

STUDIES IN MEDIUM-RING SESQUITERPENES

a thesis submitted by

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ABSTRACT

In the first part of this thesis the chemistry leading to the structure of caryophyllene is briefly discussed. The modes of transannular cyclisation observed in this system are discussed in detail together with the stereochemical implications of the cyclisation process.

The caryophyllene chlorohydrin described in the literature has been shown to be a transannular cyclisation product of the caryolane type and has been formulated as 8-chloro-1,9 dihydroxy-4;4-dimethyl tricyclo [6;3;1;0²:5] dodecane. This compound has been shown to regenerate the caryophyllene ring system by a facile 1,3 elimination which may be readily reversed to reform the chlorohydrin structure. A number of interesting reactions of the chlorohydrin have been found including a ring contraction to form a bridged eight membered ring system.

A new type of transannular cyclisation in a caryophyllene derivative is described yielding a ring system of the hydrindane type. The caryophyllene ring system has been regenerated from this system by 1,3 cleavage. Attempts at medium ring formation by 1:4 reductive cleavage have been recorded.

In the second part of the thesis the reaction of hypobromous acid with humulene has been shown to yield two products whose structures have been fully elucidated. The first, bromohumulene, is a simple humulene derivative brominated at the C₇ position, and the second, hydroxybromohumulene, is a new tricyclic system formed by a transannular reaction. The tricyclic derivative has been reconverted to the parent humulene system by a novel decyclisation process. The interconversion of humulene to caryophyllene is described by rearrangement of the hydroxybromohumulene.

ACKNOWLEDGEMENTS

The author would like to thank Dr. J. K. Sutherland for his great help and encouragement during this research.

Thanks are also due to Dr. I. H. Qurreshi and Dr. A. Torre for valuable discussion and to Professor D. H. R. Barton for the opportunity of working in his department.

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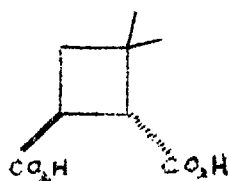
INTRODUCTION AND REVIEW

INTRODUCTION AND REVIEW

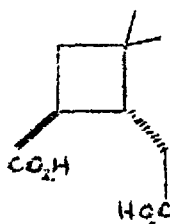
The Structure of Caryophyllene

The elucidation of the structure of caryophyllene proved to be a remarkably difficult task for, despite the extensive history of the investigations, only with the advent of pure derivatives and the application of physical methods was the structure finally determined.

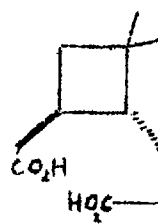
The important degradation experiments of Semmler and Mayer¹ showed that as-dimethyl succinic acid was formed on ozonolysis and later Simonsen² and co-workers discovered that an homologous series of acids containing a gem-dimethyl cyclobutane ring was formed on vigorous oxidation. The structures of these acids, (+)-trans-norcaryophyllenic (1) (+)-trans caryophyllenic (2) and (+)-trans homocaryophyllenic (3) acids were confirmed by synthesis.^{3,4,5,6.}



(1)

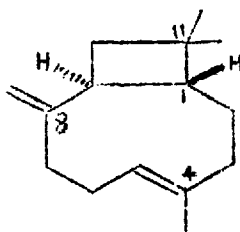


(2)



(3)

The presence of both an exocyclic methylene group and a trisubstituted double bond in caryophyllene was recognised in the early literature^{1,7} but it was not until recently that their correct location within a nine-membered ring ~~was~~ realised. Sorm and co-workers⁸ first suggested the presence of a nine-membered ring and Barton and co-workers^{9,10,11,12} elegantly demonstrated the full structure and stereochemistry of the sesquiterpene. Barton appreciated the importance of transannular cyclisations in the caryophyllene system and investigations on these tricyclic derivatives, combining both degradative and stereochemical arguments allowed the full structure of caryophyllene to be formulated as (4). The absolute



(4)

stereochemistry ~~was~~ deduced by examination of ~~the~~ molecular rotations of tricyclic derivatives.¹³

In a nine membered ring system a trans endocyclic double bond is more strained than its cis isomer¹⁴ and

caryophyllene itself was easily isomerised with nitrous acid to the more stable cis isomer, iso caryophyllene.^{10,15.} In both caryophyllene and isocaryophyllene the endocyclic double bond was shown¹¹ to be more reactive to electrophilic reagents than the exocyclic double bond whereas selective hydrogenation of the exocyclic double bond could be achieved.

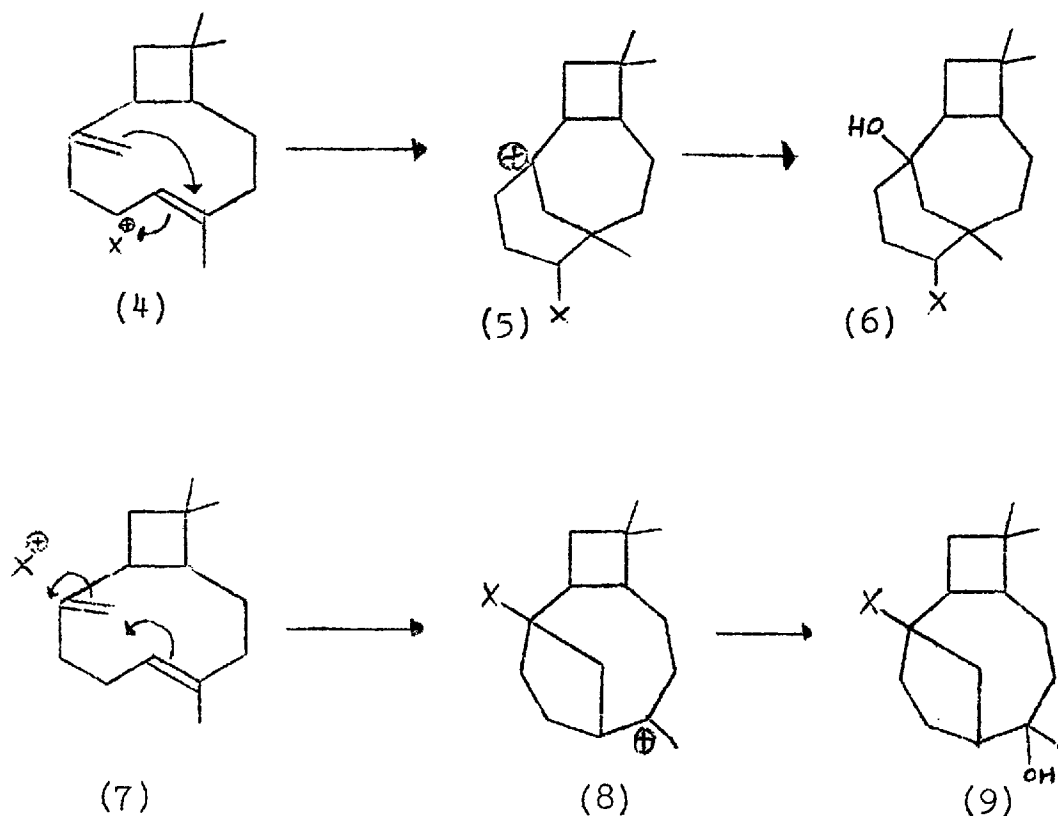
The chemical investigations on caryophyllene have been well reviewed in detail.^{16,17,18,19.}

Tricyclic Derivatives of Caryophyllene

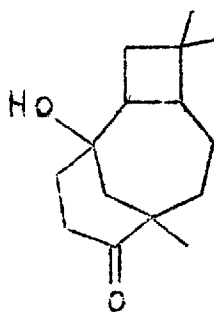
For some years it has been appreciated that medium ring cycloalkenes tended to rearrange, usually by trans-annular cyclisation, in order to remove sources of instability, namely angle strain (Baeyer strain) and trans-annular proton interactions (Pitzer strain). Caryophyllene undergoes such rearrangements under acidic conditions with remarkable ease giving tricyclic derivatives. The most important acid cyclisation products are caryolan-1-ol (β -caryophyllene alcohol), the hydrocarbon clovene and recently a new product has been isolated and has been named neoclovene. Dehydration of caryolan-1-ol yields two products pseudoclovene and isoclovene. A further cyclic product was obtained by Treibs²² as a byproduct in the epoxidation of caryophyllene using hydrogen peroxide, it is a tricyclic glycol ("Treibs glycol").

Caryolane and Clovane Cyclisations

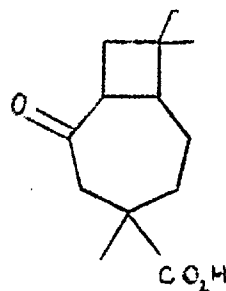
Caryolan-1-ol has been prepared from caryophyllene under a variety of mild acid hydrating conditions,^{10,20,21,22,23} formic acid yielding the formate. Barton and co-workers¹⁰ considered that a glycol, $C_{15}H_{26}O_2$, isolated by Treibs²⁴ from the action of hydrogen peroxide on caryophyllene had a common mechanism of genesis with caryolan-1-ol, in the former case the cyclisation being initiated by electrophilic attack at a double bond by H^+ and in the latter case by OH^+ .



Simple mechanistic considerations suggested two formulae (6) and (9) for caryolan-1-ol ($X = H$) and Treibs glycol ($X = OH$) by 1:4 addition across the two double bonds. Structure (9), however, requires initial electrophilic attack at the exocyclic methylene group, the least reactive to electrophiles followed by an anti-Markownikoff addition. It was shown¹⁰ that the correct mode of cyclisation was the one giving the derivatives like (6). Treibs glycol (6, $X = OH$) was simply correlated with caryolan-1-ol (6, $X = H$) by oxidation to the corresponding ketol (10) followed by Wolff-Kishner reduction.



(10)

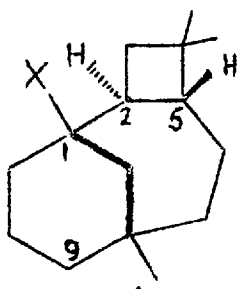


(11)

In a series of specific oxidative degradations Treibs glycol was converted to the ketoacid (11), which was shown by chemical evidence to contain a carboxyl group attached to a quaternary carbon atom, and that this acid was not a β -keto acid. From the nature of the degradations

the grouping $>\text{C}(\text{OH})-(\text{CH}_2)_2-\text{CH}(\text{OH})-$ must have been present in Treibs glycol (6, $\text{X} = \text{OH}$) and, from the known relationship between the compounds, the grouping $>\text{C}(\text{OH})-(\text{CH}_2)_3-$ in caryolan-1-ol.

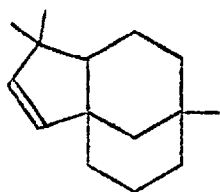
Wallach and Walker²⁵ found that caryolan-1-ol yielded a highly crystalline chloride on warming with phosphorus pentachloride. Barton's school¹⁰ established that the reaction merely effected replacement of the tertiary hydroxyl group by chlorine. This was shown by degradation to be the same keto acid (11) obtained previously during structural work on caryolan-1-ol, indicating that chlorination proceeds without inversion or rearrangement. Robertson and Todd²⁶ using this crystalline caryolan-1- chloride demonstrated by X-ray crystallography the configuration of the caryolane system (12) incorporating a trans fused cyclobutane ring with the methylene bridge on the side β and cis to the hydrogen at C_5 .



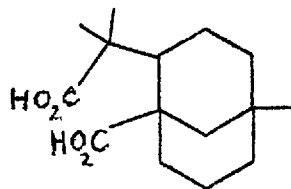
(12)

Although caryolan-1-chloride was unaffected by powerful nucleophilic reagents it was surprisingly found that sodium acetate in acetic acid gave caryolan-1-ol acetate²¹ (12, X = OAc). Since a rearside displacement (SN_2) would require an inversion of configuration at the bridgehead an SN_1 mechanism must be operative. This is of mechanistic interest²⁷ since bridgehead halides are usually exceedingly inert, in this case however, there must be sufficient flexibility in the ring system to allow an essentially planar carbonium ion at the bridgehead.

Acid catalysed hydration of caryophyllene yields a hydrocarbon clovene as well as caryolan-1-ol. The correct structure (13) for this rearrangement product was suggested independently by Eschenmoser²⁸, and Barton¹⁰ on mechanistic grounds since chemical evidence established the lack of α protons in its oxidation product clovenic acid (14).

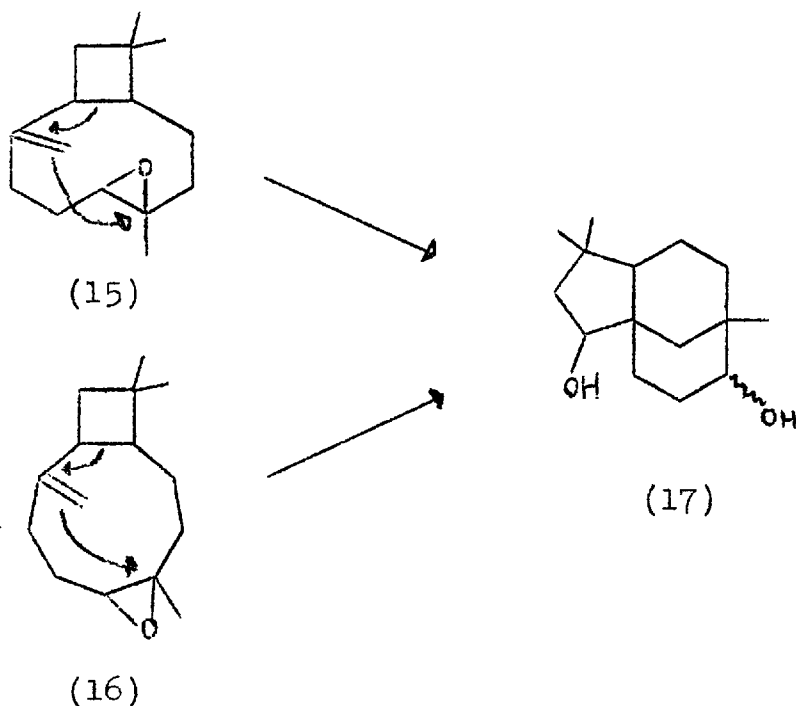


(13)



(14)

Barton¹¹ in his work illustrating the presence of a cis-endocyclic double bond in isocaryophyllene, had shown that both caryophyllene oxide (15) and isocaryophyllene oxide (16) could be cyclised to epimeric diols (17) with the clovane skeleton. This observation has been confirmed by a degradation of one of the epimeric clovane diols (17) to clovenic acid (14) and ultimately to p-cymene. In a similar degradation Lutz and Reid²⁹ obtained clovane from one of the diols (17).

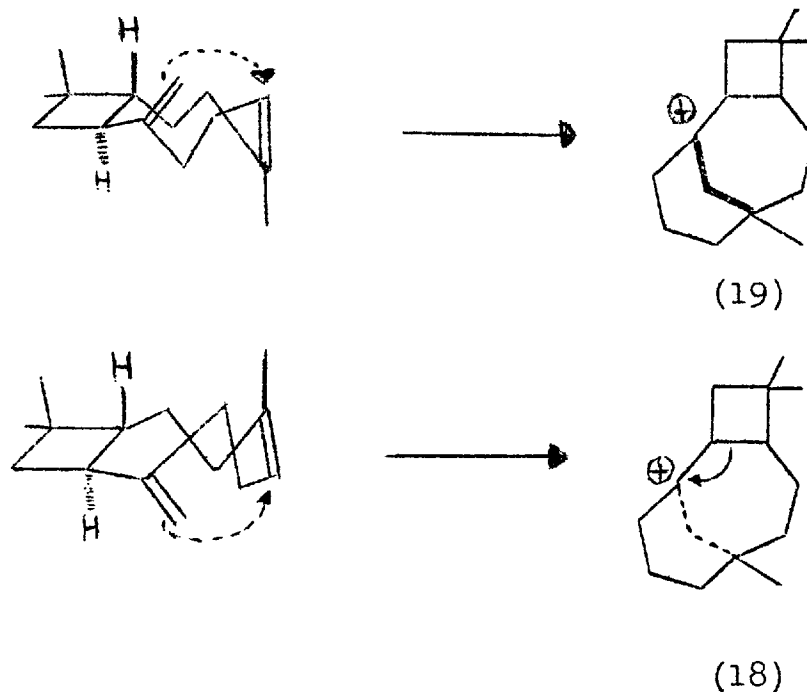


Since caryolan-1-ol is formed together with clovene in the acid catalysed cyclisation of caryophyllene it would seem reasonable that caryolan-1-ol (or some structural

equivalent in a concerted rearrangement) would be a probable intermediate in the genesis of clovene which could be formed by a simple ring expansion. In early papers^{25,30} it was reported that dehydration of caryolan-1-ol did give clovene which would support the hypothesis, however later work by Lutz and Reid²⁹ showed that this definitely was not the case, and that such treatment generated not clovene but two different hydrocarbons isoclovene and pseudoclovene.

Barton argued that since clovene was not formed from caryolan-1-ol the hydration of caryophyllene takes mutually exclusive paths involving different ionic intermediates to form the two products. It was suggested¹¹ that clovene and caryolan-1-ol belong to different stereochemical families. Conformational analysis¹² of the cyclisation products showed that in caryolane type compounds the bridging methylene group is on the β side and in clovane derivatives the bridge is on the α side of the molecule. The two modes of cyclisation may be rationalised in mechanistic terms. Models show that the endocyclic double bond lies with its plane approximately perpendicular to the plane of the four membered ring and the flexibility of the system allows the methyl group on the double bond to project either upwards or downwards. If the former, steric hinderance only allows an α -attack by the methylene

group in forming the bridge and leads to an intermediate ion (18); if the latter only β bridging is possible to yield an ion (19). The α bridged ion (18) shows a severe interaction between the four membered ring and the methylene bridge and steric acceleration of the ionic rearrangement gives, by bond migration, the more stable clovane ion with

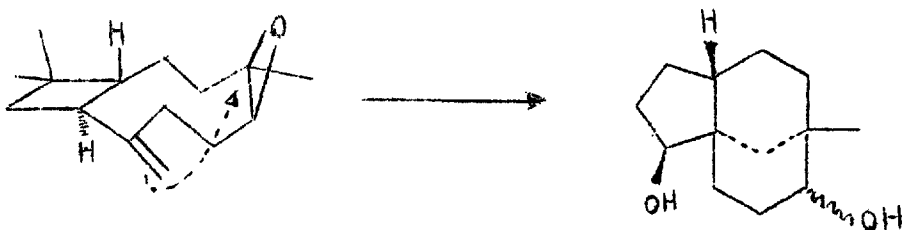


a cis-fused five membered ring. When β bridging occurs the ion formed (19) is more stable and further rearrangement does not take place. The remarkable ease of formation of this ion has already been mentioned in connection with the solvolysis of caryolan-1-chloride and it is noticeable that caryolan-1-ol can be rearranged only

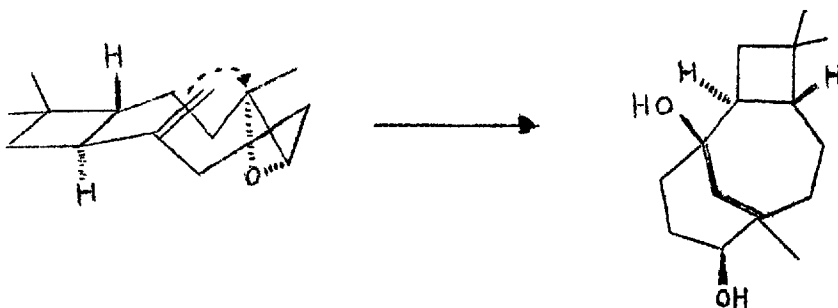
under the most drastic conditions. The stability of this ion is not fully understood as rearrangement to a β bridged caryolane system with a trans five ring fusion is not prohibited. Caryophyllene with a cis fused 4-9 ring junction (recently synthesised)⁴³ could possibly form an α bridged caryolane derivative as the prohibitive steric interaction would not force rearrangement to the clovane system.

The formation of Treibs glycol (6, X = OH) and the epimeric clovane diols (17) may be rationalised on these principles. In the reaction of hydrogen peroxide with caryophyllene Treibs glycol is obtained together with caryophyllene oxide. Electrophilic attack on the β side of the endocyclic double yields the β oxide which sterically forbids the formation of a β bridge, attack from the α side yields the (transient) α -epoxide which can undergo the caryolane cyclisation, forming a C₉ hydroxyl group in a β -axial conformation. (20).

Caryophyllene β -oxide and isocaryophyllene β -oxide similarly can only form an α bridge and after the required rearrangement the clovane diols (21) result which are epimers at C₉ because of the different stereochemistry of the two oxides. Caryophyllene oxide leads to the formation of a 9 β alcohol while isocaryophyllene oxide forms the 9 α alcohol. The deduced stereochemistry of



(21)

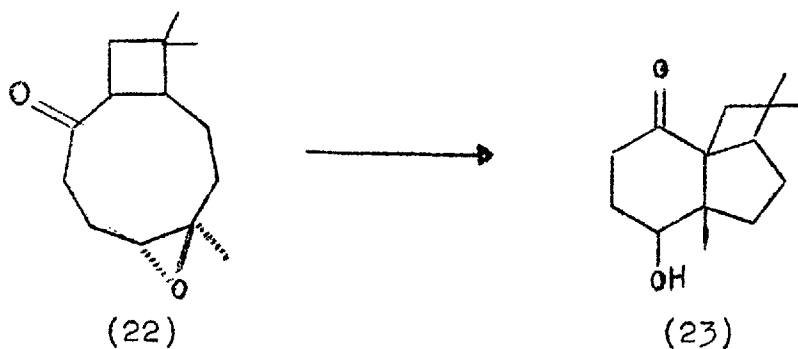


(20)

the cyclisations has been confirmed by Barton and Nickon from molecular rotation data of the tricyclic compounds.¹³ It has been shown by Warnhoff³³ that the clovane cyclisation of the epoxides proceeds by direct attack on the oxiran ring and not by an initial isomerisation to an allylic alcohol followed by a 1:4 addition across two methylene groups as found in the cyclisation of caryophyllene maleic anhydride adduct.

The oxiran ring has also been opened by transannular

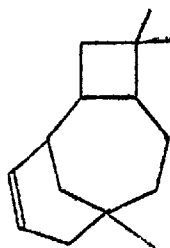
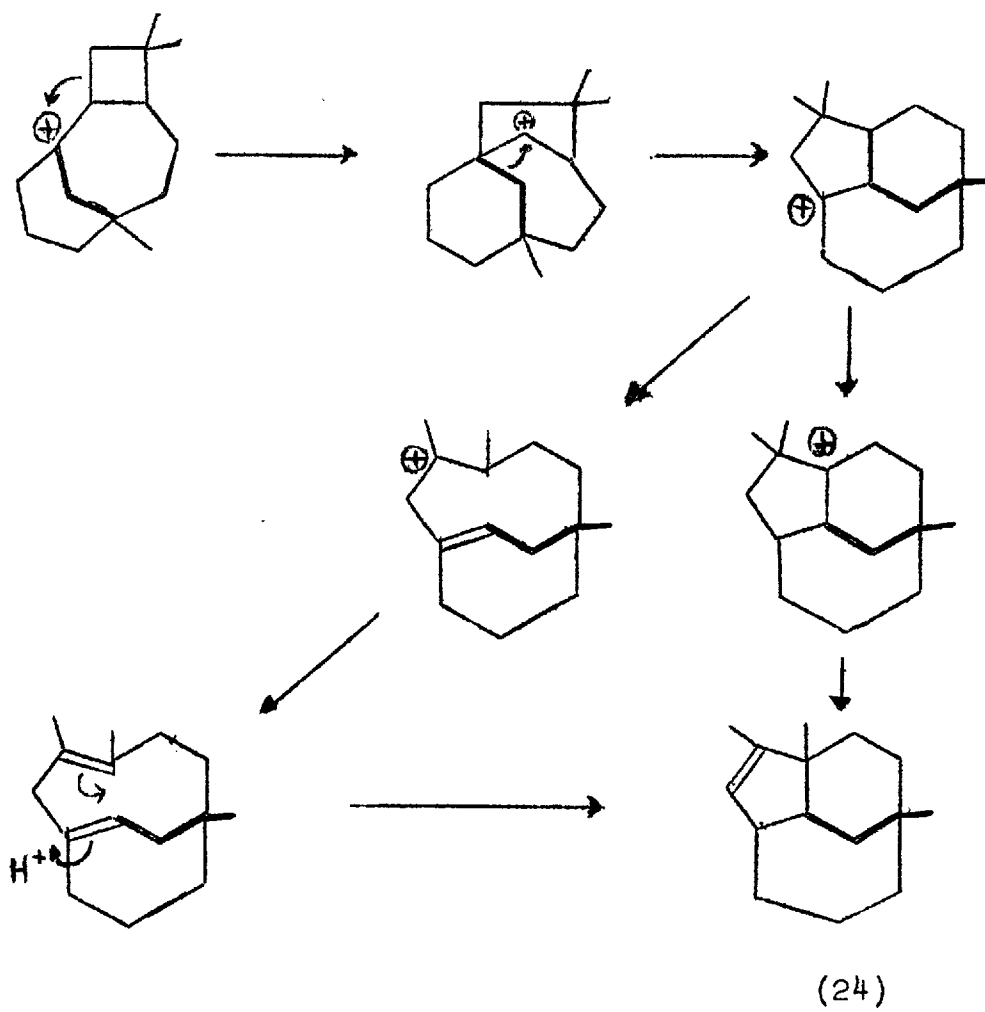
nucleophilic attack. The epoxyketone (22) in base cyclises to form a fused ring system (23) which was used extensively in the structural elucidation of caryophyllene¹⁰.



Pseudoclovene and Isoclovene

Although the bridgehead carbonium ion in the caryolane ring system is very stable rearrangement under powerful conditions has been achieved. Dehydration of caryolan-1-ol with phosphorous pentoxide gives two products isoclovene and pseudoclovene. Isoclovene was at first thought to be identical with clovene and later thought to be a double bond isomer of clovene^{29,30}, although with stereochemical information it is now realised that interconversion is impossible due to the different projections of the bridges in the two series. The elegant X-ray studies of Clunie and Robertson³¹ showed the structure to be (24) and possible mechanisms of genesis were suggested by Barton.

