STUDIES IN CARYOPHYLLENE CHEMISTRY

A Thesis presented by

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ABSTRACT

In the introductory chapter, the chemistry pertaining to the structure of caryophyllene has been reviewed. The tricyclic derivatives obtained on acid-catalysed hydration of caryophyllene and its derivatives have been summarised.

Attempted synthetic approaches to caryophyllene and its derivatives have been described and an improved method for the synthesis of 2-methylcyclopentane-1,3-dione has been recorded. Some new degradation products of caryophyllene have been investigated. Norcaryophyllene oxidoketone on treatment with dilute hydrogen iodide in acetic and propionic acids afforded a new compound, $C_{14}H_{22}O_2$. Chemical and spectral evidence leading to its formulation as 5-hydroxy-11:11-dimethyl-4-methylenebicyclo [7:2:0]-undecan-8-one is described.

The chlorohydrin and the chlorodiketone reported by Barton and Lindsey have been further investigated. The former was shown to be a dihydroxy compound and further evidence has lead to the chlorohydrin being formulated as 8-chloro-1,9-dihydroxy-4,4-dimethyltricyclo [6:3:1:$0^{2:5}$] dodecane. It is shown that the

interconversions of ketol and chlorohydrin are readily reversible transannular reactions.

Reduction of the caryophyllene derivatives mentioned above with lithium in ammonia, as well as with lithium aluminium hydride, has been studied. The chlorohydrin on reduction with lithium-ammonia solution furnished a tricyclic diol, which has been assigned the structure of 1,9-dihydroxy-4,4-dimethyltricyclo $[6:3:1:0^{2:5}]$ dodecane.

Lithium aluminium hydride reduction of the chlorohydrin gave two diols. One of these, is shown to be bicyclic compound containing an exocyclic methylene grouping and is suggested to be 5,8-dihydroxy-11,11-dimethyl-4-methylenebicyclo [7:2:0] undecane. The other product, is a tricyclic compound formulated as a ring contraction product of the chlorohydrin.

This work is dedicated to my dear mother.

I.H. Qurreshi.

ACKNOWLEDGEMENTS

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INTRODUCTION

INTRODUCTION

The sesquiterpenoid hydrocarbon mixture in the oil of cloves (from Eugenia Caryophyllata) constitutes the principal source of caryophyllene. In the older literature the terms α-, β- and ɣ- have been applied to designate specific hydrocarbons from this source. It has now been generally recognised that α-caryophyllene is identical with humulene and ɣ-caryophyllene is an artefact arising from thermal isomerisation of caryophyllene. It is now customary to refer to the main hydrocarbon, β-caryophyllene, simply as caryophyllene and to use the rational name iso-caryophyllene instead of ɣ-caryophyllene.

Caryophyllene is particularly remarkable for the ease with which it undergoes a variety of skeletal transformations. Thus it is noticeable that more effort has been put into the elucidation of the structure of this compound than of any other sesquiterpenoid.

Caryophyllene has been a subject of intensive investigation since 1834 but not much progress was made till recently when the nature of its subtle rearrangements were discovered and its chemistry properly understood. Caryophyllene has the molecular formula[1], $C_{15}H_{24}$, and contains

two ethylenic linkages, therefore it is bicyclic. The evidence for the presence of two double bonds came firstly from consideration of its physical constants by Brühl[2] and secondly from its ability to form a dihydrochloride.

Nature of first ring.

The exact nature of one of these rings has been demonstrated by the oxidative degradation of caryophyllene.[3-5] Semmler and Mayer[3] reported that caryophyllene on ozonolysis afforded two principal products, a keto acid, $C_{11}H_{18}O_3$, and a diketo acid, $C_{14}H_{22}O_4$. Both these acids on further oxidation with nitric acid afforded as-dimethyl succinic acid and a dicarboxylic acid, caryophyllenic acid, $C_9H_{14}O_4$. It had also been shown that the first two acids underwent hypobromite oxidation suggesting that each of them contained one methyl ketone grouping. Since caryophyllenic acid, $C_9H_{14}O_4$ was not obtained crystalline by these workers, this led Ruzicka, Bardhan and Wind[4] to doubt its homogeneity and later on Evans, Ramage and Simonsen[5] showed that the liquid caryophyllenic acid, obtained by Semmler and Mayer (loc. cit), is actually a mixture of two dibasic acids, one of which, caryophyllenic acid, $C_9H_{14}O_4$ (2a) or (2b) is the homologue of the other, viz. norcaryophyllenic acid, $C_8H_{12}O_4$ (1).

