material in addition to material later identified as the desired hydroxy-ketal (44).

c). P-TOLUENESULPHONIC ACID AND ETHYL ORTHOFORMATE.

A mixture of the ketol (35) (2.04 gm., 9.18 mmoles), ethylene glycol (3 ml., 53.6 mmoles), p-toluenesulphonic acid (150 mg., 0.789 mmoles) and ethyl orthoformate (6 ml.) was heated slowly in an oil bath to 150° and the ethanol and ethyl formate so produced were collected by distillation over a period of 3 hours. The reaction mixture was cooled, poured into sodium bicarbonate solution (100 ml.), extracted with ether (100 ml.), and the ether extract, after brine washing and drying was placed in the rotary evaporator to remove solvent. The residual, yellow oil (2.1 gm.) was adsorbed on basic alumina (80 gm., grade V) from ether and elution with 25% ether/petroleum ether gave the hydroxy-ketal (44) as a crystalline solid

(1.8 gm., 72%), which sublimed as needles, m.p. 100-101° ;

$\gamma_{\max.}$  (nujol mull) = 3400, 1140, 1080, 1030, 1020, 980, 950 and 920  $\text{cm}^{-1}$  ;  $\tau$  = 6.1 (singlet, 4H), 8.9 (singlet, 3H) and 9.2 (singlet, 6H). Molecular weight from mass spectroscopy was 266.

(Found : C, 72.00 ; H, 9.77% ;  $\text{C}_{16}\text{H}_{26}\text{O}_3$  requires

C, 72.14 ; H, 9.84%).

#### KETAL-TOSYLATE (45).

The hydroxy-ketal (44) (30 mg., 0.113 mmoles) and p-toluene-sulphonyl chloride (30 mg., 0.157 mmoles) were dissolved in a minimum of dry pyridine and set aside at 0°C overnight. Normal work-up omitting the mineral acid wash gave a white, crystalline solid (35 mg.) ;  $\gamma_{\max.}$  (nujol mull) = 1600, 1180, 1170, 1080, 960, 940, 920, 880, 860, 820 and 680  $\text{cm}^{-1}$  - diagnostic of the expected ketal-tosylate (45).

Without further purification this product was submitted to lithium aluminium hydride reduction.

#### LITHIUM ALUMINIUM HYDRIDE REDUCTION OF KETAL-TOSYLATE (45).

The solid tosylate (45) (35 mg., 0.083 mmoles) was dissolved in ether and added dropwise to a stirred, ice-cold solution of lithium aluminium hydride (200 mg.) in ether (15 ml.) and heated under reflux for 24 hours. Water was added dropwise to the cooled solution until no more hydrogen was evolved, and the solvent was removed in vacuo

from the filtered solution yielding a semi-solid (22 mg.). By TLC and IR comparison it was shown that the product was the hydroxy-ketal (44). This was confirmed by warming the product with 4  $\bar{N}$  hydrochloric acid for 10 minutes, ether extraction affording crystalline ketol (35) (17 mg., 90%).

CYCLOPROPYL KETONE (46).<sup>⌘</sup>

A solution of the tosylate (41) (300 mg., 0.78 mmoles) in 10% sodium ethoxide in ethanol (12 ml.) was heated under reflux for 1.5 hours, then diluted with water and extracted with ether. The combined organic extracts were washed with water, dried and the solvent removed to give the highly crystalline cyclopropyl ketone (46) (120 mg., 75%), which sublimed as long needles, m.p. 66.5-67° ;  $\gamma_{\max.}(\text{CCl}_4) = 3069, 3016, 2994, 1717, 1033, 1020 \text{ and } 1006 \text{ cm}^{-1}$  ;  $\tau = 7.61$  (triplet,  $J = 7 \text{ c.p.s.}, 1\text{H}$ ), 8.00-8.45 (broad multiplet, 8H), 8.77 (singlet, 3H), 8.85 (singlet, 3H), 9.05 (singlet, 3H) and 9.55 (quartet,  $J = 4 \text{ c.p.s.}, 1\text{H}$ ).

(Found : C, 82.50 ; H, 9.68% ;  $\text{C}_{14}\text{H}_{20}\text{O}$  requires

C, 82.30 ; H, 9.87%).

<sup>⌘</sup> This reaction was originally carried out by Mr. J.R. Stevenson<sup>33</sup>.

HYDROGENATION OF THE CYCLOPROPYL KETONE (46).

a). PtO<sub>2</sub> IN METHANOL AND 10% Pd/C IN ETHYL ACETATE.

The cyclopropyl ketone was recovered unchanged from attempted hydrogenation using either pre-reduced platinum oxide in methanol or 10% palladium/charcoal in ethyl acetate, both being conducted at room temperature and under an atmospheric pressure of hydrogen.

b). 10% Pd/C IN ACETIC ACID.

A solution of the cyclopropyl ketone (46) (200 mg., 0.98 mmoles) in glacial acetic acid (75 ml.) was shaken with 10% palladium/charcoal in the presence of hydrogen. After 10 hours one molar equivalent of hydrogen had been consumed. The filtered solution was diluted with water, neutralised with dil. sodium hydroxide solution and extracted with ether. The combined extracts were washed with water, dried and the solvent removed to give a mobile oil (201 mg., 100%). GLC on 10% Apiezon L at 150° and flow rate of 43 ml./min. showed the material to be a single compound ( $R_t = 18.0$  min., compared to starting material with  $R_t = 22.0$  min.). Small-scale distillation in a sublimation tube gave a colourless oil, shown to be the cyclopentanone (47), block temp. 100-110°/10 mm. Hg ;  $\gamma_{\max.}$  (liquid film) = 2980, 1725, 1460, 1430, 1410, 1380, 1364 and 1275  $\text{cm}^{-1}$

(Found : C, 81.69 ; H, 10.85% ; C<sub>14</sub>H<sub>22</sub>O requires

C, 81.50 ; H, 10.75%).

c). PtO<sub>2</sub> IN ACETIC ACID.

The cyclopropyl ketone (46) (70 mg., 0.343 mmoles) was added to pre-reduced Adams catalyst (50 mg.) in glacial acetic acid (15 ml.) and vigorous shaking under an atmosphere of hydrogen was maintained for 10 hours by which time approximately 2 molar equivalents of hydrogen had been consumed. Normal work-up of the reaction produced a colourless liquid (72 mg.) showing very strong  $\gamma_{\text{O-H}}$  around  $3500 \text{ cm}^{-1}$  in the IR. Examination of the liquid by GIC demonstrated the presence of at least three alcohols ( $R_t$  on 10% Apiezon L at  $150^\circ$  with flow rate of 43 ml./min. = 24.5, 21.0 and 19.3 minutes).

The crude alcohols were dissolved in Analar acetone (5 ml.) and 8  $\bar{N}$  Jones' reagent was added dropwise until a permanent orange supernatant liquid was obtained. Normal ether/water work-up yielded a yellow oil (65 mg., 90% overall) ;  $\gamma_{\text{max.}} = 1725$  and  $1710 \text{ cm}^{-1}$  (shoulder). GIC examination of this oil showed it to contain the ketones (47) and (46) in the ratio of 9:1.

LITHIUM ALUMINIUM HYDRIDE REDUCTION OF THE CYCLOPROPYL KETONE (46).

A solution of the ketone (46) (160 mg., 0.784 mmoles) in anhydrous ether (25 ml.) was treated with an excess of lithium aluminium hydride (100 mg.) and stirred for 24 hours. Normal work-up procedure for hydride reductions gave a colourless oil (153 mg.) ,  $\gamma_{\text{O-H}}$ (liquid film) =  $3500 \text{ cm}^{-1}$ , which was shown by GIC to contain two of the alcohols already obtained by platinum oxide in acetic acid

reduction of the ketone (46), these having  $R_t = 24.5$  and  $21.0$  minutes on 10% Apiezon L at  $150^\circ$  and flow rate of  $43 \text{ ml./min.}$ .

Jones' oxidation of the mixture gave back only the starting ketone (46) as a crystalline solid.

ATTEMPTED MICHAEL REACTION BETWEEN THE KETONE (46) AND THE THIOPHENOLATE ANION.

The cyclopropyl ketone (46) (14.2 mg., 0.07 mmoles) was dissolved in a mixture of ethanol and  $6 \bar{N}$  sodium hydroxide. Thiophenol (45.4 mg., 0.41 mmoles) was added and the solution was left to reflux for 72 hours. TLC and GLC analyses of the product revealed only starting material.

THE OXO-KETAL (53).

a). JONES' OXIDATION.

$8 \bar{N}$  Jones' reagent was added dropwise to a stirred, ice-cold solution of the hydroxy-ketal (44) (18 mg., 0.0676 mmoles) in Analar acetone (5 ml.) until a permanent, orange-coloured solution was obtained. Water was added and the mixture extracted with light petroleum, the extracts being washed with brine, dried and the solvent removed to furnish a colourless oil (17 mg.),  $\gamma_{\text{max.}}$  (liquid film) =  $1720 - 1680 \text{ cm.}^{-1}$ , which also showed less intense ketal absorptions between  $1000$  and  $900 \text{ cm.}^{-1}$  than would be expected. TLC confirmed that partial hydrolysis of the protecting ketal group had occurred, two

distinct spots being evident.

b). SARETT OXIDATION.

The Sarett reagent was prepared by adding chromium trioxide (35 mg.) in small portions with stirring to anhydrous pyridine (1 ml.), and to this was added a solution of hydroxy-ketal (30 mg., 0.1128 mmoles) in anhydrous pyridine (1 ml.). The reaction mixture was allowed to stand at room temperature for 5 hours, then poured into ice-water, extracted with light petroleum, washed with water, brine, dried and the petroleum ether removed under reduced pressure affording a colourless oil (25 mg.). TLC again showed two components, one being the desired oxo-ketal (53) while the second, present in very small amount, was unreacted starting material. The IR spectrum confirmed this analysis showing a strong  $\nu_{C=O}$  (liquid film) at  $1705\text{ cm}^{-1}$ , but also a much smaller  $\nu_{O-H}$  at  $3400\text{ cm}^{-1}$ .

c). SNATZKE OXIDATION.

Chromium trioxide (1.4 gm.) was added with swirling to a solution of hydroxy-ketal (44) (1.0 gm., 3.76 mmoles) in dry dimethyl formamide (50 ml.) and concentrated sulphuric acid (2 drops). The reaction mixture was allowed to stand at room temperature for 20 hours, after which it was poured into ice-water and ether. The ethereal layer was washed repeatedly with brine, dried and the solvent removed, the residual oil (950 mg.) being adsorbed on neutral alumina (40 gm., grade III) from light petroleum/ether. Elution with light



petroleum gave the crystalline oxo-ketal (53) (800 mg., 80%) which sublimed as needles, m.p. 65-66° ;  $\gamma_{\max.}$  (nujol mull) = 1705, 1190, 1135, 1115, 1075, 1020, 990, 960, 938 and 915  $\text{cm}^{-1}$  ;  $\tau$  = 5.92 (singlet, 4 H), 6.8-7.8 (complex multiplet, 4 H), 7.9-8.7 (multiplet, 7H), 8.79 (singlet, 3H), 8.89 (singlet, 3H) and 9.10 (singlet, 3H).

(Found : C, 72.46 ; H, 9.14% ;  $\text{C}_{16}\text{H}_{24}\text{O}_3$  requires C, 72.69 ; H, 9.15%).

#### KETAL (54).

A mixture of metallic sodium (50 mg., 2.188 mmoles) dissolved in redistilled diethylene glycol (2 ml.), oxo-ketal (53) (100 mg., 0.369 mmoles) and hydrazine hydrate (2 ml.) was refluxed for 1 hour and the excess hydrazine hydrate and water formed were then distilled off. After a further period of heating at 200° for 3 hours, water was added to the cooled solution and the reaction mixture extracted thoroughly with ether. The combined extracts were washed with brine, dried and the solvent removed furnishing a yellow oil (65 mg.). TIC showed three main products which were separable on a 1 mm. preparative chromatoplate using 40% ether/light petroleum as solvent. Of the two slow-running compounds, one was shown to be identical to the hydroxy-ketal (44) while the other, exhibiting a similar IR spectrum, is assumed to be the epimeric hydroxy-ketal. The fast-running material, believed to be the ketal (54), was obtained as an oil (9 mg., 9%)

showing no  $\gamma_{C=O}$  or  $\gamma_{O-H}$  but still containing the characteristic ketal absorptions in the IR.

#### TRICYCLIC KETONE (36).

An ethereal solution of the ketal (53) (9 mg., 0.0338 mmoles) was shaken for 30 minutes with 4  $\bar{N}$  hydrochloric acid (10 ml.), then washed with sodium bicarbonate solution, brine, dried and the ether removed. The residual oil (7 mg.) showed  $\gamma_{max.}$  (liquid film) = 2980, 1695, 1470, 1430, 1385, 1370, 1325 and 1290  $cm^{-1}$  and a parent ion of 206 in the mass spectrum. The mass spectral fragmentation pattern was also consistent with the tricyclic ketone (36) showing a large ion corresponding to loss of  $m/e$  55 (i.e.  $O=C-CH=CH_2$ ).

This compound has been shown by GC/MS and IR spectral comparison to be identical to the ketone (36) obtained by pyrolysis (page 71).

#### CARBONATE ESTER (56).

Redistilled ethyl chloroformate (3.5 ml., 0.0368 moles) was added dropwise to a stirred solution of the ketol (35) (4.5 gm., 0.0202 moles) in anhydrous pyridine, the temperature being maintained at approximately  $-10^{\circ}C$  by an ice-salt bath. A vigorous reaction occurred during addition giving rise to a pink solution and a heavy white precipitate of pyridine hydrochloride. The reaction mixture was stirred for a further hour, set aside at  $0^{\circ}C$  overnight, then poured into ether and water. The ethereal layer was washed with dil. mineral

acid, sodium bicarbonate solution and brine, dried and the solvent was evaporated affording a yellow, viscous oil (5.5 gm.), which was chromatographed on neutral alumina (200 gm., grade IV) with 25% ether/light petroleum as eluting solvent. This procedure gave the crystalline, white carbonate ester (56) (4.8 gm., 80%) which recrystallised from light petroleum at low temperature as prisms, m.p. 53-55° ;  $\gamma_{\text{max.}}$  (nujol mull) = 1740, 1695, 1275, 1015, 960 and 800  $\text{cm}^{-1}$ .

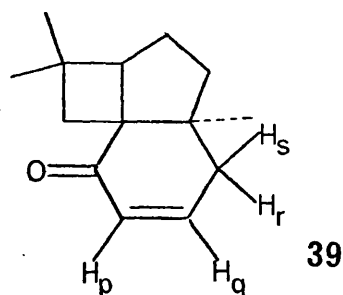
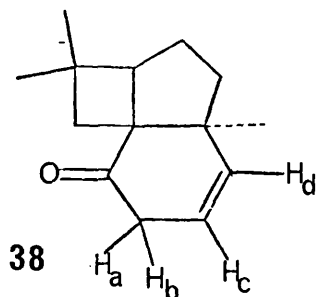
(Found : C, 69.34 ; H, 8.75% ;  $\text{C}_{17}\text{H}_{26}\text{O}_4$  requires  
C, 69.36 ; H, 8.90%).

#### PYROLYSIS OF CARBONATE (56).

The carbonate ester (56) (4.0 gm., 0.0136 moles) was refluxed in a nitrogen atmosphere at 340-350°C for 1 hour. The resultant, yellow oil was examined by TIC and IR spectroscopy, which revealed the presence of starting material and a considerable amount of a ketol identical in  $R_f$  to Barton's ketol (35), in addition to the expected keto-olefins. The oil was fractionally distilled to give an uncontaminated keto-olefin fraction (1 gm., 40%), b.p. 58-60°/0.25 mm., while the higher boiling fractions were combined, treated with ethyl chloroformate and repyrolysed. This procedure afforded pure keto-olefins in an overall yield of 65%. GIC examination of the keto-olefin fraction demonstrated the formation of two compounds ( $R_t$  on 1% S.E. 30 at 75°, flow rate of 60 ml./min. = 11.5 and 16.6 minutes), while GC/MS of these components showed both to have

molecular weights of 204. Unfortunately the complexity of the systems did not allow complete accounts of the fragmentation patterns.

NMR SPECTRA. <sup>⊗</sup>



NON-CONJUGATED ENONE (38).

Proton Irradiated	Effect on			
	H <sub>A</sub>	H <sub>B</sub>	H <sub>C</sub>	H <sub>D</sub>
none	6.85τ, td, J <sub>AB</sub> = 20, J <sub>AC</sub> J <sub>AD</sub> = 3	7.36τ, dd, J <sub>BA</sub> = 20, J <sub>BC</sub> = 3	4.47τ, td, J <sub>CD</sub> = 10, J <sub>CA</sub> J <sub>CB</sub> = 3	4.68τ, dd, J <sub>DC</sub> = 10, J <sub>DA</sub> = 3
H <sub>A</sub> <sup>↑</sup>	---	---	dd, J <sub>CD</sub> = 10 J <sub>CB</sub> = 3	d, J <sub>DC</sub> = 10
H <sub>B</sub> <sup>↑</sup>	---	---	dd, J <sub>CD</sub> = 10 J <sub>CA</sub> = 3	dd, J <sub>DC</sub> = 10 J <sub>DA</sub> = 3
H <sub>A</sub> <sup>↑</sup> and H <sub>B</sub> <sup>↑</sup>	---	---	d, J <sub>CD</sub> = 10	d, J <sub>DC</sub> = 10
H <sub>C</sub> <sup>↑</sup> and H <sub>D</sub> <sup>↑</sup>	d, J <sub>AB</sub> = 20	d, J <sub>BA</sub> = 20	---	---

CONJUGATED ENONE (39).

Proton Irradiated	Effect on			
	H <sub>P</sub>	H <sub>Q</sub>	H <sub>R</sub>	H <sub>S</sub>
none	4.11τ, dd, J <sub>PQ</sub> = 10 J <sub>PR(S)}</sub> = 3.5	3.34τ, m,	cannot be assigned, but centred at approx. 8.4τ.	
H <sub>R</sub> <sup>↑</sup> and H <sub>S</sub> <sup>↑</sup>	d(broad), J <sub>PQ</sub> = 10	d(distorted), J <sub>QP</sub> = 10	---	---

\* In these two tables showing the results of decoupling, the normal abbreviations are used, e.g. t = triplet, dd = doublet of doublet etc.. All coupling constants (J) are in c.p.s., while H<sub>A</sub><sup>↑</sup> means that the spin corresponding to proton A is irradiated.

Separation of the keto-olefins being impossible, the recorded physical data are for a mixture of the two components.  $\gamma_{\max}$ . (liquid film) = 3050, 2980, 1705, 1690 (sh.), 1660, 1450, 1310, 1290, 750 and 730 cm.<sup>-1</sup>

(Found : C, 82.04 ; H, 10.12% ; C<sub>14</sub>H<sub>20</sub>O requires  
C, 82.30 ; H, 9.87%).

TRICYCLIC KETONE (36).

Catalytic reduction of the above olefinic mixture (400 mg., 1.96 mmoles) using 10% palladium/charcoal proceeded with uptake of 48 ml. of hydrogen after 1.5 hours (approx. 1 molar equivalent). The reaction mixture was then filtered through 'Celite 535' and the solvent was evaporated to give a colourless, mobile liquid (402 mg., 99%) which was shown to be identical to the ketone (36) obtained from Wolff-Kishner reduction of the oxo-ketal (53);  $R_t$  on 1% SE 30 at 75°C with flow rate of 60 ml./min. = 24.0 mins;  $\gamma_{\max.}$  (liquid film) = 2980, 1695, 1470, 1430, 1385, 1370, 1325 and 1290  $\text{cm}^{-1}$ ;  $[\alpha]_D^{20} = -42.9^\circ$  ( $c = 0.746$  in  $\text{CHCl}_3$ ); molecular weight from mass spectroscopy = 206.

(Found : C, 81.25 ; H, 10.55% ;  $\text{C}_{14}\text{H}_{22}\text{O}$  requires  
C, 81.50 ; H, 10.75%).

TRICYCLIC TERTIARY ALCOHOL (37).

An ethereal solution of the ketone (36) (400 mg., 1.96 mmoles) was added to a stirred solution of methyl magnesium iodide (prepared from magnesium turnings (280 mg.) and methyl iodide (0.75 ml.)) in anhydrous ether (10 ml.) held at 0°C and under an atmosphere of dry nitrogen. The reaction mixture was then heated under reflux for 2.5 hours and stirred at room temperature for a further period of 48 hours. Ammonium sulphate solution (20%) was added dropwise until no further gas was evolved, and, after normal ether/water work-up,

removal of the solvent gave a red oil (400 mg.) which was adsorbed on neutral alumina (15 gm., grade IV) from ethereal solution. Elution with 25% ether/light petroleum gave material contaminated with starting ketone (80 mg.) in addition to the desired tricyclic tertiary alcohol (37) (210 mg., 47%) as a colourless oil which distilled at 50-52°/0.015 mm. ;  $\gamma_{\max.}$  (liquid film) = 3480, 1465, 1380 and 1085  $\text{cm}^{-1}$  ;  $[\alpha]_{\text{D}}^{20} = -56.5^{\circ}$  (c = 0.443 in  $\text{CHCl}_3$ ) ;  $\tau = 8.65$  (singlet, 1H, exchangeable with  $\text{D}_2\text{O}$ ), 8.80 (singlet, 3H), 8.88 (singlet, 3H) and 9.10 (singlet, 6H).

(Found : C, 80.79 ; H, 11.63% ;  $\text{C}_{15}\text{H}_{26}\text{O}$  requires  
C, 81.02 ; H, 11.79%).

#### NEOCLOVENE (9).

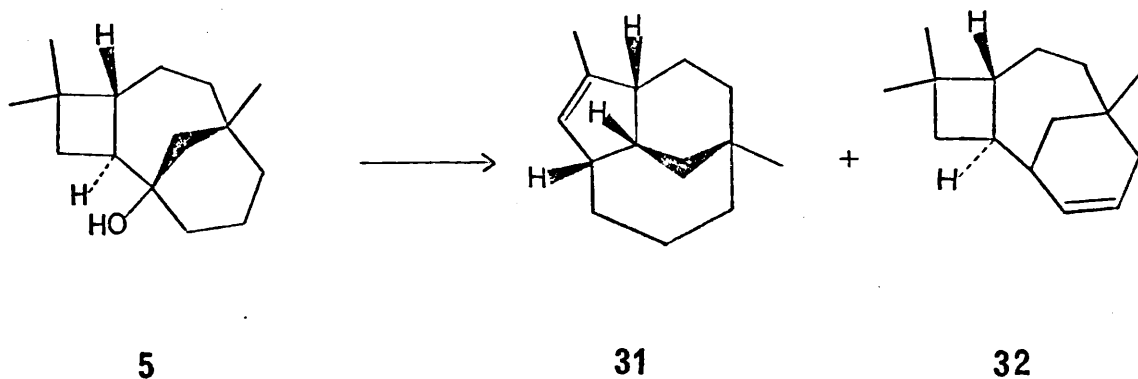
A solution of the tertiary alcohol (37) (95mg., 0.482 mmoles) in anhydrous ether (1 ml.) was added with stirring to a solution of concentrated sulphuric acid (2 ml.) in dry ether (7 ml.) held at 0°C. The reaction mixture was then stirred for 30 mins. at 0°C and 30 mins. at room temperature, diluted with ice-water and slowly neutralised with 4  $\bar{\text{N}}$  sodium hydroxide solution. Thorough extraction with ether and brine-washing of these extracts gave, on drying and removal of solvent, a colourless, mobile liquid (65 mg., 75%). Apart from a small amount of starting material (2%) which was removed by chromatography on neutral alumina with light petroleum elution, the products were entirely hydrocarbon in character. Extensive GLC examination including

50 metre capillary columns showed the product to be 99% pure neoclovene (9), which was identical in every respect to authentic neoclovene, b.p. 58-60°/0.1 mm. ;  $[\alpha]_D^{20} = -69^\circ$  (c, = 0.40 in  $\text{CHCl}_3$ ) ;  $\gamma_{\text{max.}}$  (liquid film) = 3023, 1657, 1383, 1376, 1362, 838, 812, 788 and 771  $\text{cm}^{-1}$  ;  $\tau = 4.91$  (broad multiplet, 1H), 8.80 (singlet, 3H) and 8.99 (singlet, 6H).



CHAPTER 3.THE DEHYDRATION OF CARYOLAN-1-OL.

Caryolan-1-ol is best obtained as a pure, crystalline solid by column chromatography of the products resulting from treatment of caryophyllene with sulphuric acid in ether, and its structure has been established by Robertson<sup>46</sup> from X-ray crystallographic analyses of the isomeric caryolan-1-ol. The chemical behaviour of this tertiary alcohol is not well understood despite various investigations on the reactions of caryolan-1-ol in strong, dehydrating media. The principal product from dehydration has been identified as isoclovene (31)<sup>20</sup>, the structure of which was established from the corresponding hydrochloride by a further application of the "heavy atom" method<sup>47</sup> in X-ray crystallography. Lutz and Reid<sup>23</sup> separated another olefin which they entitled pseudoclovene from this reaction and have suggested the structure (32) on rather tenuous evidence.

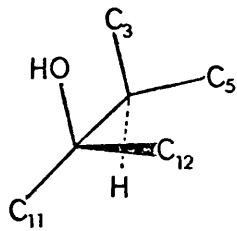
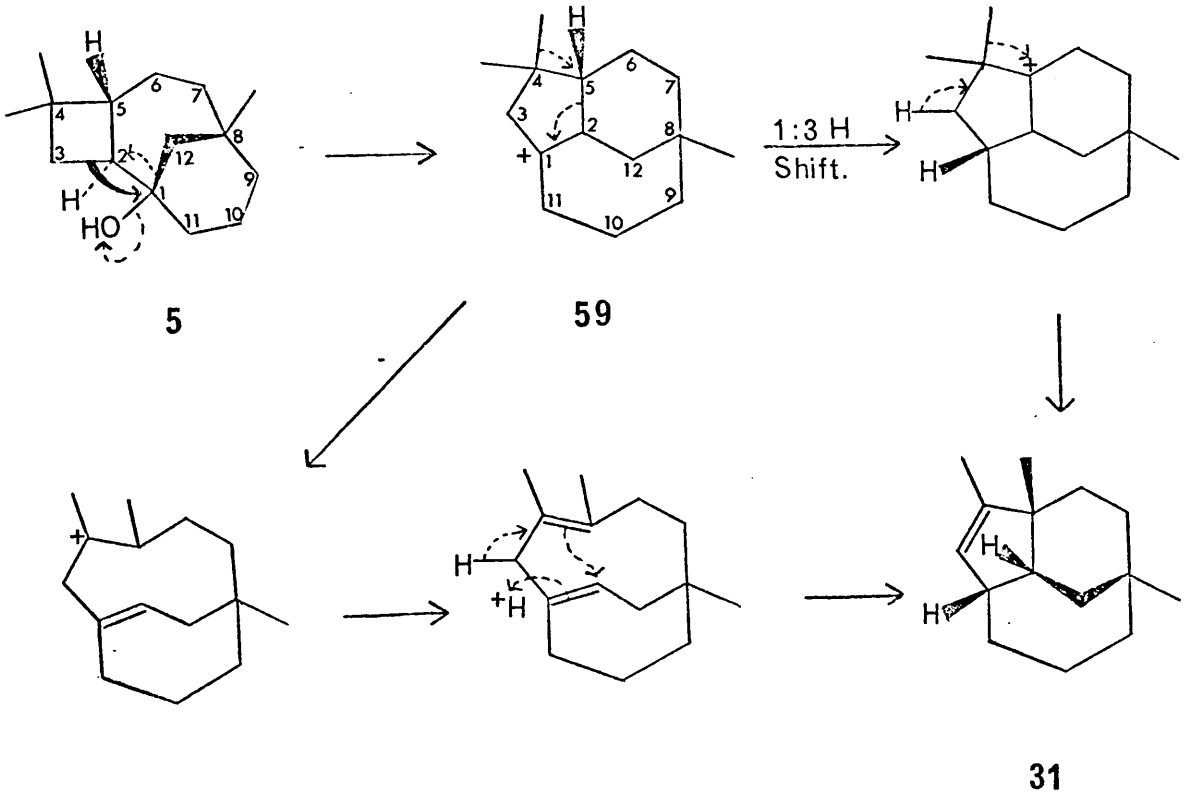


Any discussion of caryolan-1-ol chemistry demands an appreciation of the expected reactivity at bridgehead positions in bicyclo compounds, while particular consideration should be given to the unique features imposed on the bicyclo (4,3,1) decane system by the presence of a trans-fused, four-membered ring. A summary of the factors influencing the "stability" and reactivity of bridgehead carbonium ions may be found in the excellent review by Schleyer and Fort<sup>48</sup> entitled "Bridgehead Reactivity". Since substitution at the bridgehead position in the bicyclo (2,2,1) system was found to be exceedingly difficult, Bartlett<sup>49</sup> proposed that the desired bridgehead cations must be unstable. It is now realised that the most important factors in this resistance to reaction are the inability of solvent to assist in ionisation by backside solvation of the developing cation and the difficulty experienced by the cation while trying to attain its most favourable, planar configuration. From the available kinetic data it is apparent that, as the ring sizes increase, substitution becomes more facile, reflecting the easier attainment of near-planarity. No rate data are available for bicyclo (4,3,1) decane systems, but it can be predicted that carbonium ion formation should be moderately fast. Examples such as acetolysis and formolysis of caryolanyl chloride<sup>50</sup> would tend to justify this assumption.

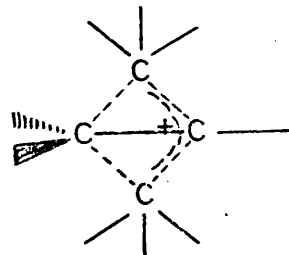
Bartlett's statement that bridgehead carbonium ions are unstable<sup>49</sup> is extremely misleading, stability being a relative term. What is really implied by Bartlett and later investigators is that

the carbonium ion is not easily formed at the bridgehead in small ring bicyclo compounds, but this does not mean that, if generated in a suitable reaction medium, i.e. with no convenient nucleophile present, the carbonium ion need not be a reasonably stable species. If produced under these circumstances prohibiting substitution, the carbonium ion undergoes rearrangement leading to a more energetically favourable carbonium ion, which may lose a proton to form an olefin, then one can fairly describe that cation initially formed as unstable. One might expect this to be the case in caryolan-1-ol, where the carbonium ion formed is adjacent to the highly strained, trans-fused, four-membered ring, opening of which would relieve some strain and may lead to a system suitable for deprotonation. In effect, the caryolanyl skeleton exhibits a rather complicated cyclobutylcarbinyll system, simple examples of which are known to rearrange to cyclopentyl carbonium ions<sup>51</sup>. Such analogous rearrangements do not seem to be observed during the acetolysis of caryolanyl chloride, and only dehydration of caryolan-1-ol with fierce reagents like phosphorus pentoxide seem to produce any rearranged material. A detailed examination of the Wagner-Meerwein shifts available to the caryolanyl cation produces some explanation for the apparent reluctance of the species to undergo molecular rearrangement. Since isoclovene (31) is the only rearrangement product of established structure, the following discussion will be centred on examining the possible mechanistic pathways leading to this olefin.