The structure of pseudoclovene is as yet unknown. Structure (25) was assigned to this compound but N.M.R. investigation has shown that this structure is definitely incorrect³².

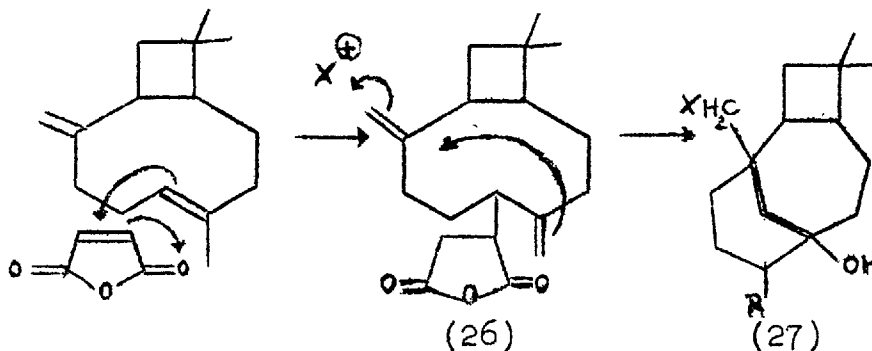


(25)

The Maleic Anhydride Adduct

Ruzicka and Zimmerman³⁴ found that reaction between maleic anhydride and caryophyllene at only 80° yielded an adduct. Ruzicka³⁵ used this derivative in attempts to elucidate the structure of caryophyllene, and related experiments³⁶ showed that adducts were also formed with acetylene dicarboxylic acid ester and azodiformic acid ester by the same mechanism.

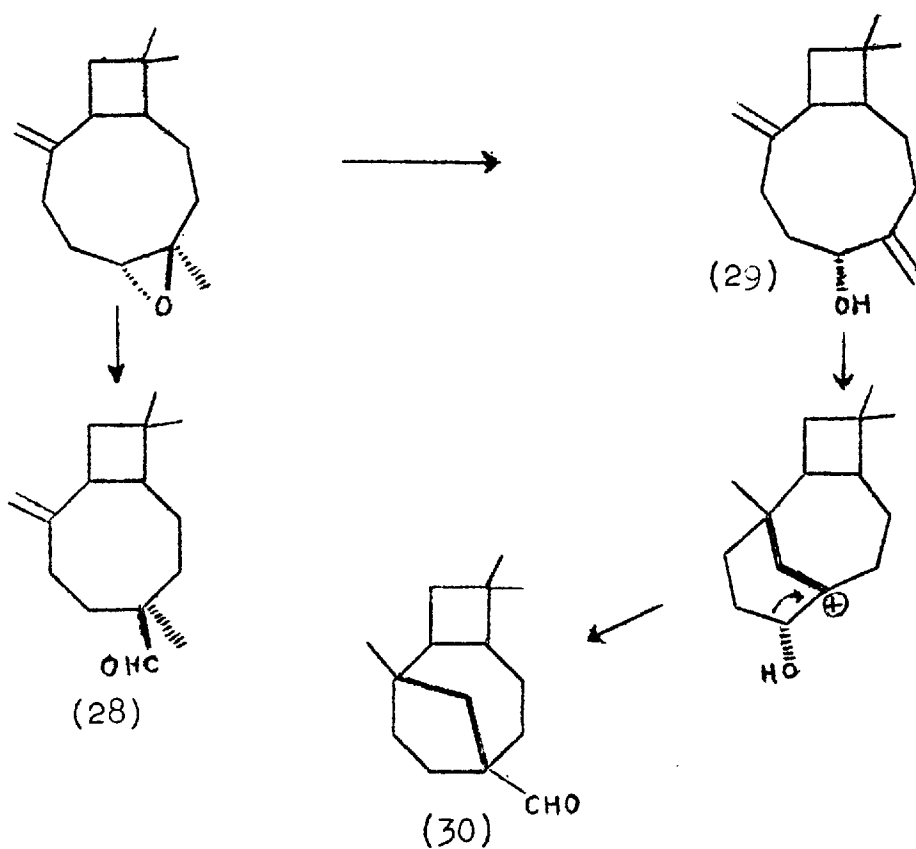
The maleic anhydride adduct cannot be formed by the normal 1:4 addition across a 1:3 diene function as this system is lacking in caryophyllene. Nickon³⁷ has shown that the reaction takes place by an allylic substitution mechanism with double bond migration. Similar reactions³⁸ are known and a cyclic transition state has been proposed. The maleic anhydride adduct (26) yields a new type of tricyclic derivative (27) with electrophilic reagents by



addition across the two double bonds in a 1,4 manner, and it is to be noticed that after isomerisation of the endocyclic double bond to an exocyclic methylene group, initial electrophilic attack then takes place preferentially at the C₈ double bond. Warnhoff³³ has also cyclised the two exocyclic double bonds in a similar manner and bridging of the caryolane type seems equally favourable from C₄ to C₈ as the reverse, that is a bridgehead carbonium ion must be as stable at C₄ as at C₈.

Ring Contraction Products

Warnhoff³³, in a recent paper, examined some of the aldehydic products obtained by acidic treatment of caryophyllene oxide. Besides the clovane diol (21) already discussed three derivatives were isolated as their 2;4 DNP's. One of them is a simple ring contraction product (28) and another is the tricyclic derivative (30) derived through the allylic alcohol (29).



The mode of cyclisation to (30) is similar to that for the cyclisation of the maleic anhydride adduct and ring contraction presumably takes place after formation of the bridged ion. The bridged eight membered ring system has already been reported³⁹ by ring contraction of a β -bridged caryolane derivative and by analogy the bridge in (30) probably has the same stereochemistry.

Ring contraction of the oxide to give the aldehyde (28) takes place even on gas chromatography⁴¹ and must be energetically very favourable.

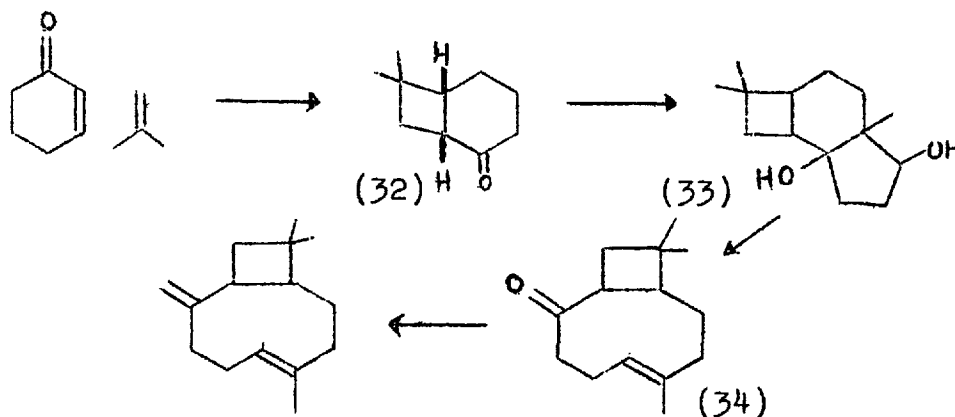
an alternative mechanism (path 2) involving two cyclobutane rearrangements has the advantage that initial electrophilic attack is at the endocyclic double bond as has been found in all the other rearrangements. These mechanisms may be tested as the quaternary methyl group and methyl group on the double bond are derived differently by the two pathways.

Synthetic Approaches

Confirmation of the basic skeleton of caryophyllene was provided by Sorm and co-workers⁴² with a synthesis of 4, 8, 11, 11 tetramethylbicyclo-(0;2;7)-undecane. This saturated hydrocarbon was elaborated from trans-homocaryophyllenic acid (3) and was shown to be identical to caryophyllane (tetrahydrocaryophyllene).

The inherent difficulties in a synthesis of caryophyllene were overcome by Corey⁴³ in an elegant preparation of d,l, caryophyllene and d,l, isocaryophyllene from cyclohex-2-eneone. Key points in the synthesis were the formation of the gem-dimethyl cyclobutane ring by photoaddition (32), the elaboration of the diol (33) and the 1,3 cleavage to the nor-caryophyllene ketone (34).

Clovene, the acid catalysed rearrangement product of caryophyllene, has also recently been synthesised⁴⁴.



THEORETICAL SECTION

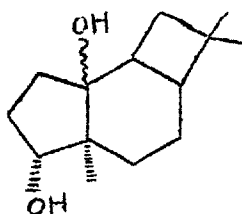
The Structure of Caryophyllene Chlorohydrin

The intrinsic difficulties associated with the structural elucidations of the medium-ring sesquiterpenes are also a factor found in synthetic approaches to medium ring systems. Unsaturated sesquiterpene medium rings are usually sterically strained and rearrangements to more thermodynamically stable structures may take place through carbonium ion rearrangements and transannular cyclisations and so attempted syntheses must produce correct double bond and fused ring stereochemistry in the absence of equilibrating conditions.

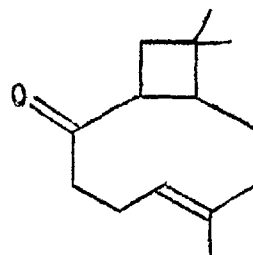
When the present work was commenced no sesquiterpenes in this category had been prepared but recently highly original and elegant syntheses of caryophyllene⁴³, longifolene⁴⁵ and the caryophyllene derivative, clovene⁴⁴ have been reported⁴⁶.

In our attempts towards a caryophyllene synthesis we recognised the danger involved in preparing the nine membered ring early in the synthesis and then having to subject it to rearrangement conditions at later stages. In order to obtain both the trans ring fusion and the thermodynamically less stable trans endocyclic double bond a preparation of the intermediate (35) seemed desirable

since on treatment with base a 1:3 cleavage would generate nor-keto caryophyllene (36) with a trans double bond.



(35)

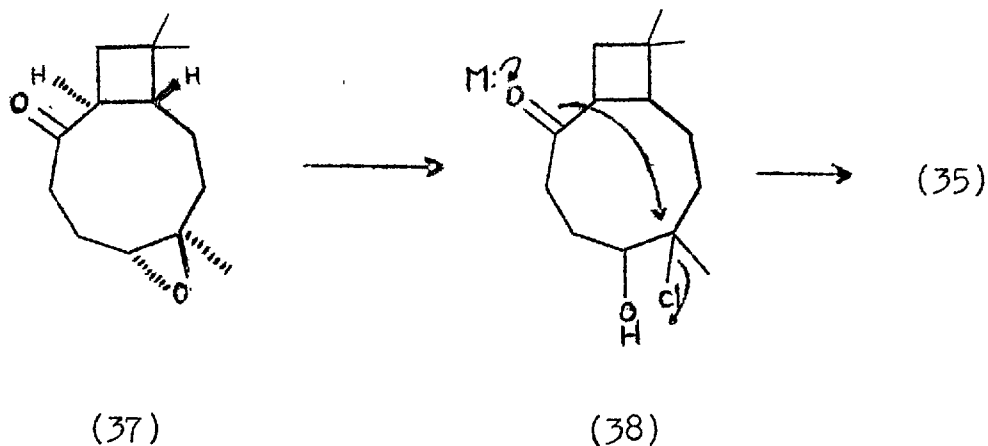


(36)

Since a synthetic preparation of (35) would certainly generate a cis fused 4-6 ring junction it would be necessary to determine whether after cleavage to (36) the cis ring fusion could be isomerised to the trans fused ketone which would then have the correct stereochemical properties for a simple conversion to caryophyllene itself.

Early attempts⁴⁷ at a direct synthesis of the intermediate (35) were largely unsuccessful and it seemed worthwhile to test the suitability of the intermediate before embarking on a long synthetic programme. Towards this end it seemed feasible to attempt conversion of suitable caryophyllene derivatives into tricyclic structures of the type (35) and then try to regenerate the caryophyllene ring system. A suitable compound for cyclisation reactions

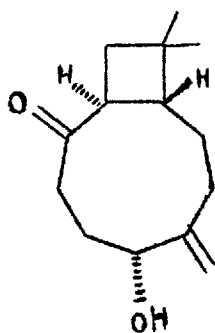
to suit our purpose appeared to be the chlorohydrin, $C_{14}H_{23}ClO_2$, prepared by Barton and his collaborators⁹ by treatment of the oxidoketone (37) with hydrogen chloride. The structure of the chlorohydrin was not proved but was expected to be (38) in which case a transannular reductive cyclisation might yield the desired intermediate (35). It was clear however that the initial assumption that the



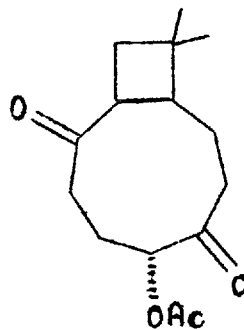
chlorohydrin was formed by a simple addition to the oxiran ring was incorrect since the product showed no typical carbonyl stretching frequency in the infra-red spectrum and the N.M.R. spectrum showed no methyl group on carbon bearing chlorine.

Structural work on the chlorohydrin showed that the oxygen functions were present in the molecule as a secondary and a tertiary alcohol, mild acetylation yielding a hydroxy

monoacetate. A characteristic reaction of the chlorohydrin was the ease with which hydrogen chloride was eliminated under a variety of basic conditions and even on passage through alumina or under catalytic reducing conditions. The product from this reaction was a ketol, $C_{14}H_{22}O_2$, which, besides hydroxyl and carbonyl groups showed the presence of a methylene function. Interestingly this ketol regenerated the chlorohydrin on treatment with hydrogen chloride, and so since both caryophyllene oxido ketone (31) and the ketol generated the chlorohydrin they must be simply related and further it seemed that the oxidoketone (37) was probably generating the ketol prior to the formation of the chlorohydrin. On these grounds structure (39) was assumed for the ketol which is formed simply from the oxidoketone (37) by isomerisation of the oxiran ring to an allylic alcohol. This seemed reasonable



(39)

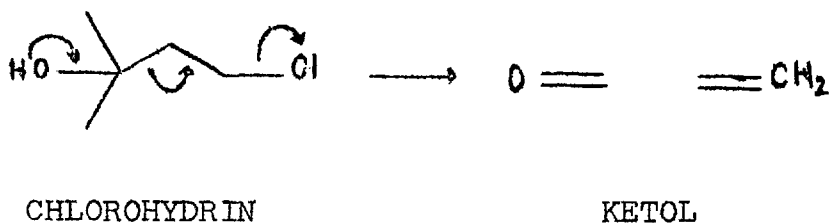


(40)

since the ketol showed the properties expected of an allylic alcohol in that it was easily oxidised with active manganese dioxide, it gave a characteristic ceric ammonium nitrate test and negative tetranitromethane test.

The intermediacy of this ketol (39) in the formation of the chlorohydrin from the oxidoketone (37) was supported when treatment of the oxidoketone with sodium iodide in acetic acid generated not an iodohydrin but the ketol (39). The isomerisation of epoxides to allylic alcohols has been observed under a variety of (usually acidic) conditions³³ and in the caryophyllene series Sorm⁸ has discovered a similar isomerisation using pyridine hydrobromide. In both humulene and caryophyllene themselves there appears to be little tendency to isomerise to their exocyclic isomers, which is in accordance with the observation that both methyl cyclononene and methyl cycloundecene are also more stable than their exocyclic isomers⁴⁸. However in the case of epoxide isomerisation both humulene⁴⁹ and caryophyllene oxides do give the allylic alcohol with the exocyclic methylene grouping. The reasons for the preferential formation of the *exo* rather than *endocyclic* double bond are not clear.

The facile conversion of the chlorohydrin to the ketol (39) was interpreted as a 1:3 cleavage reaction of the type shown in fig. 41.

FIG. 41

It was shown that in fact it was the tertiary hydroxyl group in chlorohydrin which was forming the carbonyl group in the elimination to the ketol since, on blocking the secondary hydroxyl group by acetylation to give the chlorohydrin acetate, the reaction still proceeded giving the corresponding acetate of the ketol.

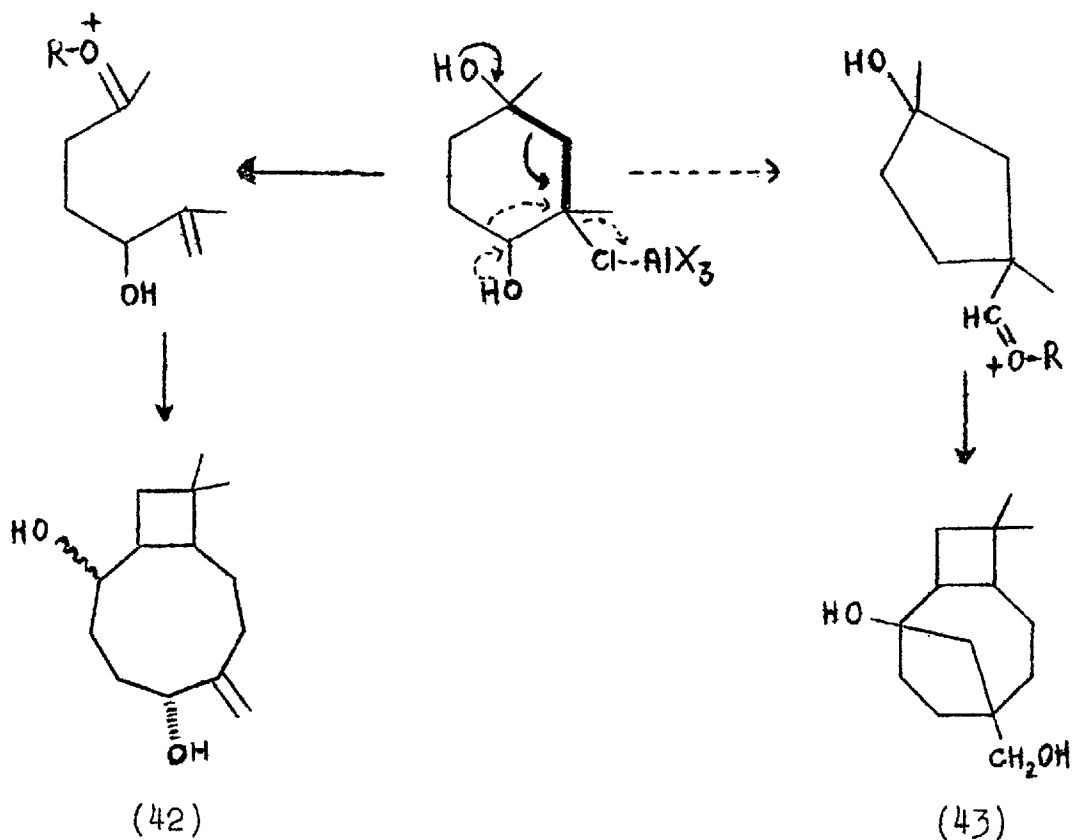
Since at this stage structure (39) was merely a working hypothesis a degradation of the ketol by ring cleavage was attempted in order to confirm the 1,4 relationship between carbonyl and hydroxyl functions. Ozonolysis of the ketol acetate yielded formaldehyde as expected together with an acetoxydione, $C_{16}H_{22}O_4$. Formation of a bis 2:4 D.N.P. (mp $135-7^{\circ}$) yielded a product lacking an acetate function and presumably this behaviour may be due to a Mattox-Kendall⁵⁰ type of elimination which would be in accord with the presumed structure of the acetoxo dione (40). Despite many attempts to deacetylate this compound

useful products were not obtained. In basic hydrolysis non-resolvable mixtures were obtained in all cases except on treatment with saturated bicarbonate at 50° for one day. This yielded a crystalline compound (mp 217-219°), $C_{13}H_{20}O_3$, ν_{max} 1695, 3500 cm^{-1} , however it is probable that this product contains a more condensed ring system formed by an intramolecular aldol condensation. The propensity of the acetoxy-dione to rearrange in this manner made it unsuitable for a degradative study.

Despite the lack of degradative evidence a further observation on the chlorohydrin allowed an extension of the part structure in fig. 41. Reduction of the chlorohydrin with lithium aluminium hydride did not yield a simple dehalogenated derivative but instead two rearranged diols were obtained. The first of these, mp 160-161°, showed four downfield protons in the N.M.R. spectrum, two protons at $\tau = 4.95, 4.94$ were ascribed to an exocyclic methylene group and a broad peak at $\tau = 5.8$ (2 protons) suggested protons on carbon bearing a secondary hydroxyl group. The existence of the exocyclic methylene group, which was confirmed by ozonolysis to yield formaldehyde, suggested that the first step in the reaction was again the same 1:3 cleavage, as had already been observed, to yield the ketol (39) (or its equivalent) followed by reduction to yield the corresponding diol (42).

The second diol mp 140-141° showed a two proton singlet at 6.64 τ which is consistent only with the presence of a $-\text{CH}_2\text{OH}$ group attached to a quaternary carbon atom. This observation was rationalised by invoking a 1:2 migration to yield an aldehydic function (or its equivalent) followed by reduction to a primary alcohol grouping (43). Mild oxidation of this product did indeed yield a liquid carboxylic acid.

In this reaction lithium aluminium hydride must first be acting as a Lewis acid and at the reductive stage of the



reaction hydride migrations in the complexes produce the diols. We were able to confirm the identity of diol (42) by lithium aluminium hydride reduction of ketol (39). Diol (42) was indeed formed in this reduction but was the minor product, the major one being the alcohol epimeric at C₈. It is interesting that this epimeric alcohol was never found in the reduction products of the chlorohydrin and it is implicit that the ketol complex generated from the chlorohydrin has a different stereochemistry from that generated by mixing the ketol (39) with lithium aluminium hydride. The exclusive formation of only one of the epimers in the reduction of the chlorohydrin could alternatively be explained by a direct hydride displacement mechanism leading to a hydroxyl configuration cis to the bond breaking in the 1:3 cleavage. This mechanism does

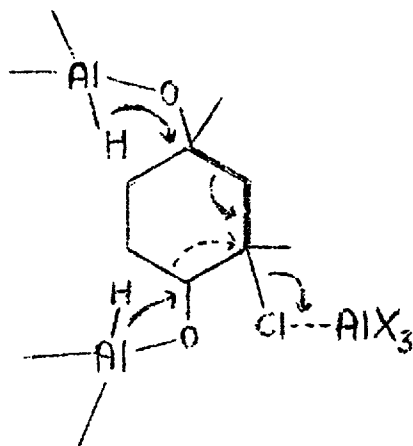
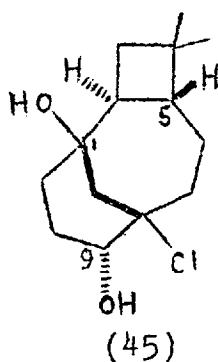


FIG. 44.

not involve in any way formation of a carbonyl complex and epimers could not be formed.

From the reactions already discussed demonstrating the relationship between the ketol of probable structure (39) and the chlorohydrin, the part structure of the latter (fig. 41) may be deduced as being contained in a six membered ring and the inferred structure for the chlorohydrin would then be (45) which has since been fully confirmed. The structures of the two diols formed on

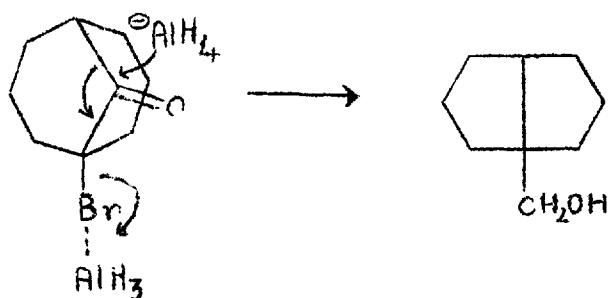


lithium aluminium hydride reduction follow from the mechanism of formation as being (42) and (43).

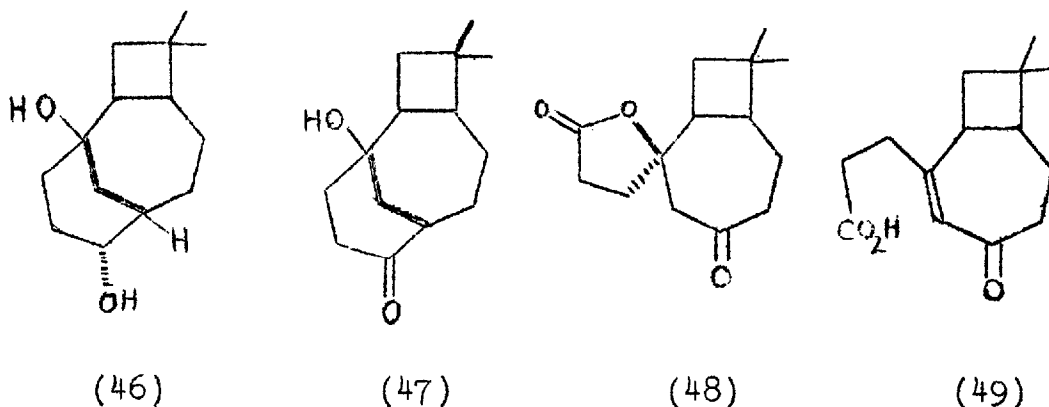
The stereochemistry of the chlorohydrin (45) may be predicted from molecular models, the only structure having no serious interactions is that in which the stereochemical integrity of the cyclobutane fusion remains trans with a β methylene group bridging to give the chair form of the

six membered ring. The stereochemistry of the 9α hydroxyl group follows from the mode of genesis from the oxido-ketone (37) of known stereochemistry.¹¹ Cyclisation to form an α bridged product shows serious interactions and this observation is in accordance with the known stereochemical requirements for cyclisation i.e. β bridging leads directly to caryolane systems, whereas an α bridge can only be formed with rearrangement to give clovane derivatives. An X-ray crystallographic determination⁵¹ has since confirmed the predicted stereochemistry as (45).