The evidence that norcaryophyllenic acid (1), is a cyclobutane derivative, as had been suggested independently by Ruzicka and Zimmermann[6] and by Ramage and Simonsen[7] is contained in the following sequence of reactions. The norcaryophyllenic acid (1) on bromination and dehydrobromination furnished dehydronorcaryophyllenic acid, $C_8H_{10}O_4$ (5), which on oxidation with chromic acid afforded as-dimethyl succinic acid (6). That dehydronorcaryophyllenic acid must be represented by (5) is proved by its ozonolysis to produce α'-keto-α:α-dimethyl glutaric acid (7), which on further oxidation with alkaline hydrogen peroxide gave as-dimethyl succinic acid (6). The constitution of norcaryophyllenic acid (1), was finally confirmed by Rydon's[8] elegant synthesis of (+)-trans-2-carboxy-3:3;dimethyl cyclobutane carboxylic acid, identical with (1). Hence it has been proven beyond any question that caryophyllene contains a cyclobutane ring with a gem-dimethyl group as part of its skeletal framework.

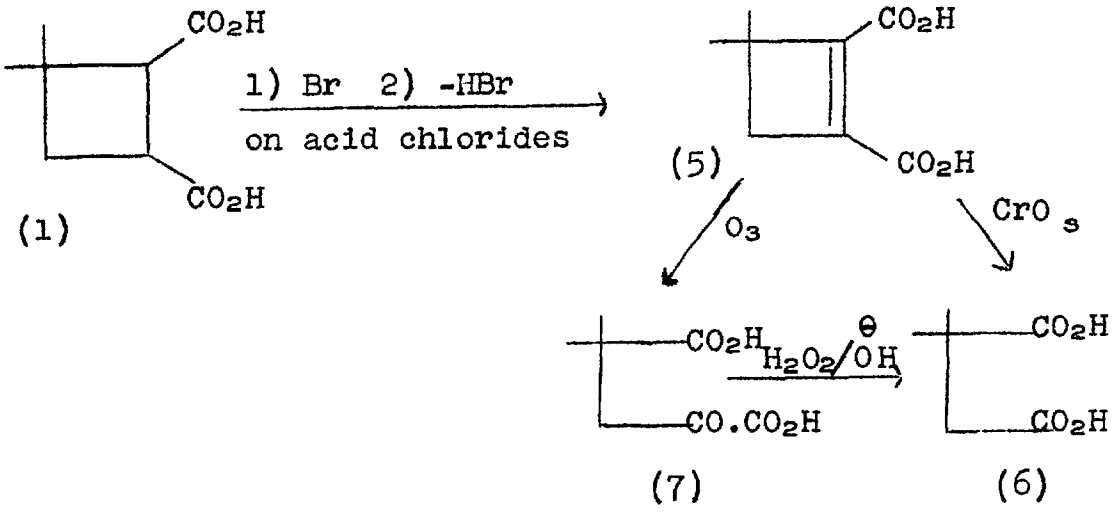
Since caryophyllenic acid, could be degraded to (+)-trans-norcaryophyllenic acid (1), (see Simonsen and Barton, ''The Terpenes'', Cambridge University Press, Vol. III, 1952), it follows that the former acid also had the configuration (+)-trans- and can be represented either by

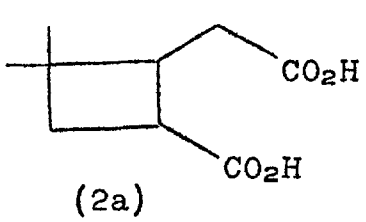
(2a) or (2b). Of the two alternatives, a decision in favour of (2a), as predicted by Barton,[9] was arrived at firstly by Dawson and Ramage's[10] synthesis of (2b), the incorrect isomer, and finally by the total synthesis and resolution of (+)-trans-caryophyllenic acid (2a) by Campbell and Rydon.[11]

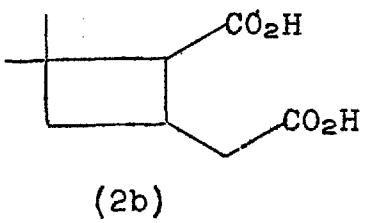
Ruzicka and Wind[12] and also Ramage and Simonsen[13] have reported that the keto acid, $C_{11}H_{18}O_3$ on treatment with sodium hypobromite afforded the next higher homologue of (+)-trans-caryophyllenic acid, i.e. (+)-trans-homocaryophyllenic acid, $C_{10}H_{16}O_4$, which can be represented by (3a) or (3b). Proof that homocaryophyllenic acid has structure (3a) was obtained by Dawson and Ramage's[14] synthesis of this compound.