Fig 3.



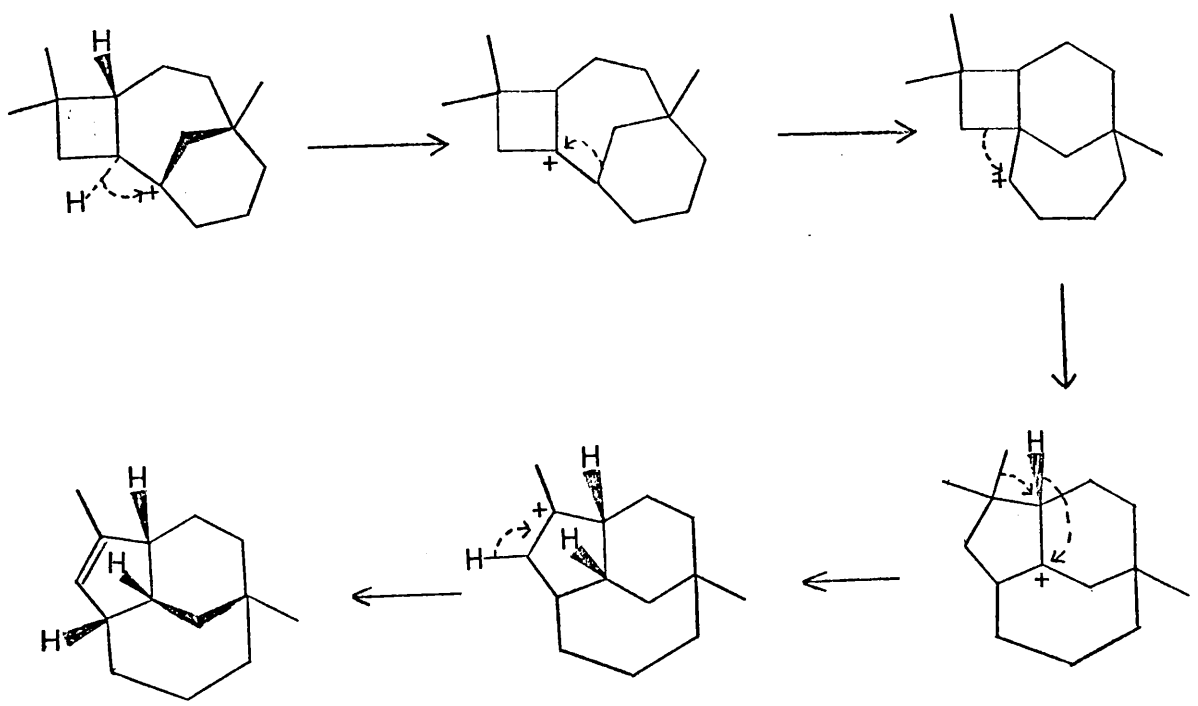
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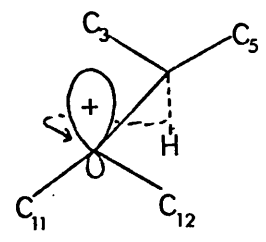
58

Barton<sup>21</sup> has postulated the two schemes shown in Fig. 3, but the initial steps in this proposal are open to criticism. The first feature apparent from an examination of molecular models is that the groups around C<sub>1</sub> and C<sub>2</sub> are in an almost totally eclipsed conformation, as shown in (57), and are held rigidly so by the four-membered ring, which limits the conformational mobility of the bicyclo (4,3,1) system. Formally the C<sub>2</sub> - C<sub>3</sub> bond is best aligned to migrate to the carbonium ion developing at C<sub>1</sub> in a cis manner, as is suggested in Barton's mechanism ; but this is impossible, since it would give rise to a trans bridged bicyclo (4,2,1) intermediate, in which the hydrogen atom attached to C<sub>5</sub> is almost touching one of the bridge hydrogens on C<sub>12</sub>. Such a strained species is hardly acceptable! One may argue that, as soon as the C<sub>2</sub>-C<sub>3</sub> bond ruptures and begins to migrate, the C<sub>1</sub> - C<sub>12</sub> bond also breaks and proceeds to move to C<sub>2</sub> simultaneously with the C<sub>3</sub> migration to C<sub>1</sub>. Such an interchange reaction obviates the formation of a trans bridged system, inversion taking place at C<sub>2</sub>. Whether or not a transition state like the one described and drawn in (58) is feasible, does not materially alter the scepticism with which Barton's mechanism is viewed. The hypothetical ion formed as a result of these migrations would be (59), in which the stereochemistry of the hydrogen at C<sub>2</sub> must be  $\alpha$ , and if one attempts to make a model of this ion with an  $\alpha$ -hydrogen atom, it is found to be impossible without causing grievous harm to the models. The structure would be perfectly acceptable with the hydrogen  $\beta$  at C<sub>2</sub>. Finally the structure of

Fig 4 .



60



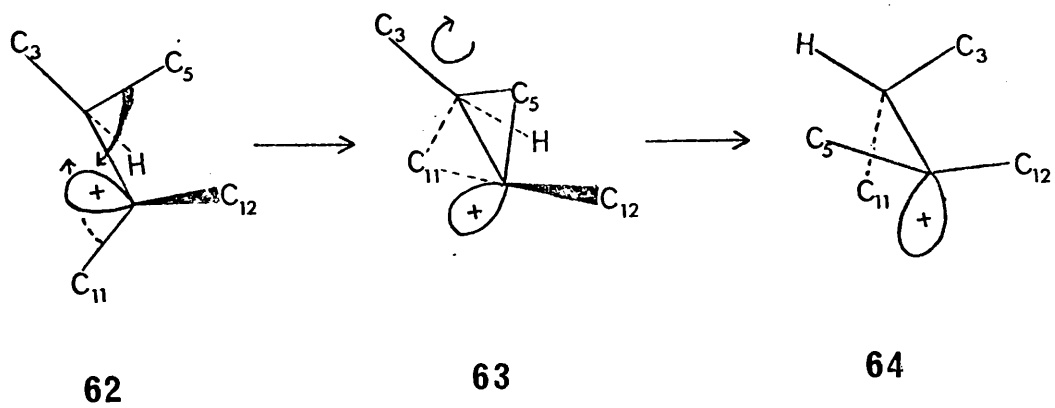
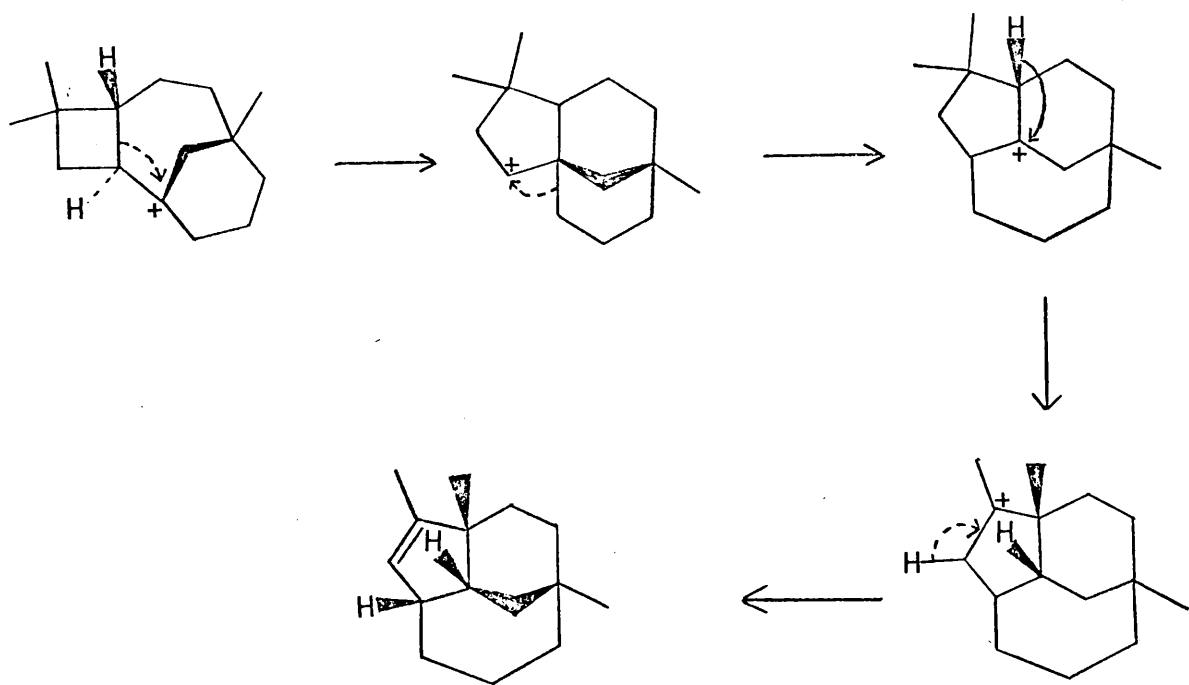
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isoclovene (31) necessitates a  $\beta$ -hydrogen at  $C_2$ , so that this interchange mechanism, were it reasonable, would predict the wrong stereochemistry for isoclovene.

A second formal mechanism may be drawn which proceeds with migration of the hydrogen atom from  $C_2$  to  $C_1$ , and is followed by interchange of the same bonds as before. This pathway is depicted in Fig. 4. Simple examination of this two dimensional representation produces two points against such a mechanism. An initial hydride migration, which creates a cyclobutyl carbonium ion, is not an energetically favourable process in the light of Brown's I-strain theory<sup>52</sup>; but rather one might expect opening of the four-membered ring with concomitant release of some strain energy to be the first step. In addition, another energetically unfavourable step is postulated in which a tertiary cation rearranges to a secondary cation. While such arguments are justifiable, it would be fallacious to dismiss this alternate mechanism without further scrutiny, since the reaction conditions are vigorous and minor energetic obstacles may be surmountable.

From the conformation of the caryolanyl cation, the most favourable migration of the hydride would occur to the backside of the  $C_1$  carbonium ion, but this would lead to another trans bicyclo (4,3,1) arrangement as a consequence of the inversion. Again the interchange reaction may be invoked, in which two centres invert simultaneously, to circumvent this difficulty, but in this case the

Fig 5.





two migrating groups i.e. H and C<sub>12</sub> are not aligned in trans-anti-parallel fashion making such a reorganisation less credible. In any case the ion formed (60) would have an  $\alpha$ -hydrogen at C<sub>1</sub>, and would again lead to the wrong stereochemistry for isoclovene. Another "possibility" would be for the hydride migration not to occur to the backside of C<sub>1</sub>, thereby avoiding inversion and the subsequent trans bridging. This would lead to isoclovene with the correct stereochemistry, but can it be accepted that during a migration a group can rotate through approximately 150° as is shown in (61) ?

The third migration, which can be introduced in a formal mechanism leading to isoclovene, involves opening of the C<sub>2</sub> - C<sub>5</sub> bond, and is illustrated in Fig. 5. The initial migration produces a secondary carbonium ion, but, since the cyclobutane ring is expanded, this may be justifiable. Unfortunately complete migration of C<sub>5</sub> to C<sub>1</sub> cannot be allowed as this would produce a trans bicyclo (3,3,1) intermediate. If this migration is accompanied by migration of C<sub>11</sub> to C<sub>2</sub>, the only way in which the correct stereochemistry could be obtained would necessitate an unlikely rotation around the C<sub>1</sub> - C<sub>2</sub> bond during the migrations. This is shown in the partial formulae (62), (63) and (64). An alternative would be for C<sub>5</sub> to migrate to the backside of C<sub>1</sub> but this would require the migrating group to move through approximately 100°, since it is far from trans antiparallel to the carbonium ion. The same problem of trans bridging is encountered, unless both groups migrate simultaneously,

10% A.P.L.; 150°; 50 ml/min.

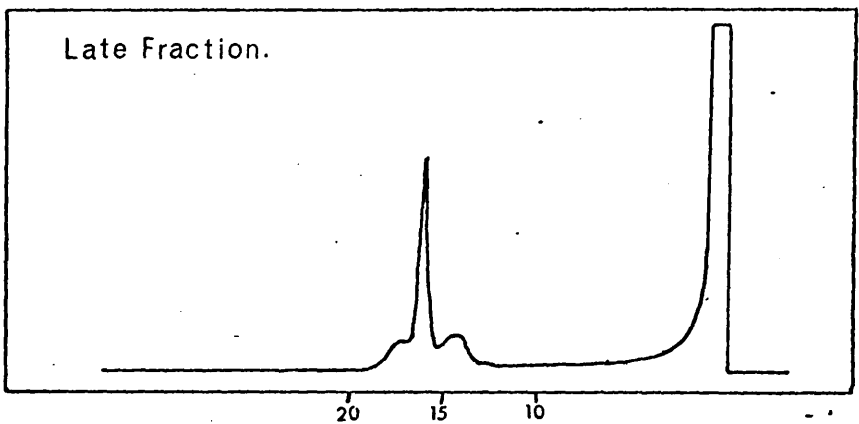
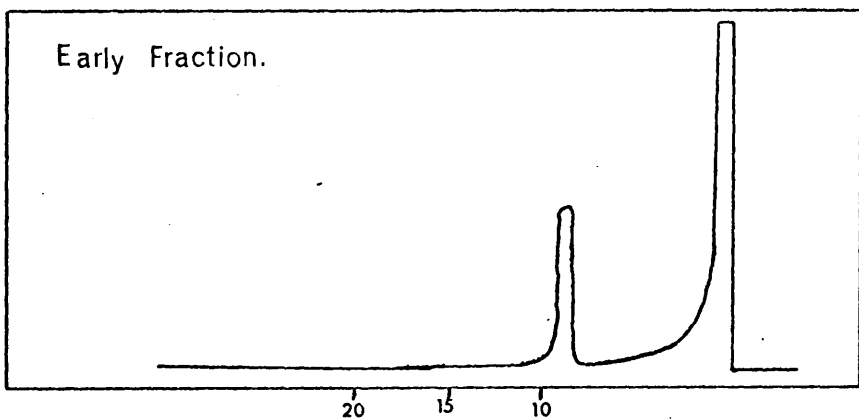
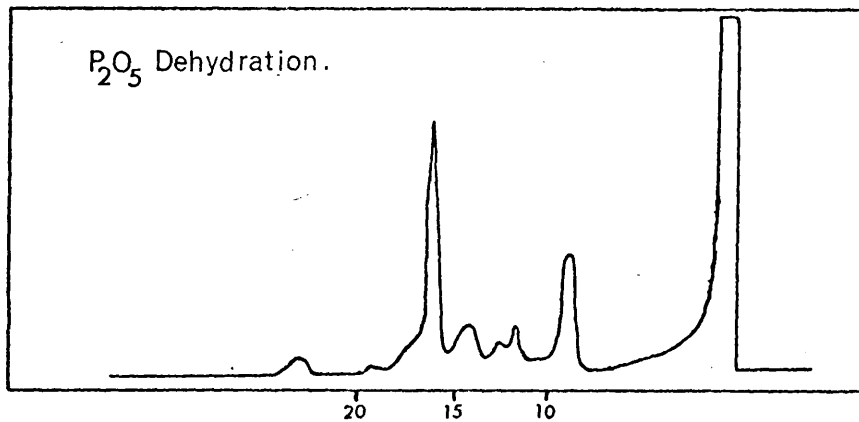


Fig. 6

and to obtain isoclovene with the correct stereochemistry, conformational flipping is required in the transition state.

This consideration of the Wagner-Meerwein migrations available to the caryolanyl cation, while not exhaustive in that 1,3 shifts are neglected, shows that formal "arrow-pushing" does not produce mechanistic pathways, which stand up to closer examination. Yet vigorous dehydration does produce isoclovene and other rearranged products by some mechanism. A more thorough investigation of the dehydration products has been initiated in the hope that some light may be cast on this mechanistic brain-teaser.

Caryolan-1-ol was dehydrated by addition of solid phosphorus pentoxide to the molten alcohol at 120°C in the manner described by Henderson, McCrone and Robertson<sup>19</sup>. A very high yield of crude hydrocarbons was obtained as a yellow oil, which, on fractional distillation through a spinning band column, gave a series of colourless liquid distillates. The earlier fractions corresponded in boiling point to pseudoclovene as obtained by Lutz and Reid<sup>23</sup>, while the late fractions were assumed to be largely isoclovene. Examination of the crude reaction mixture by GIC showed the presence of at least ten compounds, but the main products were seen to be the most and almost the least volatile components. By extremely careful distillation, samples were obtained which corresponded to greater than 90% pseudoclovene and isoclovene. Typical GIC traces of the crude mixture and of the separation obtained by distillation are shown in Fig. 6.

10% A.P.L.; 150°; 50 ml/min.

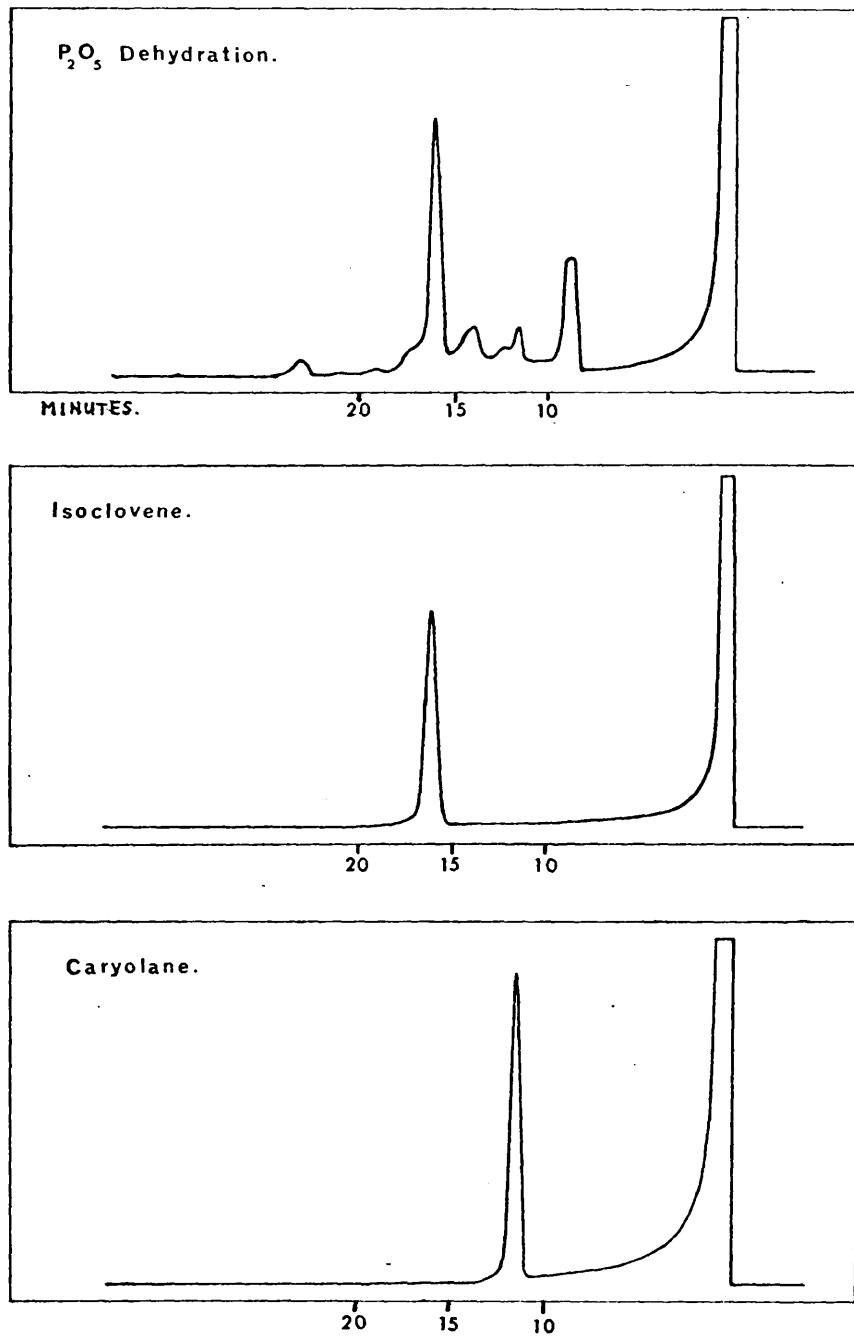


Fig. 7

On examining the experimental procedure employed to obtain a sample of isoclovene hydrochloride for X-ray crystallography, it was noted that the halide derivative could only be obtained in yields of less than 25% from late distillation fractions of the crude dehydration mixture. With GLC now available, it seemed worthwhile checking this work to ensure the correct assignment of isoclovene among the numerous products. A sample of isoclovene hydrochloride was prepared as described by Money<sup>53</sup> and purified by recrystallisation from ethyl acetate. Dehydrochlorination was effected by treatment with fused sodium acetate in refluxing acetic acid and comparison of this product with the crude dehydration products demonstrated the correctness of our assignment of isoclovene as the major product from phosphorus pentoxide treatment of caryolan-1-ol. Fig. 7 shows the purity of the isoclovene obtained in this way and correlates its retention time with that of the crude dehydration products.

Attention was now directed towards the broad peak in the GLC which was assumed to be pseudoclovene. The best material obtained from distillation was examined by IR and NMR spectroscopy, but the spectra were so complex as to be beyond first-order interpretation. From these spectra, however, it was quite apparent that the structure (32), suggested by Lutz and Reid for pseudoclovene, was unacceptable. The results of catalytic hydrogenation of pseudoclovene were also inconsistent with the structure postulated by Lutz and Reid, since two products were obtained, neither of which were

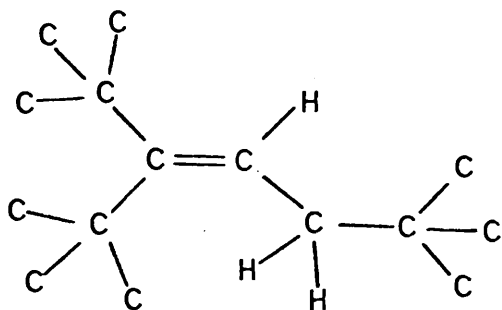
caryolane, the saturated analogue of (32). These reduction products were examined by GLC and GC/MS, which showed that one compound of different retention time from pseudoclovene had a molecular weight of 206, while the second product had a molecular weight of 204 and almost the same retention time as pseudoclovene. Since further attempts to force this reduction to completion, including the use of high pressure and elevated temperature, were totally unsuccessful, it was deduced that the material previously called pseudoclovene was really a mixture of two olefins, one of which was resistant to catalytic hydrogenation. Such an interpretation was consistent with the broad, "squared-off" appearance of the peak in GLC, and also with the complexity of the NMR and IR spectra.

The principal problem to be overcome at this stage was one of separation, both at the analytical and the preparative level. Many columns employing various stationary phases and differing sets of conditions were tested in attempts to find a suitable analytical method of separation by GLC. Apart from 50 metre capillary columns, the only phase which showed a marked resolution of the components was 1,2,3-tris(2-cyanoethoxy) propane, but at best a base line separation was never achieved. This difficult mixture was dispatched to the Varian-Aerograph Laboratories in Basel in the hope that their wider experience and range of column packings might produce a better stationary phase for this particular problem. Despite their efforts they were unable to improve on the separation obtainable with

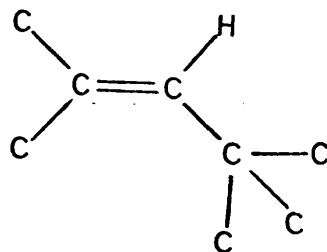
1,2,3-tris(2-cyanoethoxy) propane.

Apart from the mass spectra obtained by GC/MS, which were of little use in the elucidation of the structures of the two pseudoclovenes, no physical data could be collected for these compounds without separation of the components. Preparative GIC appeared to be the only method powerful enough to effect such a separation, hence a 20 foot stainless steel column was packed with 25% 1,2,3-tris(2-cyanoethoxy) propane for use with the Aerograph 700 Autoprep. After a considerable amount of "trial and error" experimentation, 30 milligrams of pseudoclovene A and pseudoclovene B were collected. Pseudoclovene B is that component which is eluted first from the Apiezon L analytical GIC column, while pseudoclovene A runs second on the same column. The order of elution on 1,2,3-tris(2-cyanoethoxy) propane is reversed.

The samples obtained were examined by NMR and IR spectroscopy, the two resulting spectra (NMR) being shown in Fig. 8. From these spectra partial formulae can be drawn for the two compounds, as shown by (65) for pseudoclovene A and (66) for pseudoclovene B.

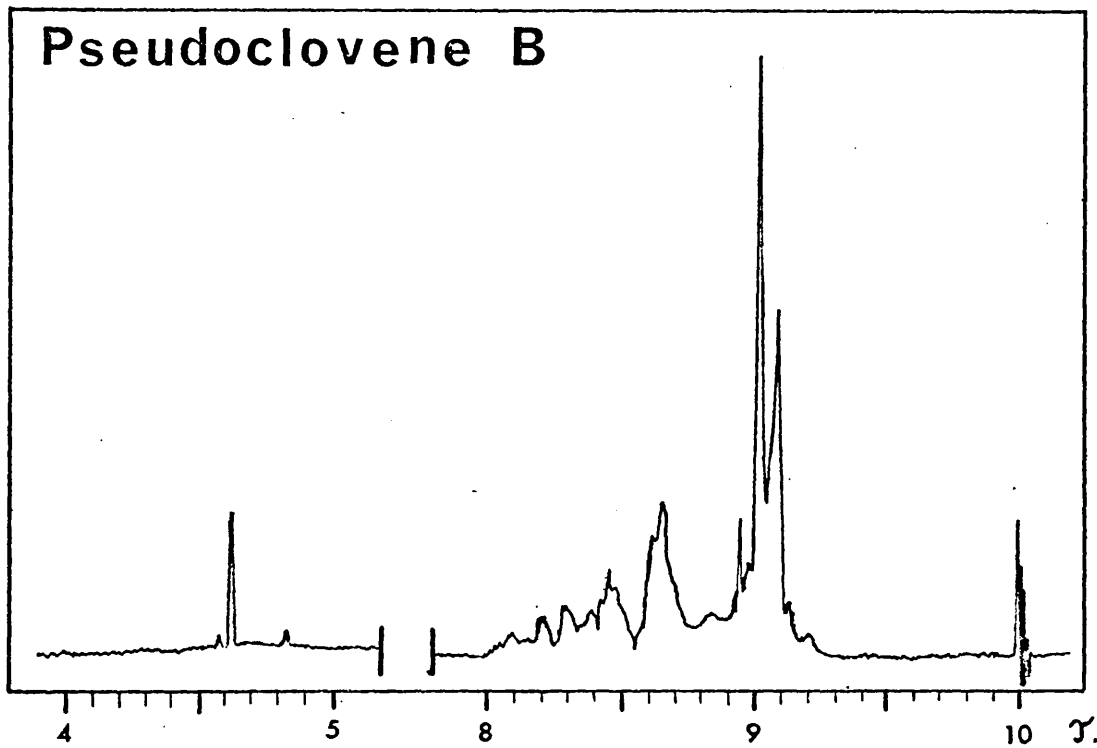
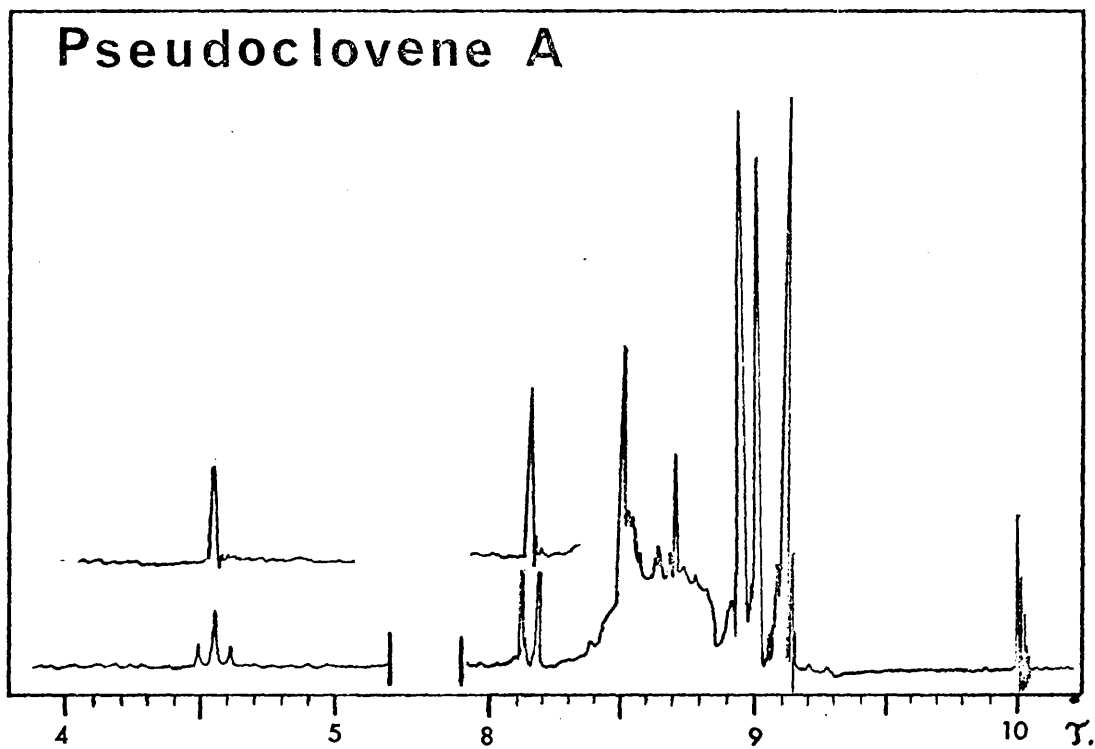


65



66

Fig 8.