The diol (42) when generated from the chlorohydrin (45) must also have a 5α hydroxyl group (9α in chlorohydrin) and the configuration of the C_8 hydroxyl is probably β if it is generated by the concerted mechanism (fig. 44) already discussed. Generation of the diol (43) by ring contraction ~~introduces~~ much strain into the system and the reasons for its formation are not clear, however a similar β -bridged eight membered ring caryophyllene derivative (30) has since been prepared by Warnhoff³³. This ring contraction without inversion at the receptor carbon atom is analogous to a reaction in the bicyclo (3:3:1) nonane system⁵² where a "push-pull" mechanism similar to our concerted displacement mechanism is postulated



Chemical confirmation of structure (45) for the chlorohydrin was obtained from a series of reactions which, by ring cleavage, demonstrated that the chlorohydrin did indeed have within it a six membered ring containing both hydroxyl groups in a 1:4 relationship. Treatment of the chlorohydrin (45) with lithium in liquid ammonia yielded a saturated tricyclic diol (46), $\text{C}_{14}\text{H}_{24}\text{O}_2$, which proved to be a simple reduction product of the chlorohydrin. This product had the expected spectral features and was characterised by oxidation to the corresponding tricyclic hydroxy ketone (47) using chromium trioxide in pyridine. The ketone showed a carbonyl stretching frequency at 1710 cm^{-1} and only two methyl groups in the N.M.R. spectrum characteristic of the gem-dimethyl function at $\tau = 8.96, 9.02$. Reduction of the tricyclic hydroxyketone (47) back to the same



tricyclic diol (46) with sodium borohydride in methanol supported the configurational assignment of the 9- α -equatorial hydroxyl group.

It was observed that electrophilic attack on the tricyclic hydroxyketone (47), although in many cases pure products were not obtained, substitution appeared to be at the bridge head position i.e. the carbonyl group was enolising preferentially towards the bridge head position. Although this would be unusual, it seemed worthwhile to attempt an α -methylation of the carbonyl group at the bridge head position which would correlate this series directly with the caryolane series (10) whose structures and stereochemistry are well documented.²⁶ This could not be achieved, methylation failing to give either 9-keto caryolan-1-ol (10) or any methylated derivative of (10).

More powerful oxidation of the tricyclic hydroxyketone (47) with chromium trioxide in acetic acid yielded a crystalline lactone to which structure (48) was assigned. This spiro- γ -lactone structure is in accordance with the infra-red spectrum which showed maxima at 1710, 1765 cm^{-1} . The formation of a γ -lactone system demonstrates conclusively the presence of a 1:4 diol system in the chlorohydrin (45) and its reduction product, the tricyclic diol (46). Further confirmation of structure was obtained by base catalysed isomerisation of the spiro- γ -lactone (48) to the unsaturated keto acid (49). Mild basic treatment of the γ lactone forms initially, by cleavage of the lactone ring, a hydroxy keto acid which by conventional β elimination forms the conjugated ene-one system λ max 246 $\text{m}\mu$ (ϵ 11,000) ν max 1710, 1650, 1620 cm^{-1} . Both the spiro- γ -lactone (48) and the keto-acid (49) were key degradation products which proved useful in later structural correlations.

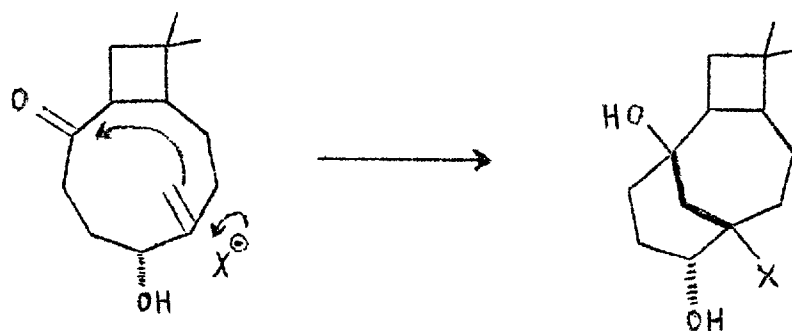
Although the chemical transformations described elucidate fully the bridged ring system present in the chlorohydrin the unchanged presence of the gem-dimethyl ring was assumed. It was shown that this assumption was justified by an oxidative degradation of the chlorohydrin (45). Acidic products from the oxidation were converted

to their methyl esters and analysis by gas chromatography showed peaks corresponding to (+)-trans caryophyllenic acid (2), (+)-trans norcaryophyllenic acid (1) and as-dimethyl succinic acid esters by comparison with genuine material obtained from a similar oxidation of caryophyllene itself. Although it was not shown that the gas column would resolve cis from trans esters, it seemed probable that the cyclobutane ring fusion was still trans in the chlorohydrin, and the full structure and stereochemistry of the chlorohydrin (45) was proposed^{39,40} which X-ray crystallography later confirmed in all details⁵¹.

The Formation of Medium Rings

During the structural work on the chlorohydrin it was observed that the transannular bridge was easily broken to regenerate the nine membered ring. We were interested in methods of generating rings both of the caryolane and hydrindane types to test the reversibility of such systems and their applicability to medium-ring sesquiterpene synthesis.

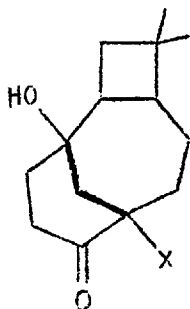
It was found that if the conditions for the isomerisation of caryophyllene oxido ketone (37) to the keto allylic alcohol (39) (sodium iodide, acetic acid) were made more vigorous a high melting product was obtained in low yield. Assuming the intermediacy of the ketol (39) in this reaction it was treated with aqueous acetic acid at 100°, the yield of product being improved by this method. The compound, $C_{14}H_{24}O_3$, showed hydroxyl absorption in the infra-red spectrum and the N.M.R. spectrum indicated only two methyl groups at 8.92, 8.95 τ . It was likely that a cyclisation analogous to the formation of the chlorohydrin was taking place to yield a tricyclic triol (50). In both cases the cyclisation is analogous to the Prins reaction (the condensation of aldehydes with olefines)

(45) $X = \text{Cl}$ (50) $X = \text{OH}$

and models reveal that a pseudo-chair conformation in the medium-ring bring both reaction centres into close proximity, an ideal position for reactions of this kind. In the triol (50), as expected, the ring system is more stable. Ring cleavage was not specifically attempted on the triol but in general reactions, ring opened material was never isolated. It is interesting that a 1:3 base cleavage on this system could equally well proceed from either end of the symmetrical 1:3 diol system, in one case regenerating the ketol (39) and in the other case an isomeric ketol with the methylene and carbonyl functions interchanged, i.e. a carbon atom would be transferred across the ring.

During our investigations on the chlorohydrin a

further interesting property of the bridged ring system was discovered. Barton and co-workers⁹ first prepared the chlorohydrin which, in the absence of spectral evidence the incorrect structure (38) might have been inferred, was characterised by oxidation to a so-called "chlorodiketone". On the new formulation for the chlorohydrin (45) this product would be a chloroketol (51). However in our hands the oxidation of the chlorohydrin yielded a chlorine free ketodiol, $C_{14}H_{22}O_3$, $\nu_{\max}$ 1705, 3450, 3620 cm^{-1} . Since the N.M.R. spectrum showed no vinylic absorption structure (52) was proposed for this product.



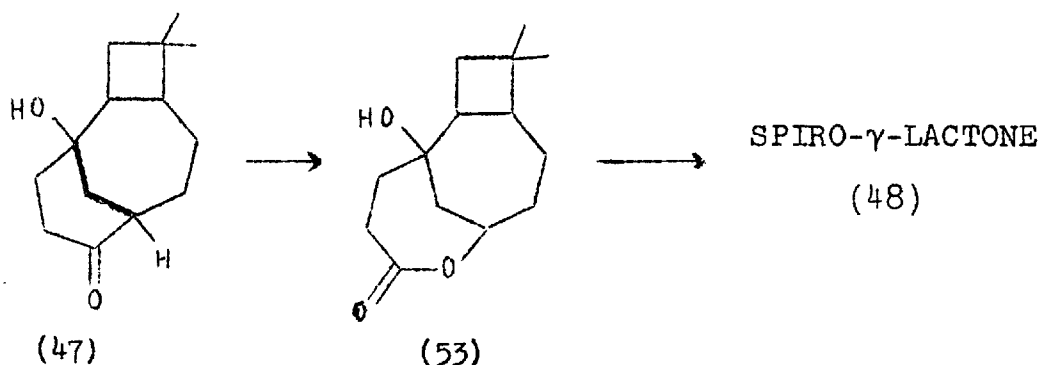
(51) $X = \text{Cl}$

(52) $X = \text{OH}$

This ketodiol (52) and the tricyclic triol (50) both bear a close structural relationship to the tricyclic hydroxyketone (47) of proved constitution, and this relationship enabled an easy confirmation of structures

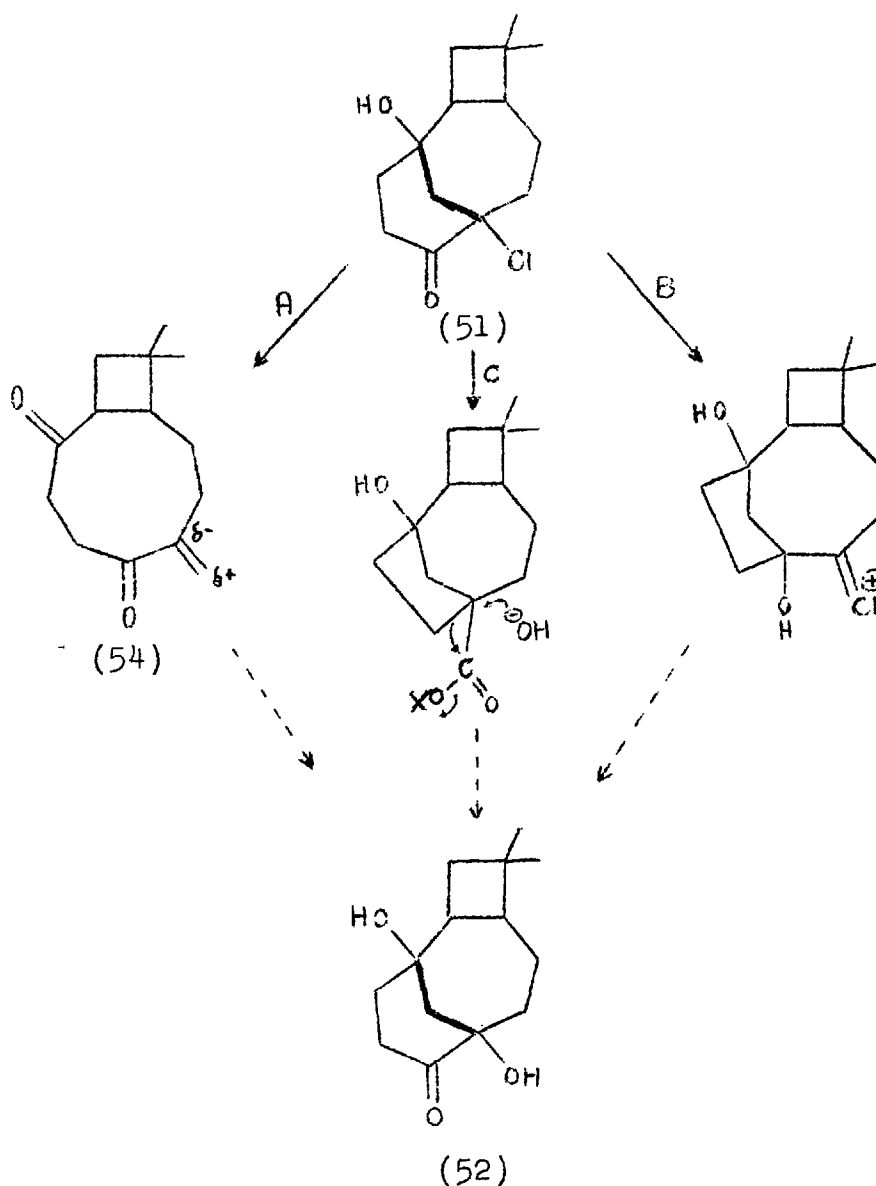
(50) and (52). The ketodiol (52) was reduced easily with sodium borohydride to give the triol (50). The reverse oxidation of (50) to (52) could not be achieved because even with Jones' reagent the triol was oxidised to (52) followed by a rapid cleavage to give the well characterised spiro- γ -lactone (48). Both the triol (50) and the ketodiol (52) were independently converted through the spiro- γ -lactone (48) to the keto acid (49).

It is to be expected that the derivatives (50) and (52) which contain the 1:2 glycol or ketol function would oxidise via a bridge head chromate ester to yield the spiro- γ -lactone, in the case of the ketol (47) however, bond fission may result by Baeyer-Villiger oxidation (53) or under the powerful chromic acid-acetic acid conditions



through hydroxylation at the bridgehead followed by cleavage. Since the existence of the chloroketol (51) had been well established by Barton⁹ the isolation of the

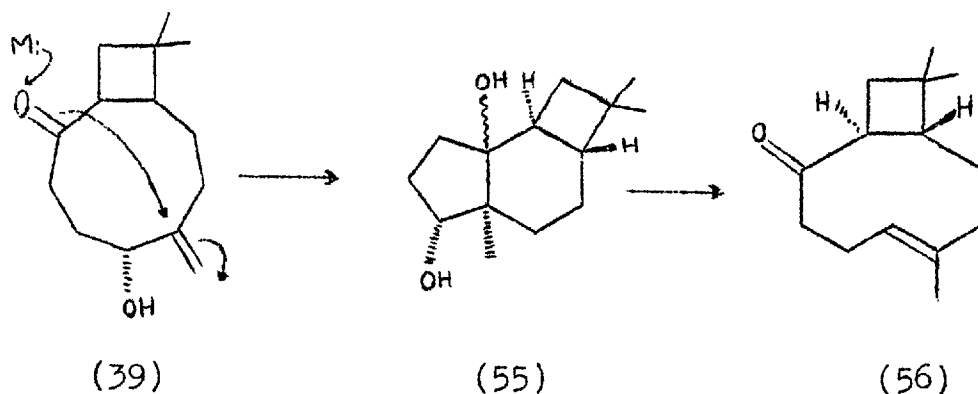
derived ketodiol (52) was unexpected, however it was found that this was due to the quality of alumina used in the purification procedure. Chromatography of the chlorohydrin oxidation product through grade V alumina did give the chloroketol (51), and on passage of this compound



through more powerful grade H alumina quantitative conversion to the ketodiol (52) occurred. The replacement of a bridgehead halogen atom by hydroxyl on alumina has no analogy in the literature and the mechanism of the reaction must be a matter of speculation. Expulsion of the chlorine atom by decyclisation would lead to the diketone (54) from which recyclisation would be improbable as the exocyclic methylene group is polarised in the wrong sense. This was tested by preparation of this diketone (54) by oxidation of the ketol (39)³³, and on passage through grade H alumina no change took place. Migration of the bridge on to the carbonyl group followed by a rapid hydrolysis and replacement of the bridge (intermediate B, kindly suggested by Professor Arigoni), or the alternative ring contraction (as observed for the chlorohydrin with L.A.H.)-ring expansion mechanism (intermediate C), are all unattractive methods of generating the ketodiol (52). A free radical or ionic mechanism is equally unenticing.

The formation of a hydrindane system (35) still seemed the most useful type of intermediate for medium-ring formation since a synthesis of this type of system would be easier than an intermediate of the caryolane type. Reductive transannular cyclisation of the chlorohydrin would not yield this system as was originally hoped

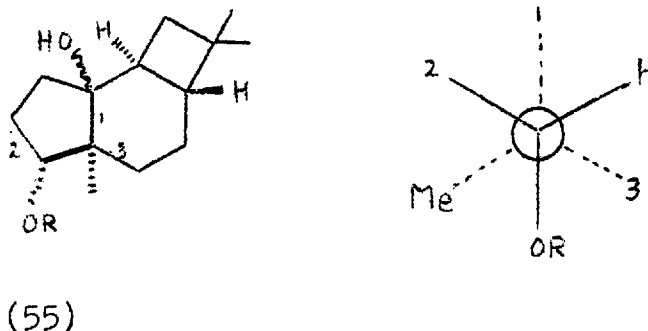
(on the old formulation (38)) but preparation of this intermediate was achieved by lithium in liquid ammonia treatment of the ketol (39). The product of this reaction



was a dihydroxy compound (55) which showed three quaternary methyl groups in the N.M.R., the gem-dimethyl group at 8.89τ and the other at 8.94τ . Mild oxidation yielded the corresponding hydroxy ketone $\nu_{\max} 1735\text{ cm}^{-1}$ which again showed two quaternary methyl groups at 8.89τ with a third shifted to 8.85τ . Although this was the desired intermediate (55) to attempt a reconstitution of the caryophyllene skeleton, at this time Corey⁴³ reported his total synthesis of caryophyllene and used a diol with the same carbon skeleton as (55) (but with a cis fused 4-6 ring junction) as an intermediate in his synthesis. Under the reaction conditions described by Corey⁴³ our tricyclic dihydroxy compound (55) was converted to the monotosylate

and, on treatment with dimethyl sulphinyl carbanion in dimethyl sulphoxide, 1:3 cleavage yielded nor-caryophyllene ketone (56), ν_{max} 1690 cm^{-1} . The N.M.R. spectrum showed besides the gem-dimethyl group, a single downfield proton at 4.75 τ and the methyl group on the double bond as a doublet at 8.22 τ .

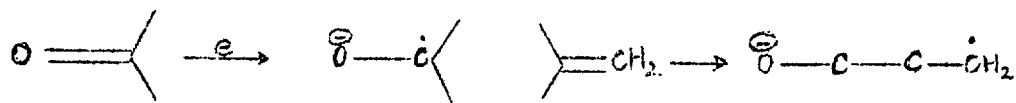
The stereochemistry of nor-caryophyllene ketone (56) (i.e. trans double bond and ring fusion) was shown by conversion to caryophyllene oxido ketone (37) of known structure. The stereochemistry of the diol (55) before cleavage may be deduced as follows: since the cleavage product nor-caryophyllene ketone contains the trans cyclobutane fusion the diol (55) must also have a trans fusion at the 4-6 ring junction, since Corey⁴³ has shown that although a cis fusion will isomerise to give a trans fusion the process is relatively slow and by gas column chromatography cis and trans fused isomeric nor-ketones may be resolved. Isolation of nor-caryophyllene ketone throughout the course of the reaction showed just one isomer present with the more stable trans fused junction. Consideration of a Newmann projection along the thickened bond shows that bonds 2 and 3 must be trans to each other since a trans double bond is formed on 1:3 cleavage, the α secondary hydroxyl group is certain since it must remain



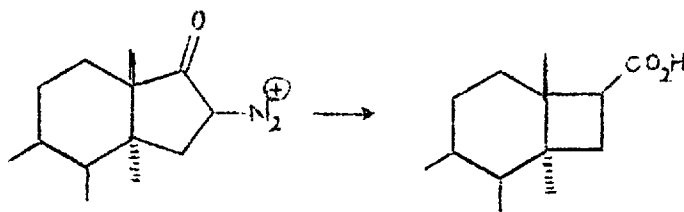
unchanged from the configuration in the ketol (39) from which the diol is generated. Similarly the angular methyl group is cis to the secondary hydroxyl group because of the requirements for forming a trans double bond. With this stereochemistry bonds 1 and -OR have favourable **co-planar** geometry for 1:3 cleavage⁵³.

The mechanism of cyclisation of the δ - ϵ unsaturated ketone function in the ketol (39) to form the diol (55) is unknown but presumably electron addition from the substrate to either the carbonyl group or the double bond is possible. It is probable that addition to the carbonyl group in fact takes place since the diol (42) (which is obtained by reduction of the ketol (39)) is quite stable to the cyclising reaction conditions, hydrogenolysis or rearranged products would have suggested electron addition to the double bond but these were not observed. The cyclisation thus probably

proceeds through addition of the radical anion⁵⁴ (derived from the carbonyl group) to the methylene group.



The stereochemistry of the diol (55) (with a trans 5-6 ring fusion) is understandable since the chair type transition state leading to this isomer shows much less H-H and H-O (of the secondary hydroxyl group) interactions. It is interesting that the diol (55) contains a trans 4-6 ring junction and only three examples of this type of fusion have been prepared, two by photolysis^{43,55} and one by ring contraction of a D-nor steroid^{56,57}.



Since nor-caryophyllene ketone (56) has a γ - δ unsaturated ketone system it was considered that this might also cyclise under conditions in which the ketol (39) generated hydrindane and caryolane derivatives however

hydrogen chloride or dilute acetic acid yielded no useful products and lithium in liquid ammonia merely reduced the ketone group.

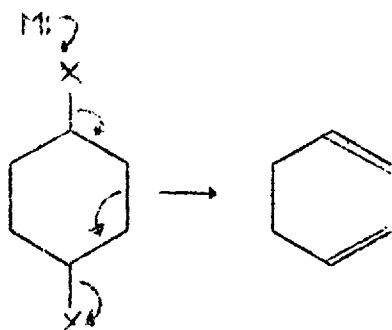
Cyclising conditions were also tested on the oxido ketone (37) to see if it was as vulnerable to transannular reactions as the derived ketol (39). As has been mentioned hydrogen chloride yields the chlorohydrin equally well from both sources but treatment of caryophyllene oxidoketone with aqueous acetic acid does not give the tricyclic triol (50) in good yield. This is presumably because acetic acid is not as good as hydrogen chloride at isomerising the oxiran ring to the allylic alcohol group prior to cyclisation. In more concentrated acetic acid isomerisation of the oxidoketone to the corresponding saturated diketone (mp, 99-100°) became dominant over the isomerisation to the



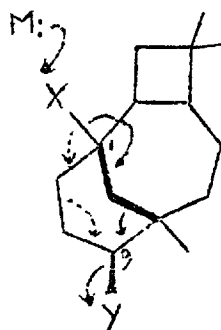
allylic alcohol. Lithium in liquid ammonia reduction of the oxido ketone (37) gave besides the oxido alcohol⁹ the tricyclic diol (46), that is the reduction product of the chlorohydrin and not the reduction product of the ketol (39). The formation of the caryolane system rather than the

hydrindane system in this reduction is surprising since the ketol (39) should be the obvious intermediate, however the addition of increasing quantities of ammonium chloride to the reduction reaction gave increasing yields of the tricyclic diol (46) at the expense of the oxido alcohol. The role of ammonium chloride in this reaction could be explained by the generation of an "equivalent chlorohydrin" from the oxidoketone prior to reduction, but mechanistically any explanation is unattractive.

As an alternative to 1:3 eliminations reductive 1:4 eliminations seemed a possible method of generating a medium ring with unsaturated linkages. Grob and Baumann⁵⁸ showed that 1:4 dihalo compounds could be cleaved generating two double bonds (fig. 57) and a similar cleavage on a suitably derived caryolane derivative would furnish



(FIG. 57)

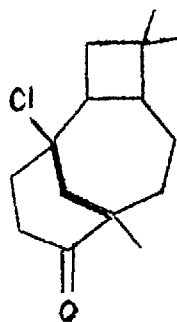


(58)

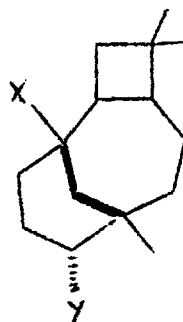
caryophyllene directly. In order to test the feasibility of such an approach to medium ring synthesis a number of derivatives of Treibs glycol (58, $X = Y = OH$) were prepared. Mesylation of the glycol followed by chlorination²⁵ of the tertiary hydroxyl group gave 1-chloro-9 β methanesulphoxycaryolane (58, $X = Cl$, $Y = -OSO_2CH_3$). Since no ring opened products were obtained on reduction with zinc in dioxan, lithium in liquid ammonia or potassium iodide in acetone the reactivity of the system was increased by preparation of dichlorocaryolane (58, $X = Y = Cl$). Again a mixture of products was obtained on reduction and this system was abandoned. It was considered that although these derivatives all contain the favourable chair conformation of the six-membered ring the 9 β axial configuration of the leaving group imparts a higher reaction energy barrier than does the co-planar 9 α -equatorial system. Also axial substituents at C₉ allow a metal ion in the reducing complex to coordinate with both substituents at C₁ and C₉ together, a situation which has been shown to favour simple reduction without cleavage and dehydrohalogenation reactions⁵⁸. In 1:4 reductive cleavage of a symmetrically substituted six membered ring, as present in (58) bond breaking can proceed in two possible ways and so it seemed necessary to achieve a system with the

lowest energy barrier in order to avoid the formation of complex mixtures. For these reasons derivatives in the 9 α equatorial caryolane series were prepared.

Treibs glycol was first acetylated and then chlorinated to yield 1-chloro-9 β acetoxy caryolane (58, X = Cl Y = -OAc), mild hydrolysis furnished the 1-chloro-9 β alcohol which was then oxidised to the chloroketone¹⁰ (59). Sodium borohydride reduction of the chloroketone gave 1-chloro-9 α



(59)

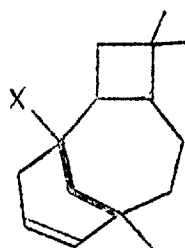


(60)

hydroxy caryolane (60, X = Cl, Y = -OH). An alternative route into the 9 α series was used as a check against possible rearrangements during the chlorination and reduction procedures. Oxidation and reduction of Treibs glycol gave immediately 9 α hydroxy caryolan-1-ol (60, X = Y = -OH) which was acetylated and chlorinated to give the corresponding chloroacetate (60, X = Cl, Y = -OAc).

This product could be converted to the same derivatives as those obtained by the first route.

With the availability of the 9 α series reductive cleavage was attempted on 1-chloro-9 α methane sulphonyl caryolane (60, X = Cl Y = -OSO₂CH₃) but under a variety of conditions no reductive fission was obtained. Similarly the chloroketone was resistant to cleavage even under powerful reducing conditions. Examination of the products from reaction with zinc in acetic acid showed that both 9 α and 9 β chloromesylates gave an identical crystalline acetate which showed downfield absorption in the N.M.R. spectrum at 4.6 τ . Since caryolane derivatives with a 9-acetoxy group (α or β) showed absorption at about 5.5 τ for the proton on carbon bearing the acetate group it was clear that a simple solvolysis of the mesylate function had not taken place and that the downfield absorption was due to vinylic protons. It was found that the zinc played no part in this reaction, acetic acid alone yielding the unsaturated acetate. It has been shown²¹ that the bridgehead chlorine atom in the caryolane series can be replaced only by acetate in solvolysis reactions and by using acetic acid as solvent in the reducing system a similar replacement of halogen by acetate together with elimination at the C₉ position

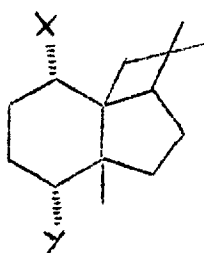


(61)

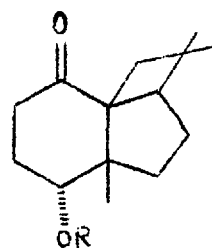
explained the reaction product (61, X = -OAC). On hydrogenation of this material one mole of hydrogen was taken up and the saturated acetate formed was shown to be identical to caryolan-1-ol acetate. Similarly attempted fragmentation of the 9 α and 9 β chloromesylates with lithium iodide in acetone gave as the major product a crude unsaturated chloride (61, X = Cl) which on hydrogenation was correlated with genuine caryolan-1-chloride. It is clear from these reactions that the bridged ring system is highly resistant to cleavage, preferential 1:2 elimination taking place as in all reductive experiments vinylic absorption appeared in the N.M.R. spectrum.