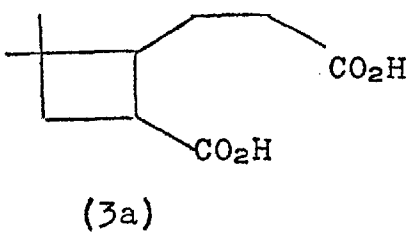
Position of double bonds.

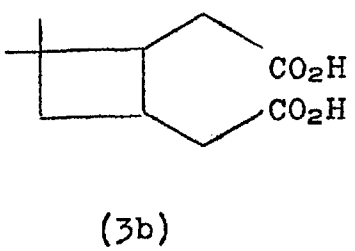
Since various oxidative experiments on caryophyllene, in particular ozonolysis, yielded formaldehyde, one of the two double bonds must be situated in an exocyclic methylene group, $\rangle C = CH_2$. Evidence that the other double bond is contained in the system $-CH=\overset{CH_3}{C}-CH_2-$ was provided by Ruzicka and Wind.[12] These workers reinvestigated the reactions of the diketo acid, $C_{14}H_{22}O_4$, originally described by Semmler and Mayer[3] and showed that the methyl ester could


CO2H
CO2H
1) Br 2) -HBr
on acid chlorides
(1)
CO2H
CO2H
(5)
O3
CrO3
CO2H
CO.CO2H
H2O2/⊖OH
CO2H
CO2H
(7)
(6)


CO2H
CO2H
(2a)


CO2H
CO2H
(2b)


CO2H
CO2H
(3a)


CO2H
CO2H
(3b)

be cyclised smoothly by sodium ethoxide to give an unsaturated keto acid, $C_{14}H_{20}O_3$, which still contained the methyl ketone grouping, since hypobromite oxidation afforded a crystalline dicarboxylic acid, $C_{13}H_{18}O_4$. These changes are represented in the sequence of partial formulae shown below:

$$C_9H_{16}\begin{cases} -CH_2.\overset{CH_3}{\overset{|}{C}}:CH. \\ \rangle C:CH_2 \end{cases} \xrightarrow{O_3} C_9H_{16}\begin{cases} -CH_2.\overset{CH_3}{\overset{|}{C}}O \quad HO_2C. \\ \rangle CO \end{cases}$$

Caryophyllene, $C_{15}H_{24}$ Diketo acid, $C_{14}H_{22}O_4$

$$\xrightarrow[\text{(on methyl ester)}]{NaOEt} C_9H_{16}\begin{cases} -C.\overset{CH_3}{\overset{|}{C}}O \quad HO_2C. \\ \rangle \overset{\|}{C} \end{cases} \xrightarrow{NaOBr} C_9H_{16}\begin{cases} -C.CO_2H \quad HO_2C. \\ \rangle \overset{\|}{C} \end{cases}$$

Keto acid, $C_{14}H_{20}O_3$ Diacid, $C_{13}H_{18}O_4$

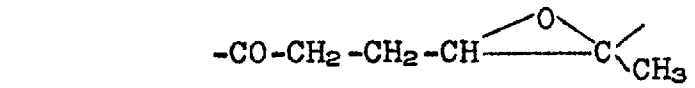
The experiments described so far were carried out starting with caryophyllene of unauthenticated homogeneity and thus the results found were of doubtful value. Subsequently crystalline caryophyllene derivatives like "β - caryophyllene nitrosite", m.p. 115°, described by Ramage and Simonsen[15] and " caryophyllene oxide", m.p. 64°, reported by Treibs[16] were employed for further degradative investigations.

Size of the second ring.