In pseudoclovene A the vinylic proton absorbs at  $4.57\tau$  as a triplet with  $J = 4$  c.p.s., being coupled with the allylic methylene group which appears as a doublet with the same coupling constant at  $8.15\tau$ . Spin decoupling confirms these assignments since irradiation at  $8.15\tau$  produces a sharp singlet at  $4.57\tau$ , while a singlet at  $8.15\tau$  is produced on irradiation at the centre of the triplet. Since integration of the area from  $8.00 - 8.30\tau$  shows the presence of only two hydrogens, it is probably fair to assume that there are no further allylic protons. The three absorptions corresponding to the methyl groups in pseudoclovene A are all distinct, appearing as singlets at  $8.93$ ,  $9.00$  and  $9.11\tau$ . Very little else can be deduced from the NMR spectrum since the methylene region appears as a broad "mush", integrating for 12 protons, between  $8.3$  and  $8.9\tau$ .

Pseudoclovene B was even less amenable to NMR analysis, since, apart from a singlet at  $4.62\tau$  (1H) and singlets at  $9.04\tau$  (6H) and  $9.09\tau$  (3H), there were no other outstanding features. Integration of the area between  $8.0$  and  $8.3\tau$  in this case gave a value of approximately 1.8 protons but the multiplicity of the absorptions in this region was so complex as to prevent any rationalisation concerning the environment of the allylic protons. To complicate matters, the sample contained a small amount ( $< 5\%$ ) of some hydrocarbon impurity, which could only be detected by capillary GLC. At no time has it been possible to prepare a sample of pseudoclovene B completely free of this contaminant. The fact that the three methyl groups in this case were

not distinct in chemical shift at first appeared interesting, but it was realised that very little could be read into this, since two of the methyl groups may very well show accidental magnetic equivalence.

The infra-red spectra of the pseudoclovenes were even less helpful from the point of view of structure assignment, since both showed a plethora of sharp absorptions even in the normally diagnostic region below  $1000\text{ cm}^{-1}$ . Pseudoclovene A did exhibit a pair of bands at  $823$  and  $807\text{ cm}^{-1}$  typical of the out-of-plane C-H deformations in a cyclic, trisubstituted olefin<sup>54</sup>, but in pseudoclovene B the strongest absorptions in this region were at  $765$  and  $750\text{ cm}^{-1}$ . The NMR spectrum of pseudoclovene B is most emphatic in favour of a trisubstituted alkene, while the IR spectrum is inconsistent with this mode of substitution. Another tricyclic sesquiterpene, copaene, has been reported to have a  $\delta_{\text{C-H}}$  value of  $785\text{ cm}^{-1}$  for a trisubstituted double bond<sup>55</sup>, this being accounted for by the highly strained nature of the olefin. If these absorptions at  $765$  and  $750\text{ cm}^{-1}$  genuinely arise from out-of-plane deformations in pseudoclovene B, then to the best of our knowledge, this constitutes the lowest reported value for a trisubstituted double bond.

Although enough material could be obtained by preparative GLC for a spectroscopic examination of the pseudoclovenes, the difficulties involved and the time spent on obtaining these samples precluded its extension to the preparation of suitable amounts for classical degradation. Several possible approaches might have been adopted at

this stage. If some method of conducting the dehydration of caryolan-1-ol could be found such that the resulting mixture was vastly simplified, then the separation problems would be accordingly easier. Various reagents and the alteration of reaction conditions were tried with this view in end, but, while this work provided some extremely interesting results which will be discussed in detail at a later stage, no method could be found which produced a simplified mixture of the pseudoclovenes.

Alternatively it was necessary to find some more efficient method of separating the pseudoclovenes. Corey had developed a technique for preparing crystalline derivatives of an olefin<sup>56</sup> and it was felt that these derivatives obtained from the pseudoclovenes might be more readily separated than the olefins themselves. The method involved making the cis diol of the olefin, which could then be converted to the crystalline thionocarbonate. If there was more steric hindrance on one side of both pseudoclovenes than on the other, then two cis diols would be expected from osmylation of the alkenes, while if neither side is particularly blocked then four diols should result. In the event, chromatography and spectroscopic examination of the products showed that all the pseudoclovene B had been converted to a single diol, whereas pseudoclovene A remained unchanged. There were small amounts of other diols formed but these constituted a negligible percentage of the total products.

By means of this selective osmylation procedure a fairly pure sample of pseudoclovene A and the diol from pseudoclovene B could be

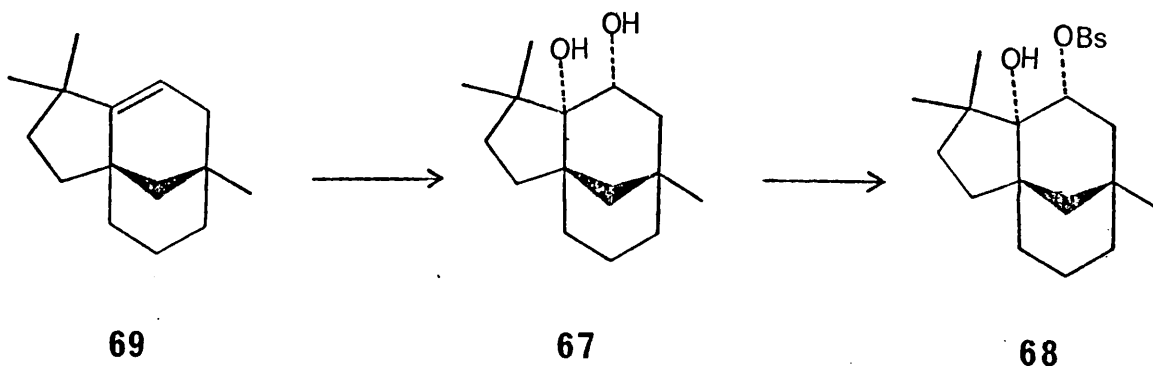
obtained. However this experiment held the clue to an even simpler separation technique. From the resistance shown by pseudoclovene A to osmylation and hydrogenation, it was reasoned that the double bond in this olefin must be hindered, while pseudoclovene B possessed an ethylenic linkage of normal reactivity. Hence silver nitrate should complex fairly effectively with pseudoclovene B, but weakly with pseudoclovene A. Chromatography on 25% silver nitrate with silica gel<sup>57</sup> confirmed this reasoning, since pseudoclovene A was eluted immediately with light petroleum while the isomer, pseudoclovene B, required the use of 10% ether/light petroleum as eluting solvent. The combination of careful distillation to separate the pseudoclovenes from the other dehydration products and silver nitrate/silica gel column chromatography proved the most convenient method of achieving pure pseudoclovene A and almost pure pseudoclovene B (The pseudoclovene B produced in this way still contained a small percentage of the impurity first noted in the NMR spectrum).

A classical degradation of  $C_{15}H_{24}$  molecules containing only one double bond presents considerable difficulties owing to the lack of functionality in the molecule. This is especially true in the pseudoclovenes where an enormous variety of tricyclic ring systems are formally possible and the double bonds are surrounded by a large number of tertiary centres. For these reasons the method of choice in their structure determination was X-ray crystallography, which has the added advantages of being unambiguous and provides detailed information

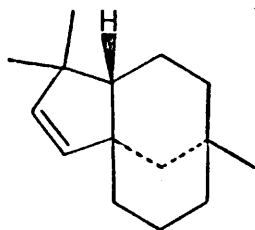
on stereochemistry, bond distances and angles etc.. A considerable amount of time was spent trying to prepare suitable heavy atom derivatives amenable to this technique.

Although osmylation of pseudoclovene A was extremely slow, treatment of the olefin with excess osmium tetroxide in ether and pyridine for seven days did yield partial conversion to the cis diol derivative, which was a poorly crystalline solid. The secondary-tertiary diol (67) could be readily converted in high yield into the corresponding mono-p-bromobenzenesulphonate ester with p-bromobenzenesulphonyl chloride in pyridine. This material was recrystallised from ether/light petroleum as needles, m.p. 94-95°C. From preliminary X-ray photographs these were found to belong to the space group  $P2_1$ , and gave well-defined reflections making them suitable for a detailed analysis. This work, conducted in association with Dr. G. Ferguson and Mr. D. Hawley, is described in Chapter 4 of this section of the thesis.

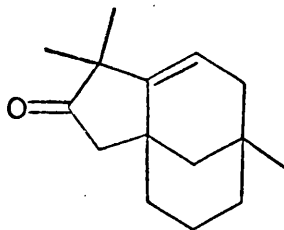
The X-ray analysis showed the brosylate to have the structure (68) which in turn assigned to pseudoclovene A the molecular structure (69).



In fact, the structure (69) had been postulated for pseudoclovene A on purely chemical grounds. During work on the synthesis of clovene (4) in these laboratories, Doyle<sup>58</sup> had synthesised the molecule (70), the intention being to hydrogenate the double bond and elaborate the carbonyl group to give clovene. However it was found that all attempts to catalytically reduce this ethylenic group failed completely, even under forcing conditions. Such behaviour had a striking resemblance to the difficulties encountered during the attempts to hydrogenate pseudoclovene A, and, while hardly conclusive evidence of structure, it was a very close analogy.



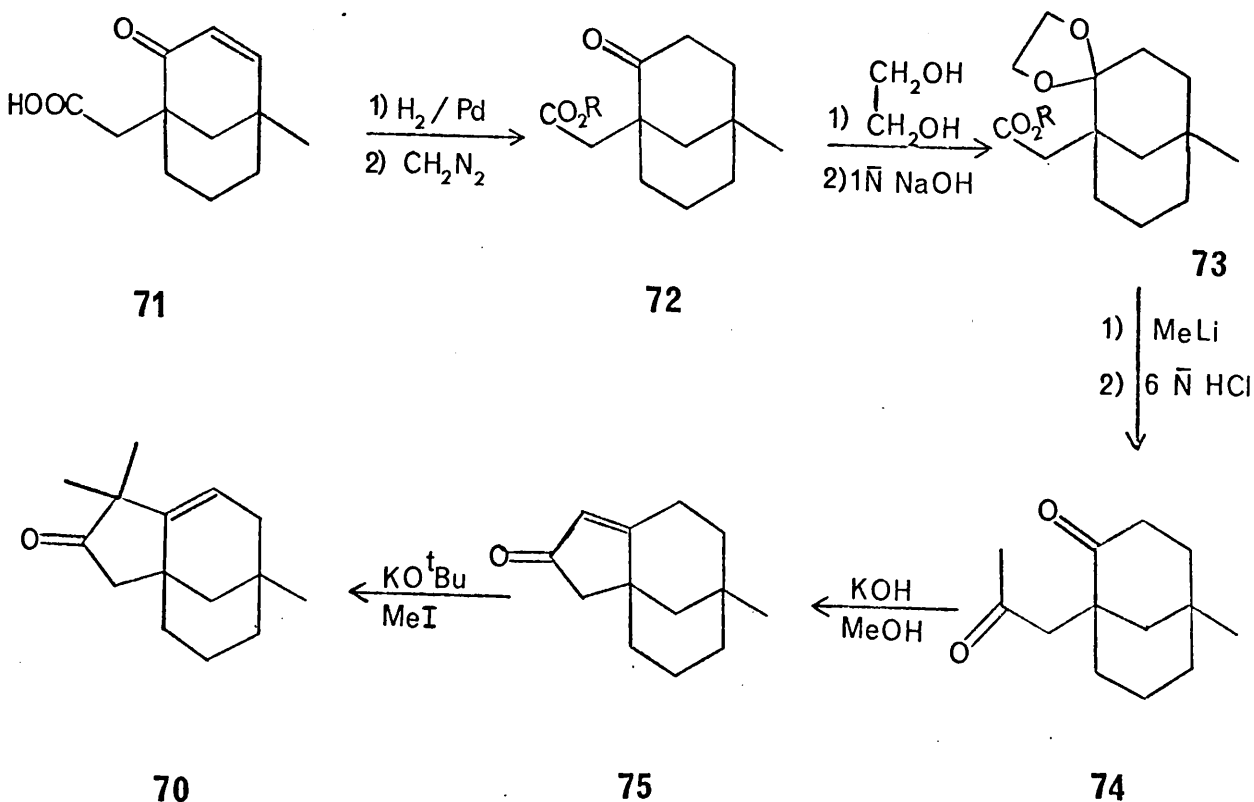
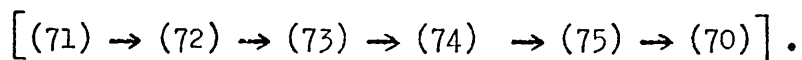
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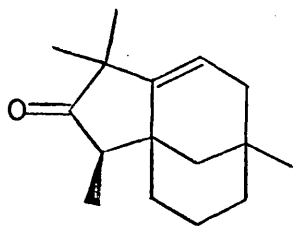
On receiving confirmation of our suspicions from the X-ray analysis, a simple synthesis of pseudoclovene A was suggested. Merely reduction of the carbonyl group in (70) to the corresponding hydrocarbon should yield racemic pseudoclovene A. Unfortunately only one milligram of the enone (70) was available and, since it had been prepared several years earlier, it was now of questionable purity. However, there was available

several grams of a precursor (71) which was used to prepare the desired enone (70) as described by Doyle<sup>58</sup> and indicated in the formulae

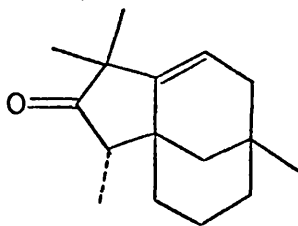


The only step which was found to present any difficulty was the methylation of the conjugated enone (75), which, according to Doyle, proceeded to give only the gem-dimethyl compound even with excess methyl iodide. In fact this was not the case, since four products resulted viz. one disubstituted enone (70), two trisubstituted

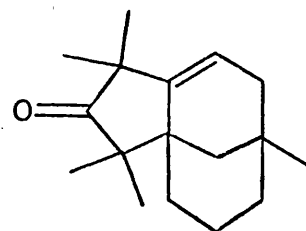
enones assumed to be (76) and (77) and one product in which four methyl groups had been inserted which is taken to be (78). Evidence for these products comes primarily from the results of GC/MS, so it is not too surprising that no mention is made of the other products by the earlier investigator. That Doyle obtained the same mixture of compounds is shown by the fact that a GC/MS comparison of a sample obtained from him was identical to the mixture obtained in this work. Fortunately the components were separable by careful column chromatography and so the synthesis was in no way hindered.



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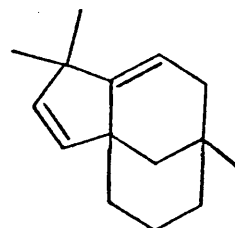


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Wolff-Kishner reduction of the enone (70) proceeded smoothly furnishing a colourless oil, which was identical in every respect except optical rotation with authentic pseudoclovene A. Another method, by which it was hoped to remove the carbonyl group in (70) was the reaction described by Caglioti<sup>59</sup>. If a tosylhydrazone is treated with lithium aluminium hydride, it is converted in good yield to the corresponding methylenic compound, but, when applied to the tosyl-



hydrazone from (70), a diene was the sole product. This compound is presumed to have the structure (79) and would be the expected product from the Bamford-Stevens<sup>60</sup> reaction in which base treatment of a tosylhydrazone leads to an olefin. Other workers have observed the formation of olefins during the Caglioti reaction and the mechanism for this decomposition is under investigation<sup>61</sup>. Catalytic hydrogenation, which was known to leave the highly hindered trisubstituted double bond unaffected, gave pseudoclovene A as expected.



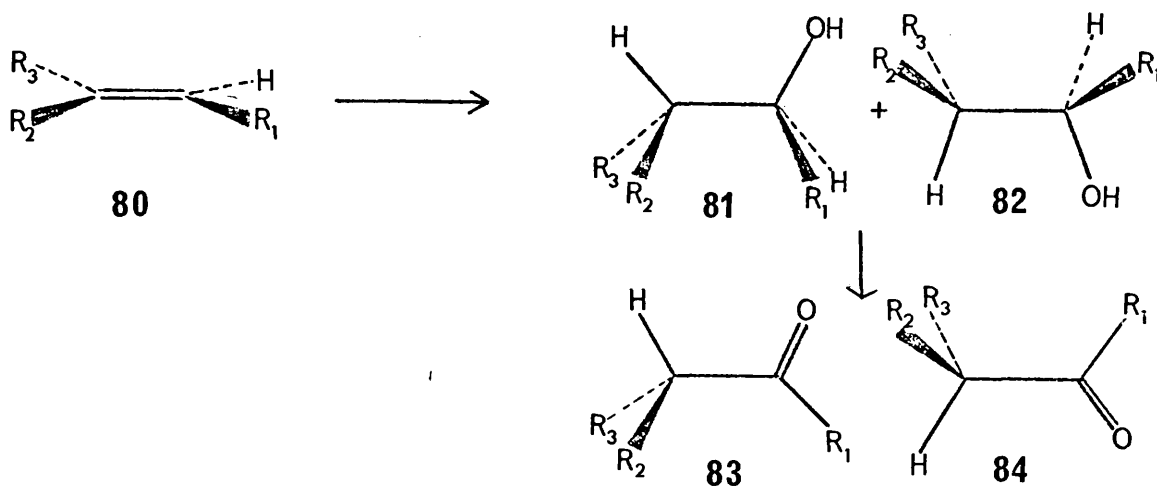
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Although it is possible to draw up formal mechanisms utilising Wagner-Meerwein shifts and hydride transfers to account for the mode of formation of pseudoclovene A, these exercises in "arrow pushing" all suffer from the disadvantages discussed in detail concerning the mechanism of isoclovene production. The mechanistic pathways will be discussed at the end of this chapter and some suggestions made to explain the co-production of isoclovene and the pseudoclovenes.

Pseudoclovene B has not as yet yielded to the attempts at structure elucidation. Fortunately the double bond in this hydrocarbon is much more reactive than in the isomer and so a classical degradative procedure is more likely to be successful. In preference to such an approach, however, efforts have principally been directed towards the preparation of a suitable crystalline derivative for X-ray diffraction

investigation. Osmylation of pseudoclovene B readily furnished the cis diol as a poorly crystalline material, which appeared homogeneous by TLC and spectroscopic examination, despite the oily appearance of the material. The p-bromobenzenesulphonate ester was prepared in the normal manner as a sharp melting crystalline solid. From the high yield of pure material it was apparent that very little impurity could have been present at the diol stage. The crystals belonged to the  $P2_1/C$  space group, which is readily amenable to crystallographic analysis, but, from preliminary photographs, it was evident from the way in which the intensity of the higher order reflections diminished, that either some packing disorder was present in the crystals or else there was considerable temperature-dependent rotation occurring. Repeated efforts to recrystallise the brosylate from different solvent systems did not improve the characteristics of the diffraction patterns, and so this derivative had to be abandoned. The di-bromoacetate was prepared from the diol by treatment with bromoacetyl bromide in benzene containing a small amount of pyridine, but this compound proved to be an oil. An alternative to formation of a derivative from the secondary-tertiary diol was to hydroborate the olefin, which, assuming it proceeded selectively from one side of the molecule, would give rise to a single secondary alcohol, elaboration of which might produce a convenient heavy atom derivative. In reality, two alcohols were formed in the ratio of 60 : 40, as identified by GLC, these alcohols being inseparable on TLC and column chromatography and giving rise to an

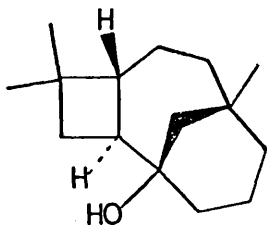
oily mixture of brosylates. Jones' oxidation of the alcohols gave two ketones as expected since hydroboration is effectively a cis hydration and will produce two alcohols epimeric at both centres. Thus an olefin represented by (80) would yield two alcohols (81) and (82) which on oxidation would furnish in turn the two ketones (83) and (84).



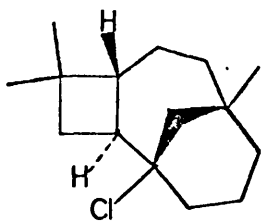
Provided the original alkene (80) has some other asymmetric centre, then (83) and (84) will be diastereoisomeric rather than enantiomeric as might at first appear. The carbonyl frequency (liquid film) in these ketones was approximately  $1705\text{ cm}^{-1}$ , which would indicate that the double bond in pseudoclovene B is in a six-membered ring rather than a cyclopentene or a cycloheptene. The intention at this stage in the work is to equilibrate the two ketones in base so that the single ketone which is thermodynamically more stable will be obtained. Some heavy atom derivative could then be made from this single ketone and the X-ray analysis performed. Unfortunately paucity

of material and even more critically shortage of time precluded the investigation of these possibilities.

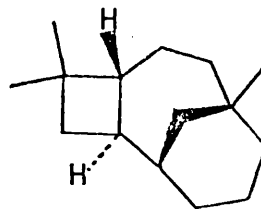
Reference has been made already to those investigations in which various sets of dehydrating conditions were applied to the reaction involving caryolan-1-ol (5) and to the interesting mechanistic implications emanating from these studies. Caryolan-1-ol itself is formed in a dehydrating medium of concentrated sulphuric acid in ether, but, when the alcohol is refluxed with a stronger solution of sulphuric acid in ether, a colourless liquid, seen by GLC to be a pure compound, is afforded in high yield. The purity of this material was established by repeated mass spectral scanning through the GLC peak. From the mass spectrum and elemental analysis, however, it was seen that this compound was a fully saturated, tricyclic hydrocarbon,  $C_{15}H_{26}$ , rather than the expected olefin,  $C_{15}H_{24}$ . Both the NMR and IR spectra confirmed the absence of a double bond. The structure of this unexpected product was established by correlation with the product from some reactions being conducted simultaneously on caryolan-1-ol chloride (85).



5



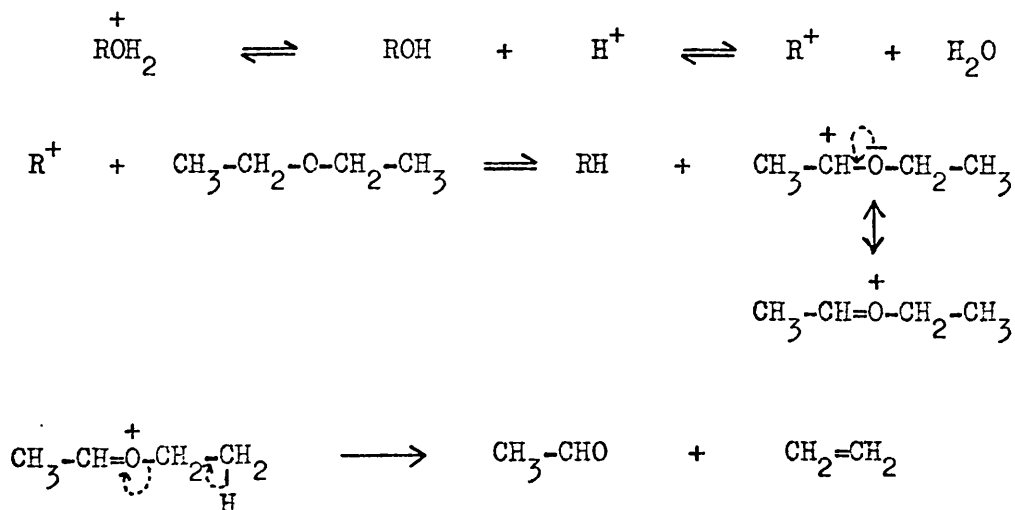
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From treatment of the chloride (85) with lithium aluminium hydride two products resulted ; one was a tertiary alcohol readily identified as caryolan-1-ol, while the second product was a saturated hydrocarbon,  $C_{15}H_{26}$ . With sodium in liquid ammonia a high yield of this hydrocarbon was obtained in a fairly pure state. The most obvious structure for this compound is that of caryolane (86), which is presumed to result from hydride attack after initial ionisation of the chloro compound. The identical nature of the two hydrocarbons formed in the above reactions was demonstrated by a variety of spectroscopic techniques in addition to GLC and mass spectral comparisons.

The mechanism of caryolane formation from caryolan-1-ol in strong, mineral acid solution is an extremely interesting one, since no analogy existed in alicyclic chemistry. From the work of Deno<sup>62</sup> and Bartlett<sup>63</sup> on triarylcarbinols the following mechanism was suggested.



Two critical factors in the success of this reaction are a) that carbonium ion formation must compete with protonation of the alcohol, and b) the stability of the carbonium ion  $R^+$  must be less than the stability of the resonance stabilised cation derived from the ether by intermolecular hydride transfer. Superimposed on these criteria is the necessity for the rate of intermolecular hydride transfer to exceed the rate of any possible rearrangement of the alkyl carbonium ion. Many other complicating factors can arise and it is clear that a fine balance in the reacting components must be achieved for successful intermolecular hydride transfer. Prior to this work on caryolan-1-ol, efficient transfer had not been reported for any tertiary alkyl carbinol, all previous examples involving aromatic systems ; but, since that time, an excellent analogy has appeared in which adamantan-1-ol gives adamantane together with adamantanone<sup>64, 65</sup>. Adamantan-1-ol and bicyclo(3,3,1)nonan-1-ol were concurrently being investigated in these laboratories as possible analogies to the caryolan-1-ol reaction, but at that time the best conditions had not been obtained for efficient intermolecular hydride transfer. It is apparent from examination of Fig. 7 (page 85.) that a small amount of caryolane is produced in the dehydration of caryolan-1-ol with phosphorus pentoxide.

Reaction with phosphorus pentoxide involves addition of the solid in small amounts over a period of 1 hour to the molten caryolan-1-ol. Such a crude, heterogeneous reaction does not permit much

10% A.P.L.; 150°; 50 ml/min.

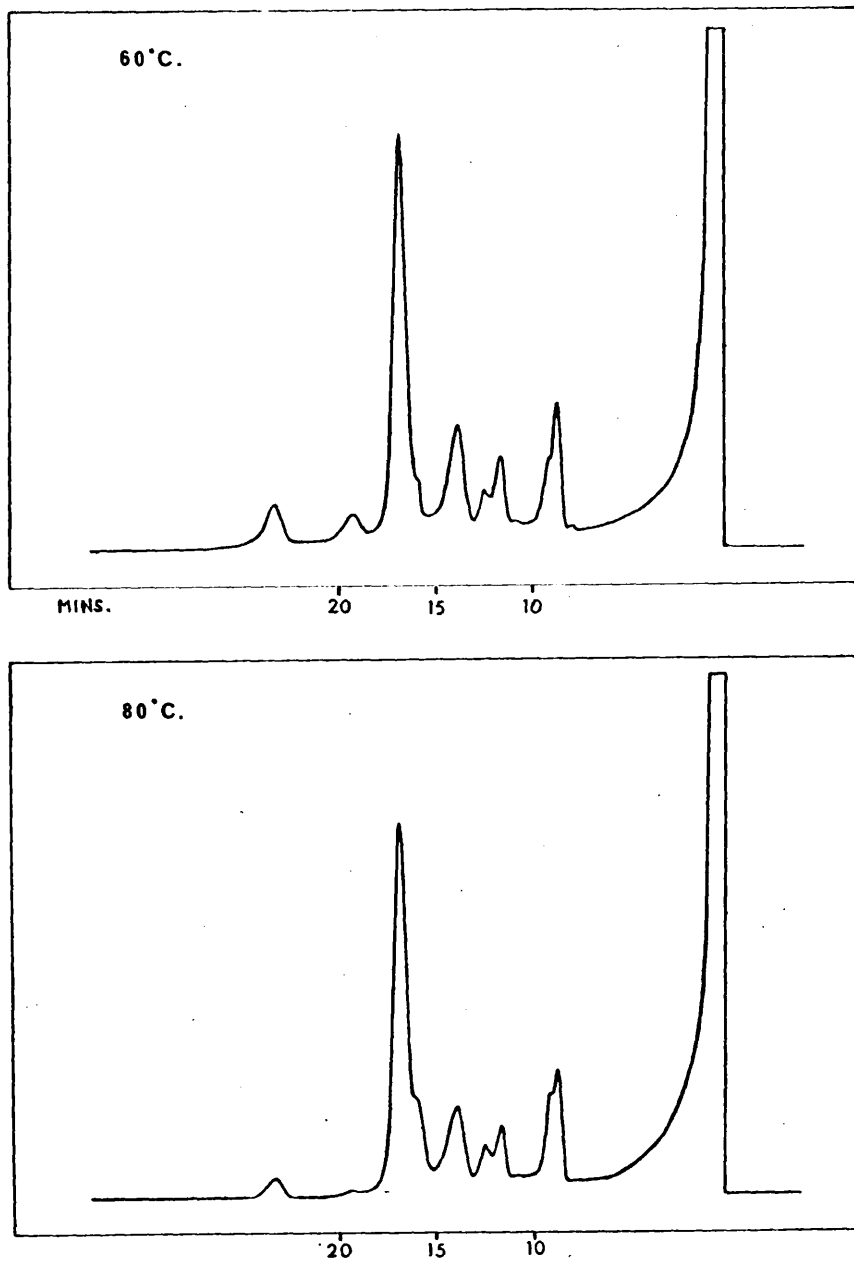
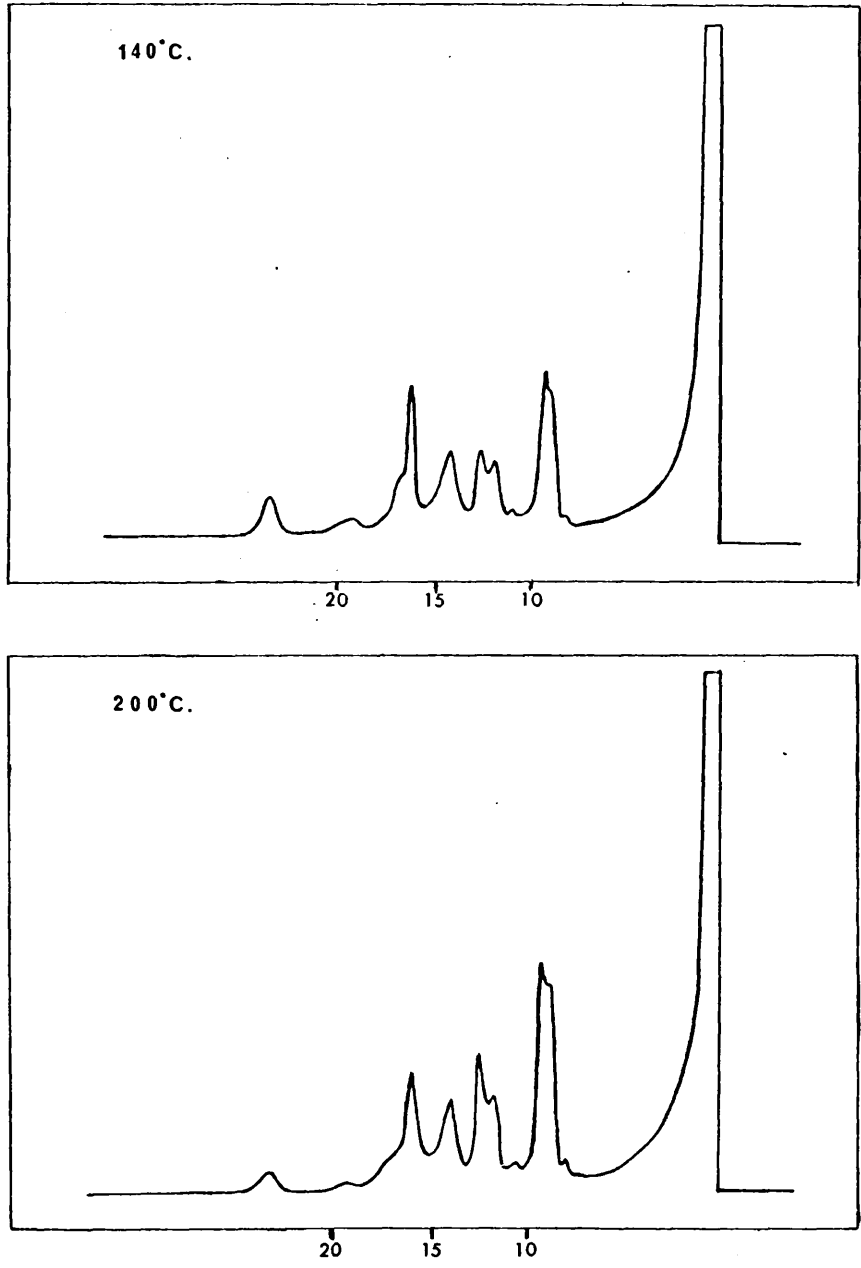