An alternative system which is open to a 1:4 reductive cleavage approach is the fused ring system (62). Base catalysed cyclisation of caryophyllene oxidoketone (37) has been shown to generate the ketol (63, R = H) by

transannular anionic attack on the oxiran ring. The mesylate derivative (63, $R = -OSO_2CH_3$) did not give any ring opened product on treatment with lithium in liquid ammonia. Sodium borohydride reduction of the ketol gave the diequatorial diol (62, $X = Y = -OH$) which was converted



(62)



(63)

to the corresponding diacetate (62, $X = Y = -OAc$). Lithium in liquid ammonia treatment of this compound regenerated the diol (62, $X = Y = -OH$) and further attempts to regenerate the medium ring from this series of compounds were abandoned.

EXPERIMENTAL

Melting points were determined on a K $\ddot{o}$ fler block and are uncorrected. Rotations were measured in chloroform. Infra-red spectra were determined on a Unicam S.P. 200 spectrometer in chloroform solution except where otherwise stated. Ultraviolet absorption spectra were determined in ethanol using a Perkin-Elmer 4000 or a Unicam S.P. 800 spectrophotometer. Nuclear magnetic resonance spectra were measured in deuteriochloroform or carbon tetrachloride on a Varian A-60 instrument. Analyses were carried out by the staff of the micro-analytical laboratory (Imperial College). Gas chromatograms were run using a Pye-Argon machine. Organic solutions were dried using anhydrous magnesium sulphate except where otherwise stated. The N.M.R. spectra of all products have been recorded and are in agreement with the structural assignments. Zanzibar Clove Oil was kindly donated by Messrs. White, Tompkins and Courage Ltd., Reigate, Surrey.

Where analytical figures are not quoted the compound has been prepared before and analytical figures obtained^{47,40}.

Isolation of Crude Caryophyllene

Clove bud sesquiterpene mixture was freed from eugenol by washing an etherial solution of the oil with aq. sodium hydroxide (5N). After drying and removal of the ether in vacuo the residual oil was fractionally distilled. A typical sample had b.p. 88-90° (2.5 mm) η_D^{22} 1.4992.

Caryophyllene Oxide (15)

Peracetic acid has been found more convenient than perbenzoic acid for this preparation²⁴.

Crude caryophyllene (50g) was stirred in ice cold chloroform solution (200 ml) and one equivalent of peracetic acid in chloroform (total volume 300 ml) was added. After stirring at room temperature the epoxide was isolated by the method of Treibs²⁴. YIELD 35% mp 61-62°

Caryophyllene Oxidoketone (37)

Caryophyllene oxide was oxidised by potassium permanganate according to the method of Treibs²⁴. The crude liquid product was purified by chromatography over alumina⁹ mp 60-62° ν max 1685 cm⁻¹.

Preparation of the Ketol (39)⁴⁷

A mixture of the oxidoketone (250 mg), sodium iodide (230 mg), sodium acetate (20 mg) and acetic acid (0.7 ml) was stood at room temperature overnight. The product was poured into saturated sodium bicarbonate solution and extracted with ether. After washing with sodium bisulphite solution the dried ether extract was concentrated to give the ketol (230 mg) from petroleum (60-80°) m.p. 110-111° $\nu_{\max}$ 1630, 1690, 3450 cm^{-1} .

The Acetate of Ketol (39)

The ketol (39) (660 mg) was dissolved in pyridine (AnalaR 5.5 ml) with acetic anhydride (AnalaR 1.75 ml). After twelve hours the solution was dissolved in ether (50 ml) and then washed with dilute hydrochloric acid (2N) and finally with saturated sodium bicarbonate solution. After drying ether was removed in vacuo and the product recrystallised from ether to give the acetate (660 mg) m.p. 127° $\nu_{\max}$ 1690, 1720 cm^{-1} .

Ozonolysis of the Ketol Acetate

The ketol acetate (500 mg) in dichloromethane (20 ml) was ozonised at 0° for two hours. The ozonide was decomposed by warming with water (10 ml) for 10 min. The organic layer was separated and the aqueous phase extracted with ether. The combined extracts were dried and concentrated in vacuo to give an oil which was crystallised from ether/petroleum (bp 40-60°). Further recrystallisation gave the acetoxy dione (400 mg). m.p. 73-76°, sublimation 78-79° $\nu_{\max}$ 1690, 1720, 1740 cm^{-1} $[\alpha]_D - 31^\circ$ (c, 0.16). (Found: C, 67.8; H, 8.5. $\text{C}_{15}\text{H}_{22}\text{O}_4$ requires C, 67.7; H, 8.3%)

Chlorohydrin (45)

Following the literature preparation⁹ the oxidoketone in chloroform was treated with hydrogen chloride. Recrystallised from chloroform/petroleum (b.p. 60-80°) m.p. 146-147°. Analogous treatment of the ketol (39) (66 mg) in chloroform (20 ml) gave the chlorohydrin (45) in quantitative yield, identified by m.p., mixed m.p., and i.r. spectrum.

Chlorohydrin Acetate

The chlorohydrin (45) (500 mg.) was left for twelve hours in pyridine (AnalaR 4.5 ml) and acetic anhydride (Analar 1.5 ml). Removal of solvents in vacuo gave a residue which was decolourised by charcoal in chloroform and then crystallised from chloroform-petroleum (b.p. 60-80°) to give the chlorohydrin acetate (460 mg) m.p. 151-153° $\nu_{\max}$ 1725, 3450, 3620 cm^{-1} .

Conversion of the Chlorohydrin (45) to the Ketol (39)

- a) The chlorohydrin (45) (100 mg) was hydrolysed at room temperature in ethanol (1ml) with 2N potassium hydroxide (1 ml) for twelve hours to give the ketol (39) (80 mg).
- b) The chlorohydrin (45) (or the acetate) was dissolved in benzene and passed through a column of Spence Grade 'H' neutral alumina to give a quantitative yield of the ketol (39) (or the acetate) identified by m.p., mixed m.p., and i.r. spectrum.

Chloroketol (51)

The chlorohydrin was oxidised in a similar way to that used by Barton and Linsey⁹ (i.e. preparation of the "chlorodiketone").

The chlorohydrin (255 mg) was oxidised by chromium trioxide (75 mg) in acetic acid (6.0 ml) and water (0.1 ml). Working up in the usual way followed by filtration through neutral alumina (Grade V) yielded after recrystallisation the chloroketol m.p. 90° $\nu_{\max}$ 1724, 3500 cm^{-1} .

Ketodiol (52)

- a) The chlorohydrin (45) (255 mg.) was oxidised as in the preparation of the chloroketol (51)⁹. After working up in the usual way the oily product was chromatographed over Spence Grade H neutral alumina. The white solid eluted with methanol was recrystallised from chloroform-petroleum (b.p. $60-80^{\circ}$) giving the ketodiol (52) (115 mg) m.p. $137-139^{\circ}$. Sublimation gave plates m.p. $138-139^{\circ}$ $\nu_{\max}$ 1705, 3450, 3620 cm^{-1} $[\alpha]_D + 64^{\circ}$ (c, 0.85). (Found: C, 70.1; H, 9.4. $\text{C}_{14}\text{H}_{22}\text{O}_3$ requires C, 70.6; H, 9.3%).

- b) Chromatography of the chloroketol (51) over Spence Grade H neutral alumina gave quantitative conversion to the ketodiol (52).

Tricyclic Triol (50)

The ketol (39) (500 mg) was dissolved in ether and a solution of acetic acid (5 ml.) and water 5 m,.) added. The ether was slowly distilled off and the temperature of the solution raised to 100°. After 30 min. the solvents were removed in vacuo and the oily residue triturated with ether to give the triol (50) (100 mg), recrystallised from ethyl acetate, m.p. 209-210° (after sublimation),

$\nu_{\max}$ 3620, 3400 cm^{-1} .

(Found: C, 69.7; H, 10.2. $\text{C}_{14}\text{H}_{24}\text{O}_3$ requires C, 70.0; H, 10.1%).

Tricyclic Diol (46)

Lithium metal (1 g.) was dissolved in liquid ammonia (500 ml) and to this well stirred solution the chlorohydrin (45) (1 g.) in tetrahydrofuran (10 ml.) was added. After stirring for two hours the excess lithium was destroyed by addition of ammonium chloride. Water (10 ml) was cautiously

added and after evaporation of the ammonia water (50 ml) and 2N hydrochloric acid were added until the aqueous residue was acidic. The solution was ether extracted and after drying and removal of solvent gave the tricyclic diol (46) (510 mg) m.p. 190-191° from chloroform ν max 3450, 3620 cm^{-1} .

Tricyclic Hydroxyketone (47)

The tricyclic diol (46) (250 mg.) was dissolved in pyridine (1.5 ml.) and after cooling to 0° chromium trioxide (375 mg) in pyridine (6 ml.) was added. After standing at room temperature for twelve hours the reaction mixture was diluted with an ice-hydrochloric acid mixture and filtered. The filtrate was ether extracted, the extract washed with saturated sodium bicarbonate solution, then water and finally dried. Evaporation of solvent and recrystallised from chloroform-petroleum (b.p. 40-60°) gave the hydroxyketone (47) (140 mg) m.p. 123-124° ν max 1710, 3450, 3650 cm^{-1} .

Reduction with sodium borohydride in aqueous methanol regenerated the tricyclic diol (46).

Spiro- γ -lactone (48)

a) Oxidation of the tricyclic triol (50)

The tricyclic triol (50) (50 mg.) was dissolved in warm acetone (4 ml.) and a solution of chromium trioxide (30 mg.) in water (0.5 ml.) with conc. sulphuric acid (2 drops) and acetone (2 ml.) was added. After standing at room temperature for twelve hours water (8 ml.) was added and the solution was then ether extracted. The extract was dried and concentrated in vacuo to give needles of the spiro- γ -lactone (48) (48 mg) recrystallised from chloroform-petroleum (b.p. 40-60°) m.p. 123-124° $\nu_{\max}$ 1710, 1765 cm^{-1} $[\alpha]_D + 20^\circ$ (c, 0.68).
(Found: C, 71.2; H, 8.4. $\text{C}_{14}\text{H}_{20}\text{O}_3$ requires C, 71.2; H, 8.5%).

b) Oxidation of the Ketodiol (52)

The ketodiol (52) (65 mg) in acetone (2 ml) was oxidised (as above) with chromium trioxide (40 mg), water (0.5 ml.), conc. sulphuric acid (1 drop) and acetone (2ml.) to give the spiro- γ -lactone (48) (55 mg.) m.p. 123-125° $\nu_{\max}$ 1710, 1770 cm^{-1} .

c) Oxidation of the Tricyclic Hydroxyketone (47)

A solution of chromium trioxide (18 mg) in water (1 drop) and acetic acid (1.5 ml) was added to a solution of the hydroxyketone (47) (25 mg) in acetic acid (0.5 ml.). The solution was stood at room temperature for 4 days. Working up in the usual manner afforded the spiro- γ -lactone (48) (18 mg.) m.p. 124-125° ν_{max} 1700, 1765 cm^{-1} .

There was no depression of m.p. between the samples and all three showed identical i.r. and t.l.c. properties.

Keto Acid (49)

N. sodium hydroxide solution was added dropwise to the spiro- γ -lactone (48) (30 mg.) in ethanol (3 ml.) until a permanent yellow colour developed (ca. 5 drops). After standing for fifteen hours water was added and the solution ether extracted. The ether extract was rejected, and the aqueous layer was acidified and reextracted with ether. This extract was dried and concentrated to give the keto acid (49) (17 mg) crystallised from chloroform-petroleum (b.p. 40-60) m.p. 128-129° ν_{max} 1620, 1650, 1710, 3300 cm^{-1} $[\alpha]_{\text{D}} + 23^{\circ}$ (c, 0.66) λ_{max} 246m μ (ϵ , 11,000).

(Found: C, 71.3; H, 8.5. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%).

Lithium Aluminium Hydride reduction of Ketol (39)

A suspension of lithium aluminium hydride (60 mg) in ether (10 ml.) was added to an ice cold solution of the ketol (39) (150 mg.) in dry ether (10 ml.). After stirring for 1 hour it was set aside at 0° overnight. A saturated solution of ammonium chloride was added to the mixture and the etherial layer separated. The aqueous portion was again extracted with ether and the combined extracts concentrated to give an oil which on trituration with chloroform-petroleum (b.p. $40-60^{\circ}$) gave a white solid (11 mg.) which was recrystallised from ethyl acetate, m.p. $159-160^{\circ}$, and shown to be identical to the diol (42) obtained from similar reduction of the chlorohydrin.

The filtrate was kept at 0° for 24 hours when the epimeric diol (42 mg.) separated m.p. $56-58^{\circ}$, from petroleum (b.p. $40-60^{\circ}$) $\nu_{\max}$ 1640, 3450, 3620 cm^{-1} $[\alpha]_D - 27^{\circ}$ (c, 1.00).

(Found: C, 74.5; H, 10.7. $C_{14}H_{24}O_2$ requires C, 75.0; H, 10.8%).

Sodium Borohydride reduction of Ketodiol (52)

The ketodiol (52) (30 mg.) was dissolved in methanol (2 ml.), water (0.2 ml), and sodium borohydride (20 mg) was added with cooling. After standing at room temperature for fifteen hours dilute hydrochloric acid (6 ml) was added and the aqueous solution was ether extracted. After drying and concentrating a white borate ester, crystallised from ethyl acetate-petroleum (b.p. 40-60°) was obtained. The borate ester was warmed in acetic acid (3 ml) and water (1 ml) for 15 min. Concentration in vacuo followed by dilution with water and extraction with ether yielded a white solid crystallised from ethyl acetate m.p. 207-210° (after sublimation) shown to be identical to the tricyclic triol (50) by mixed m.p. i.r. and t.l.c. Further confirmation was obtained by oxidation of this product to the spiro- γ -lactone (48) and conversion to the keto acid (49).

Lithium Aluminium Hydride reduction of Chlorohydrin (45)

The chlorohydrin (45) (500 mg.) in dry ether (40 ml) was refluxed with lithium aluminium hydride (156 mg.) for 30 min. and then stirred at room temperature overnight. Excess of reagent was destroyed by addition of water. The

two layers were separated and the aqueous phase extracted with ether. The combined ethereal extracts were dried and concentrated in vacuo to give an oil which was chromatographed on Grade V neutral alumina to yield two crystalline products.

a) The diol (42) (147 mg.) m.p. 160-161°, from ethyl acetate $[\alpha]_D + 39^\circ$ (c, 1.15), $\nu_{\max}$ 1640, 3450, 3600 cm^{-1} . Identical to the diol obtained by lithium aluminium hydride reduction of the ~~ketol~~ (39). Ozonolysis gave formaldehyde identified as the dimedone derivative.

b) The diol (43) (80 mg.) crystallised from ether-petroleum (b.p. 40-60°) m.p. 140-141°, $[\alpha]_D + 61^\circ$ (c 0.95), $\nu_{\max}$ 3650, 3500.

Lithium in Ammonia reduction of Oxidoketone (37)

The oxidoketone (37) (147 mg) in ether (20 ml) was added dropwise over 15 min. to a well stirred solution of lithium (150 mg) in liquid ammonia (300 ml) containing ammonium chloride (400 mg). After 2 hours the solution was worked up in the usual way. The oily product obtained was chrom. tographed over Spence Grade H alumina.

(a) Elution with benzene-ether (3:1) and

recrystallisation from ether gave the oxidoalcohol (30 mg) mp 140-141° identical to that reported⁹ for the lithium aluminium hydride reduction of the oxidoketone (37).

(b) Elution with ether and recrystallisation from ethyl acetate and chloroform-petroleum (b.p. 60-80°) gave the diol (46) (15 m.g.) identical to the tricyclic diol (46) obtained by lithium in liquid ammonia reduction of the chlorohydrin (45).

In the presence of 2 mol of ammonium chloride the ratio of oxido alcohol to diol (46) increased to 3 and in the absence of ammonium chloride was 4.

Lithium in Ammonia reduction of the Ketol (39)

Ketol (39) (200 mg) in ether (25 ml) was added over 15 min. to a well stirred solution of lithium (200 mg.) in liquid ammonia (400 ml.) After 90 min. excess reagent was decomposed by ammonium chloride and water (20 ml.) was cautiously added. After evaporation of the ammonia the reaction mixture was worked up as in previous reductions. Crystallisation from ether-petroleum (b.p. 40-60°) furnished the tricyclic dihydroxy compound (55) (60 mg) m.p. 171-172°

$\bar{\nu}_{\max}$ 3550, 3650 cm^{-1} . $[\alpha]_D + 33^\circ$ (c, 1.26). M.W. 224.
 (Found: C, 74.9; H, 10.7. $\text{C}_{14}\text{H}_{24}\text{O}_2$ requires C, 75.0; H, 10.8%).

The residue from this reaction consisted largely of saturated polymeric hydrocarbon (s) N_D^{20} 1.4500 (Found C, 86.7; H, 13.3. E.F. $\text{C}_{14}\text{H}_{26}$ requires C, 86.5; H, 13.5%).

Oxidation of Tricyclic Dihydroxy Compound (55)

The diol (55) (150 mg.) in acetone (12 ml) was added to a solution of chromium trioxide (75 mg.) in acetone (3 ml.), water (0.5 ml) and conc. sulphuric acid (2 drops). After 12 hours at room temperature the mixture was diluted with water and ether extracted. After drying concentration of the extract gave the tricyclic ketol (70 mg), from chloroform-petroleum (b.p. 40-60°), m.p. 154-155° $[\alpha]_D - 22^\circ$ (c, 0.8), $\bar{\nu}_{\max}$ 1735, 3390 cm^{-1} .
 (Found: C, 75.7; H, 9.9. $\text{C}_{14}\text{H}_{22}\text{O}_2$ requires C, 75.6; H, 10.0%).

Tosylation of the Tricyclic Dihydroxy Compound (55)

The diol (55) (300 mg) was dissolved in dry pyridine

(2 ml.) and p-toluene sulphonyl chloride (290 mg.) was added. After standing at room temperature for 12 hours pyridine was removed in vacuo and water (10 ml) and saturated sodium bicarbonate (2 ml) were added to the residue which was then warmed at 50° for 30 min. The precipitate was filtered off, then crystallised from chloroform-petroleum (b.p. 40-60°) to give the diol monotosylate (400 mg) m.p. 131-132° $[\alpha]_D - 44^\circ$ (c, 0.95), $\nu_{\max}$ 1603, 3620 cm^{-1} .
 (Found: C, 66.5; H, 7.9; $\text{C}_{21}\text{H}_{30}\text{O}_4\text{S}$ requires C, 66.6; H, 8.0%).

nor-Caryophyllene Ketone (56)

The reaction was carried out as described by Corey⁴³. Dried dimethyl sulphoxide (12 ml.) was stirred under dry, oxygen-free nitrogen. Sodium hydride (100 mg. - oil free by decantation under dry light petroleum) was added and the mixture was warmed at 60° until formation of dimethyl sulphanyl carbanion was complete⁵⁹. (ca 15 min). After cooling to room temperature the diol monotosylate (300 mg.) was added and the orange-brown solution was stirred for a further 3 hours. Water was added to the reaction mixture and the aqueous solution was ether extracted. After drying

and concentration in vacuo a light yellow oil was obtained. Petroleum (b.p. 40-60°) was added and a little diol (55) was filtered off and the residue distilled to give nor-caryophyllene ketone (56) (120 mg) as a colourless oil. b.p. 122-125° (bath. temp.)/0.3 mm n_D^{24} 1.4955 $[\alpha]_D^{25}$ -52° (c, 0.83) $\nu_{\max}$ 1690 cm^{-1} and gave a semicarbazone m.p. 177-178°.

Isolation of the nor-caryophyllene ketone (56) after 5, 15 and 180 min. gave only a single product on gas chromatography (Celite - A.D. 264 column).

Epoxidation of nor-Caryophyllene Ketone (56)

nor-Caryophyllene ketone (56) (40 mg) was treated with monoperphthalic acid (15% excess) in ether (2 ml) at 0° for 15 hours. Saturated sodium bicarbonate was added and the etherial layer was separated, dried, and concentrated to give an oil. After chromatography on Spence Grade H neutral alumina benzene fractions yielded the oxidoketone (37) m.p. 65-66° (lit m.p. 62-63°) mixed m.p. 62-64°. $[\alpha]_D^{25}$ -131° (c, 0.64) (lit. rotn. -134° (c, 4.81), $\nu_{\max}$ 1690 cm^{-1} . Identical i.r. and t.l.c. properties with genuine sample.

Oxidation of Ketol (39)³³

Ketol (39) (1 g.) was stirred with active manganese dioxide (7 g.) in chloroform (30 ml.) for 20 hours. After filtration and concentration in vacuo the oily product was crystallised from petroleum (b.p. 60-60°) to yield the diketone (54) (670 mg) m.p. 48-50°, ν max 1620, 1680, 1695 cm^{-1} .

Oxidation of the Chlorohydrin (45)

The chlorohydrin (45) was oxidised according to the method of Semmler and Mayer¹ using potassium permanganate in acetone and then conc. nitric acid. Acidic compounds formed were converted to methyl esters using diazomethane and gas chromatography on a Celite-Polyester AD 264 column showed the presence of the esters of nor-caryophyllenic (1), caryophyllenic (2) and as-dimethyl succinic acids by comparison with genuine material.

9 β -hydroxycaryolan-1-ol (Treibs Glycol) (20)

Prepared by the method of Treibs²⁴, recrystallised from benzene-petroleum (b.p. 60-80°) gave the glycol (Yield 10%) m.p. 107°.

9 β -methane sulphonyloxy caryolan-1-ol

Treibs glycol (100 mg) was dissolved in pyridine (2 ml.) and methane sulphonyl chloride (100 mg.) was added. After removal of solvents in vacuo ether was added and, after washing with dilute acid and then base the ether solution was dried and concentrated. Crystallisation from chloroform-petroleum (b.p. 40-60°) gave Treibs glycol monomesylate (58, X = -OH, Y = -OSO₂CH₃.) (100 mg) m.p. 129-130° $[\alpha]_D + 22^\circ$ (C, 1.05) $\nu_{\max}$ 3600 cm⁻¹.
(Found: C, 60.4; H, 8.5, C₁₆H₂₈O₄S requires C, 60.7; H, 8.9%).

1-chloro-9 β methane sulphonoxycaryolane

9 β methane-sulphonyloxy-caryolan-1-ol (325 mg) was chlorinated by gently warming to 100° with phosphorous pentachloride (230 mg) until reaction was complete²⁵. The resulting oil was taken into ether and washed with saturated sodium bicarbonate and water. After drying ether was removed in vacuo. Crystallisation from chloroform-petroleum (b.p. 40-60°) gave the chloro- β mesylate (58, X = Cl, Y = -OSO₂CH₃) (270 mg) m.p. 113° (dec.), $[\alpha]_D + 28^\circ$ (C, 0.93).

(Found: C, 57.6; H, 8.5. $C_{16}H_{27}ClO_3S$ requires (C, 57.4; H, 8.1%).

9 β -acetoxy caryolan-1-ol

Reibs glycol (20) (5 g.) was dissolved in pyridine (10 ml.) and acetic anhydride (5 ml) and set aside overnight. After evaporation of solvents in vacuo and crystallisation from petroleum (b.p. 60-80°) 9 β -acetoxy caryolan-1-ol (58, X = -OH, Y = -OAC) (4 g) was obtained. m.p. 103-105° $\nu_{\max}$ 1720, 3500 cm^{-1} .

1-chloro-9 β acetoxycaryolane

9 β acetoxy caryolan-1-ol (2.66g) was chlorinated with phosphorous pentachloride (2.2g) as previously. Crystallisation from petroleum (b.p. 60-80°) furnished the chloro-acetate (58, X = Cl, Y = -OAC) m.p. 124-126° $\nu_{\max}$ 1720 cm^{-1}

1-chloro-9 β hydroxy caryolane

1-chloro-9 β hydroxy caryolane (2 g) was refluxed with 5% methanolic potassium hydroxide solution (25 ml.) for 30 min. After removal of most of the methanol in vacuo

water (25 ml) was added and the aqueous solution was ether extracted. After drying and removal of ether in vacuo the 1-chloro-9 β hydroxycaryolane (58, X = Cl, Y = -OH) remained as a thick oil. $\nu_{\max}$ 3500, 3700 cm^{-1} .

1-chloro-9 keto caryolane (59)

1 chloro-9 β hydroxy caryolane (2g) was dissolved in acetic acid (15 ml) and a solution of chromium trioxide (900 mg.) in water (1 ml) and acetic acid (10 ml) was added. After 12 hours the reaction mixture was worked up as previously. Crystallisation from methanol gave the chloroketone (59) (0.6 g) m.p. 44-46 $^{\circ}$ $\nu_{\max}$ 1700 cm^{-1} .

1-chloro-9 α hydroxy caryolane

The chloroketone (59) (250 mg) was dissolved in methanol (5 ml) and water (0.2 ml). Sodium borohydride (120 mg) was added and after 12 hours at room temperature N hydrochloric acid (10 ml) was added followed by extraction with ether. After drying and evaporation of the ether the 1-chloro-9 α hydroxycaryolane (60, X = Cl, Y = -OH) was obtained as an oil $\nu_{\max}$ 3500 cm^{-1} .