The size of the second ring in caryophyllene was a subject of controversy for many years. The first clue was provided by Sörm[17] from a consideration of spectroscopic measurements on Treibs' oxido ketone, $C_{14}H_{22}O_2$. Independent chemical evidence was provided by the elegant investigations of Barton and co-workers.[18] It has been shown by Treibs (loc. cit.) that caryophyllene on treatment with hydrogen peroxide furnishes a crystalline epoxide, m.p. 64°. This compound retains the $\rangle C = CH_2$ grouping of caryophyllene, for on further oxidation with potassium permanganate it affords a crystalline C_{14}-oxido ketone. From a consideration of infra-red carbonyl frequencies of this oxido ketone and related compounds, Sörm and co-workers (loc. cit.) proposed a nine membered ring as constituting part of the caryophyllene framework, which could be tentatively represented either by (8) or (9). However, later on both of these formulae were found incorrect.

Independently Barton and Lindsey[18] demonstrated the presence of a nine membered ring in caryophyllene. Their approach established the relative positions of the two double bonds in the caryophyllene molecule in the following way. Treatment of Treibs' oxido ketone, $C_{14}H_{22}O_2$ (14)

with base induced cyclisation to a tricyclic hydroxy ketone, $C_{14}H_{22}O_2$ (15) which on oxidation with chromic acid afforded a diketone, $C_{14}H_{20}O_2$ (16). The latter on treatment with selenium dioxide furnished an ene-1:4 dione, $C_{14}H_{18}O_2$ (17) which showed a characteristic absorption spectrum ($\lambda_{max.}$ 221, 367 and 369 mμ, ϵ = 14,700; 100 and 100), suggesting the presence of the chromophore -CO-C=C-CO- in a cisoid confirmation. Further oxidation of (17) with potassium permanganate or nitric acid afforded a bicyclic dicarboxylic acid, $C_{12}H_{18}O_4$ (18), which readily formed an anhydride. The genesis of the C_{12} acid proves the presence of the grouping $-CO-CH_2-CH_2-CH(OH)-$ in the tricyclic hydroxy ketone (15), from which follows that the grouping

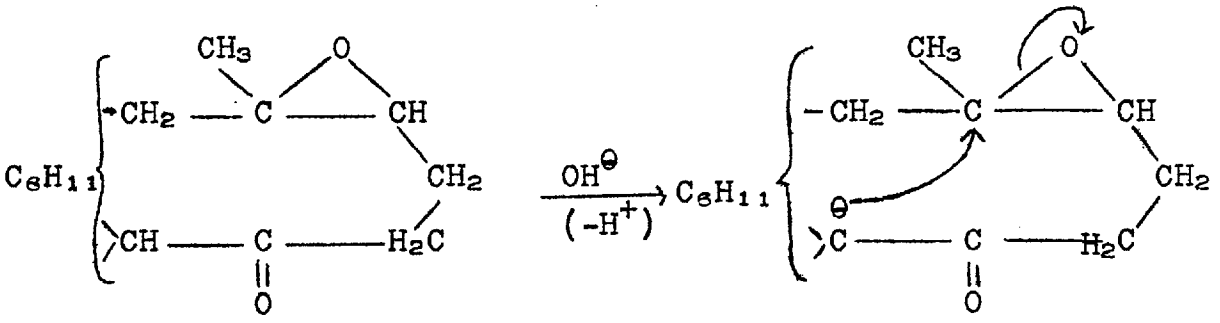


must be present in the original oxido ketone (14). In the partial formulae, six of the carbon atoms must be present in a dimethyl cyclobutane moiety. On the basis of available evidence, these workers proposed formulae (8), (9) and (10), for caryophyllene of which the first two were those originally proposed by Sörm and co-workers.[17]

At this stage Dawson and co-workers[19] reported that homocaryophyllenic acid (3a) and its precursor, the keto acid, $C_{11}H_{18}O_3$, are genuine transformation products of