Fig. 9

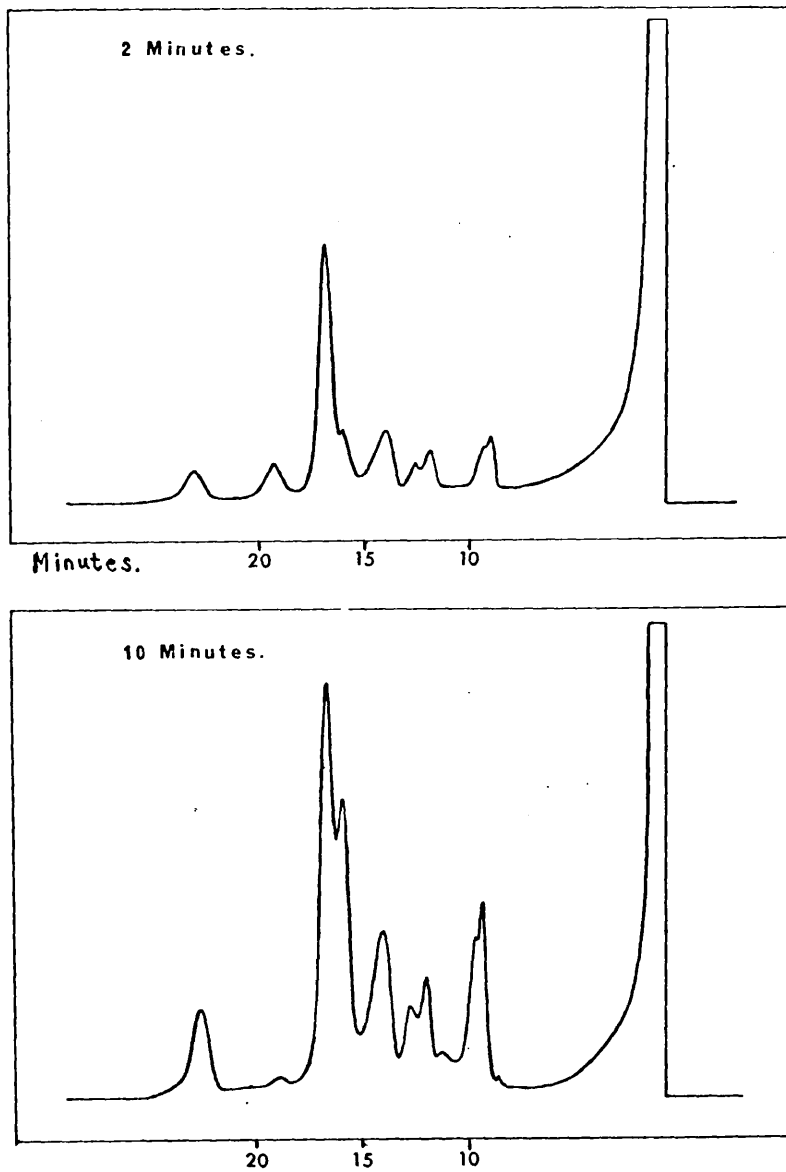


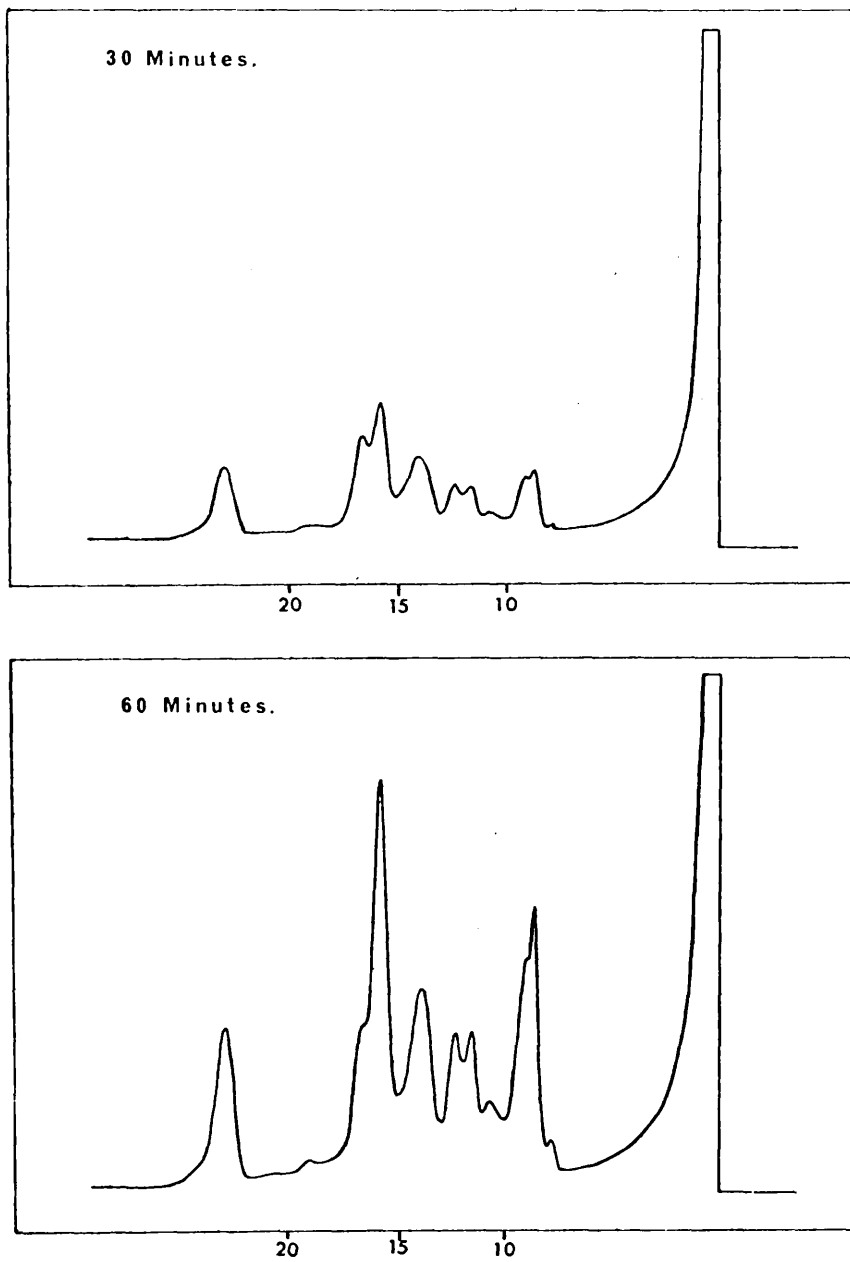
**Fig. 10**



variation of the experimental conditions and for this reason polyphosphoric acid was investigated as an alternative to phosphorus pentoxide. Initial studies showed that a similar product distribution could be obtained, although, from the detailed investigations to be discussed, distinct differences can occur. Since syrupy polyphosphoric acid becomes reasonably mobile above  $60^{\circ}\text{C}$ , greater efficiency in stirring could be effected with resultant homogeneity. The first series of experiments to be conducted involved the variation of temperature keeping all other factors constant, and the results so obtained are summarised in Figs. 9 and 10. All retention times were correlated with  $n\text{-C}_{16}\text{H}_{34}$  as internal standard and a table of the relative retention times on 10% Apiezon L at  $150^{\circ}\text{C}$  may be found preceding the experimental section of this chapter (page 114). At lower temperatures the predominant product is the compound with the relative retention of 0.62, but as the temperature increases the amount of this material diminishes, while the percentage of isoclovene ( $R_{\text{rel.}} = 0.59$ ) and the pseudoclovenes ( $R_{\text{rel.}} = 0.31$  and  $0.33$ ) increase steadily. At temperatures greater than  $130^{\circ}\text{C}$  the amount of isoclovene also begins to diminish and the pseudoclovenes become the major products, although the relative amount of the other products such as caryolane also increase. The most significant fact observed in this series of reactions is the occurrence of a probable precursor to isoclovene which may also be an intermediate in the formation of the pseudoclovenes.

10% A.P.L.; 150°; 45 ml/min.

**Fig. 11**

**Fig. 12**

A series of reactions has been conducted in which aliquots were removed from the dehydration reaction with polyphosphoric acid after various time intervals, and examined by GLC following normal work-up procedure. A typical set of results obtained for such a series conducted at 100°C is shown in Figs. 11 and 12. The material of  $R_{rel.} = 0.62$  is formed as the major product within 2 minutes at this temperature and, if the reaction is allowed to proceed, this first formed compound seems to be converted almost entirely to isoclovene. There would also appear to be a slight increase in the relative amount of the pseudoclovenes formed, but it cannot be stated with certainty that the pseudoclovenes are derived from the same precursor as isoclovene. Smaller changes in the product distribution of the other compounds formed in this reaction are also evident but, since the structures of these compounds are as yet undetermined, no further comment can be made concerning these variations.

Although this investigation did not lead to a simplified dehydration mixture as had originally been desired, the results provoked much stimulating discussion as to the nature of the isoclovene precursor. The feasibility of Wagner-Meerwein shifts in the early stages of this reaction has been appraised already in considerable detail and, since the conclusions did not favour any such migration, some alternative initiating step in the rearrangement seemed necessary. If migrations are effectively forbidden, then the next most probable action is bond cleavage. Based on such a tenet the mechanism shown in

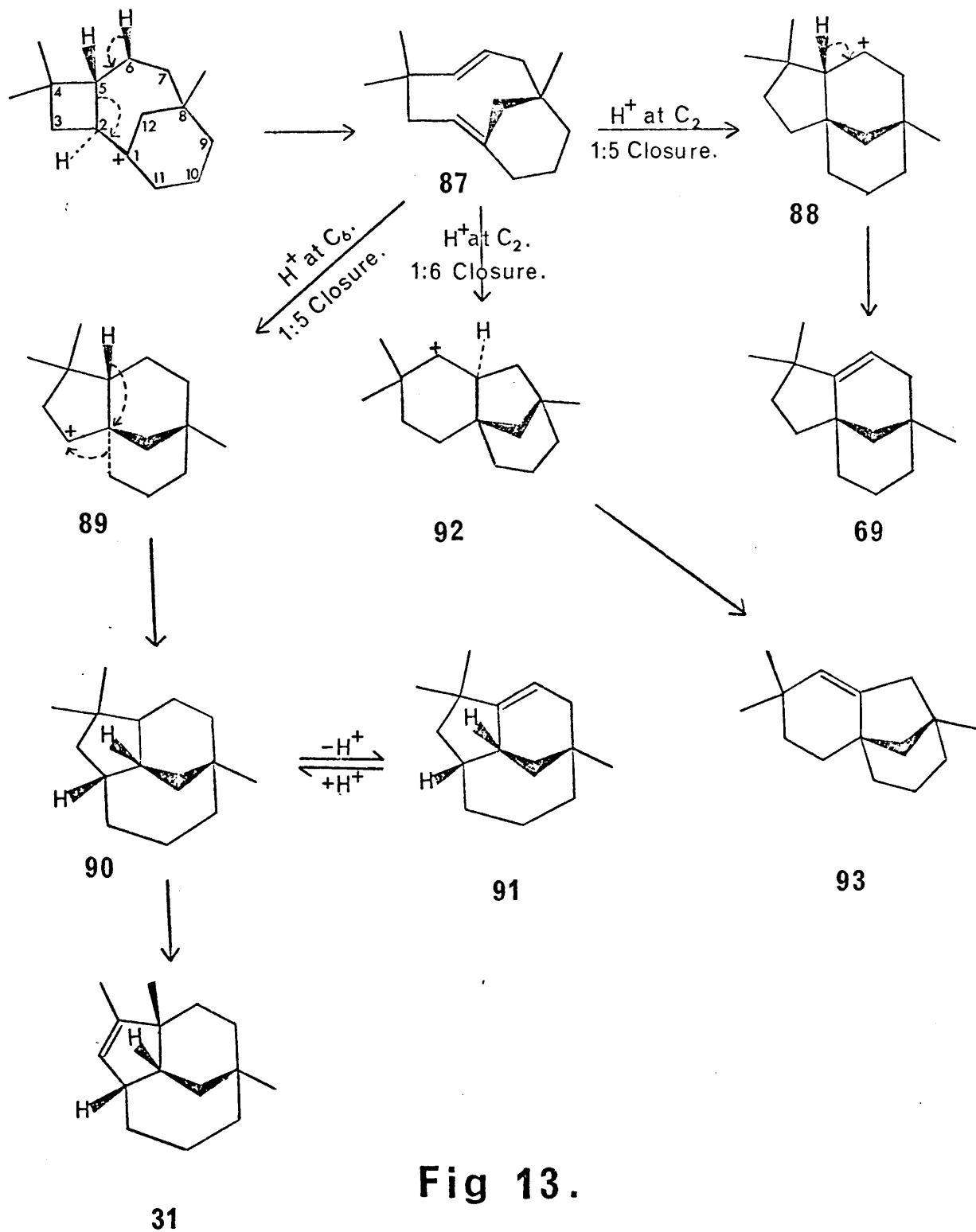


Fig 13.

Fig. 13 is proposed as a more acceptable alternative to any elaborate series of migrations. Although bond cleavage requires a considerable amount of energy, release of the inherent strain in the cyclobutane ring (calculated from combustion data to be 26 Kcal./mole<sup>66</sup>) could help to compensate. It must be borne in mind that rearrangement does not compete in rate with solvolysis or intermolecular hydride transfer, and one only observes rearranged products in a medium which does not facilitate these alternative reactions. The stereo-relationship between the cation at C<sub>1</sub> and the C<sub>2</sub> - C<sub>5</sub> bond is not particularly favourable for bond opening, which would be consistent with the relatively slow nature of rearrangement. The C<sub>2</sub> - C<sub>5</sub> bond and one hydrogen atom at C<sub>6</sub> are perfectly aligned, however, and after initial bond cleavage, formation of the diene (87) would be expected to proceed easily.

Since the orientation of the C<sub>2</sub> - C<sub>5</sub> bond and the vacant p orbital of the caryolanyl cation is not particularly good, the olefinic linkage between C<sub>1</sub> and C<sub>2</sub> may be formed with either the cis or the trans geometry. From molecular models the trans arrangement seems to be slightly favoured. So far as the mechanism of pseudoclovene A formation is concerned this point is irrelevant, but the trans,trans geometry is more convenient in explaining the stereochemistry of isoclovene formed from the diene (87). Despite the fact that a trans,trans-1,5-cyclononadiene does not seem to have been prepared, an examination of molecular models demonstrates that the system is not impossibly strained. This diene can be used as a common

intermediate to explain the formation of isoclovene (31) and pseudoclovene A (69).

Protonation of the  $C_1 - C_2$  double bond resulting in the more stable tertiary cation at  $C_1$  followed by closure between  $C_5$  and  $C_1$  would produce the cation (88), which might deprotonate to give the preferred trisubstituted double bond as required by pseudoclovene A (69). If protonation is allowed at the less likely disubstituted  $C_5 - C_6$  double bond, then closure between  $C_1$  and  $C_5$  would lead to the carbonium ion (89), which is oriented to undergo two trans antiparallel migrations leading to the cation (90). Although the  $\alpha$ -methyl group at  $C_4$  might be expected to shift to  $C_5$  in a further trans antiparallel migration, examination of the cation (90) shows this to be impossible, on account of the concave shape of this intermediate, which causes large steric repulsions on the  $\alpha$ -face. The cation (90) may deprotonate to (91) or may undergo  $\beta$ -methyl migration and deprotonation to yield isoclovene (31). Since formation of (91) could be concerted with the earlier migrations, this may very well be the observed precursor to isoclovene, and in the reaction conditions further protonation of the double bond and methyl migration could lead irreversibly in a slower process to isoclovene.

One attractive feature of this proposed mechanism is the versatility of the postulated diene intermediate, which, by permutation of the various possible closures and subsequent rearrangements, could account for the multiplicity of products. For instance, protonation

at C<sub>2</sub> followed by closure between C<sub>1</sub> and C<sub>6</sub> might lead to cation (92), deprotonation of which would yield the trisubstituted olefin (93). Such an olefin as (93) would fit all the known data on pseudoclovene B, and clearly the structure of this compound will be a test of the postulated mechanism.

Considerable interest has been attached to testing this mechanistic possibility, and at the moment work is being directed towards isolating the isoclovene precursor at an early stage in the rearrangement. A number of synthetic approaches to the interesting trans,trans-1,5-cyclonadiene (87) are also being tested in these laboratories<sup>67</sup>, but as yet this work has not been brought to a conclusion.

#### CONCLUSIONS.

The products from the dehydration of caryolan-1-ol have been examined in detail, and the structures of two of these viz. pseudoclovene A and caryolane have been established, in addition to the already known product, isoclovene. Variation of the reaction conditions is found to produce considerable changes in product distribution and, from this information together with the structures of the known products, postulates are made concerning the mechanistic pathways occurring during the reaction.



TABLE 1.

RELATIVE RETENTION DATA.

Run on 10% Apiezon L at 150° and flow rate (helium) of 50 ml./min..

COMPOUND	RETENTION TIME, $R_t$ (min.)	RELATIVE RETENTION $R_{rel.}$
$n-C_{16}H_{34}$	27.4	1.0
Caryolanyl chloride	33.4	1.22
Caryolan-1-ol	28.0	1.02
Clovene	10.0	0.35
Neoclovene	16.7	0.61
Pseudoclovene B	8.6	0.31
Pseudoclovene A	9.1	0.33
Caryolane	11.5	0.42
Isoclovene	16.2	0.59
Precursor to isoclovene	17.0	0.62
Pseudoclovane B	10.5	0.38

EXPERIMENTAL.<sup>‡</sup>CARYOLAN-1-OL (5).

The method originally described by Asahina and Tsukamoto<sup>4</sup> and modified by Lutz and Reid<sup>23</sup> was adopted. From purified caryophyllene (1000 gm., 4.9 moles) careful extraction gave a crude, yellow oil (950 gm.), which was adsorbed on neutral alumina (grade III, 10 Kgm.) from light petroleum. Elution with the same solvent yielded a colourless oil (550 gm.) while the use of 5% ether/light petroleum afforded solid caryolan-1-ol (370 gm., 34%), which was recrystallised from acetone as needles, m.p. 96-97°;  $\nu_{\max}$ . (nujol mull) = 3400, 1330, 1100, 1080 and 1024  $\text{cm}^{-1}$ ;  $\tau$  = 8.82 (singlet (broad), 1H, exchangeable with D<sub>2</sub>O), 9.00 (singlet, 6H) and 9.12 (singlet, 3H).

PHOSPHORUS PENTOXIDE DEHYDRATION OF CARYOLAN-1-OL (5).

Solid phosphorus pentoxide (35 gm., 0.246 moles) was added with stirring in small portions over a period of 1 hour to molten caryolan-1-ol (25.5 gm., 0.115 moles) at 130°. The reaction mixture was cooled, carefully neutralised with aqueous sodium hydroxide and thoroughly extracted with light petroleum. The combined extracts were dried and the solvent removed yielding a yellow oil (22.5 gm.) which was distilled through a

<sup>‡</sup> A description of the experimental procedure may be found preceding the experimental section in Chapter 2.

spinning band column. Early fractions (2 gm.) (b.p. 110-115°/11 mm.) were shown by GLC to consist almost entirely of pseudoclovene A and pseudoclovene B, while later fractions became progressively richer in isoclovene (b.p. 123-127°/11 mm.) as is evident from examination of Fig. 6 (page 83). See Table 1 (page 84) for the relative retention data on 10% Apiezon L at 150°. An early distillation fraction was also examined on at least another twenty GLC columns, and the most successful separation of the pseudoclovenes was achieved by the use of a 20% 1,2,3-tris(2-cyanoethoxy)propane column at 75° with a flow rate of 60 ml./min. ( $R_t$  pseudoclovene A = 4.7 min. ;  $R_t$  pseudoclovene B = 6.0 min.)

#### SEPARATION OF THE PSEUDOCLOVENES.

##### a) PREPARATIVE GAS-LIQUID CHROMATOGRAPHY.

The Aerograph 'Autoprep' A-700 was used to separate a mixture of the two pseudoclovenes (500 mg.) obtained by distillation of the crude dehydration products using the following set of conditions :-

Column :- 15'x $\frac{3}{8}$ " stainless steel column packed with 25% 1,2,3-tris(2-cyanoethoxy)propane on "Gaschrom".

Column Temperature :- 100°

Detector Temperature :- 175°

Collector Temperature :- 142°

Flow Rate :- 120 ml./min. (Helium).

Sample Size :- 50-60  $\mu$ l of neat liquid.

Manual injection and manual collection.

Five fractions were collected corresponding to a) fore-run, b) pseudoclovene A, c) intermediate cut, d) pseudoclovene B and e) a late cut. On account of the broad nature of the peaks and the generally poor resolution of the instrument only very small parts of each peak could be taken as pure pseudoclovene A and pure pseudoclovene B. In this manner samples of pure pseudoclovene A (30 mg.) ;  $\nu_{\max.}$  (liquid film) = 2900, 1675(w), 1452, 1379, 1373, 1358, 1321, 1281, 1021, 961, 877, 823, 806 and  $676 \text{ cm.}^{-1}$  ;  $\tau = 4.56$  (triplet,  $J = 4$  cps., 1H), 8.15 (doublet,  $J = 4$  cps., 2H), 8.25 - 8.87 (broad multiplet, 12H), 8.92 (singlet, 3H), 9.00 (singlet, 3H) and 9.11 (singlet, 3H) ; and pseudoclovene B (30 mg.) ;  $\nu_{\max.}$  (liquid film) = 2995, 2950, 1648(w), 1456, 1372, 1357, 960, 880, 872, 765 and  $750 \text{ cm.}^{-1}$  ;  $\tau = 4.61$  (singlet, 1H), 8.20 - 8.95 (multiplet, 14H), 9.02 (singlet, 6H) and 9.09 (singlet, 3H) were collected.

b) SILVER NITRATE/SILICA GEL COLUMN CHROMATOGRAPHY.

A mixture of the pseudoclovenes (1.04 gm.) was adsorbed on 25% silver nitrate/silica gel (60 gm.) from light petroleum, and elution with this solvent afforded pure pseudoclovene A (380 mg.) b.p.  $112-114^{\circ}/10 \text{ mm.}$  ;  $[\alpha]_{\text{D}}^{20} = -23.3^{\circ}$  ( $c = 1.210$ ) ; NMR and IR spectra were identical to those obtained in a).

( Found : C, 87.88 ; H, 11.98% ;  $\text{C}_{15}\text{H}_{24}$  requires  
C, 88.16 ; H, 11.84% ).

Elution with 10% ether/light petroleum yielded pseudoclovene B as a colourless oil (610 mg.) ; b.p. 111-112°/10 mm. ;  $[\alpha]_D^{20} = +33.0^\circ$  (c = 1.66). The NMR and IR spectra were almost identical to those obtained for pseudoclovene B by preparative GLC, but from detailed examination of the oil using capillary column GLC the pseudoclovene B was seen to be contaminated with approximately 5% of a further hydrocarbon.

( Found : C, 88.24 ; H, 11.92% ;  $C_{15}H_{24}$  requires  
C, 88.16 ; H, 11.84% ).

#### ISOCLOVENE HYDROCHLORIDE.

Dry HCl gas was passed through a solution of hydrocarbon consisting principally of isoclovene (1.412 gm., 6.9 nmoles) in anhydrous ether (10 ml.) until a deep red coloration was produced (approximately 5 minutes), then the reaction mixture was set aside at 0°C for 3 days. Evaporation of the solvent and excess HCl gas furnished a red, semi-solid mass (1.521 gm.) which on trituration with ethyl acetate and cooling gave almost colourless crystals of isoclovene hydrochloride, which recrystallised at low temperature from ethyl acetate as large needles, m.p. 85-87° (500 mg., 30%).

#### DEHYDROCHLORINATION OF ISOCLOVENE HYDROCHLORIDE.

Isoclovene hydrochloride (152 mg., 0.63 nmoles), fused sodium acetate (190 mg., 2.32 nmoles) and dry, glacial acetic acid (2 ml.)

were heated under reflux for 3 hours, then the cooled reaction mixture was neutralised carefully with dil. sodium hydroxide solution and thoroughly extracted with ether. The combined extracts were washed with brine, dried and the solvent was removed to give a pale yellow oil which distilled as a colourless liquid (120 mg., 92%), b.p. 125-127°/10 mm.,  $[\alpha]_D^{20} = -60.0^\circ$  ( $c = 1.523$  in  $\text{CHCl}_3$ ). GLC and GC/MS examination showed this liquid to be a single product identical in retention time and mass spectrum with the principal product from phosphorus pentoxide dehydration of caryolan-1-ol.

#### HYDROGENATION OF THE PSEUDOCLOVENES.

Hydrogenation of a mixture of pseudoclovene A and pseudoclovene B (25 mg., 0.123 mmoles) in ethyl acetate (5 ml.) and 10% Pd/C (5 mg.) proceeded with uptake of approximately 1.5 ml. of  $\text{H}_2$  (ca. 0.6 molar equivalents) after 5 hours. The reaction mixture was filtered through Celite 535 and the solvent was removed in vacuo to give a colourless oil (24 mg., 95%). GLC demonstrated the presence of two products ( $R_{\text{rel.}}$  on 10% Apiezon L at 150° = 0.33 and 0.38) and GC/MS showed the faster to have a molecular weight of 204 while the slower compound on this column had a parent ion,  $m/e = 206$ . The infra-red spectrum of the mixture showed the absence of the absorptions at 765 and 750  $\text{cm}^{-1}$ , diagnostic of pseudoclovene B, while the peaks at 823 and 806  $\text{cm}^{-1}$ , ascribed to pseudoclovene A, were still present.

ATTEMPTED HYDROGENATION OF PSEUDOCLOVENE A.

Pseudoclovene A was found to be resistant to hydrogenation under the following sets of conditions :-

- a). 10% Pd/C in ethyl acetate for 24 hours at atmospheric pressure and room temperature.
- b). PtO<sub>2</sub> in acetic acid for 10 hours at atmospheric pressure and room temperature.
- c). 10% Pd/C in ethyl acetate for 18 hours at 60° and 4 atmospheres.

PSEUDOCLOVENE A DIOL (67).

An ethereal solution of pseudoclovene A (204 mg., 1.0 mmoles) was treated with osmium tetroxide (500 mg., 1.97 mmoles) and dry pyridine (2 ml.) for 2 weeks in the dark at room temperature. Hydrogen sulphide gas was bubbled through the solution for 30 minutes causing the osmate ester to be decomposed and a heavy precipitate of osmium sulphide to form. The mixture was then filtered through glass filter paper, and normal ether/water work-up yielded a yellow oil (220 mg.), which was adsorbed on neutral alumina (20 gm., grade III) from 10% ether/light petroleum. Elution with the same solvent system yielded firstly pseudoclovene A (40 mg.), and then a poorly, crystalline semi-solid (180 mg., 75%);  $\nu_{\text{max.}}$  (liquid film) = 3550, 2980, 1472, 1455(sh.), 1380, 1060, 1020 and 960 cm.<sup>-1</sup>

THE MONO p-BROMOBENZENESULPHONATE OF PSEUDOCLOVENE A DIOL (68).

The diol from pseudoclovene A (67) (106 mg., 0.445 mmoles) and freshly recrystallised p-bromobenzenesulphonyl chloride (125 mg., 0.49 mmoles) were dissolved in a minimum of dry pyridine and left overnight at 0°C. The reaction mixture was diluted with water and thoroughly extracted with ether, the combined organic extracts being washed with 4N hydrochloric acid and brine, dried and the ether removed to furnish a white solid (175 mg., 86%) which recrystallised from light petroleum - ether as needles, m.p. 94-95°(decomp.) ;

$[\alpha]_D^{20} = +10.2^\circ$  (c = 1.29 in  $\text{CHCl}_3$ ) ;  $\nu_{\text{max.}}$  (nujol mull) = 3550, 1560, 1190, 1100, 1080, 1060, 1025, 960, 925, 905, 835, 770 and 720  $\text{cm}^{-1}$  ;  $\tau = 2.28$  (singlet, 4H), 4.92 (doublet of a doublet, 1H), 8.15 (singlet, exchangeable with  $\text{D}_2\text{O}$ , 1H), 8.96 (singlet, 3H), 9.03 (singlet, 3H) and 9.09 (singlet, 3H).

( Found :- C, 55.33 ; H, 6.49% ;  $\text{C}_{21}\text{H}_{29}\text{O}_4\text{SBr}$  requires  
C, 55.16 ; H, 6.38% ).

PSEUDOCLOVENE B DIOL.

Osmium tetroxide (500 mg., 1.97 mmoles) was added to a solution of pseudoclovene B (204 mg., 1.0 mmoles) in dry ether (10 ml.) and pyridine (2 ml.), and the reaction mixture was set aside at room temperature for 24 hours in darkness. Work-up, as described for pseudoclovene A diol, yielded a semi-solid (230 mg.) which, although it appeared homogeneous by TIC, could not be obtained in a crystalline



state even after chromatography ;  $\nu_{\text{max.}}$  (liquid film) = 3500, 2980, 1465, 1455, 1380, 1080 and 1000  $\text{cm}^{-1}$

MONO p-BROMOBENZENESULPHONATE OF PSEUDOCLOVENE B DIOL.