1-chloro-9 α methane sulphonoxycaryolane

1-chloro-9 α hydroxycaryolane was mesylated in pyridine as previously to give the 1-chloro-9 α mesylate (60, X = Cl, Y = -OSO₂CH₃) crystallised from petroleum (b.p. 60-80°) m.p. 119° (Yield 90%).

1-chloro-9 α acetoxycaryolane

1-chloro-9 α hydroxy caryolane was acetylated in pyridine as previously to give the 1-chloro-9 α acetoxy-caryolane (60, X = Cl, Y = -OAc) crystallised from methanol m.p. 78-79° $\nu_{\max}$ 1730 cm⁻¹ $[\alpha]_D$ - 12° (C, 1.12). (Yield 100%).

9-keto caryolan-1-ol (10)

Treibs glycol (20) was oxidised using chromium trioxide acetic acid by the method of Barton¹⁰. The keto alcohol (10) was recrystallised from chloroform-petroleum (b.p. 60-80°) m.p. 104° $\nu_{\max}$ 1695, 3450, 3650 cm⁻¹. (Yield 70%)

9 α hydroxy caryolan-1-ol

9-keto caryolan-1-ol (10) (1.56 g) was dissolved in methanol (7 ml.) containing water (0.5 ml.) and sodium borohydride (350 mg.) was added at 0°. After 15 hours the resulting solution was taken into ether and washed with 2N sodium hydroxide solution. After drying ether was evaporated and the residue crystallised from chloroform to give 9 α -hydroxy caryolan-1-ol (60, X = Y = OH) (1.5 g) m.p. 161-163° $[\alpha]_D - 5^\circ$ (C, 0.77) $\nu_{\max}$ 3450, 3650 cm^{-1} .

9 α -acetoxy caryolan-1-ol

9 α hydroxy caryolan-1-ol was acetylated using acetic anhydride and pyridine as previously. Crystallisation from petroleum (b.p. 40-60°) gave 9 α acetoxycaryolan-1-ol (60, X = OH, Y = -OAC) m.p. 105° $[\alpha]_D - 22^\circ$ (C, 0.97) $\nu_{\max}$ 1730, 3650 cm^{-1} .

(Found: C, 73.2; H, 10.4. $\text{C}_{17}\text{H}_{28}\text{O}_3$ requires C, 72.8; H, 10.1%).

Chlorination of this material in the usual way with phosphorous pentachloride gave 1 chloro-9 α acetoxy-caryolane identical to that obtained previously by acetylation of 1 chloro-9 α hydroxy caryolane.

Methods of Attempted 1:4 Reductive Cleavages

1-chloro-9 β methanesulphonoxycaryolane was treated with lithium in liquid ammonia, lithium iodide in acetone, zinc in refluxing pyridine, zinc in refluxing acetic acid, magnesium in refluxing ether.

9-keto-caryolan-1-ol was treated with zinc in refluxing dioxane and zinc in refluxing acetic acid.

1-chloro-9 α methane sulphonoxycaryolane - treated as for the β epimer.

Acetic acid on the 9 α , and 9 β chloromesylates

The 1-chloro-9 α (or 9 β) methane sulphonoxy caryolane (3 g.) was refluxed in glacial acetic acid (20 ml) for 24 hours. After removal of solvent in vacuo the oily residue was crystallised from methanol to give the 1-acetoxy (Δ_9) caryolene (61, X = -OAc) (300 mg.) m.p. 76-77°, $[\alpha]_D + 44^\circ$ (C, 1.08) $\nu_{\max}$ 1720 cm^{-1} . (Found: C, 78.0; H, 10.1. $\text{C}_{17}\text{H}_{26}\text{O}_2$ requires C, 77.8; H, 10.0%).

Hydrogenation in ethanol using Adam's catalyst gave an uptake of hydrogen corresponding to 1 mole and yielded a

saturated acetate m.p. 39-40° $\nu_{\max}$ 1730 cm^{-1} $[\alpha]_D$
 + 45° (C, 0.60) shown to be 1-acetoxy caryolane by mixed
 m.p. i.r. and t.l.c. properties.

Lithium iodide on the 9 α , and 9 β chloromesylates

The 1-chloro-9 α (or 9 β) methane-sulphonoxycaryolane
 (1 g.) was refluxed in acetone (50 ml.) with lithium iodide
 (5 g.) for 3 days. Acetone was removed in vacuo and water
 was added followed by ether extraction. The ether solution
 was washed with sodium metabisulphite solution, dried and
 evaporated to give an oil which was chromatographed over
 Spence Grade H neutral alumina. The petrol eluant yielded
 an oily product which was hydrogenated in ethanol using
 Adam's catalyst. After 1 mole uptake the isolated product
 was a saturated chloride m.p. 62-63° $[\alpha]_D$ + 9° (C, 0.72)
 shown by mixed m.p., i.r. and t.l.c. properties to be
 1-chloro caryolane. (12, X = Cl).

Cyclisation of Oxido-ketone (37)

Base catalysed cyclisation of oxido ketone (37) to
 the cyclic ketol (63, R = H) was carried out by the method
 of Barton⁹ m.p. 146-147° $\nu_{\max}$ 1690, 3500 cm^{-1} . The

mesylate (63, $R = \text{SO}_2\text{CH}_3$) and tosylate (63, $R = \text{SO}_2\text{C}_6\text{H}_4\text{CH}_3$) were prepared in pyridine and both were oils.

Reduction of the Cyclic Ketol (63, $R = \text{H}$)

The cyclic ketol (63, $R = \text{H}$) (100 mg) was reduced in methanol (3 ml), water (0.25 ml.) with sodium borohydride (36 mg.). After 12 hours ether was added and after washing with 2N sodium hydroxide, drying and evaporation of the ether the cyclic diol (62, $X = Y = -\text{OH}$) (100 mg) was obtained. Crystallised from ethanol-petroleum (b.p. $60-80^\circ$) m.p. $164-165^\circ$, $[\alpha]_D - 64^\circ$ (C, 1.0). (Found: C, 74.9; H, 10.8. $\text{C}_{14}\text{H}_{24}\text{O}_2$ requires C, 75.0; H, 10.8%).

Cyclic Diacetate (62, $X = Y = -\text{OAC}$)

The cyclic diol (62, $X = Y = -\text{OH}$) was acetylated in pyridine at room temperature as before to give the cyclic diacetate (62, $X = Y = -\text{OAC}$). Crystallised from methanol m.p. $83-84^\circ$ $[\alpha]_D - 46^\circ$ (C, 1.73), $\nu_{\text{max}} 1730 \text{ cm}^{-1}$. (Yield 100%).

Methods of Attempted 1:4 Reductive Cleavage

Cyclic ketol tosylate (mesylate) was treated with lithium in liquid ammonia for 5 hours.

Cyclic diacetate was treated with lithium in liquid ammonia, only the cyclic diol (62, $X = Y = -OH$) was recovered.

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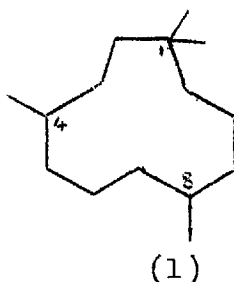
HUMULENE

Introduction and Review

The Structure of Humulene

Humulene was first isolated by Chapman¹ from hop oil (Humulus lupulus L) and has since been isolated from many sources^{2,3}. Significantly, it was shown by Deussen⁴ to be present in "caryophyllene oil" from oil of cloves and comparison of derivatives showed that humulene was identical to α -caryophyllene from this source. Recently Sorm⁵ confirmed this by comparison of the infra-red spectra of humulene and α -caryophyllene and their fully hydrogenated derivatives.

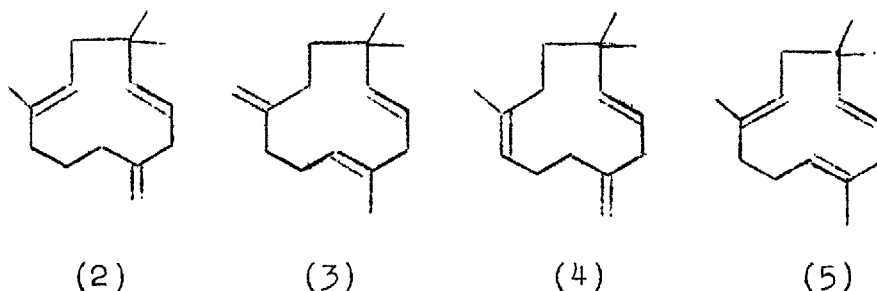
Clemo and Harris⁶ proved the presence of three double bonds in humulene from quantitative hydrogenation and titration with perbenzoic acid and thus the hydrocarbon was known to be monocyclic. The lack of ultraviolet absorption showed that the ethylenic bonds could not be conjugated. Oxidative degradation^{7,8} showed that the basic skeleton of humulene was 1:1:4:8-tetramethylcyclo-undecatriene, but the precise location of the double bonds caused controversy. Sorm and co-workers⁹ fully confirmed the humulene skeleton by synthesising 1:1:4:8 tetramethylcycloundecane by two independent routes and showed it to be identical to humulane (hexahydrohumulene) (1).



Fawcett and Harris¹⁰ at this time also demonstrated the humulene skeleton by unambiguous synthesis of a humulene degradation product.

While at this time the nature of the carbon skeleton had been well demonstrated there was no agreement as to the location of the double bonds for several years. This was mainly because workers in the field were not using pure humulene in their degradative experiments. Distillation or available chromatographic techniques were inadequate for purification of the hydrocarbon.

Characterised oxidation products of humulene included laevulinic acid, laevulinic aldehyde, as-dimethylsuccinic acid and formaldehyde. Mainly from these oxidation products various structures (2)¹¹, (3)¹², (4)¹², (5)¹³, were proposed for humulene but any one structure could not account for all the observed oxidation products.



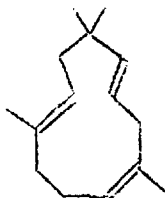
Sorm and coworkers¹¹ believed structure (2) represented humulene primarily because of the isolation of as-dimethylsuccinic acid on oxidation together with a high yield of formaldehyde and formic acid suggesting a structure containing exocyclic methylene group. Infrared absorption at 890 cm^{-1} confirmed their view which was in part shared by Fawcett and Harris¹² who however suggested structures (3) and (4) as alternatives. Both groups of workers were incorrect and it was suggested by Dev¹⁷ that formaldehyde arose from an abnormal ozonolysis. This suggestion is certainly incorrect and these erroneous results presumably arise because of a contaminant in their humulene which has since been shown by Sorm¹⁹ to occur naturally in crude humulene oil and probably has structure (2). This compound is now called β -humulene.

Clark and Ramage¹³ suggested structure (5) on the basis of oxidative degradation of some crystalline

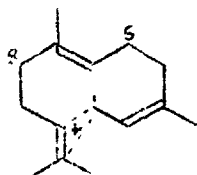
derivatives and this structure received support from Sutherland and co-workers¹⁴ who by reductive cleavage of humulene ozonide obtained butane 1:3 diol and two other components, presumably the glycols of laevulinic and asym-dimethyl succinic acids.

In 1961 Sutherland¹⁵ isolated pure humulene as a crystalline silver nitrate adduct, $C_{15}H_{24} \cdot 2AgNO_3$, and showed that the pure hydrocarbon could be regenerated by steam distillation or treatment with aqueous ammonia without rearrangement. The pure humulene obtained showed neither an exocyclic methylene group in its infra-red spectrum nor gave formaldehyde on ozonolysis¹⁶ and fully confirmed structure (5) for humulene. This structure is also in full accordance with the N.M.R. spectrum^{17,18}.

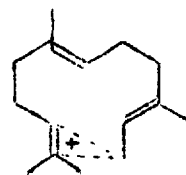
Recently^{20,21}. X-ray analysis of the silver nitrate adduct has shown that humulene has an all trans stereochemistry of the double bonds. Until this X-ray determination several workers had speculated about the humulene stereochemistry. Dev¹⁸ wrote humulene as being derived from trans-cis (6-7)-trans farnesol (6) while Hendrickson²²



(6)

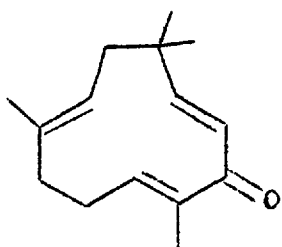


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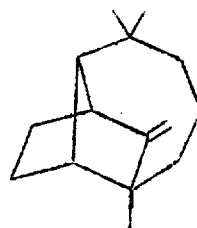


(8)

thought from a consideration of steric and electronic properties that humulene (and caryophyllene) should be generated from trans-trans-cis (2-3) farnesyl cation (7). However Sutherland¹⁶ also on steric considerations reached the conclusion that the all-trans farnesyl cation (8) was the correct humulene precursor. This view was supported by Naves²⁶ who from examination of sesquiterpene mixtures concluded that all-trans farnesol was initially formed in the biogenesis and that this would cyclise before it could rearrange to a progenitor with a cis double bond. Since humulene is now known to have the all trans stereochemistry presumably it is derived from the all trans farnesyl cation (8) and caryophyllene is most likely generated by cyclisation of humulene. Zerumbone (9)²⁸ and longifolene (10), besides



(9)



(10)

caryophyllene, are known to exist with humulene in nature and it would not be surprising if these sesquiterpenes were also derived from humulene.

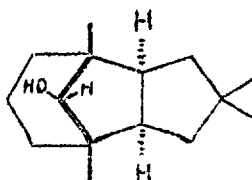
It has recently been reported^{29,30.} that two humulene monoepoxides (epoxidised at C 3-4 and C 7-8), humulene dioxide and a humulene alcohol exist in nature. It is probable that these are, like caryophyllene oxide, biological oxidation products of the parent sesquiterpene.

Cyclisation Products of Humulene

There is only one humulene cyclisation product so far recorded in the literature. This is probably because of the relatively short chemical history of this sesquiterpene compared with caryophyllene rather than for any inherent stereochemical, or thermodynamic reasons.

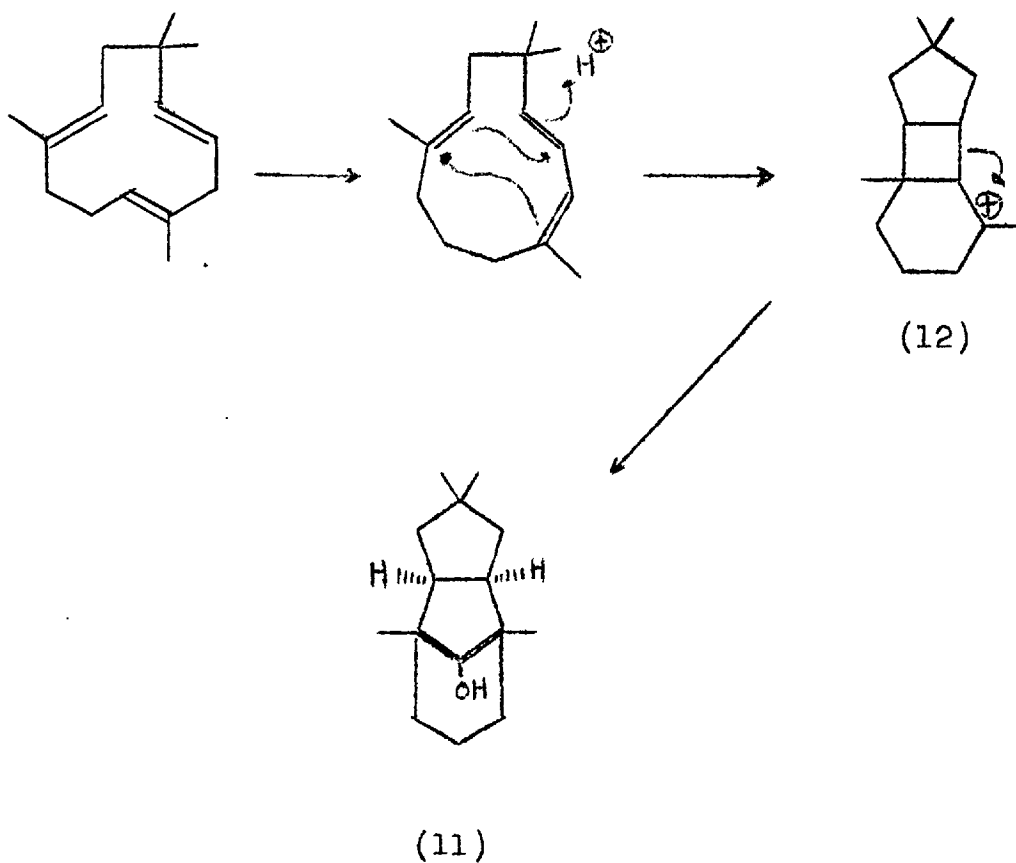
Acid catalysed hydration of crude caryophyllene has for some time been known to generate ' α -caryophyllene alcohol' in low yield. It has now been shown that this is a humulene cyclisation product (which is known to be present in crude clove-oil caryophyllene), pure humulene generating the compound in high yield and pure caryophyllene giving none²³.

Nickon and co-workers²⁴. by an elegant use of the Barton reaction showed that (11) represented the structure and stereochemistry of ' α -caryophyllene alcohol'. This has been confirmed by an X-ray structural determination²³.

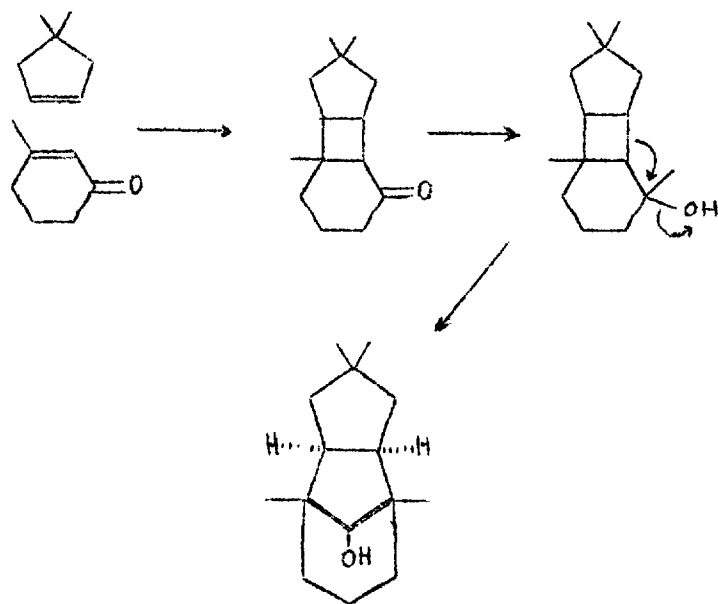


(11)

It has been suggested that α -caryophyllene alcohol may be generated by a series of transannular reactions through an intermediate of type (12)



Corey²⁵ in an ingenious synthesis prepared an intermediate of type (12) which, on acidic treatment gave α -caryophyllene alcohol.

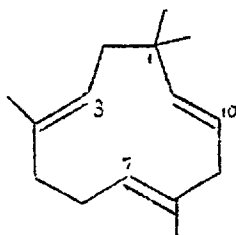


(11)

THEORETICAL SECTION

Introduction

Although only one cyclisation product of humulene has so far been recorded²⁴, there has been little work on transannular cyclisations in this system but with the presence of three double bonds cyclisations may be expected to proliferate as in the related system caryophyllene. With caryophyllene, tricyclic derivatives formed by easily reversible transannular reactions are useful models for an attempted synthesis and the preparation of a polycyclic system which similarly regenerated humulene with the incorporation of three trans double bonds would also be a useful synthetic model for this system.



(5)

It is also likely the humulene is the biogenetic precursor of caryophyllene, since a simple cyclisation between the double bonds at C₃ and C₁₁ would generate a

4-9 ring fusion with the correct trans- stereochemistry as found in caryophyllene. A simple chemical transformation between these two related sesquiterpenes would in itself, not be conclusive of an in vivo relationship, but would show that such a transformation is at least feasible. No experimental evidence for a link between this pair of sesquiterpenes has been reported so far.

The humulene used in this work was obtained from a crude sesquiterpene mixture by isolation through the silver nitrate adduct¹⁵. In new experiments doubly purified humulene was used, which showed a single peak on g.l.c., but in repetition experiments yielding crystalline products humulene containing small quantities (< 5%) of caryophyllene was used.

Since humulene contains two 1, 5 diene systems the simplest transannular reaction possible should be bond isomerisation as in the Cope³¹ rearrangement. Using temperatures up to 250° no rearrangement products of any type were found which is in contrast to the facile Cope rearrangement of germacrone³² and germacrene³³.

The N.M.R. spectrum of humulene was well resolved and so most useful for the identification of groups in reaction products, the gem-dimethyl group appeared at 8.96 τ , the C₄ methyl at 8.35 τ (doublet), the C₈ methyl

at 8.57 τ and a characteristic vinylic proton pattern at 4.39, 4.50, 4.61, 4.75 and 5.01 τ . The resolved nature of the spectrum probably implies that rigidity is imparted by the three endocyclic double bonds, a situation which was not found in any derivatives of this system.

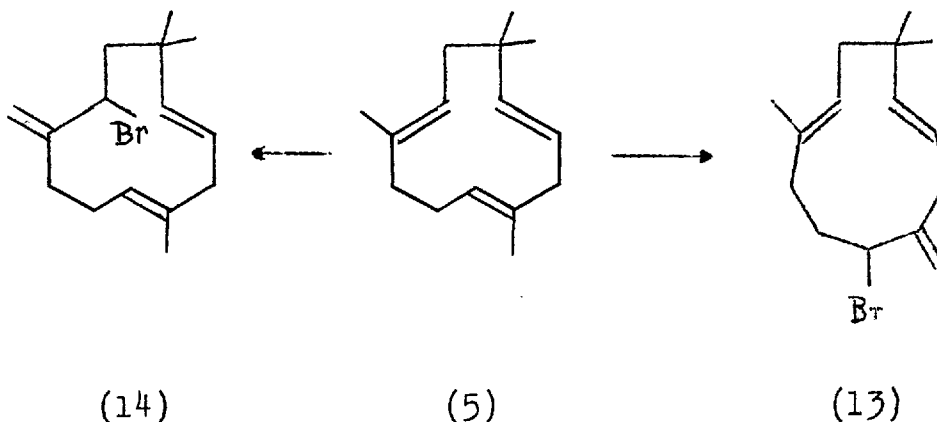
Early experiments on humulene³³ were concerned with cyclisation of the molecule using bromine in carbon tetrachloride as a condensing agent but crude products were obtained which even after extensive chromatography were non-homogeneous and showed considerable vinylic absorption in the N.M.R. which suggested monocyclic bromo derivatives. Bromination of humulene using N-bromosuccinimide (N.B.S.) in aqueous acetone was more successful, crystalline products being isolated. The reaction between molar equivalents of N.B.S. yielded after work up an oil from which was isolated a high melting solid, $C_{15}H_{26}O_2$, which we have named dihydroxyhumulene, and chromatography of the residue yielded hydroxybromohumulene, $C_{15}H_{25}BrO$, and a third crystalline component bromohumulene, $C_{15}H_{23}Br$. The N.M.R. spectra of dihydroxy and hydroxybromohumulene showed considerable similarities, namely the presence of four methyl groups and the absence of vinylic protons and both were considered to be cyclisation products. The simple relationship between these two compounds was

indicated by the hydrolysis of the hydroxybromo derivative to the dihydroxyhumulene. The structures of these compounds have been elucidated and will be discussed in full later.

Bromohumulene showed considerable absorption in the vinylic region and with the probability that it was a simple humulene derivative chemical investigation of the structure was commenced.

The Structure of Bromohumulene

The N.M.R. spectrum of crystalline bromohumulene, $C_{15}H_{23}Br$, showed the presence of the gem-dimethyl group at 8.92 τ , a methyl group on a double bond at 8.42 τ , a single proton as a triplet centred at 5.85 τ which may be assigned to the $-CHBr$ system, and vinylic absorption between 4.83 and 5.05 τ (5 protons). The absence of the characteristic vinylic splitting pattern of humulene coupled with the disappearance of one of the humulene methyl groups on a double bond indicated the probable rearrangement of a methyl group to an exocyclic methylene group on formation of the ~~bromo~~ derivative. Assuming a simple reaction without rearrangement the probable structures which could be deduced immediately were (13) and (14).



The presence of three double bonds in bromohumulene was shown by catalytic hydrogenation, after three moles had been consumed the liquid product still contained bromine. A rather more convincing demonstration of the degree of unsaturation was obtained by treatment of the bromohumulene in ether with peracid. After three days back titration showed that two moles of peracid had been consumed and a crystalline diepoxide, $C_{15}H_{23}BrO_2$, $\nu_{\max} 1640\text{ cm}^{-1}$, was isolated. Both the bromodiepoxide and bromohumulene itself gave high yields of formaldehyde (as the dimedone derivative) on ozonolysis, and further treatment of the bromodiepoxide with peracid showed that a third mole was slowly consumed over fourteen days. The presence of three double bonds in bromohumulene, one of them as an exocyclic methylene group was thus well established.

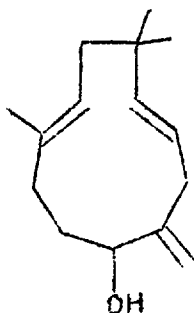
It was necessary however, to relate bromohumulene to the parent hydrocarbon as the possibility of ring contraction or methyl migration could not be ignored. This was achieved by reduction of bromohumulene using lithium in liquid ammonia, the product from this reaction contained no halogen and gas chromatography showed just a single peak corresponding to genuine humulene, but from the N.M.R. spectrum the product was shown to be a mixture of humulene (5) and apparently its exocyclic analogue β -humulene (2). Hydrogenation of

this hydrocarbon mixture gave a total take-up corresponding to three moles and the saturated product showed identical i.r. and retention volume on g.l.c. with an authentic specimen of hexahydrohumulene (humulane (1)). A separation of the reduction mixture was effected on a silver nitrate-silica gel preparative plate, pure humulene being isolated and characterised by i.r., g.l.c., and N.M.R., the isomeric β -humulene however, when isolated rapidly autoxidised in air.