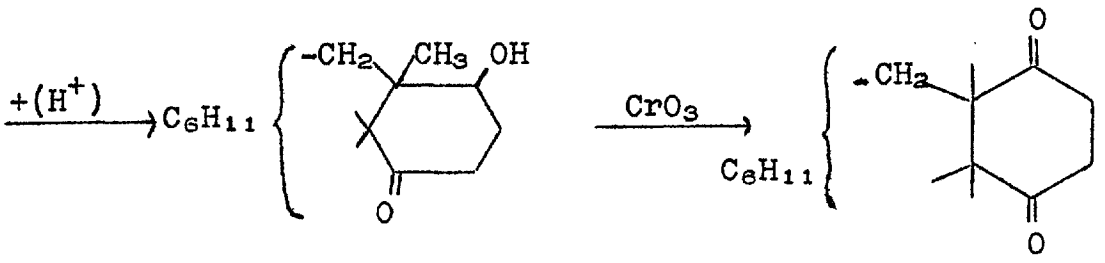
caryophyllene. They demonstrated it by using the blue crystalline nitrosite of caryophyllene, which on oxidation with potassium permanganate gave the keto acid, $C_{11}H_{18}O_3$. Since homocaryophyllenic acid (3a), is obtained from the keto acid by hypobromite oxidation, it follows that the latter must contain one methyl ketone grouping and could be represented by structure (4a) or (4b). These workers also reported that the keto acid, $C_{11}H_{18}O_3$, on oxidation with potassium permanganate furnished caryophyllenic acid (2a). This evidence favours formulation (4a) for the keto acid which suggests that there should be two methylene groups between the cyclobutane ring fusion and the methyl group. On the basis of this requirement, formulae (8) and (9) for caryophyllene can be excluded. These workers also proposed another alternative structure (11) for caryophyllene, which too is not valid as it does not contain the grouping $-CH=\overset{CH_3}{\overset{|}{C}}-CH_2-$ so explicitly proved by Ruzicka and Wind[12] and would give the least likely structure for homocaryophyllenic acid.

The dicarboxylic acid, obtained by Barton's degradation, would, on the basis of formulae (10) and (11), be (12) and (13) respectively. Barton and his collaborators,[20] however, demonstrated that the dicarboxylic acid is di-tertiary as in (12) and not secondary-tertiary as in (13).



(14)

Treib's $C_{14}H_{22}O_2$ oxido-ketone

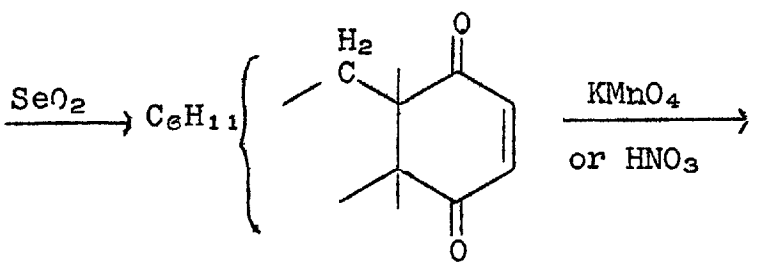


(15)

$C_{14}H_{22}O_2$ hydroxy-ketone

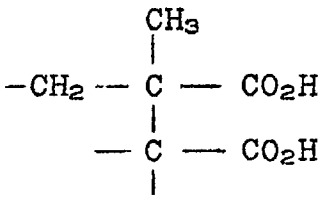
(16)

$C_{14}H_{20}O_2$ diketone



(17)