The diol of pseudoclovene B (119 mg., 0.5 mmoles) on analogous treatment with p-bromobenzenesulphonyl chloride to that of pseudoclovene A diol yielded a white solid (207 mg., 90%) which recrystallised from light petroleum - ether as fine needles, m.p. 109-110° ;

$\nu_{\text{max.}}$  (nujol mull) = 3550, 2980, 1580, 1475, 1460, 1360, 1190, 1100, 1080, 1020, 925 and 750  $\text{cm}^{-1}$ .

( Found :- C, 55.24 ; H, 6.40% ;  $\text{C}_{21}\text{H}_{29}\text{O}_4\text{SBr}$  requires  
C, 55.16 ; H, 6.49% ).

DI-BROMOACETATE OF PSEUDOCLOVENE B DIOL.

Bromoacetyl bromide (1 ml.) was added dropwise to a solution of pseudoclovene B diol (55 mg., 0.27 mmoles) in anhydrous benzene (14 ml.) containing pyridine (8 drops), the temperature being maintained at 5°C. The reaction mixture was stirred at room temperature for 4 hours, then poured on to ice and extracted with ethyl acetate, the extracts being washed with brine, dried and the solvent evaporated. The resultant brown oil (107 mg.) showed only one spot on TLC apart from a brown stain at the base line. Preparative TLC yielded a colourless oil (90 mg., 80%) which solidified at 0°C but melted at approximately 5°C ;

$\nu_{\text{max.}}$  (liquid film) = 2950, 1740, 1460, 1420, 1380, 1290, 1180, 1120,

1060 and 1000  $\text{cm}^{-1}$ . N.B. no  $\nu_{\text{O-H}}$  indicating the formation of the dibromoacetate.

#### HYDROBORATION OF PSEUDOCLOVENE B.

A 1.0 molar solution of diborane in tetrahydrofuran was prepared as described by Brown<sup>68</sup>, and this solution (1 ml.) was added dropwise to a stirred solution of pseudoclovene B (204 mg., 1.0 mmoles) in dry tetrahydrofuran (5 ml.). After stirring for 30 minutes at room temperature, the excess diborane was destroyed by careful addition of water till effervescence stopped. The reaction mixture was heated to 40°C and 3N sodium hydroxide solution (1 ml.) and 30% hydrogen peroxide (1 ml.) were added. After a further hour of stirring at room temperature, potassium carbonate (3 gm.) was added and the tetrahydrofuran layer decanted. The residues were extracted with tetrahydrofuran (2X15 ml.) and the combined extracts were dried, removal of solvent yielding a yellow oil (218 mg.). TLC showed three spots, one of which appeared to be at least 80% of the total products, and this material was separated by preparative TLC as a colourless oil (150 mg.). GLC, however, indicated this single spot by TLC to be a mixture of two compounds in the ratio of 7:3 ( $R_t$  on 10% Apiezon L at 150° and flow rate of 50 ml./min. = 33.4 min. and 31.6 min.). The infra-red spectrum showed no indication of unchanged olefin but a strong  $\nu_{\text{O-H}}$  at 3400  $\text{cm}^{-1}$  and  $\nu_{\text{C-O}}$  at 1040  $\text{cm}^{-1}$ .

JONES' OXIDATION OF ALCOHOLS FROM HYDROBORATION.

8N Jones' reagent was added dropwise to a stirred, ice-cold solution of the alcohols obtained above (50 mg., 0.225 mmoles) in Analar acetone (3 ml.) until a permanent, orange-coloured supernatant liquid was obtained. Water was added and the mixture was extracted with ether, the extracts being washed with brine, dried and the solvent removed to furnish a colourless oil (47 mg.) ;  $\nu_{\max.}$  (liquid film) = 3950, 1705, 1465 and 1380  $\text{cm}^{-1}$ . TLC showed only one spot, but GLC showed a 7:3 mixture of two ketones ( $R_t$  on 5% Q.F. 1 at 150° and flow rate of 45 ml./min. = 10.7 min. and 11.4 min.).

CONCENTRATED SULPHURIC ACID IN ETHER DEHYDRATION OF CARYOLAN-1-OL.

Concentrated sulphuric acid (6.67 ml.) was added dropwise to a solution of caryolan-1-ol (5 gm., 0.0225 moles) in dry ether (17 ml.) and the mixture was heated under reflux for 1 hour, then allowed to cool. The products were poured into ice-cold water, neutralised with 20% sodium hydroxide solution and thoroughly extracted with light petroleum. The combined extracts were dried and the solvent evaporated to give a dark yellow oil (4.4 gm., 95%) which was distilled yielding pure caryolane (86) as a colourless liquid, b.p. 62-64°/2 mm. ;  $[\alpha]_D^{25} = -31.0^\circ$  ( $c = 3.53$  in  $\text{CHCl}_3$ ) ;  $\nu_{\max.}$  (liquid film) = 2950, 1460, 1380, 1360, 1300, 1258, 1160, 990, 962, and 900  $\text{cm}^{-1}$  ;  $\tau = 8.1 - 8.95$  (multiplet, 17H), 9.02 (singlet, 6H) and 9.18 (singlet, 3H).

Molecular weight from mass spectroscopy was 206.

( Found :- C, 87.24 ; H, 12.68% ;  $C_{15}H_{26}$  requires  
C, 87.30 ; H, 12.70% ).

LITHIUM ALUMINIUM HYDRIDE REDUCTION OF CARYOLANYL CHLORIDE.

An ethereal solution of caryolanyl chloride (85) (1 gm., 4.08 mmoles) was added to lithium aluminium hydride (4 gm.) in anhydrous ether (50 ml.), and the reaction mixture was heated under reflux for 36 hours. Moist ethyl acetate was added dropwise to the cooled solution until all evolution of hydrogen had ceased and normal ether/water work-up gave, on removal of the solvent, a semi-solid, which was adsorbed on silica gel (35 gm.) from light petroleum. Elution with light petroleum gave a colourless oil (250 mg., 34%) which was identical in every respect with caryolane as obtained above. Elution with 25% ether/light petroleum gave a colourless solid (520 mg., 56%) which, on crystallisation from acetone, had m.p. 93-94° and was shown by mixed m.p. and spectral comparison to be identical to caryolan-1-ol.

REDUCTION OF CARYOLANYL CHLORIDE WITH LITHIUM IN AMMONIA.

A solution of caryolanyl chloride (500 mg., 2.04 mmoles) in liquid ammonia (100 ml.) and anhydrous ether (100 ml.) was treated with lithium metal (750 mg.) over a period of 10 minutes. After stirring for a further 15 minutes, ethanol was added slowly until the blue colour was discharged. Normal ether/water work-up gave caryolane (86) (420 mg., 98%) as the only product.

TRICYCLIC KETONE (75).

The tricyclic ketone (75) was prepared as described by Doyle<sup>58</sup> from a sample of the keto-acid (71) kindly supplied by him.

METHYLATION OF TRICYCLIC KETONE (75).

A suspension of potassium t-butoxide (2.8 gm., 0.025 moles) in benzene (60 ml.) and the tricyclic ketone (75) (1.00 gm., 0.0053 moles) was heated under reflux for 1 hour and then cooled to 0°C. A solution of methyl iodide (10 ml.) in benzene (10 ml.) was added and refluxing resumed for a further 2 hours, after which brine was added to the cooled solution and the mixture extracted with light petroleum. The combined extracts were dried and the light petroleum evaporated affording a yellow oil (850mg.) which was adsorbed on neutral alumina (50 gm., grade I) and eluted with light petroleum. The first material to be eluted was shown by GC/MS to have a molecular weight of 246 corresponding to substitution of four methyl groups, while the next few fractions contained two isomeric compounds of molecular weight 232, i.e. trisubstituted, and the last material to be eluted with light petroleum was the desired disubstituted compound of molecular weight 218. The material so obtained was a colourless oil (120 mg.) which was distilled in a sublimation tube (block temperature 125-135°/10 mm.) ;  $\nu_{\text{max.}}$  (liquid film) = 1740, 1385 and 1365  $\text{cm}^{-1}$  ;  $\tau$  = 4.28 (distorted triplet, J = 4 cps., 1H), 7.73 (singlet, 2H), 8.04 (doublet, J = 4 cps., 2H), 8.91 (singlet, 6H) and

9.07 (singlet, 3H).

The orange 2,4-dinitrophenylhydrazone was prepared and was shown to be identical in m.p. and mixed m.p. 156-158° with that obtained in previous investigations.

TOSYLHYDRAZONE OF TRICYCLIC KETONE (75).

The ketone (70) (36 mg., 0.165 mmoles) and recrystallised tosyl hydrazine (33 mg., 0.177 mmoles) were heated with dry ethanol (1 ml.) on the steam-bath for 1 hour, allowed to cool and set aside for 2 hours. Water and chloroform were added and the organic layer was separated, washed with 5% hydrochloric acid, dried and the solvent was removed to yield a tacky oil (64 mg.) which showed almost no  $\nu_{C=O}$  in the infra-red spectrum. Preparative TIC gave a pure sample of the desired tosylhydrazone as a colourless, crystalline material (22 mg.), m.p. 151-152° ;  $\nu_{max.}$  (nujol mull) = 3200, 1620, 1600, 1520, 1160 and 820  $cm^{-1}$

PSEUDOCLOVENE A FROM THE TOSYLHYDRAZONE.

A solution of the tosylhydrazone obtained above (10 mg.) in dry tetrahydrofuran (3 ml.) was heated under reflux with an excess of lithium aluminium hydride (25 mg.) for 8 hours. Water was added dropwise to the cooled solution until all hydrogen evolution had ceased and the resultant supernatant liquid was decanted, the residues being further extracted with tetrahydrofuran. The combined

extracts were washed with dilute hydrochloric acid and brine, dried and the solvent was removed affording a colourless oil (4 mg.) which was seen from GC/MS to be a single compound of molecular weight 202.

Catalytic reduction of this material for 1 hour using 10% Pd/C in ethyl acetate gave a single olefin (4 mg.) which was shown to be identical by GC/MS to authentic pseudoclovene A and also to the material obtained from Wolff-Kishner reduction of the ketone (70).

#### PSEUDOCLOVENE A FROM WOLFF-KISHNER REDUCTION OF THE KETONE (70).

The ketone (70) (100 mg., 0.46 mmoles) was added to hydrazine hydrate (0.11 ml.) and metallic sodium (40 mg.) in distilled diethylene glycol (5 ml.) and the mixture was heated under reflux for 1.5 hours. Excess hydrazine hydrate and water were then distilled off and refluxing was continued for a further 3 hours. The cooled reaction mixture was neutralised with 6N hydrochloric acid and extracted with light petroleum. The combined extracts were washed with brine, dried and the solvent was removed to furnish a pale yellow oil (65 mg.) which was adsorbed on neutral alumina (2 gm., grade I) and on elution with light petroleum, pure pseudoclovene A (56 mg., 60%), b.p. 112-114°/10 mm., identical in all spectral comparisons to authentic pseudoclovene A, was obtained.

DEHYDRATION OF CARYOLAN-1-OL WITH POLYPHOSPHORIC ACID.a). VARIATION OF TEMPERATURE.

Caryolan-1-ol (1 gm., 4.9 mmoles) was added to polyphosphoric acid (15 ml.) at 60°C and vigorous stirring was maintained for 30 minutes at this temperature. The reaction mixture was then poured on to ice-water and stirred until all the polyphosphoric acid had dissolved. After neutralising with dilute sodium hydroxide solution, the organic material was extracted with light petroleum yielding, on evaporation of the solvent, a yellow oil (850 mg, 96%) which showed only hydrocarbon absorptions in the infra-red spectrum and was examined by GLC.

Identical experiments were conducted at 80°, 100°, 120°, 140° and 200°C, the results of some of these being shown in Figs. 9 and 10 (see pages 104 and 105).

b). VARIATION OF TIME.

Caryolan-1-ol (3 gm., 14.7 mmoles) was added to stirred polyphosphoric acid (45 ml.) at °C and aliquots (2 ml.) of the reaction mixture were removed after 2, 4, 10, 20, 30 and 60 minutes. The aliquots were worked-up as described above and examined by GLC, the results being shown in Figs. 11 and 12 (see pages 107 and 108).



CHAPTER 4.THE STRUCTURE OF PSEUDOCLOVENE A.

(An X-ray analysis of the mono-*p*-bromobenzenesulphonyl ester of pseudoclovene A diol).

The mono-brosylate of pseudoclovene A diol was prepared as described in Chapter 3 and examination of a single crystal by normal X-ray diffraction and chemical techniques afforded the following data.

CRYSTAL DATA.

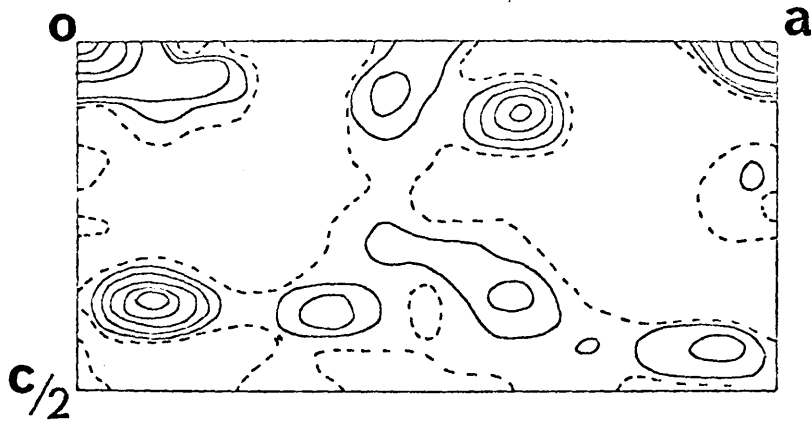
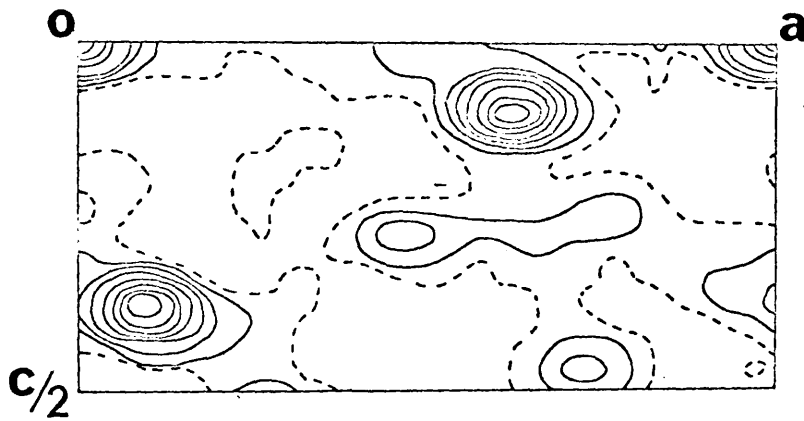
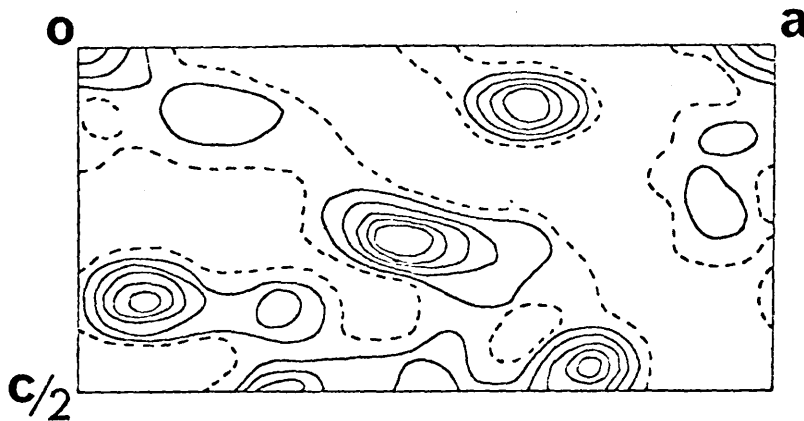
Molecular Formula	$C_{21}H_{29}O_4SBr$
Molecular Weight, M	457.5
Crystal System	Monoclinic
Cell Dimensions, a	$9.97 \pm 0.02 \text{ \AA}$
b	$21.41 \pm 0.03 \text{ \AA}$
c	$9.97 \pm 0.02 \text{ \AA}$
$\beta$	$90 \pm 0.17^\circ$
Unit Cell Volume, V	$2128 \text{ \AA}^3$
Density Measured, $D_m$	1.42 gm./cc.
No. of Molecules/Unit Cell, Z	4
Density Calculated, $D_x$	1.43 gm./cc.
No. of Electrons/Unit Cell, F(000)	952
Space Group	$P2_1$
Absorption Coefficient for X-rays ( $\lambda = 1.542$ ), $\mu$	$39.7 \text{ cm.}^{-1}$

CRYSTALLOGRAPHIC MEASUREMENTS.

Oscillation and Weissenberg photographs were obtained from crystals rotated about the a and b axes using Cu K<sub>α</sub> radiation ( $\lambda = 1.5418 \text{ \AA}$ ) and precession photographs were taken using Mo K<sub>α</sub> radiation ( $\lambda = 0.7107 \text{ \AA}$ ). The cell dimensions, systematic absences (Ok0, only present if  $k = 4n$ ) and the number of molecules per unit cell originally led us to believe that the crystals were tetragonal, space group P4<sub>1</sub> or P4<sub>3</sub>. Detailed examination of higher layer Weissenberg photographs, however, showed significant differences between  $xkl$  and  $xk\bar{l}$  reflexions which were of too great a magnitude to result from anomalous dispersion effects. Thus the crystals were monoclinic and must have the space group P2<sub>1</sub>, since the alternative P2<sub>1</sub>/m was precluded on the basis of the optical activity of the derivative.

The intensity data were collected by means of equi-inclination, multiple-film Weissenberg exposures<sup>69</sup> taken with Cu K<sub>α</sub> radiation on a small, single crystal bathed uniformly in the X-ray beam. In all, 3072 independent reflexions were measured by visual comparison with a calibrated wedge. From the exposure times the data were placed on approximately the same scale and corrections for Lorentz polarisation and the rotation factors appropriate to the upper layers were made at this stage. No allowance was made for "unobserved" reflexions.

Fig 14.

 $v=0$  $v=1/4$  $v=1/2$

STRUCTURE DETERMINATION.

A three-dimensional Patterson map showed that the four molecules in the unit cell, or at least their heavy atoms, were related by a pseudo four-fold screw axis as had been suspected from the crystal data. The presence of this symmetry property was employed wherever possible in determining the initial bromine and sulphur coordinates. The true Harker section at  $v = \frac{1}{2}$  displayed the expected pseudo four-fold axis and other correlating peaks were identified on the sections at  $v = 0$  and  $v = \frac{1}{4}$ . Fig. 14 shows these sections.

The structure analysis was continued by the phase-determining heavy atom method<sup>47</sup>. In the first Fourier synthesis the structure factors were weighted in order to reduce phase-angle errors<sup>70</sup>. After two cycles of structure factor and electron density calculations, all the non-hydrogen atoms constituting both molecules in the asymmetric unit were clearly resolved. A further two rounds of Fourier refinement improved the values for all the atomic coordinates and the residual (R) was lowered to 0.25.

Fig 15.

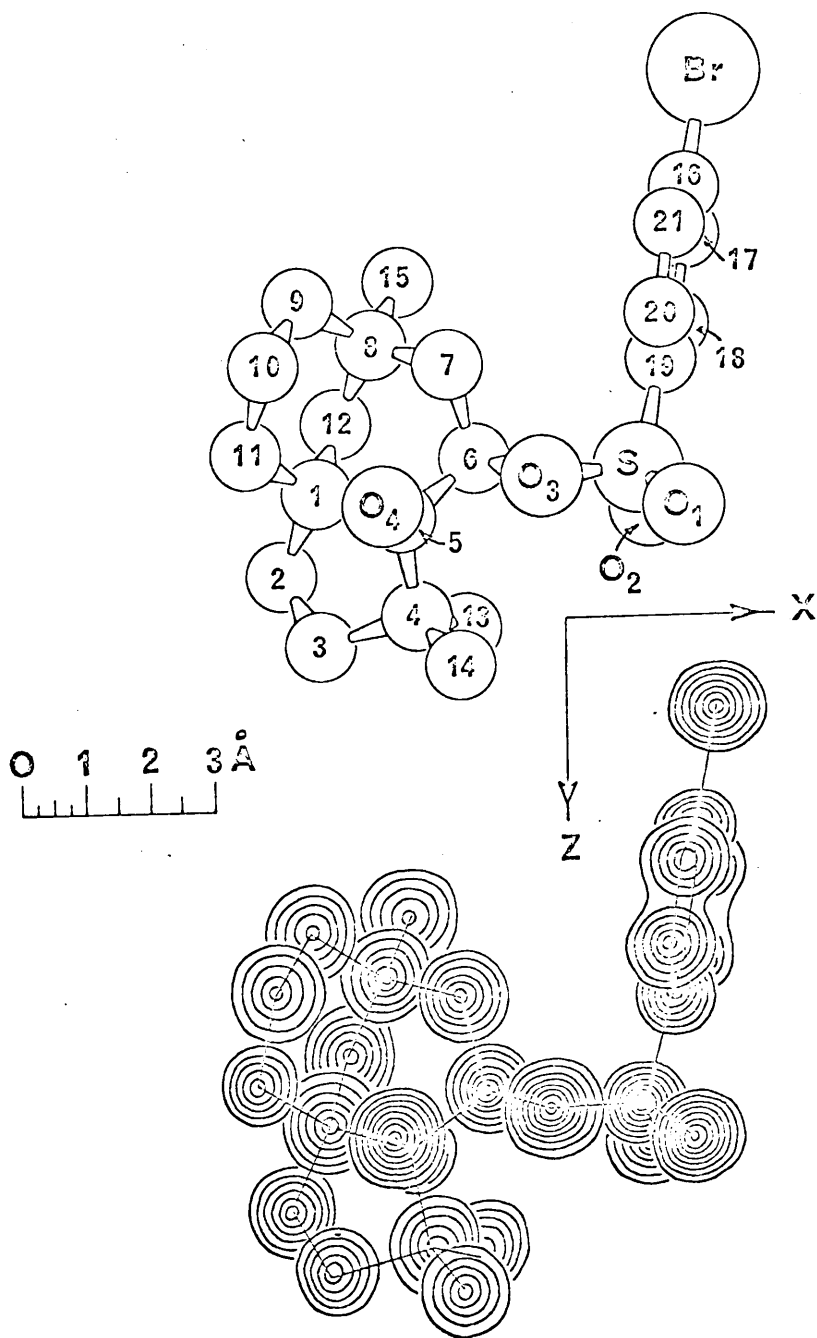
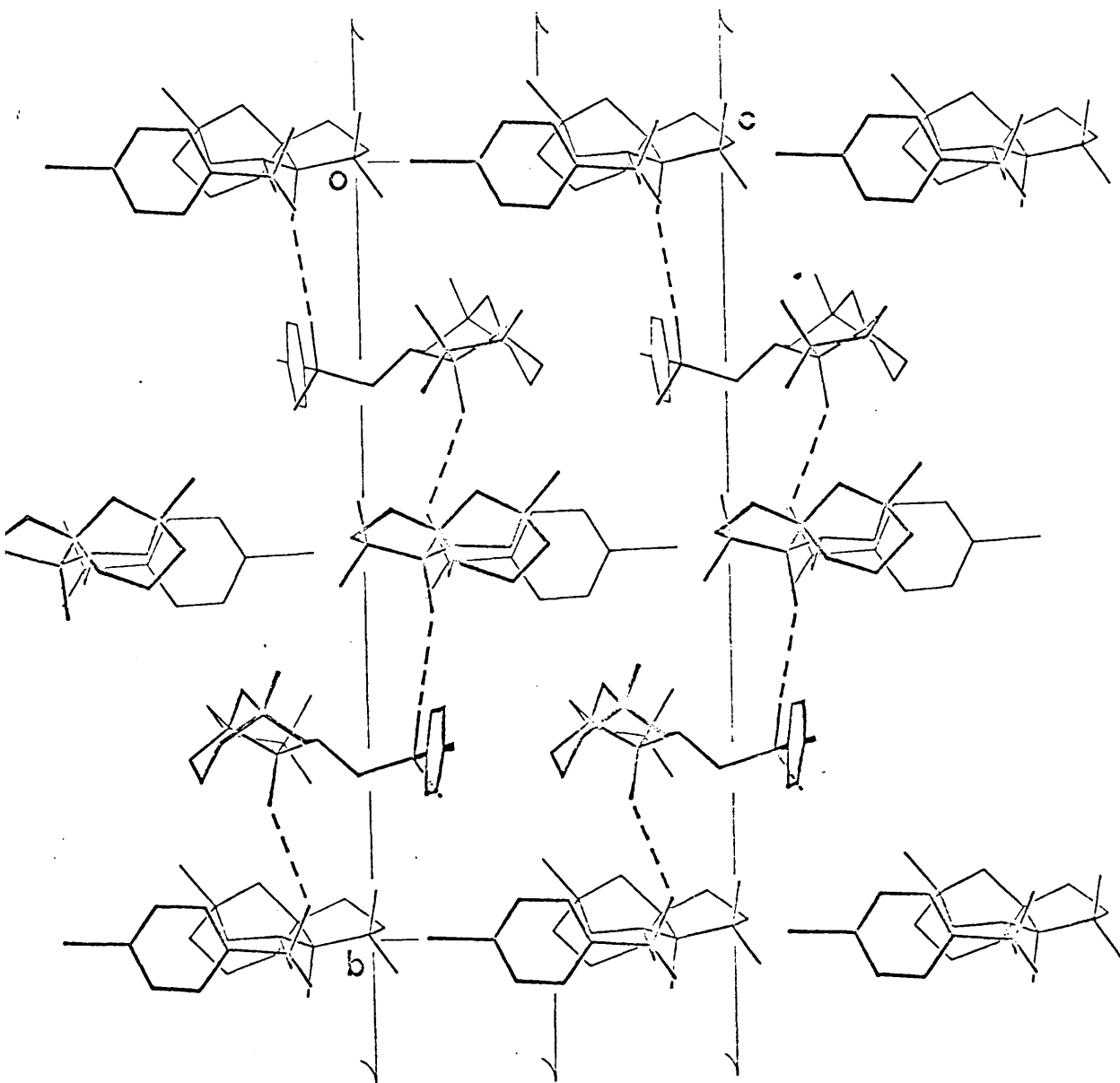


Fig 16.



0 1 2 3 Å

STRUCTURE REFINEMENTS.<sup>‡</sup>

Using a block-diagonal approximation to the least squares matrix of normal equations, seven cycles of least squares refinement were carried out to improve the positional and isotropic thermal parameters of the atoms. The data were then placed on a common scale by means of the layer scale factors obtained at the end of isotropic refinement. Six further cycles of least squares refinement during which anisotropic vibration of the atoms and the new scale factors were taken into account. At convergence, when the shifts were all less than one fifth of the estimated standard deviations, R had become 0.087. The shifts in the scale factor and temperature parameters had also become insignificant at this stage.

A composite view of the final electron density distribution over a single molecule is shown in Fig. 15 together with a diagram showing the corresponding atomic arrangement and numbering scheme adopted in the analysis. The average values for the bond lengths and angles over the two molecules in the asymmetric unit are presented in Table 2 together with their estimated standard deviations in parentheses. The contents of the unit cell when viewed along the  $a$  - axis are illustrated in Fig. 16.

<sup>‡</sup> The refinement was conducted by Mr. D.M. Hawley and Dr. G. Ferguson and is mentioned here only to record the accuracy of the final structure determination.

## Fig 17

Bijvoet pairs used in the anomalous-dispersion calculations.

h	k	l	$I_k/I_{\bar{k}}$	$F_k^2/F_{\bar{k}}^2$	h	k	l	$I_k/I_{\bar{k}}$	$F_k^2/F_{\bar{k}}^2$
1	2	3	0.54	0.75	3	4	-7	1.33	1.69
1	6	4	0.73	0.88	4	3	-2	0.64	0.58
2	1	9	1.24	1.24	4	3	-7	0.77	0.91
2	1	7	1.22	1.09	4	4	5	0.83	0.98
2	1	-6	0.50	0.49	4	4	3	0.76	0.99
2	1	-7	0.80	0.99	4	5	4	0.73	0.92
2	1	-8	1.50	1.49	5	1	3	0.42	0.66
2	3	4	0.50	0.57	5	3	4	0.74	0.74
2	3	-6	1.10	1.05	5	3	3	1.30	1.26
2	4	3	0.69	0.85	5	3	2	0.50	0.51
3	1	8	0.85	0.78	5	4	4	0.57	0.81
*3	1	6	1.25	0.96	6	1	2	0.64	0.50
3	1	-5	0.55	0.74	*6	5	4	0.81	1.04
3	3	-5	1.40	1.31	7	2	-2	0.63	0.76



ABSOLUTE CONFIGURATION.

Although the absolute configuration of several caryophyllene derivatives had been deduced by the method of molecular rotations<sup>71</sup> and also by the asymmetric synthesis method<sup>27</sup>, X-ray crystallography is known to be the most reliable method of assignment, and it was deemed worthwhile establishing the absolute configuration of pseudoclovene A. The intensities of 28 Bijvoet pairs<sup>72</sup> ( $hkl$  and  $h\bar{k}l$ ) were estimated visually and structure factors were calculated taking into account the anomalous dispersion corrections for bromine and sulphur given in the International Tables<sup>73</sup>. The results of the calculations are presented in Fig. 17 which shows only 2 Bijvoet pairs (marked by an asterisk) differing in direction between the calculated and observed structure factors. It follows that the structure in Fig. 15 correctly represents the absolute stereochemistry of the mono-*p*-bromobenzenesulphonyl ester of pseudoclovene A diol.

DISCUSSION.

Both molecules in the asymmetric unit adopt similar conformations and are closely related by a pseudo four-fold axis. Thus if the coordinates of the first molecule are transformed by the symmetry operation appropriate to a four-fold screw axis ( $x, y, z, \rightarrow z, \frac{1}{4} + y, \bar{x}$ ), to a good approximation, the coordinates of the corresponding atoms of the second molecule are obtained. Within experimental error, almost all the bond angles and bond lengths of molecule 1 are identical to

those in molecule 2. One or two differences which appear to be significant in terms of the estimated standard deviations are most likely to indicate a slight underestimation of errors rather than inherent differences between the molecules of the asymmetric unit. Hence the dimensions in both molecules have been averaged and the mean values are given in Table 2. In the following discussion mean values are quoted where appropriate.