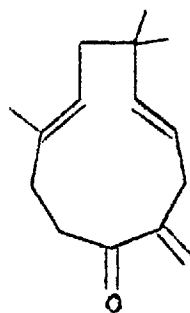
The reduction of allylic halides with lithium in liquid ammonia is thought to proceed through the carbanion and kinetic control of the protonation leads to the two isomers found. Reduction with chromous ion proceeds not through the allylic anion but by a radical mechanism and stereochemical control is decisive. Under these conditions only β -humulene (2) is formed in the reduction which is probably the product of thermodynamic control since it has been claimed that humulene may be isomerised to presumably the more stable β -humulene on basic alumina¹⁹. Since simple conversion back to the humulene skeleton reasonably precludes the possibility of rearrangement in the formation of bromohumulene, an apparently simple decision between the probable structures (13) and (14) must be made. The elimination of one of these structures

in fact proved most difficult due to the symmetry of the two possibilities and the ease of rearrangement of the allylic halide.

N.B.S. in aqueous solution is an effective source of hypobromous acid and addition of bromonium ion to the most reactive double bond would be expected in the formation of bromohumulene. It has been shown³⁰ that humulene may be selectively epoxidised at the C₇ double bond indicating its greater reactivity to electrophilic reagents and on this basis bromohumulene would be (13). A simple correlation with the corresponding alcohol, humulenol (15), which has been made by isomerisation of humulene monoxide²⁹, was attempted.



(15)



(16)

The preparation of humulene monoxide using perphthalic acid gave an essentially pure monoxide. Rearrangement to

the allylic alcohol (15) using neutral grade 1 alumina has been reported^{29,35}. however in our experiments acid washed alumina gave higher yields of humulenol (15). In the case of caryophyllene oxide a similar isomerisation was effected using acidic reagents and this behaviour which was first observed in transcyclodecene epoxide³⁶ may be characteristic of medium ring oxirans. It was significant that humulene epoxide did not show the doubly allylic protons at C₉ but these reappeared in the humulenol (15) indicating that the epoxide was truly formed at C₇. The humulenol (15) showed a very similar N.M.R. spectrum to bromohumulene, in particular both showed a methyl group on a double bond at 8.40 τ , and this was assignable to the C₄ methyl group supporting structure (13) for bromohumulene.

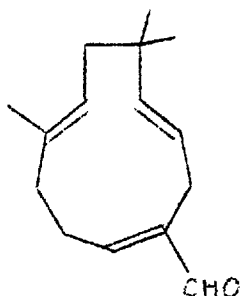
Hydrolysis of bromohumulene to humulenol (15) was attempted using silver salts in aqueous organic solutions and a variety of other mild reagents but in all cases the product appeared to consist of allylic primary alcohols with both cis and trans endocyclic double bonds. Allylic rearrangements was also observed when displacement with acetate or benzoate ions was attempted. Correlation of hexahydrobromohumulene with hexahydrohumulenol³⁵ was also impossible since elimination to give the alkene rather than hydrolysis took place in basic solution, and similarly,

attempted conversion of humulenol (15) to bromohumulene gave only complex products.

Humulenol (15) is reported as yielding a low melting humulene ketone (16)²⁹. on oxidation with manganese dioxide which has been characterised as the 2:4 dinitrophenyl-hydrazone (2, 4 DNP) m.p. 190-191⁰, and since allylic halides may be oxidised to the corresponding carbonyl compound using dimethyl sulphoxide³⁷ a correlation between bromohumulene and humulene ketone (16) was sought.

Oxidation of humulenol gave ketonic material in moderate yield which, despite extensive chromatography, could not be crystallised but did yield a 2, 4 DNP (m.p. 193-194⁰) as described. Oxidation of bromohumulene with dimethyl sulphoxide gave crude oxidised material which was converted directly to the 2, 4 DNP derivative. The isolated 2,4 DNP (m.p. 198-199⁰) was not identical to humulene ketone 2,4 DNP in its physical properties and the alternative structure (14) for bromohumulene seemed feasible. However, examination of the filtrate from the preparation of the 2,4 DNP (m.p. 198-199⁰) showed on thin layer chromatography the presence of humulene ketone 2,4 DNP in low yield. In successive oxidations on larger quantities of bromohumulene it was possible to separate both the 2,4 DNP's by fractional crystallisation.

The normal oxidation product of bromohumulene, humulene ketone (16) was thus being formed in small amounts and the 2,4 DNP in major yield has been shown to be derived from humulene aldehyde (17), generated by an S_N2' oxidation of bromohumulene. Purification of the oxidation mixture from



(17)

bromohumulene by chromatography gave a colourless oil which although showing only a single spot on silica gel thin layer chromatography could be resolved into two on silver nitrate-silica gel. A separation of humulene aldehyde (17) from humulene ketone (16) was not achieved and separation through fractional crystallisation of the 2,4 DNP's was always necessary. After resolution of the 2,4 DNP mixture confirmation of structures (16) and (17) and thus of (13) for bromohumulene was sought by degradation of both 2,4 DNP's.

Humulene aldehyde 2,4 DNP and humulene ketone 2,4 DNP from the oxidation experiments were ozonised in acetic acid

and, after oxidation with hydrogen peroxide according to the method of Sutherland and Waters¹⁶, acidic products were isolated. Thin layer chromatography showed the presence from both derivatives of dimethylsuccinic (or succinic), malonic and laevulic acids and after conversion to the methyl esters gas chromatography confirmed the presence of dimethyl succinic (50%), laevulic (30%) and only small amounts of malonic (< 5%) and succinic (< 15%) acids. The generation of laevulic acid from both the 2,4 DNP's, a critical degradation product which can only be derived from structural types (15) and (16), means that bromohumulene is derived from reaction at the C₇ double bond and has structure (13). The formation of succinic acid is slightly surprising but it is possibly generated from laevulic acid by oxidation. In a separate experiment humulene ketone 2,4 DNP gave formaldehyde whereas humulene aldehyde 2,4 DNP gave none.

The N.M.R. spectrum of humulene aldehyde 2:4 DNP shows similar downfield absorption to crotonaldehyde 2,4 DNP and in particular an extra downfield proton (2.92 τ) assignable to the aldehydic proton can be recognised in comparison with the spectrum of the humulene ketone derivative.

During work on the tricyclic derivatives of humulene key products were these same two 2,4 DNP's already discussed

and the characteristic differences in thin layer RF's and in the shape of the U.V. curves of these compounds were ideal for characterisation purposes.

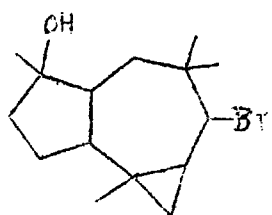
The Structure of Hydroxybromohumulene

The cyclisation of humulene using aqueous N-bromo-succinimide (NBS) gives rise to two compounds, hydroxybromohumulene and dihydroxyhumulene. Since it was easily shown that hydroxybromohumulene was hydrolysed to give dihydroxyhumulene it was reasonable to assume a simple relationship between them and that hydroxybromohumulene was being hydrolysed to dihydroxyhumulene under the reaction conditions. The close similarities in the N.M.R. spectra of the two compounds confirmed this simple connection and chemical elucidation of the basic skeleton of the cyclic system was performed on either compound as desired.

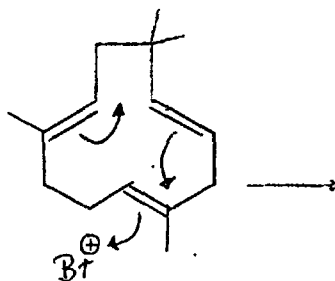
The N.M.R. spectra of these compounds gave useful structural information; hydroxybromohumulene showed no vinylic absorption, methyl groups at 8.88 (6H), 8.90 (3H) and 8.94 (3H) τ , a single downfield proton centred at 6.15 τ as a triplet, and absorption corresponding to three protons from 9.3 to 9.9 τ . This spectrum may be interpreted as showing that all three of the humulene double bonds had taken part in the cyclisation process and in so doing formed a substituted cyclopropane ring (broad A-B-C

pattern at high field). Dihydroxyhumulene showed essentially the same N.M.R. features but the single downfield proton was at 6.8 τ which indicated that dihydroxyhumulene has one secondary and one tertiary hydroxyl and in hydroxybromohumulene one tertiary hydroxyl group and, from the difference in the downfield proton position, one secondary bromine atom. The tertiary nature of the hydroxyl group in the hydroxybromo derivative was confirmed by its inability to either form an acetate or oxidise to a ketone whereas dihydroxyhumulene easily gave these derivatives.

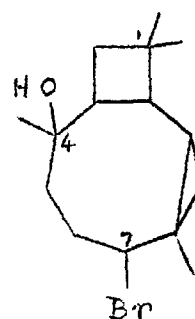
Many cyclisation products of humulene may be envisaged but, accepting a direct cyclisation without Wagner-Meerwein skeletal rearrangement and the formation of a three membered ring together with one secondary and one tertiary substituent, only two structures may be derived as working possibilities. Of these two possibilities structure (18)



(19)



(5)



(18)

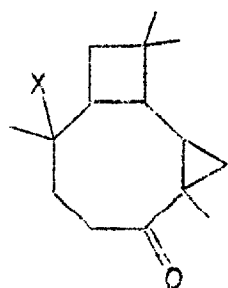
must be favoured on mechanistic grounds since it is derived by initial attack by bromium ion at the most reactive bond to electrophilic attack (i.e. C_7), as is the case in the formation of the monocyclic derivative bromohumulene (13), whereas structure (19) would be generated by attack at the C_{10} double bond which is the least reactive of the three double bonds.

Although the cyclopropane ring is polarised by the presence of an α -electronegative substituent ring opening was not readily brought about. Hydrogen chloride in chloroform (or thionyl chloride in pyridine) gave by replacement of the hydroxyl group a chloro-bromohumulene, $C_{15}H_{24}BrCl$, from hydroxybromohumulene and similarly a dichlorohumulene, $C_{15}H_{24}Cl_2$ from dihydroxyhumulene. Chlorobromohumulene showed in the N.M.R. all the features of its progenitor except that one methyl group was shifted downfield to 8.48τ on chlorination of the tertiary hydroxyl group. Similarly in dichlorohumulene one methyl group was shifted to 8.53τ on replacement of the tertiary hydroxyl and the single downfield proton was displaced to 6.57τ on replacement of the secondary hydroxyl group. These changes in the N.M.R. spectra are consistent with the groups $>C(OH)CH_3$ and $>CHBr$ being present in hydroxybromohumulene.

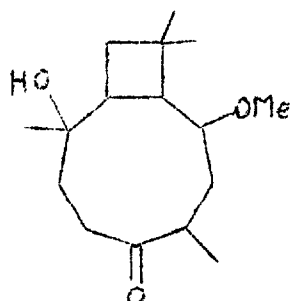
Under these halogenation conditions the cyclopropane

ring remained intact and this inertness was reflected in the resistance to hydrogenation, since ring opening could only be achieved together with general decomposition of the system. Electrophilic ring opening of the postulated cyclopropane ring was vital in order to have confidence in the proposed structure (18). Towards this end dihydroxyhumulene was oxidised gently to the corresponding humulene hydroxyketone (20, X = -OH) which showed an ultraviolet absorption maximum at 213 m μ , a typical value for a carbonyl group conjugated to a cyclopropane ring. Importantly in this hydroxyketone, while most of the groups remained in their usual positions in the N.M.R. spectrum, one methyl group was shifted downfield to 8.56 τ and this may be assigned to the methyl group on the cyclopropane now deshielded by the presence of an α carbonyl group.

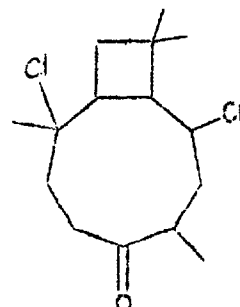
This system, as expected, was far more susceptible to addition across the three membered ring because of the high polarity of the carbonyl group. In characterising the hydroxy ketone (20, X = OH) a 2,4 DNP derivative was prepared in acidic methanol and isolation after two days gave a product containing a methoxyl group by addition of methanol across the cyclopropane ring (21). In the N.M.R. spectrum this methoxyl group appeared at 6.62 τ and a single downfield proton centred at 4.9 τ suggested the single



(20)



(21)



(22)

proton in a $-CHOMe$ function. Significantly all cyclopropane absorption had disappeared from the spectrum and it may be noted that ring opening of the ketol derived from the alternative working structure (19) would generate a tertiary methyl ether.

In order to obtain further evidence for the presence of a three membered ring addition of hydrogen chloride to the cyclopropane function in humulene hydroxyketone (20, $X = -OH$) was investigated. Initial treatment with hydrogen chloride in chloroform gave the corresponding chloroketone (20, $X = Cl$) which, on more vigorous treatment using hydrogen chloride in methanol, yielded a liquid dichloroketone that could be generated directly from humulene hydroxyketone (20, $X = -OH$) under these more powerful conditions. It was clear from the N.M.R. spectrum that

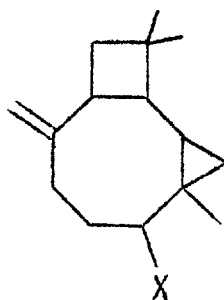
the chloroketone initially formed resulted from replacement of the tertiary hydroxyl group since the cyclopropane absorption was still present but a single methyl group was displaced downfield to 8.53τ . The dichloroketone (22) however showed no absorption above 9.1τ but again showed a proton at 6.5τ assignable to the presence of a $-\text{CHCl}$ grouping. The carbonyl stretching frequency was noticeably shifted from 1685 cm^{-1} to 1700 cm^{-1} on cleaving the three membered ring.

The authenticity of the cyclopropane ring seemed reasonably well established by the formation of two ring opened derivatives. The groups present in hydroxybromohumulene in which confidence could be placed at this stage were a gem- dimethyl group, a methyl group on carbon bearing a hydroxyl group ($>\text{C}(\text{OH})\text{Me}$) and a secondary bromine atom flanking a methyl cyclopropyl ring, but no evidence yet to suggest that the basic carbon skeleton of humulene was intact. This latter proof was obtained when it was found that the tricyclic hydroxybromohumulene could be decyclised to yield a known monocyclic humulene derivative which is discussed in full later. The regeneration of the humulene skeleton implies that the tricyclic compounds retain the basic humulene skeleton and so structure (18) for hydroxybromohumulene seemed likely.

A chemical proof of the cyclobutane ring in the tricyclic derivatives seemed desirable and towards this end the formation of the "caryophyllenic acids" ((1), (2) and (3)) was attempted. A direct nitric acid oxidation of dihydroxyhumulene did not yield the desired acidic products and this may be ascribed to the resistance of the three membered ring to oxidative fission. Preparation of a derivative lacking the cyclopropane ring and suitable for oxidative degradation was not achieved, reduction of the dichloroketone (22) failing to remove all the halogen from the molecule.

Since degradation was unproductive a direct conversion of hydroxybromohumulene (18) to caryophyllene (or some stereo isomer) was conceived as the simplest method of establishing the presence of the cyclobutane ring and at the same time providing supporting evidence for an intact humulene skeleton in the tricyclic derivatives. Treatment of hydroxybromohumulene (18) with phosphorus oxychloride in pyridine yielded an oily bromoalkene (23, X = Br) formed by elimination of the hydroxyl group to generate an exocyclic methylene function. From the analytical figures this compound contained about 15% of the chloroalkene (23, X = Cl) by halogen exchange with the reagent. Similar treatment of dihydroxyhumulene under these conditions gave the pure

chloroalkene (23, X = Cl). Although the spectral data supported the assigned structure (23) experience had shown that rearrangements may be initiated easily in this tricyclic system using dehydrating agents and a variation of



(23)

the method of preparing these alkene halides was used in order to eliminate this possibility. Dihydroxyhumulene was acetylated to give an oily product which was shown to consist of 80% monoacetate together with some 20% diacetate. Dehydration gave the liquid alkene acetate (23, X = -OAC) which, like the alkene halides, gave formaldehyde on ozonolysis but only consumed 80% of the theoretical quantity of hydrogen due to the presence of the diacetate. Hydrolysis of this product (23, X = -OAC) gave a mixture of the alkene alcohol (23, X = -OH) and regenerated dihydroxyhumulene (20%) which could be separated at this stage. The alkene alcohol (23, X = -OH)

was a crystalline product which was fully characterised and yielded formaldehyde in good yield on ozonolysis. Since greater confidence was enjoyed in the structure of this crystalline product reassurance as to the structures of the alkene halides was obtained when halogenation of the alkene alcohol gave the same alkene halides as found previously. These halides could also be hydrolysed to the alkene alcohol (23, X = -OH).

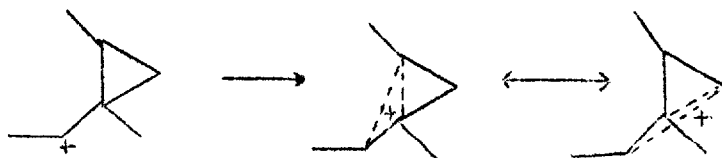
It was interesting, though not definitive, that the residues from the ozonolysis of the alkene derivatives (23) all showed a carbonyl stretching frequency in the infra-red at 1690 cm^{-1} , a value typical of a medium ring ketone whereas the alternative structure (19) would, after such a series of reactions, have generated a five membered ring ketone.

With the assured authenticity of the alkene halide structure (23) conversion to the caryophyllene ring system was attempted. Roberts³⁸ observed that cyclopropyl carbinyl halides rearranged on forming a Grignard reagent to give the corresponding allyl derivative by isomerisation of the carbanion. The factors affecting the stability of a carbanion α to a cyclopropane ring are not well understood as nor-tricyclene Grignard derivatives are quite stable³⁹, however a similar rearrangement was attempted. The hydrocarbon

product obtained after protonation of the Grignard complex showed several peaks on gas chromatographic examination, one of them corresponding to caryophyllene or isocaryophyllene.

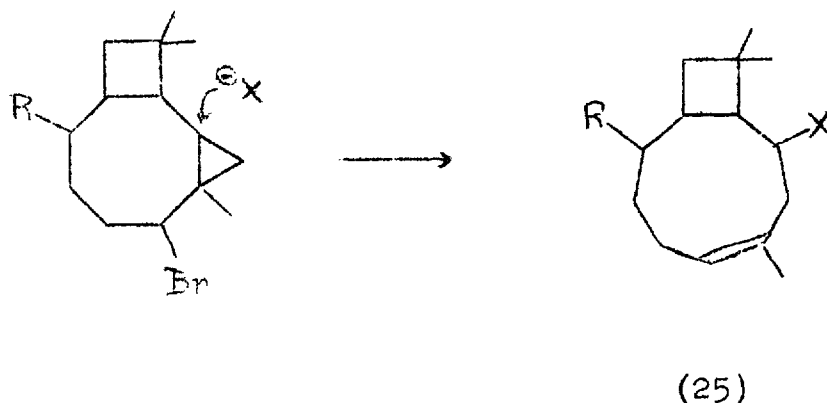
Instead of rearrangement of the anion derived from hydroxybromohumulene (18) the caryophyllene ring system should in principle be derivable by similar rearrangement of the carbonium ion. Roberts^{38,39} has shown that solvolysis of cyclopropylcarbinyl halides gives rearranged products and this has been interpreted as non classical ion formation by the cyclopropyl carbinyl cation. It has been postulated that a "bicyclobutonium" ion, readily interconvertible with other such bicyclobutonium ions, is first formed⁴⁴ and then on solvation of such a species a variety of products may be generated such as allyl carbinol, cyclobutanol and cyclopropyl carbinol. In hydroxybromohumulene (18) ionisation of the halogen atom would give rise to a unsymmetrically substituted cyclopropylcarbinylcation and by delocalisation of this ion six different bicyclobutonium ions may be formed (two are shown in fig. 24).

Charge neutralisation of these ions could give rise in principle to three cyclobutane, three cyclopropane and six unsaturated products. Such a rearrangement would perhaps not be expected to give all twelve products since thermodynamic and steric forces would probably control the

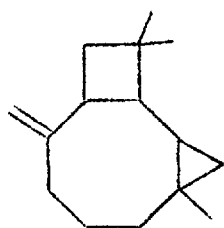
FIG. 24

interconversion of these bicyclobutonium ions⁴⁵. To obtain the caryophyllene ring system formation of unsaturated derivatives from the cyclopropyl system is desired and of these six possible products, if thermodynamic control were dominant, two would be unlikely since they generate disubstituted double bonds.

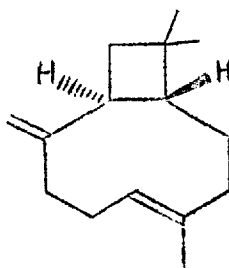
Julia^{40,41,42} has shown that rearrangement of secondary cyclopropyl carbinols to the homoallylic bromide may be achieved with hydrobromic acid, and further, such treatment gives a trans double bond (25). Such treatment of hydroxybromohumulene (18) however gave non-resolvable mixtures. It has also been shown⁴³ that ionisable halides may be reduced to give hydrocarbons using sodium borohydride in aqueous diglyme and by using this reaction



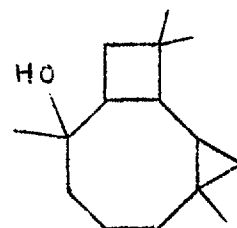
it was hoped that the reduction of the non classical ion would preferentially be at the homoallylic position. However under aqueous conditions dihydroxyhumulene was the major product and under anhydrous conditions sodium borohydride in the presence of boron trifluoride tended to hydroborate the double bond as it was formed. As a modification of this procedure reduction using a high excess of lithium aluminium hydride in strictly anhydrous conditions gave useful products. Reduction of the bromoalkene (23, X = Br) gave a mixture of hydrocarbon products which, on gas chromatographic examination, was shown to consist of compounds corresponding to humulene (5) and β -humulene (2) 15% , caryophyllene or isocaryophyllene 30% and an unknown product 50% which seemed probably (and was later shown) to be the tricyclic hydrocarbon (26) formed by direct



(26)



(27)



(28)

reduction of the alkene bromide without rearrangement.

Humulene and β -humulene were removed from the hydrocarbon mixture by washing with aqueous silver nitrate solution. The presence of humulene (5) in the reduction mixture was indicated by the characteristic vinylic splitting pattern in the N.M.R. spectrum but the presence of β -humulene (2) was only inferred because the hydrocarbon product tended to autoxidise on standing and on mechanistic grounds the hydrocarbon could well be "iso- β humulene" (3). These products have yet to be fully characterised.

After removal of these humulenes the hydrocarbon mixture contained the tricyclic hydrocarbon (26) and caryophyllene (27) together with several small impurities. Separation of the two main products proved to be most difficult, chromatography employing silica gel tending to rearrange the tricyclic hydrocarbon (26) and apparently,

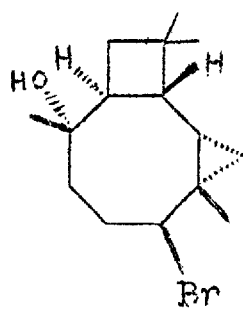
due to the presence of contaminants, polymerise or decompose the caryophyllene. Preparative thick layer chromatography on a silica gel-silver nitrate system has given both the tricyclic hydrocarbon (26) and caryophyllene (27) better than 95% pure and preparative gas chromatography gave almost completely pure products.

The N.M.R. spectrum of the tricyclic hydrocarbon (26) is in full agreement with the assigned structure and similarly the caryophyllene fraction (27) corresponds in both infra-red and N.M.R. spectra with a genuine sample of caryophyllene. Epoxidation of (27) has given crystalline material which has an almost superimposable infra-red spectrum with caryophyllene oxide and significantly, isocaryophyllene and its derived oxide have different spectral characteristics. The isolation of caryophyllene demonstrates clearly that reductive opening of the cyclopropane ring has generated a trans endocyclic double bond and importantly the presence of a cyclobutane ring in the tricyclic derivatives which is fused trans to the medium ring.

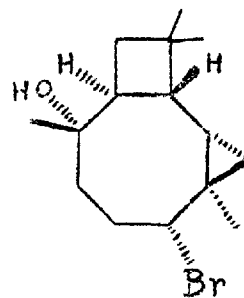
The general sensitivity of the tricyclic system to rearrangement (as in the decyclisation reactions discussed later) was also reflected in the ease of rearrangement of tricyclic hydrocarbon (26), which, on passage through a

column of grade 1 silica gel, was converted quantitatively and stereospecifically to humulene (5). Reduction of hydroxybromohumulene (18) with lithium borohydride in acetonitrile did not give ring opened products but yielded exclusively the hydroxytricyclic (28). Elimination of water from this molecule might be expected to yield the tricyclic hydrocarbon (26) but this was only obtained in low yield, humulene being the major product. Again this is an example of cleavage of the cyclobutane ring and a similar cleavage on a hydroxy caryophyllene would also generate the humulene system. This would then constitute the reverse conversion of the one already achieved between the two sesquiterpenes humulene and caryophyllene.

The stereochemistry of the tricyclic humulene derivative hydroxybromohumulene (18) is as yet unknown but the conversion to d,l, caryophyllene means that the cyclobutane ring fusion is certainly trans. Decyclisation processes have been shown to regenerate the humulene system stereospecifically (see later) and conversely an all trans cyclisation process would be probable. On these grounds two relative configurations are possible, (18a) and (18b). Of these two, (18b) contains a trans fused cyclopropane ring which, from models, appears to be rather strained and (18a) is probably the more likely stereochemistry.



(18a)



(18b)

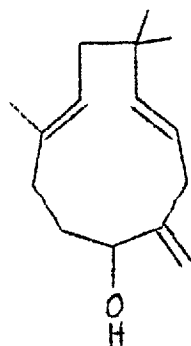
The Mechanism of Decyclisation

It had been noticed that the yields of humulene cyclisation products in the reaction with N.B.S. were dependent on such factors as acidity, the ratio of water to acetone used as solvent, length of reaction and speed of isolation of the products. An investigation as to the precise sequence of reactions occurring was commenced.