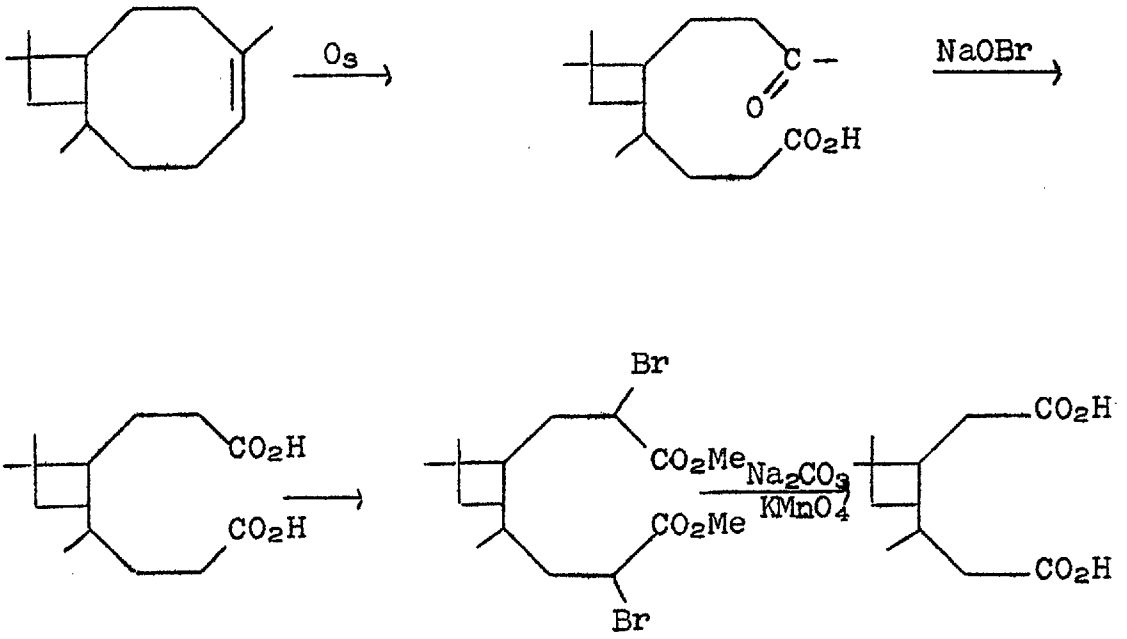
$C_{14}H_{18}O_2$ ene-1:4-dione



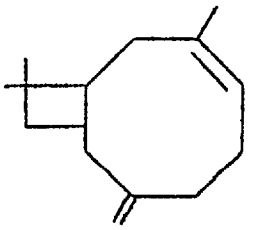
(18)

$C_{12}H_{18}O_4$ diacid

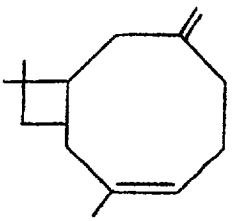
This evidence favours Barton's formulation (10) for caryophyllene. Further support for this structure was given by the oxidative degradation of dihydro caryophyllene carried out by Atwater and Reid[21] which is shown below:



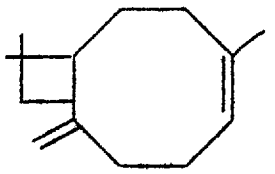
Such a degradation is not possible from (11).



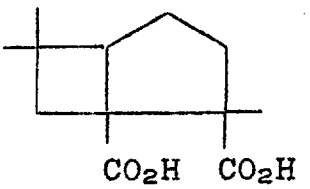
(8)



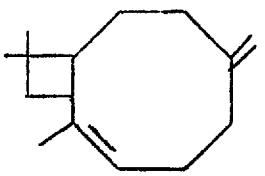
(9)



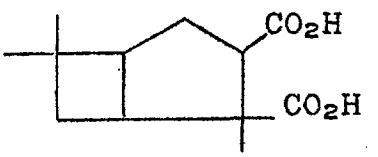
(10)



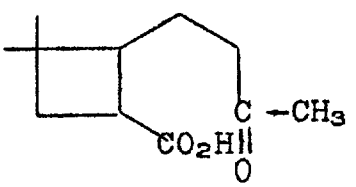
(12)



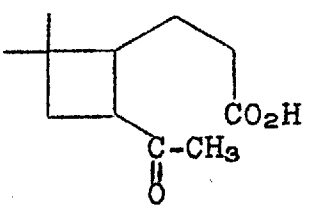
(11)



(13)



(4a)

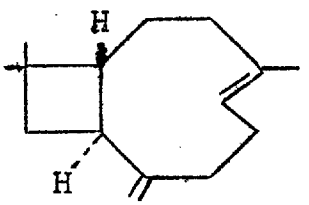


(4b)

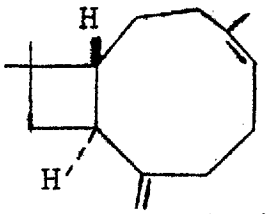
Iso-caryophyllene.

The existence of an isomer of caryophyllene in clove oil has been a matter of controversy for a long time. It is now generally accepted that they are different chemical entities. Iso-caryophyllene is obtained as a by-product in the preparation of caryophyllene nitrosite or when the latter is heated in ethanol. Barton and his collaborators[22] also reported its formation from caryophyllene during the catalytic reduction (Pd) of the exocyclic methylene group to dihydrocaryophyllene, which is, thus dihydro isocaryophyllene. The exact nature of isocaryophyllene has been rigidly demonstrated by Barton and his collaborators (loc. cit.) in the following way. On treatment with per acid, isocaryophyllene furnished a crystalline oxide (23), isomeric with the caryophyllene oxide (19), which on mild acid catalysed hydration afforded a crystalline diol (20). The latter on oxidation with chromic acid gave first the ketol (21) and then the diketone (22). Under similar sequence of reactions isocaryophyllene oxide (23) cyclises to give a stereoisomeric diol (24) which oxidises first to the ketol (25) and finally to the diketone (22). The fact that the same diketone (22) is obtained in both cases suggests that the two stereo-