The pseudoclovene A derivative is a substituted tricyclo - (6,3,1,0<sup>1,5</sup>) dodecane system and shows some interesting conformational properties. The cyclopentane ring adopts the envelope conformation and is cis-fused to a cyclohexane ring, which, in turn, constitutes six atoms of the bicyclo(3,3,1)nonane skeleton. In idealised conformations these rings would produce a highly strained species and the deformations undergone by the molecule to relieve this strain are marked. As might be expected, especially in the light of the recent strain calculations<sup>74</sup>, bond elongation does not contribute significantly to strain minimisation, the C(sp<sup>3</sup>) - C(sp<sup>3</sup>) bond distances being very close to those quoted by Sutton et al<sup>75</sup>.

X-ray investigations of carbocyclic<sup>76</sup> and heterocyclic<sup>77</sup> bicyclo(3,3,1)nonane systems show the preferred conformation in the solid state to be a flattened chair-chair arrangement ; but, in this instance, the cyclohexane cis-fused to the cyclopentane ring prefers to adopt a boat conformation. This may be due to the increased interaction across the bridge ring system between the endo substituents

on atoms C(3) and C(10) as a result of a brosylate group replacing a hydrogen atom ; in which case this result is of considerable importance in considerations of the solvolytic behaviour of the tosylates from exo and endo bicyclo(3,3,1)nonan-3-ol<sup>78</sup>. While the endo bicyclo(3,3,1)nonan-3-ol tosylate may indeed be in a boat-chair conformation, direct correlation between this molecule and the brosylate of pseudoclovene A diol may not be assumed, since the presence of the cis-fused cyclopentane ring and the tertiary hydroxyl group will undoubtedly play a part in determining the overall conformation.

Even in the boat-chair conformation there is still considerable strain present owing to the mutual repulsions between the C(5) hydroxyl group and the C(7) and C(10) endo methylene hydrogen atoms, in addition to the "bow-sprit" interaction of the hydrogens attached to C(6) and C(12). The interactions of C(10) with O(4) and C(7) are partially relieved by a flattening of the cyclohexane chair so that C(10) is only displaced by 0.55 Å from the best plane through C(1), C(11), C(8) and C(9). In an ideal chair conformation with tetrahedral angles this displacement would be 0.73 Å<sup>76</sup>. The bridge atom C(12) is constrained by the adjacent boat ring, hence its deviation (0.75 Å<sup>76</sup>) from the plane does not differ significantly from the ideal value. Similar ring flattening effects have been observed in the tricyclo-(5,3,1,1<sup>2,6</sup>)dodecane system<sup>79</sup> in addition to the heterocyclic and carbocyclic bicyclo(3,3,1)nonane systems previously mentioned.

Interaction of the "bow-sprit" hydrogens is relieved by a slight flattening of the boat ring so that the C(6) to C(12) separation is increased from  $2.57 \overset{\circ}{\text{\AA}}$ , the value expected for an undistorted boat ring, to  $2.64 \overset{\circ}{\text{\AA}}$ . Further relief is afforded by a significant twisting of the two cyclohexane rings as is evidenced by the non-equality of the C(9) to C(5) ( $3.75 \overset{\circ}{\text{\AA}}$ ) and the C(11) to C(7) ( $3.49 \overset{\circ}{\text{\AA}}$ ) distances. No such twisting of the molecular framework has been observed in the twin-chair conformations of carbocyclic and heterocyclic bicyclo(3,3,1)nonane systems nor in the tricyclo(5,3,1,1<sup>2,6</sup>)dodecane skeleton. The twist conformation, in addition to reducing steric interaction between the "bow-sprit" hydrogens, minimises the overcrowding which would result from the proximity of the C(5) hydroxyl group and the endo methylene hydrogen bonded to C(10). A necessary result from this flattening and twisting in the bicyclo(3,3,1)nonane skeleton is the appreciable increase in the valency angles of the ring at atoms C(10) and C(11), the average value being  $114.9^\circ$ .

The cyclopentane ring has an envelope conformation with C(3) displaced  $0.63 \overset{\circ}{\text{\AA}}$  from the best plane through carbon atoms C(1), C(2), C(4) and C(5). The average valency angle in the ring ( $104.3^\circ$ ) is in good agreement with the usual mean angle ( $105^\circ$ ) in five-membered rings<sup>80</sup>.

The C(5)-C(1)-C(11) valency angle ( $114.4^\circ$ ) has been increased to minimise the steric interactions between the hydroxyl O(4) and C(11) and the torsional interaction about the C(5)-C(1) bond (the non-

bonded separation O(4) to C(11) is 2.62 Å while the torsional angle O(4)C(5) - C(1)C(11) is 5°. The non-bonded interaction of the hydroxyl O(4) with the methyl group C(14) (the distance between O(4) and C(14) is 2.81 Å) has been relieved by an increase in the C(14)-C(5)-O(4) angle to 116.4°. No accompanying increase in the C(4)-C(5)-O(4) angle (109.2°) is observed and this is not altogether unexpected since any increase would push the hydroxyl group closer to the endo methylene hydrogen on C(10) (see Fig. 15) and so worsen the severe steric strain already present between these centres. On the other hand the steric interaction between C(13) and C(6) is relieved by increases in both the C(13)-C(4)-C(5) and C(4)-C(5)-C(6) angles which are 112.2° and 115.7° respectively.

The carbon atoms of the benzene ring and the sulphur and bromine atoms are coplanar within experimental error. Bond lengths and angles in this part of the molecule are normal with the exception of those around C(16'). These discrepancies are probably a result of the uncertainty in the position of C(16') caused by diffraction effects from the adjacent bromine atom.

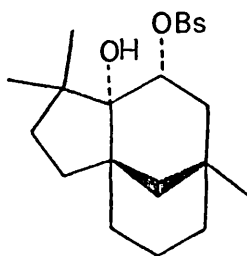
#### MOLECULAR PACKING.

All the intermolecular distances are close to or greater than the normal Van der Waals distances with the exception of O(2)...O(4') and O(4)...O(2') which have a value of 3.00 Å, probably as a result of intermolecular O...H - O hydrogen bonding. Such an analysis is

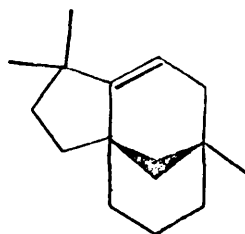
supported by a difference in the S - O(1) (1.394 Å) and S - O(2) (1.445 Å) bond lengths. The lengthening of the S - O(2) bond, if significant, is presumably caused by a partial loss in the double bond character resulting from its participation in hydrogen bonding. The molecules in the crystal are linked together by hydrogen bonds and form spirals parallel to the b direction.

### CONCLUSIONS.

A three-dimension X-ray analysis of the mono-*p*-bromobenzene-sulphonate of pseudoclovene A diol shows it to have the structure (68). This, in turn, leads to the assignment of structure (69) to the parent olefin, and from examination of anomalous dispersion effects the absolute stereochemistry is also established to be that shown in (69).



68



69

Thanks are due to Professor D.W.J. Cruickshank, Drs. D.R. McGregor, K.W. Muir, J.G. Sime and Messrs. D.R. Pollard and J.G.F. Smith whose programmes were used in the calculations carried out on the University K.D.F.9 computer.

## Table 2.

(a) Average bond lengths with e.s.d.s.(Å).

Br -C(16)	1.921(12)	C(4)-C(14)	1.506(21)
S -O(1)	1.394(10)	C(5)-C(6)	1.535(16)
S -O(2)	1.445( 9)	C(6)-C(7)	1.517(17)
S -O(3)	1.584( 7)	C(7)-C(8)	1.549(20)
S -C(19)	1.766(10)	C(8)-C(9)	1.562(23)
O(3)-C(6)	1.464(13)	C(8)-C(12)	1.506(19)
O(4)-C(5)	1.435(14)	C(8)-C(15)	1.537(25)
C(1)-C(2)	1.542(21)	C(9)-C(10)	1.519(27)
C(1)-C(5)	1.552(16)	C(10)-C(11)	1.524(26)
C(1)-C(11)	1.525(19)	C(16)-C(17)	1.307(20)
C(1)-C(12)	1.534(19)	C(16)-C(21)	1.335(21)
C(2)-C(3)	1.488(21)	C(17)-C(18)	1.415(18)
C(3)-C(4)	1.555(18)	C(18)-C(19)	1.365(17)
C(4)-C(5)	1.570(17)	C(19)-C(20)	1.387(18)
C(4)-C(13)	1.525(18)	C(20)-C(21)	1.360(21)

## (b) Average valency angles with e.s.d.s.(°)

O(1) S O(2)	118.9( 5)	C(4)C(5)C(6)	115.6( 9)
O(1) S O(3)	104.4( 5)	O(3)C(6)C(5)	106.7( 8)
O(1) S C(19)	110.9( 5)	O(3)C(6)C(7)	109.2( 9)
O(2) S O(3)	109.8( 5)	C(5)C(6)C(7)	113.8(10)
O(2) S C(19)	107.4( 5)	C(6)C(7)C(8)	110.4(11)
O(3) S C(19)	104.5( 5)	C(7)C(8)C(9)	109.7(13)
S O(3)C(6)	121.1( 7)	C(7)C(8)C(12)	111.6(11)
C(2)C(1)C(5)	104.4(11)	C(7)C(8)C(15)	109.4(13)
C(2)C(1)C(11)	107.4(10)	C(9)C(8)C(12)	108.4(11)
C(2)C(1)C(12)	112.6(10)	C(9)C(8)C(15)	109.0(13)
C(5)C(1)C(11)	114.3(10)	C(12)C(8)C(15)	108.7(13)
C(5)C(1)C(12)	110.7(10)	C(8)C(9)C(10)	109.8(13)
C(11)C(1)C(12)	107.3(11)	C(9)C(10)C(11)	114.8(16)
C(1)C(2)C(3)	104.9(11)	C(1)C(11)C(10)	114.9(12)
C(2)C(3)C(4)	105.4(11)	C(1)C(12)C(8)	110.3(11)
C(3)C(4)C(5)	98.8( 9)	Br C(16)C(17)	118.2(11)
C(3)C(4)C(13)	108.8(10)	Br C(16)C(21)	116.8(11)



c(3)c(4)c(14)	111.9(11)	c(17)c(16)c(21)	125.0(13)
c(5)c(4)c(13)	112.2(10)	c(16)c(17)c(18)	119.1(13)
c(5)c(4)c(14)	116.4(11)	c(17)c(18)c(19)	116.2(11)
c(13)c(4)c(14)	108.3(11)	s c(19)c(18)	119.4( 9)
o(4)c(5)c(1)	107.8( 9)	s c(19)c(20)	117.6( 9)
o(4)c(5)c(4)	109.2(10)	c(18)c(19)c(20)	123.0(11)
o(4)c(5)c(6)	106.1( 9)	c(19)c(20)c(21)	117.6(13)
c(1)c(5)c(4)	107.8(10)	c(20)c(21)c(16)	119.1(13)
c(1)c(5)c(6)	110.0(10)		

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INTRODUCTION.

The rate determining step in an SN<sub>2</sub> reaction is the initial ionization process. In the gas phase this stands very high energy but in the presence of a polar solvent the activation energy is lower. The mechanism may be affected in two distinct ways. Since several leaving groups (X) are electron withdrawing, the C-X bond will be polarized even in the ground state, and polar solvent molecules are capable of stabilizing this charge separation. In the S<sub>N</sub>2 mechanism lengthening the C-X bond in the transition state will

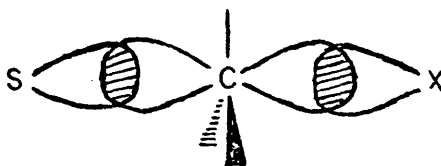
## Section Two.

become even more important, with the result that the energy of the transition state will be much lower than in the ground state, thereby producing a net lowering of the activation energy. The effect will be more marked if the leaving group is a poor one, and the developing carbocation will be more dependent on the group. It is a common mistake to think of this as a typical (SN)<sub>1</sub> displacement reaction, this involves a concerted leaving group back side extraction (anti-periplanar) to the C-X bond, and the partial carbocation (or intermediate) is described as having an



CHAPTER 1.INTRODUCTION.

The rate determining step in an  $SN_1$  reaction is the initial ionisation process. In the gas phase this demands very high enthalpies, but in the presence of a polar solvent the activation energy is lowered. The reaction may be affected in two distinct ways. Since normal leaving groups (X) are electron withdrawing, the C - X bond will be polarised even in the ground state, and polar solvent molecules are capable of stabilising this charge separation. As the C - X bond lengthens the charge separation will increase and solvation will become even more important, with the result that the energy gained from solvation in the transition state will be much larger than in the ground state, thereby producing a net lowering in the activation energy. The second role played by solvent involves stabilisation of the developing carbonium ion from the opposite side to the departing group, in a manner analogous to the incoming nucleophile in a direct ( $SN_2$ ) displacement mechanism. This transition state concept invoking back side solvation leads logically to the hypothesis of a penta-covalent carbonium ion intermediate (1) as described by Doering and Zeiss<sup>1</sup>.





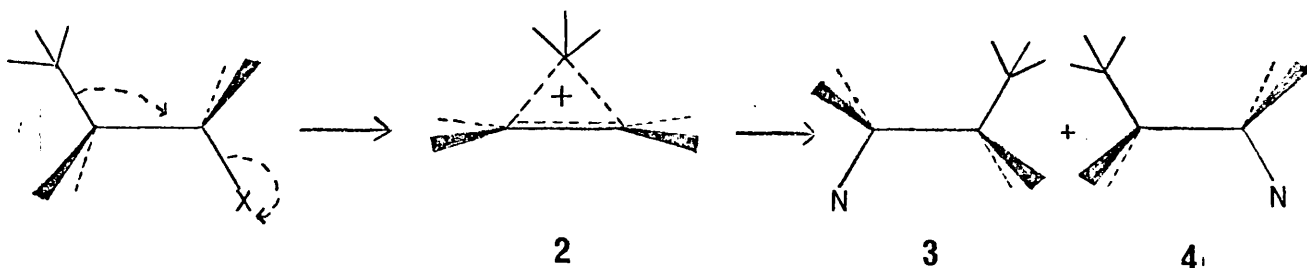
In many cyclic systems it is sterically impossible for solvation to occur at the rear of the developing carbonium ion and such an interpretation has been employed, at least in part, to account for the low solvolysis rates of substituted bridgehead compounds<sup>2</sup>.

In a large class of systems, not only cyclic in nature, it is commonly believed that the role of solvent in back side stabilisation is assumed in whole or in part by some nucleophilic function, which is itself part of the molecule undergoing substitution. This internal driving force in solvolysis, resulting from participation by a neighbouring group, is ascribed the name of "anchimeric assistance"<sup>3</sup>.

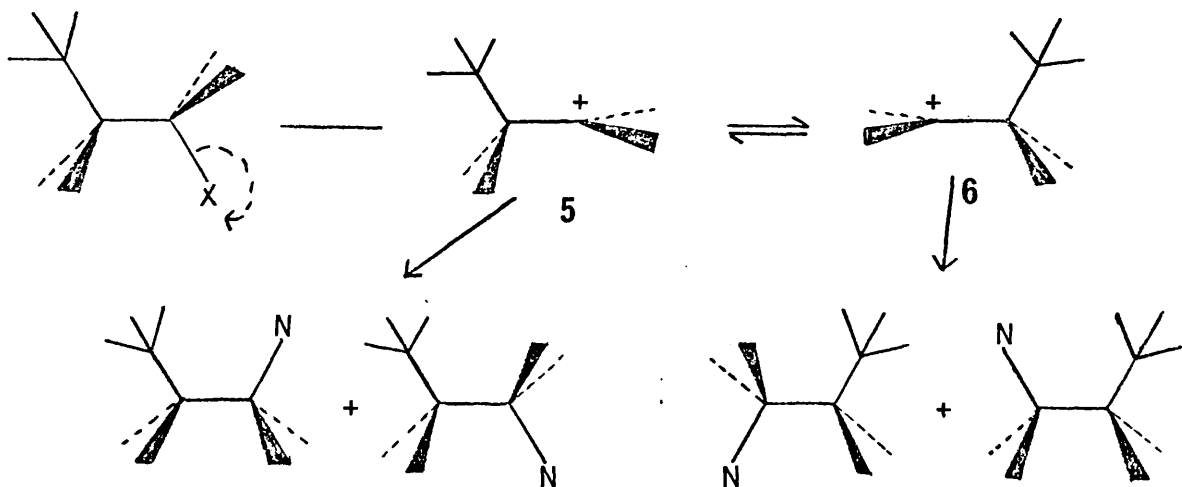
Functional groups which would be expected to behave as good internal nucleophiles, and especially those containing nitrogen, sulphur or oxygen, are commonly accepted as participating in the ionisation step during solvolysis<sup>4,5</sup>, although unanimous agreement does not exist on the subject of carbon acting as the nucleophile. The whole question of carbon participation is intimately bound up in the controversy over non-classical carbonium ions and, while it is not apposite to annotate the arguments for and against such intermediates, brief mention must be made of some points relevant to these investigations.

Winstein and many other investigators argue that in a variety of circumstances a carbon atom can participate in the initial ionisation step giving rise to a bridged "non-classical ion" (2), which

undergoes nucleophilic attack to give products (3) and (4) stereospecifically.



Brown, on the other hand, prefers to regard the initial ionisation as proceeding independently to the classical cation (5), which may undergo rapid equilibrium with the other classical cation (6), and formally give rise to four products as shown.



If anchimeric assistance is operating, then three phenomena should result :- a) considerable rate enhancement, b) rearranged products, and c) marked stereospecificity in the products. The interpretation of rate data shows an enormous difference in viewpoint

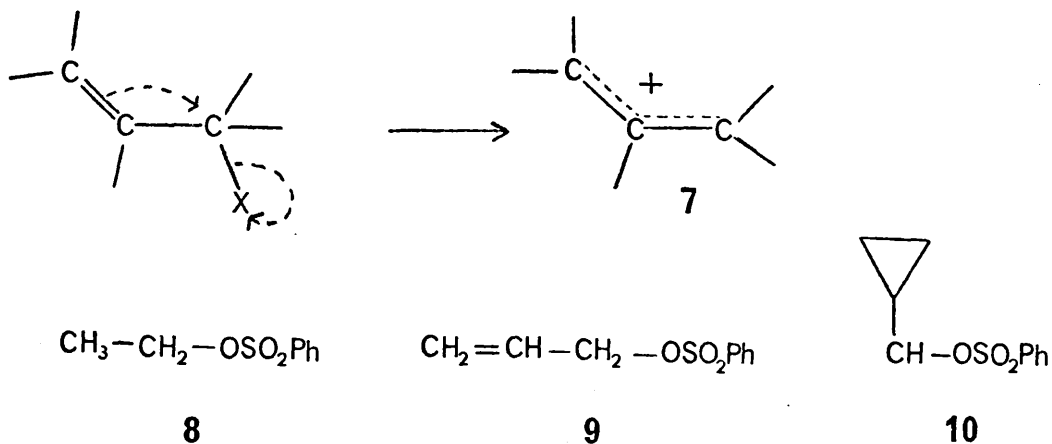
since the question, "Rate enhancement relative to what?" must be answered before any meaning can be derived from individual rate measurements. The problem of what constitutes a good model is a major obstacle in attaining a final answer to the question of non-classical ions, since Brown argues that the apparently fast rates observed in many systems are in fact normal and that the selected model often solvolyses slowly as a result of steric factors. That the last two expected phenomena are indeed observed, sheds little light on the issue, as Brown<sup>6</sup> has presented a cogent argument to account for these without invoking non-classical ions. A review article by Sargent<sup>7</sup> presents most of the available data and argues forcibly in favour of non-classical ions, while concise accounts of Brown's views have also been published<sup>6,8</sup>.

To a large extent the controversy centres on whether C - C single bonds can participate in ionisation and there is little doubt that a carbon atom may provide anchimeric assistance when it is part of an aryl ring, an olefin or a cyclopropane. In the investigation which follows an attempt is being made to estimate the relative efficiencies of a double bond and a cyclopropyl ring in participation within a semi-rigid bicyclo(3,3,1) system.

It is possible to classify the reported examples of cyclopropyl and double bond participation according to the relative situation of the developing carbonium ion to the neighbouring group under examination. Thus one can consider as separate classes an allylic carbonium ion together with a cyclopropyl carbinyll cation, a homoallylic with a

$\beta$ -cyclopropanyl carbonium ion, and those systems in which the double bond or cyclopropane ring is separated by two or more carbon atoms from the carbonium ion. A fairly extensive coverage of all these systems is described by Eakin<sup>9</sup> and only a representative sample is now considered to enable the bicyclo(3,3,1) system to be placed in perspective.

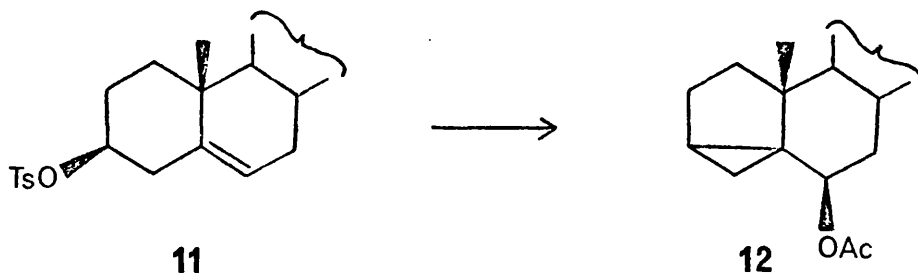
The delocalised representation of the allylic cation (7) is of course well-known and Hughes<sup>10</sup> seems to have first suggested that the double bond should greatly facilitate unimolecular displacement.



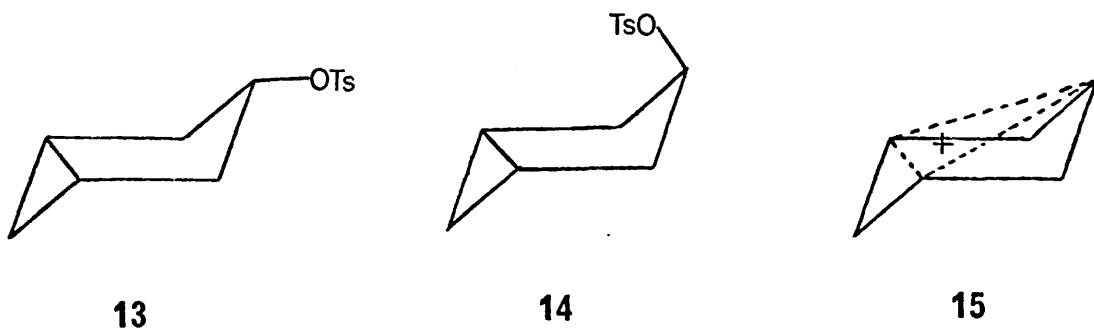
This effect turned out to be much smaller than anticipated ; for instance, the solvolysis rate of allyl chloride in aqueous formic acid is only 25 times faster than n-propyl chloride<sup>11</sup>. More striking is the rate of solvolysis in cyclopropyl carbinyl systems, which unexpectedly were found to be faster than the corresponding allylic systems. In the series of ethyl, allyl and cyclopropyl carbinyl benzenesulphonates [(8), (9) and (10)] the relative rates were found to be 1 to 36 to 500<sup>12,13</sup>. A similar order of reactivity has been observed for the

halo derivatives<sup>14</sup>.

Numerous examples of a double bond or a cyclopropane ring participating in solvolysis reactions have been reported for structural cases in which a methylenic group is interposed between the cation and the functional group. Probably the classic case of homoallylic participation is the earliest reported one, in which 3- $\beta$ -cholesteryl tosylate (11) gives the i-cholestane (12) with a rate 40 times faster than solvolysis of the saturated compound<sup>15</sup>.

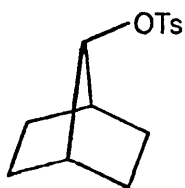


The first example of homocyclopropyl participation was described by Winstein<sup>16</sup> in the solvolysis of cis- and trans-3-bicyclo(3,1,0)-hexyl tosylates (13) and (14).

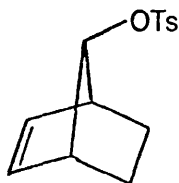


While the results obtained by other investigators<sup>17,18</sup> seemed to cast doubt on the interpretation of these results, a re-examination by Winstein's group<sup>19</sup> has confirmed the earlier results and would seem to indicate the intermediacy of the tris-homocyclopropenyl cation (15) in the solvolysis of the cis compound (13).

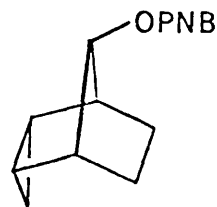
One system in which it is possible to obtain a direct comparison between homoallyl and homocyclopropyl participation is found in the norbornyl system. The solvolytic rates for anti-7-norbornyl tosylate (16), anti-7-norbornenyl tosylate (17) and endo-anti-bicyclo(3,2,1,0<sup>2,4</sup>)-octan-8-yl p-nitrobenzoate (18) have been measured<sup>20,21</sup>. It is found that both the double bond and the cyclopropane ring provide very marked anchimeric acceleration. Once again the cyclopropyl derivative is found to be more reactive than the corresponding olefin.



16



17



18

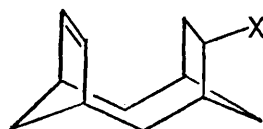
Relative  
Rates.

1

 $10^{11}$  $10^{14}$

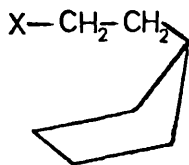
In the third sub-division of participation to be considered, systems in which the functional group is several carbon atoms distant from the potential carbonium ion centre, an enormous variety of structural types is possible and it is hardly surprising that the degree of anchimeric assistance can vary from none to extremely pronounced. In those examples in which the functional group is held very close to the potential carbonium ion, as a consequence of a fixed geometry, marked participation can be observed. A good example of geometrical proximity leading to large rate enhancement is found in the half-cage structure (19) which is found to solvolyse 13 times faster than the corresponding anti-7-norbornenyl derivative<sup>22</sup>.

In more flexible systems, however, it is common to encounter only very small rate enhancements both for cyclopropyl and double bond participation.

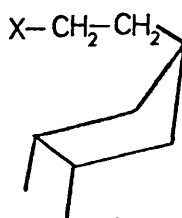


19

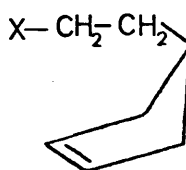
Sargent has recently examined the nucleophilic efficiencies of a remote cyclopropane ring and a double bond in intramolecular displacement reactions for 2-(cyclopentyl)-ethyl derivatives<sup>23</sup>.



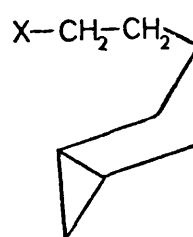
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21



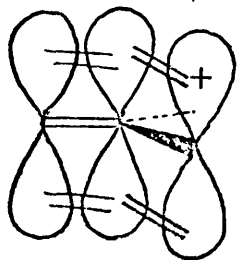
22



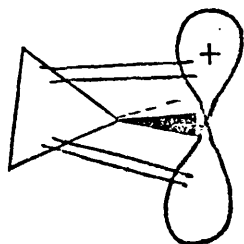
23

Thus he compared the rates of acetolysis of the tosylates (20), (21), (22) and (23) and found that the cyclopropyl compound showed no anchimeric assistance, having a rate almost identical to the two saturated model compounds, while the olefin did show some participation, exhibiting an 87-fold increase in rate. These results were interpreted in terms of differing steric interactions in the transition state. From this and other work it is evident that as a participating group, a cyclopropane ring is more sensitive to environmental factors than is a double bond.

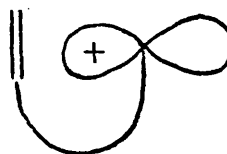
At this juncture it must also be noted that there are two extreme forms of functional group participation with a cation plus a multitude of intermediate cases. In the allyl cation, stabilisation is presumed to result from largely  $\pi$  interactions as shown in (24) and it has been proposed that the cyclopropyl carbinyl cation (25) is similarly stabilised in a  $\pi$  or pseudo- $\pi$  manner<sup>24,25</sup>. The other extreme forms of double bond and cyclopropyl participation are shown in (26) and (27), the interactions in these examples being purely  $\sigma$  in character.