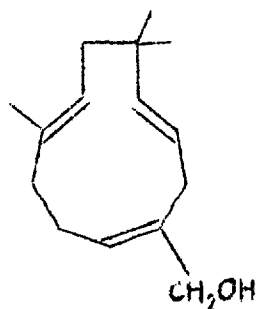
It was found that after addition of the N.B.S. the hypobromous acid formed reacted exceedingly quickly with the humulene, and quenching of the reaction by addition of chloroform after only one minute gave a maximum yield of hydroxybromohumulene, (18), little if any dihydroxyhumulene, and also the monocyclic bromohumulene (13). Stirring the reaction for one hour after the addition of N.B.S. gave a different composition of products, the yield of hydroxy bromohumulene was reduced but this loss of yield was in part accounted for by the isolation of dihydroxyhumulene. There was no change in the amount of monocyclic bromohumulene (13) isolated but an increase in the quantity of oily residue from the reaction was obtained. In a similar experiment a reaction mixture was stirred at room temperature overnight and after the isolation of products

bromohumulene was obtained in normal yield but no tricyclic products. The major reaction product was a crude liquid alcohol and the evidence from these three reactions suggested that bromohumulene once formed was stable under the reaction conditions but hydroxybromohumulene (18) was easily hydrolysed to dihydroxyhumulene and the ultimate product from the tricycles was a liquid alcohol. The structure of the liquid alcohol and the stabilities of the crystalline humulene derivatives were investigated to support these suppositions.

After reacting humulene with N.B.S. overnight the liquid alcoholic product was purified by chromatography until it showed essentially a single spot on thin layer chromatography. It was clear that a number of other products were formed in minor quantities but these could not be isolated in pure form. The N.M.R. spectrum of the alcoholic product showed vinylic absorption centred at 5τ and together with three methyl groups, one of them situated at 8.40τ which may be ascribed to the C_4 methyl in the humulene system. The N.M.R. and I.R. spectra showed considerable similarities with those for humulenol (15), which had already been prepared by isomerisation of humulene epoxide in connection with the work on bromohumulene (see before). In characterising the isolated alcohol it did



(15)



(29)

indeed show an allylic alcohol spot test (ceric ammonium nitrate) but oxidation and formation of the 2,4 DNP gave the derivative corresponding to humulene aldehyde (17) and only a trace of the humulene ketone (16) derivative could be detected on thin layer chromatography. It is therefore clear that the allylic alcohol formed in the reaction of humulene with N.B.S. overnight is actually "isohumulanol" (29) with only a trace of humulanol (15) itself.

Since the 2,4 DNP's of the oxidation products of these two isomeric allylic alcohols have been fully characterised previously, especially by their thin layer chromatograms and characteristic ultraviolet spectra, all experiments yielding such mixtures were characterised in this way. It is necessary however to interpret results from these

experiments with caution because yields of the two 2,4 DNP's may not accurately reflect the proportions of allylic alcohols present since their relative rates of oxidation may be different, although there is no evidence to suspect that this is the case.

As the overnight reaction of humulene with N.B.S. did not give the tricyclic products hydroxybromo- and dihydroxyhumulene but did give a new product isohumulanol (29) with traces of humulenol (15), it was suggestive that the tri-cycles were decyclising under the reaction conditions. The stabilities of reaction products were tested in isolation with an acetone-water-succinimide system designed to reflect the conditions actually existing in the N.B.S. reaction after the hypobromous acid had reacted with the humulene, as far as was concomitant with the solubilities of the compounds.

Hydroxybromohumulene (18) in the presence of acetone-water-succinimide at room temperature overnight gave a little dihydroxyhumulene together with an allylic alcohol portion but little starting material. Oxidation of the allylic alcohol fraction and conversion to the 2,4 DNP's gave, surprisingly, mainly humulene ketone 2,4 DNP with only a small quantity of the humulene aldehyde derivative, just the reverse of what had been observed under the actual

reaction conditions. Under more dilute conditions the yields of dihydroxyhumulene increased at the expense of the allylic alcohols and in the absence of succinimide, which is a weak acid, only a little decyclisation to the allylic alcohols took place.

Dihydroxyhumulene showed similar behaviour but in the presence of succinimide a large proportion of starting material was recovered and, in the absence of succinimide or under more dilute conditions the rate of decyclisation was very ~~slow~~. Again, as in the case of hydroxybromohumulene, the composition of the allylic alcohol fraction as estimated by oxidation and isolation of the 2:4 DNP's showed that humulenol (15) was mainly present and isohumulenol (29) was present in only trace quantities. From these two experiments it is quite clear that since decyclisation of dihydroxyhumulene is much slower than for hydroxybromohumulene most of the allylic alcohols formed must be generated directly from hydroxybromohumulene and only a little from dihydroxyhumulene. A reaction scheme may be presented as in fig. 30.

The generation of two allylic alcohols may be explained on the assumption that humulenol (15) is formed initially which may then be isomerised to give isohumulenol (29). It was shown that oxidation of pure humulenol (obtained

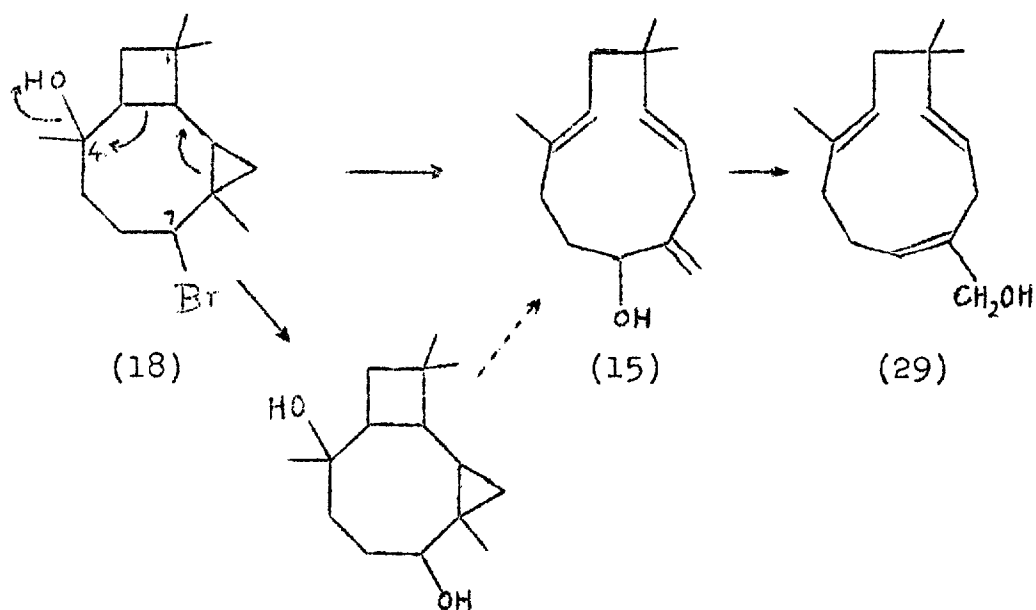


FIG. 30.

from isomerisation of humulene epoxide) gave only humulene ketone as identified by formation of the 2,4 DNP, thin layer chromatography did not detect any humulene aldehyde 2,4 DNP and so isomerisation of humulenol (15) could not be due to the isolation and estimation procedure employed. Instead it was shown that humulenol (15) dissolved in acetone-water-succinimide did in fact isomerise slowly to give isohumulenol (29) which would account for the small quantities of the latter obtained from decyclisation of both hydroxybromo- and dihydroxyhumulene. However in the reaction of humulene with N.B.S. overnight humulene aldehyde (17) was the major

product, and presumably this is due to the increased acidity of the reaction medium in this case over the artificial conditions employed to study the stabilities of the individual components. This is supported by the observation that hydroxybromohumulene in decyclisations always generated more isohumulenol (29) than did a corresponding decyclisation of dihydroxyhumulene, and this would be accounted for by the formation of hydrogen bromide during the decyclisation of the former which, due to the increased acidity of the reaction medium, would then more efficiently isomerise humulenol (15) to isohumulenol (29).

The mechanism of decyclisation became interesting when it was found that the obvious intermediate in the formation of humulenol, namely the monocyclic bromohumulene (13) (see fig. 30), was in fact not involved in this reaction. Bromohumulene was shown to be very stable under acetone/water/succinimide conditions, no humulenol was formed by hydrolysis and so it was quite clear that hydroxybromohumulene (18) could not first decyclise to give bromohumulene (13) prior to the formation of humulenol. This might have been deduced from the knowledge that the yields of bromohumulene were virtually independent of the reaction time with N.B.S. and that decyclisation of hydroxybromohumulene never gave bromohumulene in isolatable quantities. The formation of

bromohumulene (13) thus must be by simple addition to the C₇₋₈ double bond and must in no way be involved in the cyclisation-decyclisation reactions occurring alongside it.

Since dihydroxyhumulene was known to generate the monocyclic allylic alcohols at a much slower rate than hydroxybromohumulene, hydrolysis could not precede decyclisation and to account for these observations a new reaction scheme (fig. 31) was proposed:

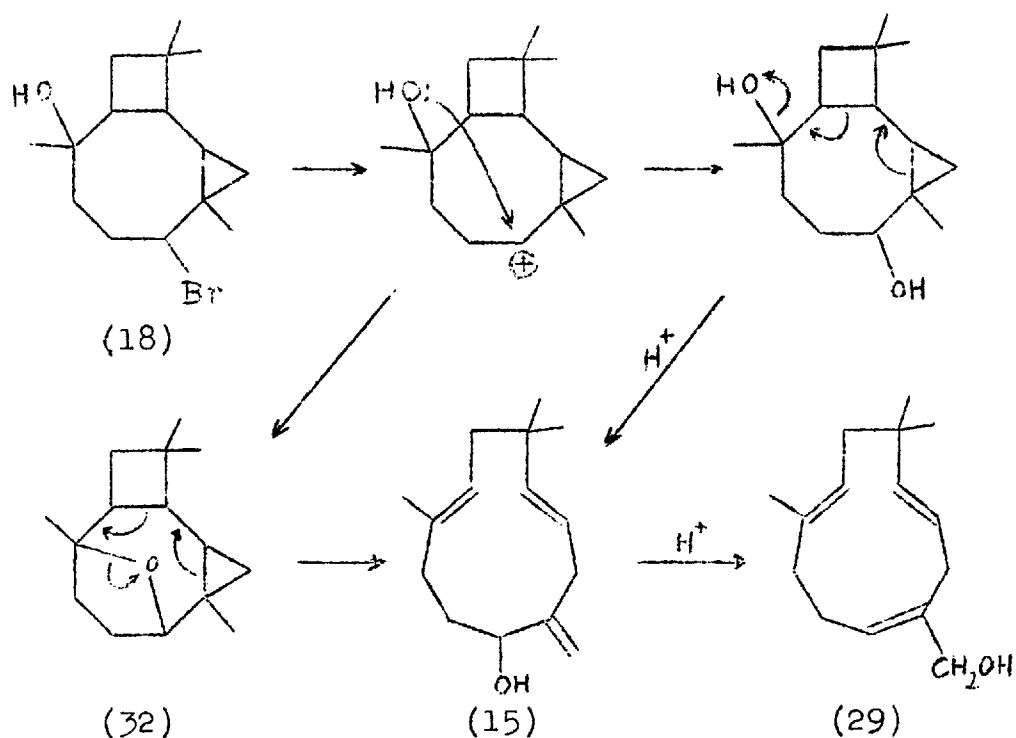


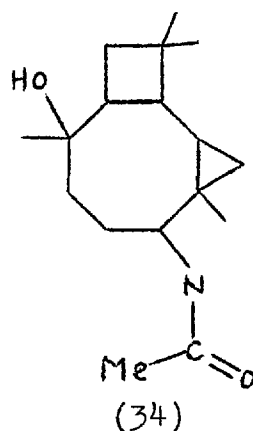
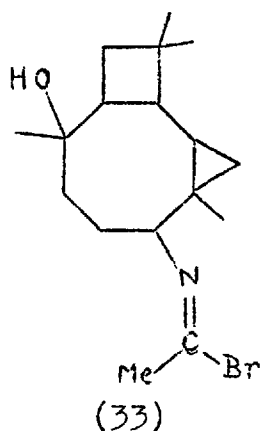
FIG. 31

Important features of this scheme were confirmed in full by the following experiments. Hydroxybromohumulene was

solvolysed in both acetone/water and acetone/saturated bicarbonate solution for both five and forty minutes. It was found that on isolating the products from the solvolyses in both neutral and basic solution the composition of products was nearly identical. After forty minutes nearly all the hydroxybromohumulene had reacted in both cases, and the insensitivity of the reaction rate to added base strongly suggests an S_N1 mechanism. In fact in basic solution slightly higher yields of dihydroxyhumulene and slightly lower yields of the monocyclic alcohols were recorded, which is to be expected as in basic solution the hydrobromic acid liberated in the reaction is removed and can not catalyse the decyclisation of the dihydroxyhumulene.

The acid catalysed nature of the decyclisation of the dihydroxyhumulene was confirmed by analysis of products after reaction in solutions of varying acidity. It was found the more acidic the solution, the more complete was the formation of the monocyclic allylic alcohols, whereas in basic solution dihydroxyhumulene was quite stable. A simple bond migration without cyclic ether formation adequately explains this decyclisation (fig. 31). It is interesting that in 0.3N solution a new cyclic product was obtained which is probably due to the recyclisation of the generated humulenol (15) under these conditions.

A key experiment to confirm the possible intermediacy of the cyclic ether (32) in the decyclisation of hydroxybromohumulene was performed. Hydroxybromohumulene was dissolved in carefully dried acetonitrile and after three days products from the reaction were isolated. As one would expect in anhydrous solution no dihydroxyhumulene was isolated, however, a crystalline product was obtained which was formed by reaction of acetonitrile with hydroxybromo-humulene. This product, the hydroxybromo imine (33), must be formed by solvent insertion after the formation of the hydroxyhumulene carbonium ion since acetonitrile is insufficiently nucleophilic to displace bromine by an S_N2



mechanism, that is, the initial stage in the decyclisation process is confirmed as being the ionisation of the secondary bromine atom. The N.M.R. spectrum of the C-bromo

imine (33) showed two downfield protons corresponding to the group $=NH - CH <$ and the methyl group on carbon bearing bromine appeared at 8.03τ as a singlet. Mild hydrolysis of this product easily generated the hydroxy-7-acetamido tricyclic compound (34).

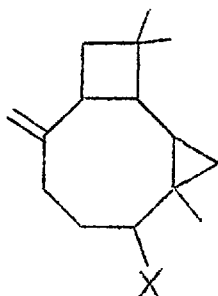
Importantly, in this reaction in acetonitrile, after chromatography a fraction containing the monocyclic allylic alcohols was obtained and so confirmation of the trans-annular formation of the cyclic ether (32) and its rearrangement (fig. 31) was confirmed since under anhydrous conditions the hydroxyl group at C_4 is the only source of the hydroxyl group ultimately appearing at C_7 in the decyclised product. A bimolecular reaction where the hydroxyl group of one molecule is donated to a monocyclic carbonium ion of a second molecule is electronically unfavourable and in this case some dihydroxyhumulene should be formed by neutralisation of the carbonium ion before rearrangement. In fact, the monocyclic allylic alcohol portion isolated and examined in the usual way by oxidation and conversion to the 2:4 DNP's, showed that isohumulenol (29) was the main product present with only traces of humulenol (15) itself. This might have been expected from our previous observations that under acidic conditions (hydrogen bromide is released during the decyclisation) humulenol (15) tended to

slowly isomerise to isohumulene (29) and the duration of this reaction was sufficient for nearly total isomerisation. The relative stereochemistry of the hydroxyl group at C₄ with respect to the cyclobutane ring fusion is unknown but it is clear from models that an ether bridge between C₄ and C₇ may be accommodated on either the α or β side of the molecule without undue strain. The 5-7-3 ring system (19) which was the only other likely possibility for the tricyclic products could not, for steric reasons, decyclise through a cyclic ether intermediate.

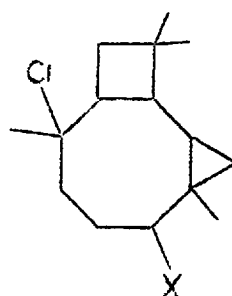
It is noticeable that in the solvolysis of hydroxy-bromohumulene (18), apart from the monocyclic alcohols, the major product obtained was dihydroxyhumulene formed by direct replacement of the halogen atom. Recent work however has suggested that ionisation of cyclopropyl carbonyl halides involves non-classical intermediates involving as extreme forms cyclobutyl and homoallylic cations⁴⁴. On this basis solvolysis would be expected to generate the most strain free system. In our case this is not so, and it has been observed in other systems^{39,45,46} that a strained cyclopropyl ring can survive S_N1 reactions at the α -carbon atom without rearrangement. It is known that the substitution pattern of the cyclopropane ring critically decides the reaction products

although carbonium (and carbanion) rearrangements of the cyclopropyl carbinyll system are not well understood.

The abnormally rapid S_N1 solvolysis of cyclopropyl carbinyll halides³⁸ is well appreciated and the rate of solvolysis of hydroxybromohumulene (18) reflected this enhanced reactivity. An approximate initial rate constant $k_1 = 1 \times 10^{-3} \text{ sec}^{-1}$ was obtained by product analysis which is of similar order to those values recorded for this type of system. The possibility that the initial step in the reaction was not a simple ionisation but was initiated by transannular anchimeric assistance from the hydroxy group at C_4 , either by direct displacement or by "solvation" of the formed ion, was not ignored. Humulene alkene bromide (23, $X = \text{Br}$) was solvolysed under S_N1 conditions and it was found that the rate of hydrolysis was about half that of hydroxybromohumulene (18). More convincingly, chlorobromohumulene (35, $X = \text{Br}$) was hydrolysed to dihydroxyhumulene



(23)



(35)

at least 70% as fast as hydroxybromohumulene and so the hydroxyl group at C₄ seems to play only a minor role in the ionisation of the bromine atom and a pure neighbouring group displacement seems unlikely. An "internal solvation" of the formed ion would be an acceptable mechanism to account for the small rate increase in the presence of a C₄ hydroxyl group.

In interpreting the solvolysis rate of chlorobromohumulene (35, X = Br) it is important that the ionisation of the bromine atom at C₇ should precede that of the chlorine atom at C₄, as if it does not then hydroxybromohumulene would be the intermediate after the first ionisation and the rate of formation of dihydroxyhumulene would be expected to be the same from both chlorobromo- and hydroxybromohumulene, and an internal neighbouring group displacement mechanism could not be ruled out. This does not seem likely as it was found that dichlorohumulene (35, X = Cl) was rather slowly hydrolysed and some starting material was recovered even after twelve hours. This recovery of starting material implies firstly that the initial step in the hydrolysis of the dihalides (35) is ionisation at C₇ (as dichloro- was slower than chlorobromohumulene), and secondly that ionisation of the tertiary halogen atom is then facilitated by the hydroxyl group at C₇ again by an internal solvation mechanism.

To summarise, a hydroxyl group at C_4 may assist ionisation at C_7 to a small extent (as in the hydrolysis of hydroxybromohumulene), and similarly a hydroxyl group at C_7 may assist ionisation at C_4 to a greater extent (as in the solvolysis of the dihalohumulenes (35)).

The monocyclic alcohols were again found to a small extent in the solvolysis of chlorobromohumulene (35, $X = Br$) and the decyclisation process is best formulated in the same way as the acid catalysed decomposition of dihydroxyhumulene i.e. without invoking a transannular ether linkage (fig. 36).

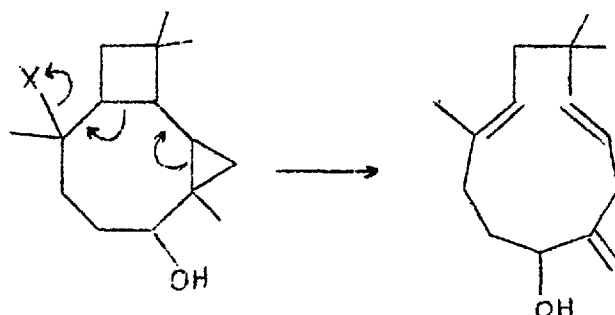


FIG. 36

The decyclisation in fig. 36 could have been formulated in the same manner as the decyclisation of hydroxybromohumulene in fig. 31, that is by initial neighbouring group displacement from C_7 to form the same oxygen bridged compound (32) so represented in fig. (31). This mechanism however suffers from the disadvantage that the cyclic ether (32) contains the

equivalent of a tetrahydrofuran ring which under the solvolytic conditions, unless special steric or thermodynamic forces act, should be a quite stable species although it has never been isolated.

Previously it has been said that dihydroxyhumulene cannot be the intermediate in the decyclisation of hydroxybromohumulene since it forms the monocyclic alcohols at a much slower rate under the same acetone-water-succinimide conditions. If however hydrolysis to dihydroxyhumulene does take place then the solution would effectively contain hydrogen bromide and the reaction conditions are then no longer equivalent. It may be that the small increase in acidity could strikingly catalyse the decyclisation of dihydroxyhumulene (as it does the isomerisation of humulenol to isohumulenol) in which case the deduction from the rate of decyclisation would be invalid. In opposition to this idea hydroxybromohumulene appears to yield more monocyclic alcohols than dihydroxyhumulene even in basic conditions although the difference is not dramatic and a resolution of the mechanism will require more accurate methods of rate determination and product analysis.

To conclude, the decyclisation of dihydroxyhumulene and its halogenated derivatives may be adequately explained by conventional bond movements (fig. 36). Hydroxybromohumulene

(18) on the other hand, certainly does not decyclise to bromo-humulene (13) before generating humulenol (15) and a trans-annular cyclic ether mechanism, although in many ways unattractive, accounts for the observed reactions, especially the formation of monocyclic alcohols in anhydrous solution although special mechanisms may operate under these conditions.

The general sensitivity of the humulene system is well typified by these cyclisation and decyclisation processes taking place in the N.B.S. reaction and it may be mentioned that humulenol (15), the product of the initial cyclisation-decyclisation reaction, has been shown to recyclise again with more N.B.S. and as yet the full complexity of this monocyclic system is unrevealed.

EXPERIMENTAL

Melting points were determined on a K f ler block and are uncorrected. Infra-red spectra were determined on a Unicam S.P. 200 spectrometer in chloroform solution except where otherwise stated. Ultraviolet absorption spectra were run in ethanol using a Unicam S.P. 800 spectrophotometer. Nuclear magnetic resonance spectra were measured in deuteriochloroform on a Varian A60 instrument. Analyses were carried out by the staff of the microanalytical laboratory (Imperial College). Gas chromatograms were run using a Pye-Argon machine and preparatively using an Aerograph "autoprep" instrument. Organic solutions were dried using anhydrous magnesium sulphate. The N.M.R. spectra of all compounds have been recorded and are in agreement with the structural assignments. Crude humulene oil was obtained from The Glidden Co., Jacksonville, Florida.

Purification of Humulene^{15.}

Crude humulene oil (35% humulene) (75g) was taken into petroleum (b.p. 60-80°) (200 ml) and extracted three times with 50% aqueous silver nitrate (30 ml.). The aqueous extracts were combined, decomposed with excess 880 ammonia and extracted. After drying concentration of the extract gave humulene (14g) containing some 10% impurity. This product was used for the preparation of crystalline compounds known to be humulene derivatives.

A second purification as above gave pure humulene (10g) or by partial evaporation of the aqueous silver nitrate extract in vacuo the crystalline silver nitrate adduct was obtained. Crystallised from ethanol-petroleum (b.p. 60-80°) mp. 175-176° dec. Decomposition of this adduct as above also gave pure humulene as a colourless oil (6.5 g.).

Humulene and N-bromosuccinimide (N.B.S.)

a) Humulene (3.47g) was stirred in acetone (16ml.), water 4ml.) and after cooling to 0° N-bromo succinimide (3.22g.) was added over 1 min. After the final addition of N.B.S. the reaction products were removed immediately by extraction with chloroform (30ml.). After washing the extract with 2N sodium hydroxide solution, water, and drying, solvent was evaporated

giving a liquid product. Petroleum (b.p. 40-60°) was added and on cooling hydroxybromohumulene (18) (1.37g) crystallised from petroleum (b.p. 40-60°) m.p. 134° $\nu_{\max}$ 3550 cm^{-1} . (Found: C, 60.0; H, 8.4; Br, 26.7. $\text{C}_{15}\text{H}_{25}\text{BrO}$ requires C, 59.8; H, 8.4; Br, 26.5%).

The residue from the preparation of hydroxybromohumulene was concentrated to an oily liquid which was chromatographed on Spence Grade H neutral alumina (30g.) to give, on elution with petroleum (b.p. 40-60°), bromohumulene (13) (1.24g) crystallised from methanol m.p. 48°, $\nu_{\max}$ 1660, 1640, 980, 910 cm^{-1} .

(Found: C, 63.7; H, 8.2; Br, 28.3. $\text{C}_{15}\text{H}_{23}\text{Br}$ requires C, 63.6; H, 8.1; Br, 28.3%).

b) Isolation of products after 15 min, 30 min. and 2 hr. showed that the yield of bromohumulene (13) was constant while the yield of hydroxybromohumulene (18) decreased at the expense of increasing yields of dihydroxyhumulene.

Hydroxybromohumulene was separated from dihydroxyhumulene. using hot petroleum (b.p. 60-80°) the latter being insoluble.

c) After stirring the reaction mixture at room temperature overnight an oily product was obtained which was chromatographed over Spence Grade H neutral alumina (30g.). The petroleum (b.p. 40-60°) eluant yielded bromohumulene (1.15g). No tricyclic products were obtained but elution with chloroform

gave isohumulanol (29) which was identified by oxidation with manganese dioxide in chloroform and conversion of the humulene aldehyde (17) formed into the 2,4 DNP (m.p. 197-199°) as described. This derivative was identified by mixed m.p., i.r., U.V. and thin layer chromatograms.

Ozonolysis of Bromohumulene (13)

Bromohumulene (13) (100 mg) in methylene dichloride (10ml) was ozonised for 1 hr. at 0°. The solution was then steam distilled into saturated aqueous dimedone to give the formaldehyde derivative m.p. 189-191° in good yield.

Double bond determination of Bromohumulene (13)

a) Bromohumulene (29.5 mg.) was hydrogenated at atmospheric pressure in ethanol (8ml) using Adams' platinum oxide catalyst. After hydrogen uptake corresponding to three moles the saturated liquid product still contained bromine.

b) Bromohumulene (13) (101mg.) was treated with excess perphthalic acid in ether. After 3 days at 0° two moles of peracid were consumed (determined by back titration) and a crystalline diepoxybromide was isolated, crystallised from ether m.p. 128-130° $\nu_{\max}$ 1640 cm^{-1} .

(Found: C, 57.4; H, 7.4. $\text{C}_{15}\text{H}_{23}\text{BrO}_2$ requires C, 57.2; H, 7.4%). Ozonolysis in methylene chloride at 0° gave

formaldehyde, isolated as the dimedone derivative, m.p. 192° , in good yield.

After further treatment with peracid at 0° for 2 weeks the diepoxybromide consumed a third molar equivalent.

Lithium in ammonia reduction of Bromohumulene (13)

Bromohumulene (13) (0.5g.) in dry ether (20ml.) was added to a stirred solution of lithium (0.75g) in liquid ammonia (700 ml.). After $3\frac{1}{2}$ hr. the excess lithium was destroyed by ammonium chloride and water (30ml) was **cautiously** added. After evaporation of ammonia the residue was ~~ether~~ extracted to give a mixed hydrocarbon product (350mg.). The mixed hydrocarbons (50 mg.) were chromatographed on a silica gel-silver nitrate preparative thick layer plate (silica gel 72g., silver nitrate 15g.). Elution of the plate with benzene-acetone (4:1) and isolation of the products by separation of the plate into strips which were washed with 880 ammonia and ether extracted gave humulene (10 mg.), identified by i.r., N.M.R. and gas chromatographic properties. Isomeric β -humulene (2) was isolated but rapidly autoxidised in air. Hydrogenation of the mixed ~~hydro~~carbons (β -humulene (2) and humulene (5) 2:1) in ethanol with Adam's platinum oxide catalyst gave, after the consumption of three moles of hydrogen, a single product identical to humulane (1) in i.r. and gas chromatographic properties.

Chromous ion reduction of Bromohumulene (13)

Chromic sulphate (5g.) was stirred under nitrogen in water (32ml) with zinc dust (1.5g.) to generate a blue solution of chromous sulphate. The aqueous solution was decanted into a solution of bromohumulene (450 mg.) in dimethyl formamide (20 ml.). After 5 min. the solution was diluted with water and ether extracted. The extract was dried and concentrated to give β -humulene (2) (250 mg.) which autoxidised on contact with air.

Oxidation of Bromohumulene (13)

Bromohumulene (4.5g.) was dissolved in dry dimethylsulphoxide (30ml.) and sodium carbonate (2g) was added. After stirring at 70° for 4 hr. dimethyl sulphoxide was removed in vacuo and, after addition of water to the residue, products were isolated by ether extraction. After drying concentration of the extract gave an oily residue which was chromatographed twice on silica gel to yield the oxidised products (3.2g.) $\nu_{\max}$ 1630, 1680 cm^{-1} . Thin layer chromatography on silica gel-silver nitrate system showed two spots. Ozonolysis in methylene dichloride gave a low yield of the formaldehyde-dimedone derivative on steam distillation.

Isolation of the 2;4 DNP's of (16) and (17)

The bromohumulene oxidation product (550 mg.) was converted to the corresponding 2,4 DNP derivative in methanol using Brady's reagent. The reaction solution showed the presence of two derivatives on alumina thin layer chromatography (eluted with benzene) with similar R_F values. Crystalline products were collected from the reaction solution in crops over 24 hr. and thin layer chromatography was used to identify pure fractions. The initial crops consisted of pure humulene aldehyde 2,4 DNP (560 mg.), crystallised from chloroform-ethanol m.p. 198-199° $\lambda_{\max}^{\text{EtOH}}$ 255 (ϵ , 16, 100), 290 (ϵ , 9,800), 380 $m\mu$ (ϵ , 28,800).

(Found: C, 63.3; H, 7.0. $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_4$ requires C, 63.3; H, 6.6%). Later fractions to crystallise from the mother liquors contained humulene ketone 2,4 DNP (125 mg.) re-crystallised from chloroform-ethanol m.p. 193-194°, $\lambda_{\max}^{\text{EtOH}}$ 285 (ϵ , 9,700 shoulder), 250 (ϵ , 16,100), 370 $m\mu$ (ϵ , 28,600). (Found: C, 63.0; H, 6.4. $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_4$ requires C, 63.3; H, 6.6%). Identified by mixed m.p., i.r. and thin layer chromatogram with genuine material. The ultra violet spectra of the two derivatives were definitive, the peaks for the aldehydic derivative being more pronounced.

Ozonolysis of the Carbonyl derivatives¹⁶

Humulene aldehyde 2;4 DNP (or humulene ketone 2,4 DNP) (200 mg) in acetic acid (7 ml.) was ozonised to excess over 3 hr. at room temperature. Hydrogen peroxide (7 ml, 15%) was added and, after standing for 48 hr. the solution was added dropwise to boiling water (10 ml.). After concentration in vacuo the solution was made basic with saturated sodium bicarbonate. Neutral products were then removed by ether extraction and, after reacidification with conc. hydrochloric acid, acidic products were isolated by continuous chloroform extraction for 48 hr.

Thin layer chromatograms were run on silica gel eluting with benzene-ether-formic acid (17.5; 5; 2.5) and developed by spraying with bromo cresol green solution (40 mg. in 96% ethanol (100 ml)). The acidic oxidation products from both 2,4 DNP derivatives gave identical chromatograms corresponding to laevulic acid, dimethyl succinic (and/or succinic acid), malonic acid and two uncharacterised products. After conversion to the methyl esters gas chromatograms on Celite-Peg H again showed identical product composition from both 2,4 DNP derivatives corresponding to the methyl esters of laevulic (30%), as-dimethyl succinic (50%), succinic (< 15%) and malonic acids (< 5%) together with two uncharacterised products. In a separate ozonolysis experiment humulene

ketone 2,4 DNP gave formaldehyde and none was obtained from humulene aldehyde 2,4 DNP.

Humulene monoepoxide³⁰

Humulene (1.02 g.) was epoxidised with one equivalent of monoperphthalic acid in ether (20 ml) at 0° for 12 hr. Chromatography on Spence Grade H neutral alumina (25 g) gave on elution with benzene essentially pure liquid humulene monoxide (0.8g), $\nu_{\max}$ 1650 cm^{-1} .

Humulenol (15)

Humulene monoepoxide (1.0 g.) was stirred in refluxing petroleum (b.p. 60-80°) (25 ml) with acid washed Spence Grade H alumina (2.25 g.) for 15 hr. The mixture was filtered, the alumina washed with ether, and the combined filtrate evaporated in vacuo. The residue was then chromatographed on Spence grade H neutral alumina (25 g) to give essentially pure liquid humulenol (15) (0.65g.), $\nu_{\max}$ (liquid film) 1640, 3400 cm^{-1} .

Humulene Ketone (16)

Humulenol (0.5g) was stirred with active manganese dioxide (3.5g.) in refluxing chloroform (20 ml.) for 12 hr. The resulting mixture was filtered and concentration of the

filtrate yielded a crude liquid product which was chromatographed on silica gel (15g.) to yield essentially pure liquid humulene ketone (0.35g.). Reaction with Brady's reagent in methanol in the usual manner gave humulene ketone 2,4 DNP, crystallised from chloroform ethanol m.p. 193-194°. No humulene aldehyde 2,4 DNP could be detected on thin layer chromatography of the reaction solution.

Hydrolysis of Hydroxybromohumulene (18)

Hydroxybromo-humulene (18), (0.75g.) was stirred in acetone (12 ml.) with saturated sodium bicarbonate solution (4 ml.) for 3 hr. Water (20 ml.) was added and, after extraction with chloroform and concentration of the extract, dihydroxyhumulene (510mg.) was obtained. Crystallised from acetone or chloroform-petroleum (b.p. 40-60°) m.p. 205-206° ν_{max} (nujol) 3350 cm^{-1} .

(Found: C, 75.3; H, 11.0. $\text{C}_{15}\text{H}_{26}\text{O}_2$ requires C, 75.6; H, 10.9%).

Humulene hydroxyketone (20, X = -OH)

Chromium trioxide (85mg.) in water (0.1ml.), conc. sulphuric acid (3 drops), and acetone (3ml.) was added to dihydroxyhumulene (145mg.) dissolved in acetone (10ml.).

After 15 hr. the solution was diluted with water and extracted

with ether. After drying, concentration of the extract yielded a colourless oil. From petroleum (b.p. 60-80°) m.p. 52-54° $\nu_{\max}$ 1685, 3500 cm^{-1} $\lambda_{\max}^{\text{EtOH}}$ 213 μ (ϵ 1,260). Removal of solvent of crystallisation in vacuo yielded the pure liquid humulene hydroxyketone (20, X = -OH).

A solution of the hydroxyketone (20, X = -OH) in methanol with Brady's reagent in the presence of a little sulphuric acid gave after 2 days a methoxy 2,4 DNP (21), crystallised from chloroform-ethanol m.p. 178-181° $\nu_{\max}$ 1595, 1630, 3350, 3500 cm^{-1} .

(Found: C, 59.7; H, 7.0; N, 12.3. $\text{C}_{22}\text{H}_{32}\text{N}_4\text{O}_6$ requires C, 59.1; H, 7.2; N, 12.5%).

Humulene chloroketone (20, X = Cl)

A rapid stream of dry hydrogen chloride was passed through a solution of humulene **hydroxyketone** (20, X = -OH) (100mg) in chloroform (10ml.) for 20 min. After standing the saturated solution at room temperature overnight solvent was removed in vacuo. The residue was taken into ether, dried, and after decolourisation with charcoal concentration gave humulene chloroketone (20, X=Cl) (55 mg.) crystallised from petroleum (b.p. 60-80°) m.p. 114-116° $\nu_{\max}$ 1685 cm^{-1} . (Found: C, 70.8; H, 9.2. $\text{C}_{15}\text{H}_{23}\text{ClO}$ requires C, 70.7; H, 9.1%).

Humulene dichloroketone (22)

Humulene chloroketone (20, X = Cl) (75 mg.) in methanol (5 ml.) was saturated with dry hydrogen chloride at 0°. After standing at room temperature for 15 hr. methanol was removed in vacuo. The residue was taken into ether and, after drying and decolourisation with charcoal, concentration gave the liquid humulene dichloroketone (22) (65mg) ν max 1700 cm⁻¹. In the same way this product could be made directly from ~~humulene~~ hydroxyketone (20, X = -OH). A solution of the dichloroketone (22) in methanol with Brady's reagent gave a dichloro 2,4 DNP, crystallised from chloroform-ethanol m.p. 258-260°. (Found: C, 53.8; H, 6.0; Cl, 15.0. $C_{21}H_{28}N_4Cl_2O_4$ requires C, 53.5; H, 6.0; Cl, 15.0%).

Chlorobromohumulene (35, X = Br)

a) Hydroxybromohumulene (18) (355 mg.) was dissolved in pyridine (2 ml.) and thionyl chloride (0.5g) was added at 0°. After leaving at 0° overnight the solution was diluted with ice. The product was isolated by extraction with ether and, after washing with 2N hydrochloric acid, saturated sodium bicarbonate solution and drying, concentration gave chlorobromohumulene (35, X = Br) (150mg). Crystallised from petroleum (b.p. 60-80°) m.p. 147-150°, M.W. 319 (mass. spec.)

(Found: C, 56.6; H, 7.3. $C_{15}H_{24}BrCl$ requires C, 56.4; H, 7.6%).

b) Hydroxybromohumulene (18) (250mg.) in chloroform (10ml.) was treated with dry hydrogen chloride for 45 min. Evaporation of the solvent in vacuo and crystallisation from petroleum (b.p. 60-80°) gave chlorobromohumulene (35, X = Br) (160mg.) m.p. 147-150°.

c) Chlorobromohumulene (35, X = Br) (100 mg) on hydrolysis in 2N sodium hydroxide solution (aqueous-ethanol, 1:2) at room temperature yielded dihydroxyhumulene (35mg.).

Dichlorohumulene (35, X = Cl)

a) Dihydroxyhumulene (150 mg.) was dissolved in pyridine (4ml) and thionyl chloride (0.5g) at 0°. The product was isolated as for chlorobromohumulene. Crystallisation from petroleum (b.p. 60-80°) gave dichlorohumulene (35, X = Cl) (55mg.) m.p. 143-146° M.W. 275 (mass. spec.)

(Found: C, 65.4; H, 8.8. $C_{15}H_{24}Cl_2$ requires C, 65.5; H, 8.8%).

b) Dihydroxyhumulene (150 mg.) in chloroform (10ml) was treated with a rapid stream of dry hydrogen chloride for 45 min. Evaporation of the solvent in vacuo and crystallisation from petroleum (b.p. 60-80°) gave dichlorohumulene (35, X = Cl) (55mg.) m.p. 145-146°.

Alkene bromide (23, X = Br)

Hydroxybromohumulene (18) (2g.) was dissolved in pyridine (15 ml.) and phosphorous oxychloride (1.7 ml) was added dropwise to the ice-cold solution. After 12 hr. at 0° the solution was diluted with ice and extracted with chloroform. After drying, concentration of the extract gave the liquid alkene bromide (1.58 g.) $\nu_{\max}$ 1640 cm^{-1} containing about 15% of the alkene chloride (23, X = Cl). Treatment of hydroxybromohumulene (18) similarly with phosphorous oxybromide gives the pure alkene bromide (23, X = Br) $\nu_{\max}$ 1640 cm^{-1} . Ozonolysis at 0° in dichloromethane gave formaldehyde, isolated as the dimedone derivative, in good yield.

Alkene chloride (23, X = Cl)

Dihydroxyhumulene was treated with phosphorous oxychloride in pyridine and isolated as for the alkene bromide. Concentration of the solvent extract gave the pure liquid alkene chloride, (23, X = Cl) $\nu_{\max}$ 1640 cm^{-1} . Ozonolysis at 0° in dichloromethane gave formaldehyde, identified as the dimedone derivative, in good yield.

Humulene hydroxyacetate

a) Dihydroxyhumulene (200 mg.) was dissolved in pyridine

(6 ml.) and acetic anhydride (500 mg.) and, after standing at room temperature overnight, concentration in vacuo gave an oily liquid. The residue was taken into ether and washed with 2N hydrochloric acid, saturated sodium bicarbonate solution and then water. After drying evaporation of solvent yielded an oily humulene hydroxyacetate (180 mg) $\nu_{\max}$ 1720, 3650 which was shown to contain 18% humulene diacetate.

b) Hydrolysis of the acetate mixture (130 mg.) in N sodium hydroxide solution (aqueous-ethanol, 1:1 (4 ml.) overnight at room temperature gave dihydroxyhumulene (71 mg.)

Alkene acetate (23, X = -OAC)

Humulene hydroxyacetate (160 mg) was treated with phosphorous oxychloride (0.5 g.) in pyridine (2 ml.) at 0° for 30 hr. The products were isolated as for the alkene bromide. Concentration of the solvent extract gave the oily alkene acetate (23, X = -OAC) (140 mg.) $\nu_{\max}$ 1640, 1720 cm^{-1} containing about 18% of humulene diacetate. Hydrogenation of the crude alkene acetate (115 mg.) in ethanol (5 ml.) with Adam's platinum oxide catalyst (7 mg.) gave a take up corresponding 82% alkene acetate.

Alkene Alcohol (23, X = OH)

The crude alkene acetate (23, X = -OAC) (410 mg.) was hydrolysed by stirring in N sodium hydroxide solution (aqueous-ethanol 1:1, (6 ml.)) at room temperature for 10 hr. Water was then added and the solution was chloroform extracted. The organic extract was dried and evaporated to yield an oily residue which was diluted with petroleum (b.p. 40-60°) and the precipitated dihydroxy-humulene (50 mg.) was removed by filtration. Evaporation of the filtrate gave a viscous oil which crystallised on scratching. Chromatography through Woelm grade 1 silicagel gave the pure alkene alcohol (23, X = -OH) (265 mg.) m.p. 68-72°, ν max 1640, 3500, 3650 cm^{-1} . (Found: C, 81.3; H, 11.0. $\text{C}_{15}\text{H}_{24}\text{O}$ requires C, 81.7; H, 11.0%). Ozonolysis of the alkene alcohol (23, X = -OH) (70 mg.) in dichloromethane (5 ml.) at 0° gave formaldehyde, isolated as the dimedone derivative, in good yield.

Bromination of Alkene alcohol (23, X = -OH)

The alkene alcohol (23, X = OH) (265 mg.) was dissolved in ice-cold pyridine (5 ml) and phosphorus tribromide (0.3ml.) was added. After leaving at room temperature overnight and evaporation of solvents in vacuo the product was isolated in the way described for the alkene bromide previously. Concentration of solvent in vacuo gave the oily alkene bromide

(23, X = Br) (200 mg) identified by i.r., N.M.R. and thin layer chromatograms.

The alkene bromide could likewise be hydrolysed under mild aqueous conditions to give the alkene alcohol (23, X = OH).

Reduction of the Alkene bromide (23, X = Br)

The alkene bromide (23, X = Br) (1.3g) was dissolved in dried tetrahydrofuran (150 ml.) and lithium aluminium hydride (1.1 g.) was added. After refluxing for 2 days the solution was cooled to 0° and the excess reagent was destroyed by cautious addition of N sodium hydroxide dropwise. The product was then filtered through Celite, water was added to the filtrate which was then chloroform extracted. After drying, concentration of the extract gave a liquid residue which was passed through a column of Spence Grade H neutral alumina (10g) with petroleum (b.p. 40-60°). Evaporation of the eluant gave the mixed hydrocarbons (720 mg) shown to consist of humulene (5) and (2) or (3) (15%), caryophyllene (27) (30%), and the tricyclic hydrocarbon (26) (50%) (Found; C, 88.4; H, 11.7. $C_{15}H_{24}$ requires C, 88.2; H, 11.8%).

Separation of the hydrocarbons

Complete removal of humulene (5) (and double bond isomers

(2) or (3)) was effected by washing a petroleum (b.p. 40-60°) solution of the hydrocarbons with 50% silver nitrate solution. A preparative thick plate was prepared from silica gel (Merck G.F. 254, 70g), silver nitrate (15g) and water (120 ml). After air drying for 2 days the hydrocarbons (125 mg.) were applied and chromatographed using benzene-acetone (4:1). Products were isolated in strips by decomposition of silver nitrate with ammonia (880) and extraction of products into ether. Both the tricyclic hydrocarbon (26) and caryophyllene (27) were obtained in better than 95% purity.

Alternatively a double pass through a poly-propylene-glycol adipate preparative gas chromatographic column gave pure tricyclic hydrocarbon (26) and caryophyllene (27).

d,l Caryophyllene (27) prepared by this method showed identical i.r. spectrum with natural caryophyllene and the derived oxides showed identical thin layer chromatograms and infra red spectra.

Humulene from the Tricyclic hydrocarbon (26)

The tricyclic hydrocarbon (25mg.) was passed through a short column of Woelm grade 1 silica gel (3g) with petroleum (b.p. 40-60°). Evaporation of the eluant gave pure humulene (5) (25mg.) identified by i.r., N.M.R. spectrum. The humulene silver nitrate adduct was prepared by addition to ethanolic silver nitrate m.p. 175-176°.

Hydroxy tricycle (28)

Hydroxybromohumulene (18) (300 mg.) was added to dry acetonitrile (25 ml) containing lithium borohydride (100 mg.). After refluxing for 12 hr. water was added dropwise to decompose excess reagent. The solution was then filtered through Celite, water was added and the aqueous solution then extracted with ether. The extract was washed with N hydrochloric acid, saturated sodium bicarbonate solution, dried and concentrated in vacuo to yield the liquid hydroxy tricycle (28) (230 mg) $\nu_{\max}$ 3500, 3650.

Dehydration using phosphorous oxychloride in pyridine as already described gave a hydrocarbon mixture which, from the N.M.R. spectrum and gas chromatography evidence contained humulene (30%) and tricyclic hydrocarbon (26) (10%).

Solvolysis Experiments under N.B.S. Reaction Conditions

- a) Bromohumulene (13) (750mg.) was shaken overnight in acetone (9ml.), water (2ml.) and succinimide (400mg.). After dilution with N sodium hydroxide the product was isolated by chloroform extraction. Bromohumulene (740mg.) was recovered.
- b) Hydroxybromohumulene (18) (1g.) was dissolved in acetone (8ml.), water (2ml.) and succinimide (500mg.). After standing

overnight products were isolated by extraction with chloroform. No dihydroxyhumulene was isolated and the oily product was chromatographed on alumina (15g). Oxidation of the eluted alcohols with manganese dioxide in chloroform and conversion of carbonyl compounds to the 2,4 DNP derivatives gave humulene ketone 2,4 DNP (120mg) together with humulene aldehyde 2,4 DNP (10mg). Under more dilute conditions (e.g. fifteen fold dilution) up to 60% dihydroxyhumulene was isolated.

c) Humulenol (15) (700mg.) was shaken for 2 days in acetone (8ml), water (2ml.) and succinimide (400mg.). Isolation of alcohols, oxidation and conversion to the 2,4 DNP's showed that the product was humulene ketone 2,4 DNP contaminated with a small amount of humulene aldehyde 2,4 DNP detected in the mother liquors by thin layer chromatography.

d) Dihydroxyhumulene (310mg.) was dissolved in acetone (8ml.), water (1ml.) and succinimide (200mg.). After 12 hr. dihydroxyhumulene (145mg.) and oily monocyclic alcohols (157mg.) were isolated. Oxidation of the alcohols and conversion to the 2,4 DNP allowed the isolation of humulene ketone 2,4 DNP but no humulene aldehyde 2,4 DNP was detected. Under more dilute conditions (fivefold dilution) up to 80% of dihydroxyhumulene could be isolated.

Hydrolysis Reactions on Humulene Derivatives

a) Hydroxybromohumulene (18) (1g.) was dissolved in acetone (15 ml.) and water (5 ml.) (in another experiment saturated sodium bicarbonate (5 ml) was added. After 5 min. (in another set of experiments 40 min.) the solution was diluted with water and immediately chloroform extracted. The products were isolated by precipitation of dihydroxyhumulene from chloroform solution using petroleum (b.p. 40-60°). Evaporation of the filtrate and addition of petroleum (b.p. 40-60°) allowed the crystallisation of starting material. Evaporation of the filtrate gave the residual monocyclic alcohols.

<u>Experiment</u>	<u>Time</u>	<u>Diol</u>	<u>Products</u> <u>HBH (18)</u>	<u>Monocycles</u>
Water	5 min	40 mg (5%)	940 mg	---
Bicarbonate	5	55 (7)	920	---
Water	40	640 (81)	66	63 mg
Bicarbonate	40	680 (86)	66	33

Approximate ionisation rate constant in acetone 3:1 at room temperature is $k = 1 \times 10^{-3} \text{ sec}^{-1}$.

b) Dihydroxyhumulene (174 mg.) in acetone (15 ml) and water (3ml) saturated with sodium bicarbonate was stirred overnight.

Products were isolated in the usual way and dihydroxyhumulene (162mg. 93%) was recovered.

c) Dihydroxyhumulene (174mg.) was dissolved in acetone (15ml), water (0.3ml.) and 2N sulphuric acid (2.7ml.). After leaving overnight products were isolated in the usual way. Dihydroxyhumulene (48mg) was crystallised and the residue (125mg) consisted of monocyclic alcohols. A new cyclisation product m.p. 180° was isolated in low yield from this reaction. In more dilute acidic solution the rate of decyclisation of dihydroxyhumulene was slower.

d) Dichlorohumulene (35, X = Cl) (107mg.) in acetone (5ml.), water (1ml.) and sodium bicarbonate (33mg., 1 mole) was stood overnight. Products were isolated in the usual way giving dihydroxyhumulene (36mg, 40%) and starting material (35mg.)

e) Chlorobromohumulene (35, X = Br) (193mg.) in acetone (8ml), water (1.5ml.) and sodium bicarbonate (51mg, 1 mole) overnight gave dihydroxyhumulene (90mg, 63%) and some monocyclic alcohols.

f) Chlorobromohumulene (35, X = Br) (193mg.) in acetone (9ml), water (3ml) and excess sodium bicarbonate gave after

40 min. dihydroxyhumulene (100mg., 69%) and oily products containing a little monocyclic alcohol but no starting material.

g) Alkene bromide (23, X = Br) (180mg.) containing some 15% alkene chloride was solvolysed in acetone (4.5ml) with water (1.5ml) for 40 min. After products were isolated in the usual way N.M.R. examination showed about 50% conversion to the alkene alcohol (23, X = -OH).

Solvolysis in Acetonitrile

Hydroxybromohumulene (18) (1g.) was dissolved in dry acetonitrile (25ml.) and after 3 days at room temperature solvent was removed in vacuo to give a viscous oily residue which was extracted with hot petroleum (b.p. 60-80°) (25ml. x 5). On standing at 0° the petroleum extract deposited humulene hydroxybromoimine (33) (145mg.) crystallised from chloroform-petroleum (b.p. 60-80°) m.p. 151-152° χ_{max} 1665, 3450cm⁻¹. (Found: C, 59.6; H, 8.1. C₁₇H₂₈NBrO requires C, 59.6; H, 8.2%). After removal of all the bromoimine evaporation of the petroleum filtrate yielded an oil (655mg) which was chromatographed on Woelm grade 1 alumina. Elution with petroleum (b.p. 40-60°) gave a crude oil (330mg.) containing hydrocarbons and probably some bromohumulene (13). The

ether eluant contained hydroxybromohumulene (18) (67mg.) and elution with acetone gave the alcoholic products (200mg). The alcohols were oxidised in chloroform (12ml) with manganese dioxide (1.2g.) and carbonyl products were converted to the 2,4 DNP's. The products obtained were humulene aldehyde 2,4 DNP (> 95%) and a little humulene ketone 2,4 DNP (< 5%) characterised by i.r., u.v. mixed m.p. and thin layer chromatographic properties.

Humulene hydroxy-7 acetamido tricycle (34)

The hydroxybromoimine (33) (50mg.) was dissolved in acetone (2.5ml.) and silver nitrate (200mg) in water (2.5ml) was added with stirring. After 2 hr. 2N hydrochloric acid (2ml.) was added and after filtration the aqueous solution was extracted with ether. After drying concentration of the extract yielded a viscous oil. Precipitation from chloroform-petroleum (b.p. 40-60°) gave an amorphous hydroxy amide (34) (42mg.), ν max 1660, 3450, 3600 cm^{-1} .

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