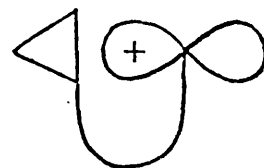
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25



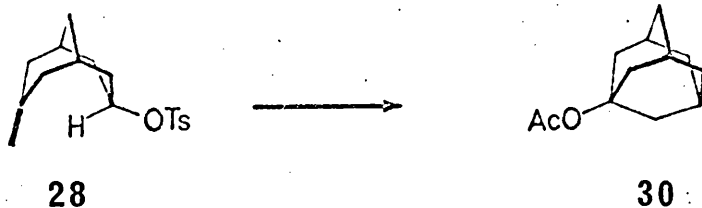
26



27



## Fig 1 .

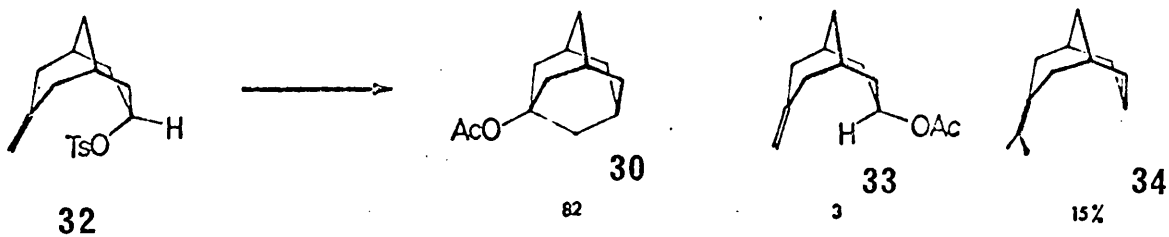
ACETOLYSIS PRODUCTS AND  
KINETIC DATA.

$$k = 6.56 \times 10^{-4} \text{ at } 25^\circ\text{C}$$

$$k = 1.15 \times 10^{-2} \text{ at } 50^\circ\text{C}$$

$$\Delta H^\ddagger = 21.7 \text{ Kcal./ Mole}$$

$$\Delta S_{25}^\ddagger = -1.5 \text{ e.u.}$$

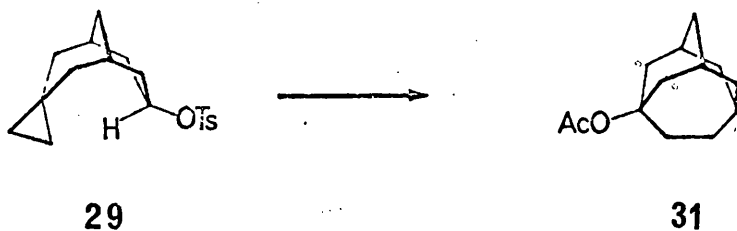


$$k = 4.05 \times 10^{-5} \text{ at } 25^\circ\text{C}$$

$$k = 7.45 \times 10^{-4} \text{ at } 50^\circ\text{C}$$

$$\Delta H^\ddagger = 21.7 \text{ Kcal./ Mole}$$

$$\Delta S_{25}^\ddagger = -5.6 \text{ e.u.}$$



$$k = 2.14 \times 10^{-4} \text{ at } 25^\circ\text{C}$$

$$k = 3.98 \times 10^{-3} \text{ at } 50^\circ\text{C}$$

$$\Delta H^\ddagger = 21.8 \text{ Kcal./ Mole}$$

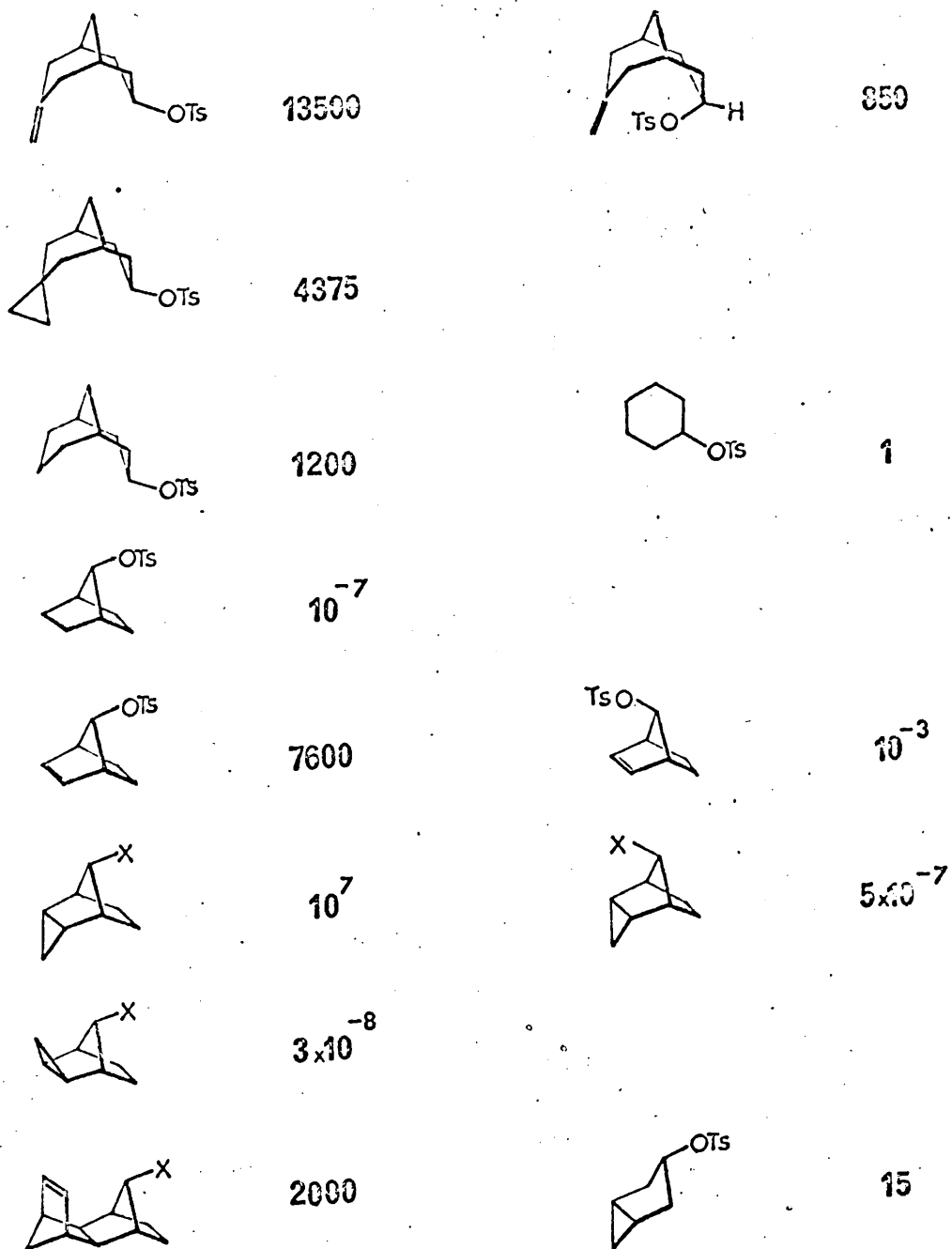
$$\Delta S_{25}^\ddagger = -2.3 \text{ e.u.}$$

An excellent opportunity of examining transannular participation, which is purely  $\sigma$  in nature, is afforded in the bicyclo(3,3,1) systems (28) and (29) (see Fig. 1). Eakin has synthesised these tosylates and obtained kinetic data for their solvolyses in buffered acetic acid<sup>26</sup>. The only products resulting from such treatment are adamantyl acetate (30) and homoadamantyl acetate (31), hence one of the expected phenomena resulting from participation, viz. rearranged products is observed. The syn-exomethylene tosylate (32) on acetolysis was found to yield 82% of adamantyl acetate (30), 3% of anti-exomethylene acetate (33) and 15% of the diene (34). Provided participation is equally important in the two transition states, it is evident from the rate data in Fig. 1 and the relative rates shown in Fig. 2 that the double bond is providing more anchimeric assistance than the cyclopropane ring. Other phenomena such as relief of steric interactions will be playing an important part during solvolysis, but a fuller discussion of the implications arising from this rate data will be deferred until Chapter 3.

Although kinetic studies can often provide strong evidence in favour of neighbouring group participation, inherent difficulties, such as the choice of suitable model systems, lead to conflicting interpretations. The questions of non-classical carbonium ions and anchimeric assistance have so fired the minds of organic chemists that numerous alternative methods of tackling the problems are being examined. Three of these are of particular note. Considerable success

## Fig 2.

RELATIVE SOLVOLYTIC REACTIVITY AT 25°C.



is being achieved in observing the intermediate carbonium ions directly by spectroscopic techniques. A chief exponent of this approach is Olah<sup>27</sup>, who has succeeded in generating carbonium ions at low temperature by means of a "magic acid" (often a mixture of fluoro-sulphuric acid in antimony pentafluoride) and, by studying the nuclear magnetic resonance spectrum, can usually gain otherwise unavailable information concerning the nature of the species in solution and their subsequent reactions. One limitation imposed on this method is the finite nature of the nuclear magnetic resonance time scale, which means that one may be observing either an averaged effect or else reasonably long-lived intermediates.

A second modern approach makes use of quantitative determinations of the steric effects operative in molecules, as first described by Westheimer<sup>28</sup>. In outline, the method consists of taking the equilibrium conformation of the species undergoing solvolysis and the expected classical carbonium ion derived therefrom, calculating the sum of the strain terms

$$E_{\text{total}} = E_{\text{bond length}} + E_{\text{bond angle}} + E_{\text{torsional}} + E_{\text{nonbonded interaction}}$$

for both molecular species, and by subtraction, obtaining the difference in strain in going to the carbonium ion. It is found that a fairly linear relationship exists between this  $\Delta E_{\text{strain}}$  and the logarithm of the relative rate constants for the solvolyses of a

number of compounds, which are believed to proceed without anchimeric assistance. Large deviations from this linear relationship are taken to indicate neighbouring group participation<sup>29</sup>. Although such an approach accounts for most of the steric interactions involved and would seem to undermine Brown's objections to non-classical ions, it is argued that this calculation is incomplete unless some term can be included to take measure of the less well-defined steric inhibition to ionisation.

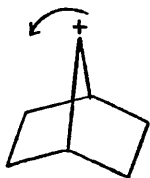
Without doubt the last method is the most promising one, but at the same time it is the most difficult and the least likely to yield immediately useful results. This approach embodies some quantum mechanical calculation of the progress of the simulated reaction, and by consideration of the possible transition states e.g. classical or non-classical, together with observations on the behaviour of the charge distribution, it should be possible to plot out the most likely course of reaction. In principle, this is both aesthetically satisfying and scientifically more realistic than either of the earlier methods, but as a consequence of the necessary simplifications and assumptions the final validity of current results may be seriously in question.

Although fully aware of these possible deficiencies, we elected to attempt a correlation between the observed rate data and the results of Extended Hückel calculations for the bicyclo(3,3,1)nonane derivatives already discussed.

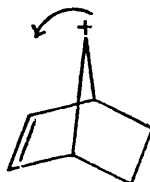
CHAPTER 2.THE METHOD OF CALCULATION.Simulation of the Reaction Pathway.

Complete ab initio calculations are as yet intractable for molecular systems of such size as the bicyclo(3,3,1) tosylates which form the subject of this investigation. The developments in ab initio calculations on small molecules and the progress in the analysis of the effects produced on introducing various assumptions<sup>30</sup>, however, have provided a means of developing semi-empirical procedures. One such approximate Molecular Orbital Calculation, which has achieved a good deal of success, is the Extended Hückel Method (EHM) introduced by Longuet-Higgins and Roberts<sup>31</sup> and popularised of late by Hoffmann<sup>32</sup>.

It is especially noteworthy that this method has been employed in calculations on carbonium ions and has yielded what are purported to be "chemically" meaningful results<sup>33</sup>. Of particular relevance to the present problem are those calculations on the 7-norbornyl (35), 7-norbornenyl (36) and endo-bicyclo(3,2,1,0<sup>2,4</sup>)octan-8-yl (37) cations, in which the cation at C<sub>7</sub> was rotated in an arc towards the single bond, the double bond or the cyclopropane ring respectively<sup>33,34,35</sup>.



35



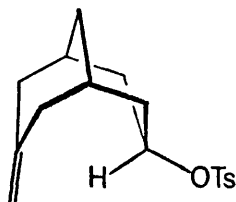
36



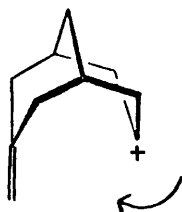
37

As the cation is moved towards the double bond or the cyclopropane ring a pronounced minimum in the total energy results. This energy change is accompanied by a transfer of positive charge from the  $C_7$  position to the atoms  $C_2$  and  $C_3$ . These phenomena have been interpreted as evidence for non-classical cation formation, but the most striking feature is that the cyclopropane ring seems to be more efficient than the double bond in stabilising the system. Since the publication of these calculations, the rates of solvolyses of three anti derivatives corresponding to the cations (35), (36) and (37) have been compared and it would appear that the cyclopropane ring does in fact participate more efficiently than the double bond<sup>20,21</sup>.

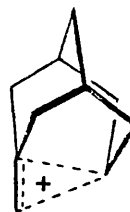
Perhaps participation in solvolysis can be examined in the bicyclo(3,3,1) systems by this method. It was felt that merely moving the carbonium ion at  $C_3$  towards the double bond in (38) in an analogous fashion to the norbornenyl calculations was unrealistic since the arrangement (39) was unlikely to resemble the probable transition state during solvolysis.



28

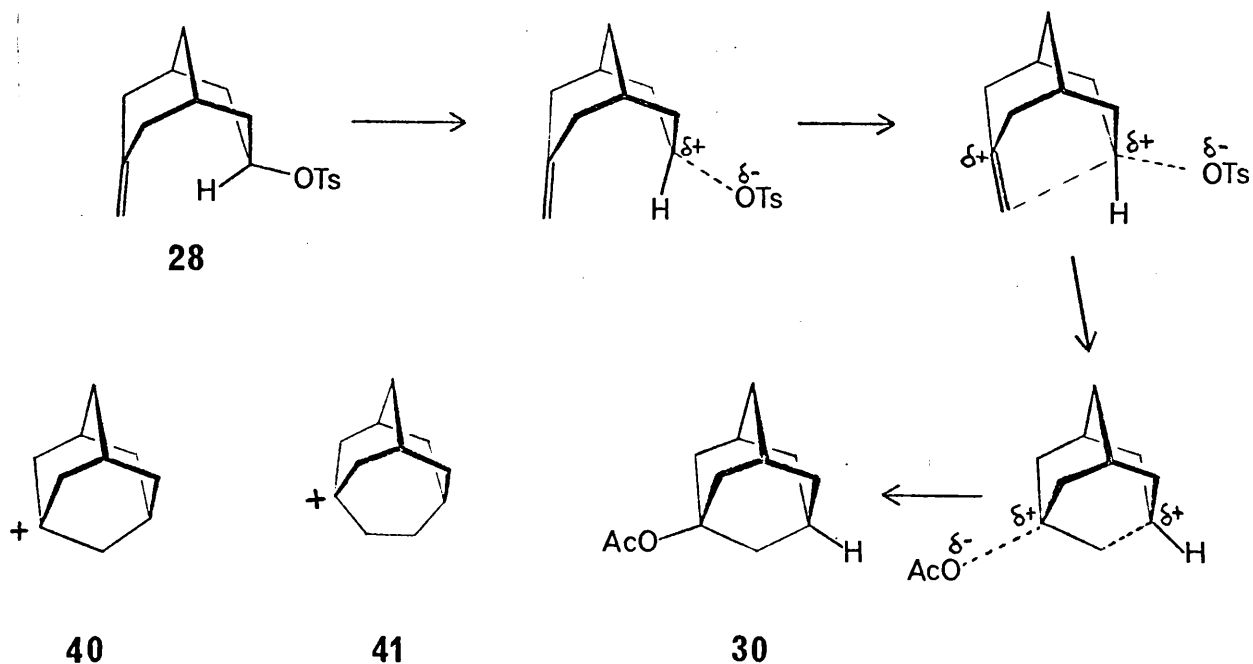


38



39

The structural reorganisation (28)  $\rightarrow$  (30) is a more probable representation of the reaction pathway, provided the double bond is participating at an early stage in the transformation.



If the above representation is accurate, then clearly the double bond is participating with only a partial positive charge developed at  $C_3$  and one may reason that the energy gained by delocalisation should be greater if one begins with a fully developed carbonium ion. Hence the simplified approach used in the subsequent calculations commences with a trigonal carbonium ion at  $C_3$  and the double bond or cyclopropane group is rotated towards the carbonium ion until the adamantyl (40) or homoadamantyl cation (41) is attained.



### The Extended Hückel Theory.

The Extended Hückel Theory utilises the linear combination of atomic orbitals expansion for a molecular orbital  $\Psi_i$  in terms of

$$\Psi_i = \sum_{j=1}^n c_{ij} \phi_j$$

On minimising the total energy the secular equations are obtained, i.e.

$$\sum [H_{ij} - ES_{ij}] c_{ij} = 0$$

In their solution the following approximations are made. The basis set of atomic orbitals containing the 1s orbitals of the hydrogen atoms and the 2s and 2p orbitals for each carbon atom are represented by Slater functions. The coulomb integrals,  $H_{ii}$ , are usually selected from valence state ionisation potentials, and the off-diagonal matrix elements are approximated by use of the expression first discussed by Mulliken<sup>36</sup> and used by Wolfsberg and Helmholtz<sup>37</sup>.

$$H_{ij} = 0.5 K (H_{ii} + H_{jj}) S_{ij}$$

Several values of K have been employed by different investigators and a systematic examination has been conducted into the effects caused by variation of K in the case of ethane<sup>32</sup>.

Having determined the matrix elements, solution of the secular determinant gives the eigenvalues and eigenvectors. A Mulliken population analysis<sup>38</sup> of the resultant wave functions yields the overlap populations and the effective charges. The total energy of the system is approximated as the sum of one-electron energies. To examine the reliability of this procedure, Hoffmann has considered the behaviour of this sum of one-electron energies over a wide range of internuclear distances. The complete Hamiltonian may be written as the sum of electron-electron, electron-nuclear and nuclear-nuclear energies,

$$H = \sum_{ee'} H_{ee'} + \sum_{en} H_{en} + \sum_{nn'} H_{nn'}$$

In the "Hückel Theory, these values are never calculated explicitly but rather  $H$  is approximated by a sum of one-electron effective Hamiltonians, whose matrix elements we endeavour to estimate systematically.

$$H = \sum_e H_{\text{eff.}}$$

Hoffmann argues from the observed behaviour of the one-electron energies at different internuclear separations that this systematic guessing of effective one-electron Hamiltonians includes nuclear

repulsions at small distances. If one superimposes nuclear-nuclear interactions on the one-electron energies the minimum in the energy curve completely vanishes.

Slater has also advanced a theoretical argument to justify the total energy being approximated as the sum of one-electron energies<sup>39</sup>. The total Hartree-Fock molecular energy for a neutral molecule may be written as

$$E = 2 \sum_i e_i + \sum_{n,n'} E_{nn'} - \sum_{e,e'} E_{ee'}$$

where  $e_i$  are one-electron energies,  $\sum E_{nn'}$  is the sum of nuclear-nuclear interactions and  $\sum E_{ee'}$  is the sum of electron-electron repulsions.

Slater shows that the last two terms cancel each other approximately, or at least their difference is believed to vary slowly with inter-nuclear distance.

In the case of cationic species, however, this argument clearly does not hold since a one electron deficiency exists, thereby reducing the electron-electron repulsion term and creating a decided imbalance in the last two terms. In spite of these theoretical objections, Hoffmann's calculations do show an energy minimum for charged species and from the published work it would appear that some meaningful results are obtainable.

The Computer Programme.

An Algol Extended Huckel programme written by J. Danielson, to whom I am indebted, was employed and the calculations were performed on Glasgow University's K.D.F. 9 computer.

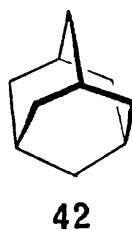
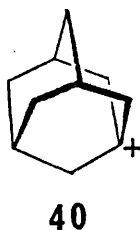
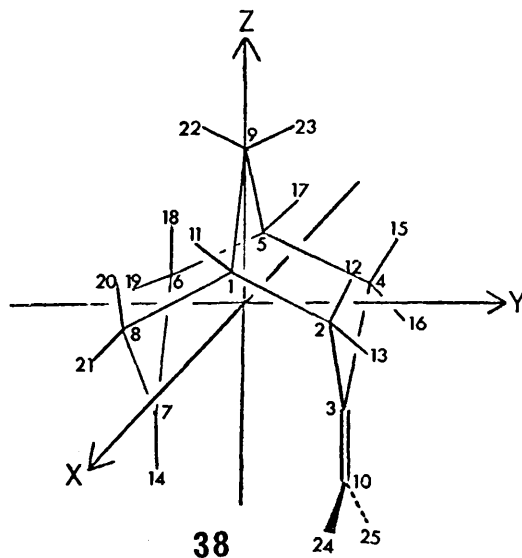
The essential input data are :-

- a) For each atom ;
  - 1. A basis set of Slater orbitals.
  - 2. The Cartesian co-ordinates.
- b) For each orbital ;
  - 1. The effective nuclear charge.
  - 2. The coulomb integral.

The programme is in three parts and output may be obtained corresponding to each stage of the calculation. Thus the overlap matrix, the eigenvectors and eigenvalues, and the complete population analysis are all available as output if desired. The computing time required is largely dictated by the number of orbitals. For a 25 orbital problem the computing time is approximately 10 minutes, whereas a 55 orbital calculation such as the adamantyl cation requires approximately 80 minutes.

Choice of Geometry.A) Exomethylene Closure.

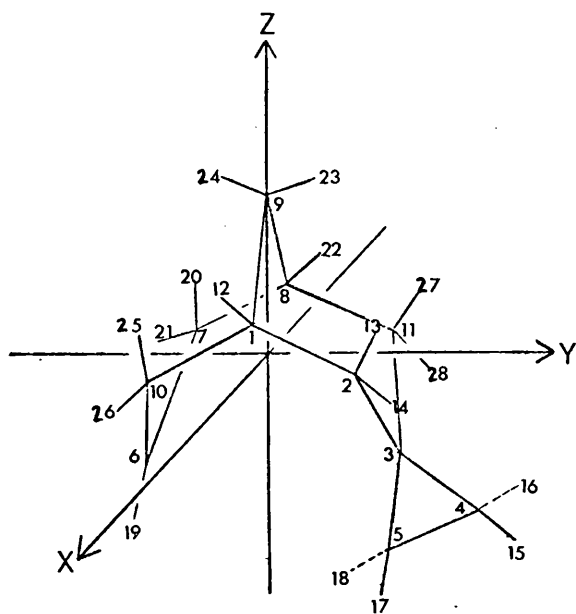
Bicyclo(3,3,1) compounds are known to exist preferentially as twin-chair conformers, but X-ray crystallography has demonstrated that the potentially severe interactions between the endo substituents at C<sub>3</sub> and C<sub>7</sub> are minimised by flattening of the two chairs<sup>40</sup>. In the completely closed form one has the adamantyl cation (40) which is predicted from strain calculations<sup>41</sup> to show several significant differences in bond lengths and angles from the symmetrical, saturated analogue, adamantane (42).



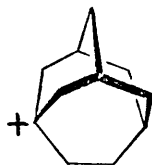
The bond lengths employed were largely those suggested by Dewar<sup>42</sup> and the numbering scheme adopted is shown in (38). The following approximations were then taken :-

- 1) The carbon atoms  $C_1$  to  $C_9$  were assumed to form a perfect twin-chair skeleton with all C - C bond lengths equal to  $1.539 \overset{\circ}{\text{Å}}$ , C - H lengths equal to  $1.093 \overset{\circ}{\text{Å}}$ , and all angles taking the tetrahedral value of  $109^{\circ}28'$ .
- 2) During the simulated closure these C and H atoms were regarded as fixed so that in the closed form (40) three perfect chairs were obtained.
- 3) The bond lengths  $C_7-C_{14}$ ,  $C_{10}-C_{24}$  and  $C_{10}-C_{25}$  were set at  $1.083 \overset{\circ}{\text{Å}}$  and the bond angle  $H_{24}-C_{10}-H_{25}$  at  $120^{\circ}$  in the exomethylene cation (38).
- 4) As closure proceeds the following changes occur :-
  - a)  $C_3-C_{10}$  increases from  $1.337$  to  $1.539 \overset{\circ}{\text{Å}}$ .
  - b)  $C_7-H_{14}$ ,  $C_{10}-H_{24}$  and  $C_{10}-H_{25}$  increase from  $1.083$  to  $1.093 \overset{\circ}{\text{Å}}$ .
  - c) the angle  $H_{24}-C_{10}-H_{25}$  decreases from  $120^{\circ}$  to  $109^{\circ}28'$ .

These changes were regarded as varying linearly with  $\theta$  (the angle  $C_{10}-C_9$  or  $C_7-H_{14}$  makes with the negative direction of the Z-axis).



43



44

B) Cyclopropyl Closure.

A similar approach was adopted for this series of calculations, although several complicating features exist in this case.

Diagram (43) shows the atomic numbering scheme employed throughout.

Since the product in this closure is homoadamantyl cation (44), one cannot retain the basic system used above, but by lengthening the  $C_3-C_6$  distance to  $2.975 \text{ \AA}$  and keeping the positions of  $C_1, C_2, C_7, C_8, C_9, C_{10}$  and  $C_{11}$  constant one obtains a skeleton which can be fixed throughout the closure. Such a modification involves changing the bond angles  $C_2-C_3-C_{11}$  and  $C_7-C_6-C_{10}$  to  $113^\circ 12'$  and contracting the bond lengths  $C_2-C_3, C_3-C_{11}, C_6-C_7$  and  $C_6-C_{10}$  to  $1.506 \text{ \AA}$ . The internal C-C-C angles of the cyclopropane ring are assumed to be  $60^\circ$  while a value of  $118^\circ$  is attributed to the external H-C-H angles based on the values obtained in a number of electron diffraction studies on cyclopropanes. If the angle  $\theta$  is defined in this instance as the angle between  $C_6-H_{19}$  and the negative direction of the Y-axis, it is seen to assume the value of  $73^\circ 56'$  in the cyclopropyl cation (43). Apart from  $C_4, C_5, H_{15}, H_{16}, H_{17}, H_{18}$  and  $H_{19}$  all the atomic positions are regarded as stationary during the simulated closure and a linear relationship is assumed between  $\theta$  and the various bond length and angle changes which occur. In the closed homoadamantyl cation the bond lengths  $C_6-C_5, C_5-C_4$  and  $C_4-C_3$  are all  $1.539 \text{ \AA}$ , and angles  $C_5-C_4-C_3$  and  $C_4-C_5-C_6$  are assigned the value of  $117^\circ 48'$  as suggested by Schleyer's strain calculations<sup>41</sup>. Thus in the closed form  $\theta$  is equal to  $7^\circ 48'$ .



CHAPTER 3.RESULTS AND DISCUSSION.Selection of Parameters.

Numerous calculations have been performed on methane and ethylene. Consequently these two molecules are well suited to employ as a gauge of the adequacy of the computer programmes and the choice of parameters. Apart from the bond lengths and angles, the variables in the input data are the Slater orbital exponents, the coulomb integrals and the constant K in the equation,

$$H_{ij} = 0.5 K (H_{ii} + H_{jj}) S_{ij}$$

The Slater orbital exponents for H(1s) and C(2s) and (2p) are 1.00 and 1.625 respectively. The selection of values for the coulomb integrals and K, however, represents the point of departure in many calculations employing the Extended Hückel Method. Hoffmann in his original paper assumed the coulomb integrals to be of value

$$C(2s) = - 21.4 \text{ eV,}$$

$$C(2p) = - 11.4 \text{ eV,}$$

$$\text{and } H(1s) = - 13.6 \text{ eV}$$

which are based on the valence state ionisation potentials of Skinner and Pritchard<sup>43</sup>. In the same investigation Hoffmann also

Table 1.

Method	$H_{ii}$ (-eV)		K	$e_i$ (-eV)	$e_i$ (-eV)		e. density	
	C(2s)	C(2p)			$a_1$	$t_2$	$q_C$	$q_H$
E.H.M.	19.32	11.70	1.75	137.9	23.38	15.19	4.486	0.879
E.H.M.	19.32	11.70	1.80	139.9	23.83	15.38	4.489	0.878
E.H.M.	19.32	11.70	1.88	143.0	24.55	15.65	4.493	0.877
E.H.M.	21.40	11.40	1.75	139.6	24.87	14.98	4.532	0.867
I.E.H.M.	---	---	1.75	133.8	23.96	14.32	4.100	0.975
Semi-empirical S.C.F.	---	---	--	---	---	13.88	3.692	1.077
S.C.F. (Krauss)	---	---	--	139.6	25.63	14.72	---	---
S.C.F. (Woznick)	---	---	--	140.4	25.84	14.79	---	---

examined the effect of the variation of  $K$  on the orbital energies and the population analysis and suggested  $K = 1.75$  was the optimum value. Using these parameter values together with the "rounded off" bond lengths used by Hoffmann, calculations on methane and ethylene yielded results which were in complete agreement with Hoffmann's determination of the sum of one-electron energies, the ionisation potential and the charge distribution.

More recent estimates of valence state ionisation potentials<sup>44,45</sup> differ slightly from Skinner and Pritchard's results. To examine the effect of variations in the parameters, values for  $C(2s)$  and  $C(2p)$  of  $-19.32$  and  $-11.70$  eV, based on Self-Consistent Field calculations, were employed in a series of calculations, in which  $K$  was allotted a range of values. Table 1 summarises the results of these calculations together with those obtained by an iterative Extended Huckel Method<sup>46</sup>, a semi-empirical Self-Consistent Field approach<sup>42</sup> and the results of two recent Self-Consistent Field calculations<sup>47,48</sup>. From these data, taken in conjunction with Hoffmann's investigations, the following observations may be noted :-

- 1) Increasing  $K$  causes an increase in the sum of one-electron energies.
- 2) Increasing  $K$  causes  $e(a_1)$  to increase much more than  $e(t_2)$ .
- 3) Increasing  $K$  causes only a small increase in the electron density centred on carbon.
- 4) An increase in the coulomb integral for  $C(2s)$  causes the energy of the  $a_1$  orbital to increase by the same order of magnitude,

while a decrease in  $C(2p)$  coulomb integral lowers the energy of  $t_2$  by approximately the same amount.

It is clear from the calculated data that, by application of Koopmans Theorem<sup>49</sup>, which equates the ionisation potentials to the orbital energies, it should be possible to select parameter values which would give orbital energies exactly matching the observed ionisation potentials. Three considerations suggested that such an exercise would be unprofitable,

- a) While an accurate value of 12.99 eV has been determined for the first ionisation potential of methane there is no such reliable measurement of the second ionisation potential as far as we are aware, and this would certainly be necessary to minimise the number of "correct" permutations of the variables.
- b) Optimisation of the parameters in this way would produce values which would not retain a theoretical basis such as valence state ionisation potential, and would almost certainly fail to reproduce the ionisation potentials for larger molecules.
- c) The available data shows that the sum of one-electron energies and the population analysis are not grossly affected within the range of parameters examined.

For these reasons the calculations on adamantyl and homoadamantyl cation formation were commenced with this choice of parameters.

$\theta$	0°	10°	20°	30°	40°	54°44'
$e_i$	-939.4	-939.3	-939.1	-938.9	-938.6	-937.4
$C_1$ and $C_5$	3.958	3.964	3.969	3.967	3.958	3.944
$C_2$ and $C_4$	4.220	4.215	4.208	4.197	4.183	4.155
$C_3$	3.829	3.811	3.765	3.687	3.602	3.562
$C_6$ and $C_8$	4.174	4.178	4.185	4.193	4.204	4.219
$C_7$	3.533	3.572	3.648	3.756	3.862	3.944
$C_9$	4.224	4.225	4.225	4.224	4.223	4.219
$C_{10}$	4.272	4.239	4.203	4.177	4.165	4.156
$H_{11}$ and $H_{17}$	0.916	0.917	0.917	0.917	0.916	0.913
$H_{12}$ and $H_{15}$	0.886	0.887	0.887	0.887	0.888	0.895
$H_{13}$ and $H_{16}$	0.899	0.899	0.897	0.899	0.898	0.895
$H_{14}$	0.905	0.906	0.906	0.905	0.907	0.913
$H_{18}$ and $H_{20}$	0.869	0.867	0.869	0.875	0.882	0.892
$H_{19}$ and $H_{21}$	0.900	0.900	0.899	0.898	0.898	0.900
$H_{22}$	0.900	0.900	0.900	0.898	0.896	0.892
$H_{23}$	0.898	0.899	0.900	0.900	0.900	0.900
$H_{24}$ and $H_{25}$	0.897	0.897	0.896	0.896	0.896	0.895

Table 2.

The values employed were:-

$$\alpha \text{ C}(2s) = -19.32 \text{ eV,}$$

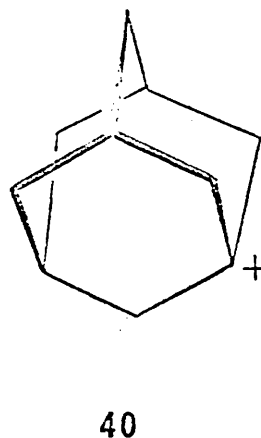
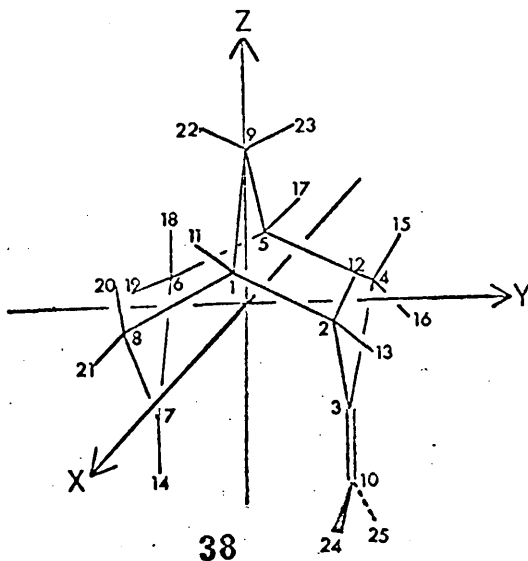
$$\alpha \text{ C}(2p) = -11.70 \text{ eV,}$$

$$\alpha \text{ H}(1s) = -13.60 \text{ eV,}$$

and  $K = 1.80.$

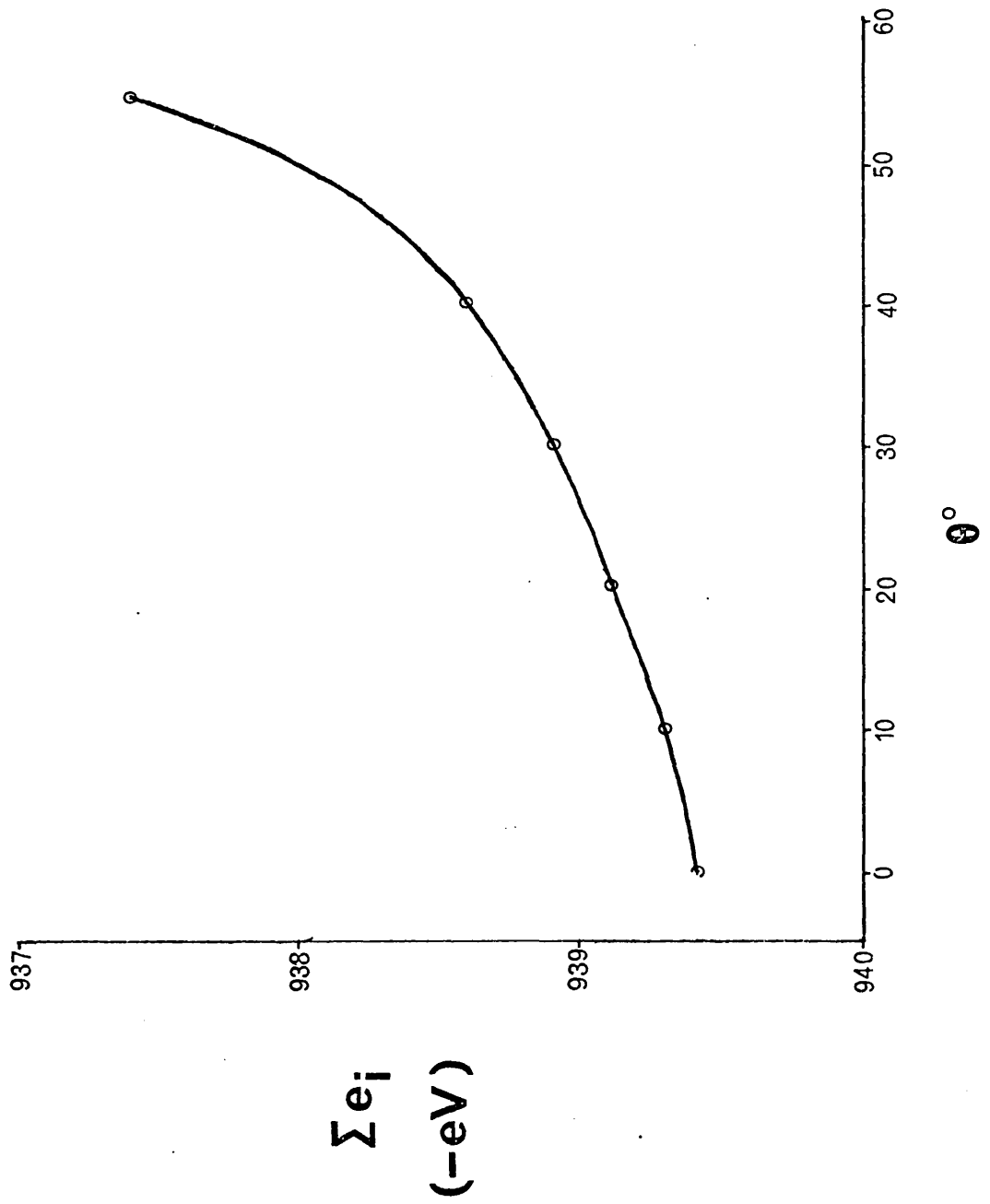
### Adamantyl Cation Formation.

Using the bond lengths and angles discussed in Chapter 2, the Cartesian co-ordinates of all the atoms for each position during the closure of (38) to (40) were calculated employing the right-handed orthogonal axes shown in (38). The atomic numbering scheme also indicated in (38) was maintained throughout the calculation and corresponds to that used in Table 2.



The various intermediate geometries are designated according to  $\theta$ , the angle  $\text{C}_3\text{-C}_{10}$  (or  $\text{C}_7\text{-H}_{14}$ ) makes with the negative direction of the Z-axis, so that initially  $\theta = 0^\circ$  while in the adamantyl cation

Fig 3.



$\theta = 54^{\circ}44'$ . Calculations were further performed for  $\theta = 10, 20, 30$  and  $40^{\circ}$  the resultant sum of one-electron energies and the charge densities being shown in Table 2. Fig. 3, derived from this data, is a graph of the sum of one-electron energies against  $\theta$  and in Fig. 4 the charge densities at  $C_3, C_7$  and  $C_{10}$  are plotted against  $\theta$ .

The energy plot shows no "dips" which may have indicated non-classical ion formation, but increases smoothly to give the apparently less stable adamantyl cation. Such a result is surprising and certainly unexpected in the light of the known chemical behaviour of adamantanes. This and other closures are known to proceed extremely smoothly to give the adamantyl skeleton<sup>50</sup> and Schleyer has shown that treatment of a variety of saturated hydrocarbons such as nujol with strong Lewis acids leads to substituted adamantanes<sup>51</sup>. From a simple hybrid orbital approach, the closure reaction being calculated may be viewed as a double bond i.e. 1  $\sigma$  plus 1  $\pi$  bond rearranging to 2  $\pi$  bonds, and from an elementary calculation such a process should make the adamantyl cation more stable than the open species. It superficially seems that the chemical and simple bonding rationale is more reliable than the Extended Hückel Calculation.

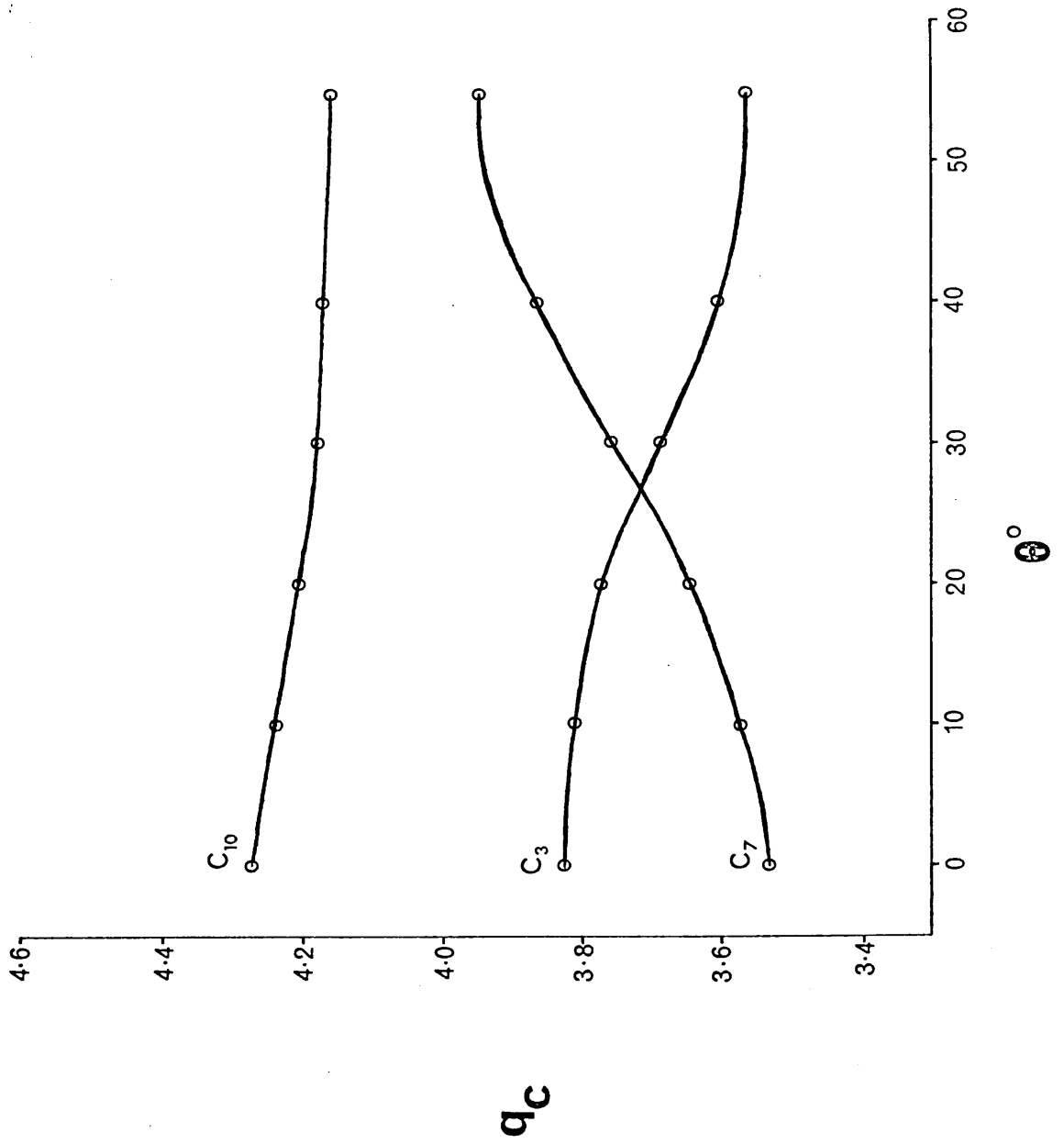
The explanation for the anomalous results almost certainly lies in the extreme approximations adopted in the calculation, especially the assumption that the sum of one-electron energies may be equated to the total molecular energy. As discussed in Chapter 2, Slater's explanation for this frequently observed correlation breaks down for



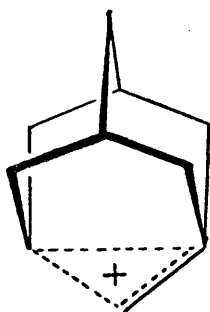
charged species, and it was only the success achieved by Hoffmann for a number of cations, which encouraged us to neglect the obvious objections.

Yet some attempt must be made to explain Hoffmann's success in view of the failure obtained with the adamantyl system. Two points might be relevant in this sense. Extended Hückel Calculations on ethane fail to predict the correct equilibrium bond lengths and yield a C - C distance of 1.92 Å, rather than the experimental value of 1.54 Å<sup>32</sup>. The second point is the observation that, in both Hoffmann's and the present investigation, the geometrical changes undergone by the species involves bringing various atoms nearer to each other, thereby presumably increasing nuclear-nuclear interactions. In the 7-norbornenyl cation, rotation of C<sub>7</sub> towards the double bond may very well lower the C<sub>2</sub>-C<sub>7</sub> and C<sub>3</sub>-C<sub>7</sub> distances to below 2.0 Å, which, if one can extrapolate from the ethane results, might produce a false energy minimum, before nuclear-nuclear interactions dominate the energy terms. In the adamantyl cation formation, C<sub>10</sub> will approach C<sub>7</sub> and might also be expected to show this false minimum. In this case, however, as C<sub>10</sub> is rotated the nuclear-nuclear repulsions between C<sub>10</sub> and all the other C and H atoms will be increasing and may "swamp" such an effect. This explanation of the discrepancy in results is mere hypothesis and while it may contain some semblance of the truth, the final analysis will almost certainly be more complex.

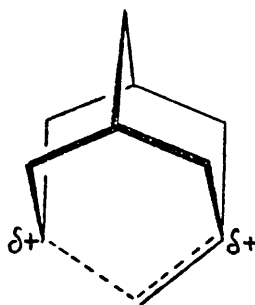
Fig 4 .



Although the behaviour of the total energy during closure is unacceptable, the population analysis may be much less affected by the assumptions in the calculation. Fig. 4 shows a smooth transfer of positive charge from  $C_7$  to  $C_3$  as reaction proceeds but  $C_{10}$  is seen to undergo very little change in its gross atomic population. Hence the non-classical representation (45) can be ruled out and the more realistic formula (46) substituted. One feature of the adamantyl cation which has been of considerable interest is the unusual NMR spectrum<sup>52</sup> showing three protons very low downfield. It had been hoped that the calculation on the adamantyl cation would yield charge densities which might be correlated with the observed NMR spectrum, but this does not appear to be the case. At least no first-order correlation between the charge densities on the hydrogen atoms and the NMR spectrum seems to exist.



45

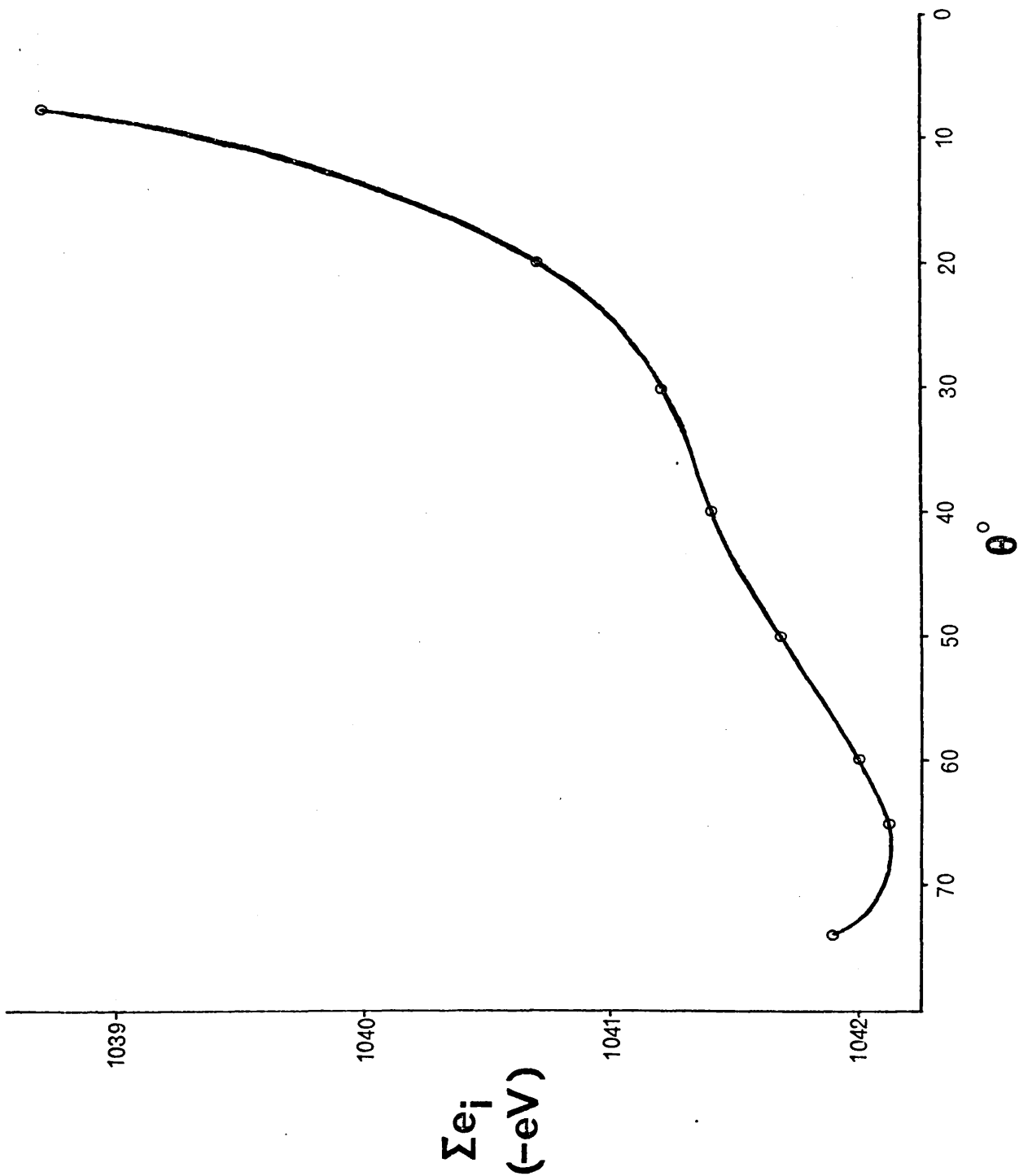


46

Table 3.

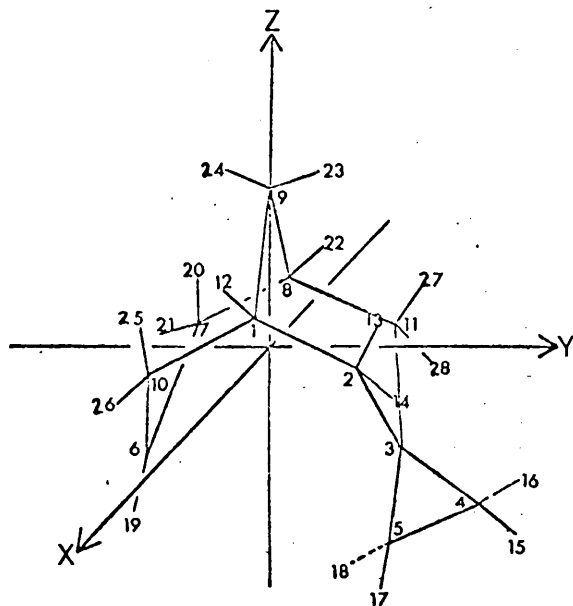
$\theta$	$73^{\circ}56'$	$65^{\circ}$	$60^{\circ}$	$50^{\circ}$	$40^{\circ}$	$30^{\circ}$	$20^{\circ}$	$7^{\circ}48'$
$\sum e_i$ (-eV)	1041.9	1042.1	1042.0	1041.7	1041.4	1041.2	1040.7	1038.7
$C_1$ and $C_8$	3.995	4.003	4.007	4.010	4.007	3.996	3.981	3.962
$C_2$ and $C_{11}$	3.995	4.003	4.007	4.010	4.007	3.996	3.981	3.962
$C_3$	4.232	4.224	4.219	4.209	4.199	4.194	4.190	4.183
$C_4$	4.234	4.182	4.161	4.133	4.123	4.128	4.147	4.197
$C_5$	4.222	4.273	4.299	4.331	4.324	4.284	4.224	4.171
$C_6$	3.501	3.536	3.572	3.691	3.842	3.955	4.016	4.046
$C_7$ and $C_{10}$	4.159	4.159	4.160	4.168	4.182	4.199	4.214	4.228
$C_9$	4.221	4.220	4.220	4.220	4.220	4.220	4.221	4.219
$H_{12}$ and $H_{22}$	0.917	0.917	0.917	0.917	0.917	0.917	0.916	0.915
$H_{13}$ and $H_{27}$	0.882	0.879	0.875	0.867	0.858	0.853	0.854	0.863
$H_{14}$ and $H_{28}$	0.898	0.897	0.897	0.896	0.897	0.899	0.900	0.901
$H_{15}$ and $H_{16}$	0.909	0.907	0.906	0.904	0.901	0.898	0.895	0.886
$H_{17}$ and $H_{18}$	0.907	0.905	0.902	0.897	0.894	0.893	0.894	0.890
$H_{19}$	0.911	0.912	0.912	0.912	0.912	0.912	0.910	0.898
$H_{20}$ and $H_{25}$	0.835	0.836	0.838	0.846	0.859	0.872	0.681	0.886
$H_{21}$ and $H_{26}$	0.899	0.897	0.896	0.895	0.896	0.897	0.899	0.902
$H_{23}$	0.900	0.901	0.901	0.901	0.902	0.901	0.901	0.901
$H_{24}$	0.901	0.901	0.901	0.901	0.901	0.900	0.898	0.896

Fig 5.

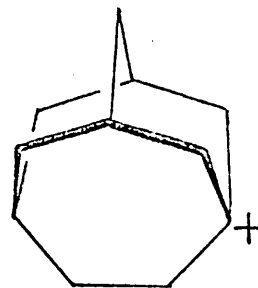


Homoadamantyl Cation Formation.

During the closure of the cyclopropyl cation (43) to homoadamantyl cation (44)  $\theta$  is defined as the angle between  $C_6-H_{19}$  and the negative direction of the Y-axis and calculations were conducted for  $\theta = 73^\circ 56'$  (corresponding to (43) ),  $65^\circ$ ,  $60^\circ$ ,  $50^\circ$ ,  $40^\circ$ ,  $30^\circ$ ,  $20^\circ$  and  $7^\circ 48'$  (corresponding to (44) ).



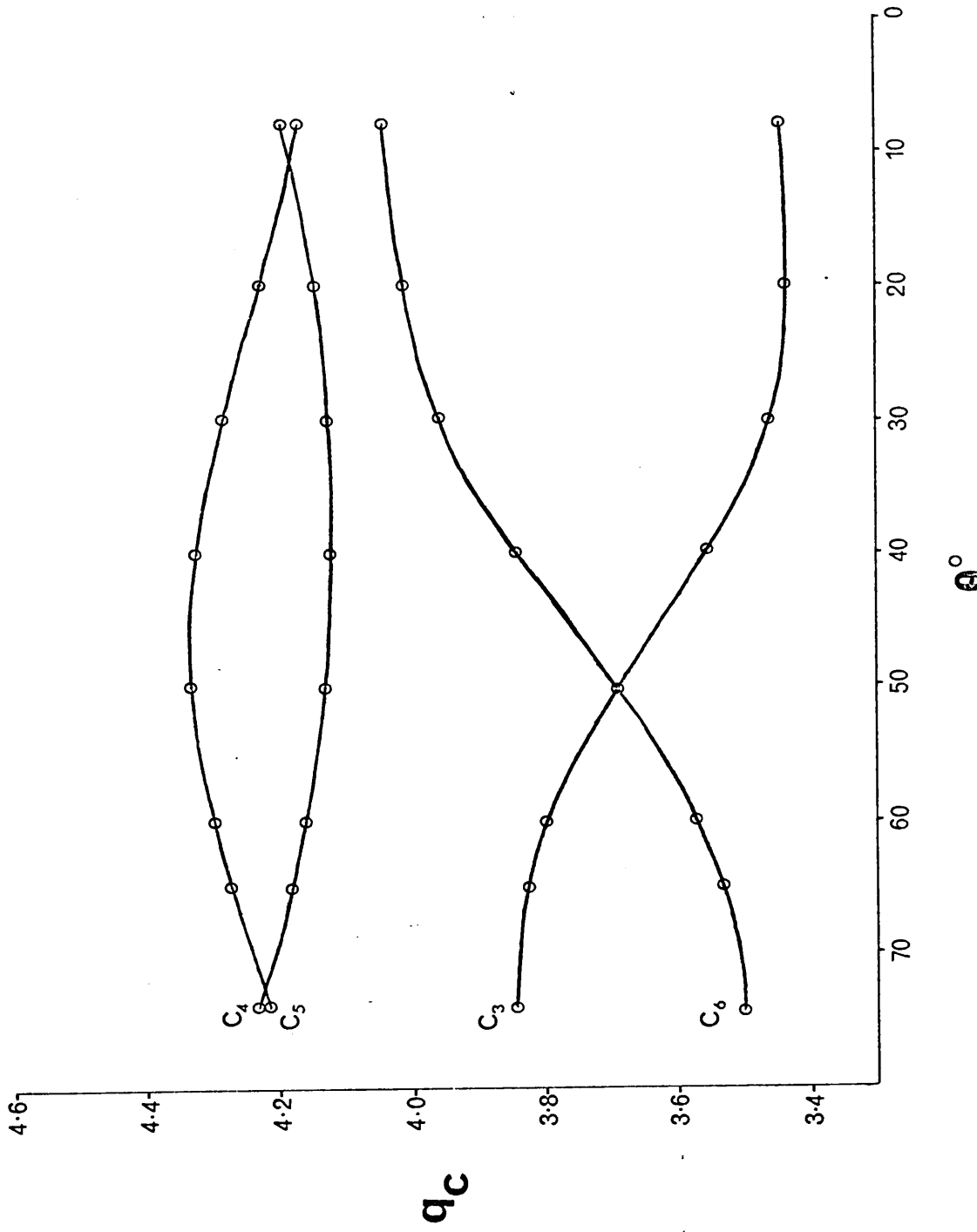
43



44

The results are summarised in Table 3 and Fig. 5 is a graph of the sum of one-electron energies against  $\theta$ . In this instance, the energy does not increase smoothly but exhibits a shallow minimum of 0.2 eV before increasing to homoadamantyl cation. The arguments already outlined apply equally to this situation and it would be fallacious to interpret the energy "dip" as indicative of formation of a stable non-classical species. Presumably the balance of forces in this example

Fig 6.



favours an initial increase in bonding energy before going to the apparently less stable closed system, but as already emphasised, these forces are not properly weighted in Extended Hückel Calculations and hence very little can be deduced with confidence from the energy plot.

The electron distribution at C<sub>3</sub>, C<sub>6</sub>, C<sub>4</sub> and C<sub>5</sub> are shown in Fig. 6 as a function of  $\Theta$ , and as was expected, charge is transferred from C<sub>6</sub> to C<sub>3</sub>. As compared with the adamantyl system the positive charge is transferred more quickly in this case, which probably reflects the fact that the C<sub>3</sub>-C<sub>5</sub> bond is nearer to C<sub>6</sub> in this system than the C<sub>3</sub>-C<sub>10</sub> double bond is to C<sub>7</sub> in the exomethylene cation.

#### Methods of Improving the Calculations.

Considerable effort has been expended in designing Iterative Extended Hückel Methods<sup>46,53</sup> which is effectively a parallel to the  $\omega$ -technique in  $\pi$ -electron systems. The diagonal elements are considered as a function of the net atomic charge and the orbital population and the calculation is iterated on charges to consistency. The Slater orbital exponents may also be varied according to the charge on the atoms. Attempts were made to incorporate an iterative procedure into the calculations already described but these were unsuccessful on account of considerable computational difficulties. The amount of computing time for each cycle (approximately 1½ hours) was also a factor weighing heavily against the use of an iterative procedure. From the published results obtained by iterative procedures, it would



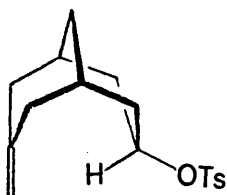
appear that some improvement can be obtained for charged species, although for neutral molecules the results from the basic calculation are often better than those from iterative procedures. Further refinements suggested for Extended Hückel Calculations include the use of Self-Consistent Field atomic orbitals in preference to Slater orbitals and the replacement of the Wolfsberg-Helmholtz expression for the non-diagonal elements by Cusachs' relationship<sup>54</sup>,

$$H_{ij} = S_{ij} (2 - S_{ij}) (H_{ii} + H_{jj}) / 2.$$

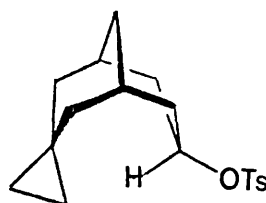
These improvements, however, do not eliminate the chief cause of the deficiencies, namely the complete neglect of electron repulsions. A semi-empirical theory, recently described by Dewar and Klopman<sup>42</sup>, at least in part tackles this problem, but it is not sufficiently developed to be of use in the calculations of the size described above.

#### Comments on the Solvolyses Rates.

The purpose of this investigation was to examine proposed reaction pathways for the solvolyses of anti-7-exomethylene-bicyclo(3,3,1)-nonan-3-yl tosylate (28) and the anti-7-spirocyclopropylbicyclo(3,3,1)-nonan-3-yl tosylate (29).



28



29

While the calculations have not yielded results directly applicable to the interpretation of the observed solvolysis rates, it is worthwhile commenting on the possible interpretation of this kinetic data in view of the interest in the relative merits of a double bond and a cyclopropane ring in anchimerically accelerating a reaction.

The exomethylene tosylate is found to solvolyse approximately 3 times faster than the cyclopropyl tosylate and one may interpret this as a reflection of the relative stabilities of the classical adamantyl and homoadamantyl cations formed. In effect this suggestion means that the transition states are related at least energetically to the completely closed cations. Certainly Schleyer's strain calculations on these cations would support such an argument, since he finds the homoadamantyl system to contain more strain energy than the adamantyl system<sup>41</sup>. Eakin<sup>9</sup> has applied Schleyer's approach to the exomethylene tosylate and finds that the strain factors are not enough to account for the observed reactivity. The rate enhancement is therefore attributed to double bond participation in the transition state. Unfortunately, a lack of experimental data did not permit him to calculate the strain effects for the cyclopropyl cation but, in qualitative terms, it is evident that the proximity of the cyclopropyl group and the endo hydrogen at C<sub>7</sub> will increase the steric contribution to the rate by a sizeable factor. Thus in the cyclopropane case participation is almost certainly less than in the exomethylene tosylate and indeed it may play little or no role in the solvolysis.

Such a conclusion is in contradiction to the well-documented norbornyl example of cyclopropyl participation and it follows that thorough examination of the criteria for efficient participation is needed. While the organic chemist is providing the experimental basis for such an investigation, the empirical and the theoretical methods must be developed if the problem is to be satisfactorily concluded.

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