isomeric diols (24) and (20) differ only in the configuration of the hydroxyl at C_9. Since this hydroxyl is obtained on fission of the epoxide ring, it follows that the configuration of one carbon of the epoxide and therefore of the double bond, is the only difference between caryophyllene and isocaryophyllene. This evidence firmly establishes that caryophyllene and isocaryophyllene are geometrical isomerides about the endocyclic double bond. On the basis of experimental evidence that caryophyllene is less stable and more reactive towards electrophillic reagents than its isomer, Barton and his collaborator[22] assigned the trans-configuration to caryophyllene (26) and the cis-configuration to isocaryophyllene (27). These assignments are in agreement with Prelog's[23] observation that trans-



(26)

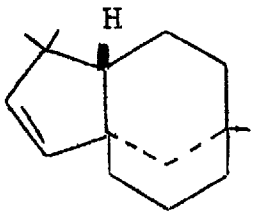


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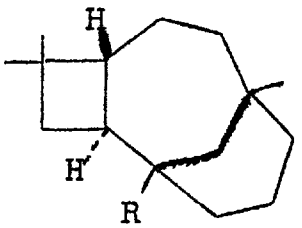
cyclononene, being more strained, is more reactive than the cis-isomer. Further support for these views is obtained from the study of the tricyclic derivatives of caryophyllene by Barton and his collaborators (loc. cit.).

Rearrangements.

Caryophyllene on treatment with acid, undergoes a number of interesting cyclisations yielding, among other products, the hydrocarbon clovene (28) and caryolan-1-ol (29; R=OH) (formerly known as β-caryophyllene alcohol).



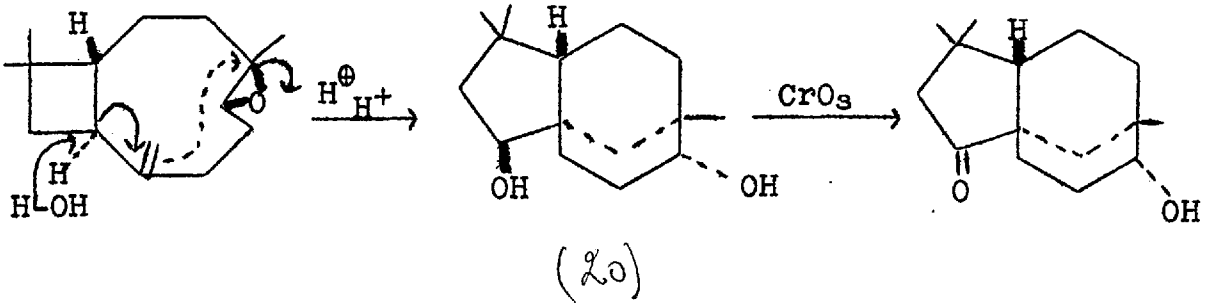
(28)



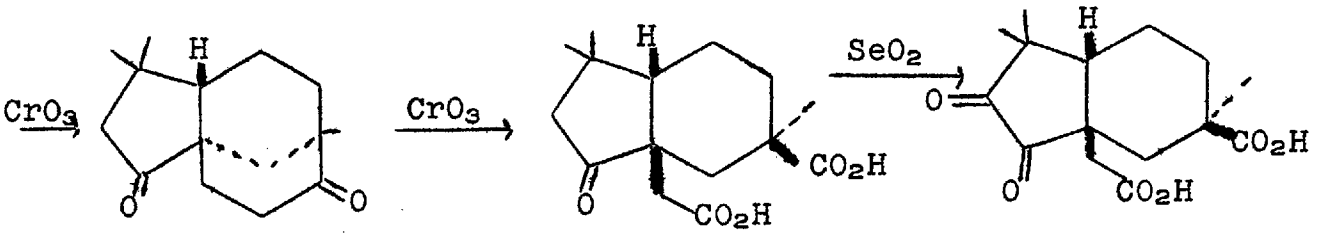
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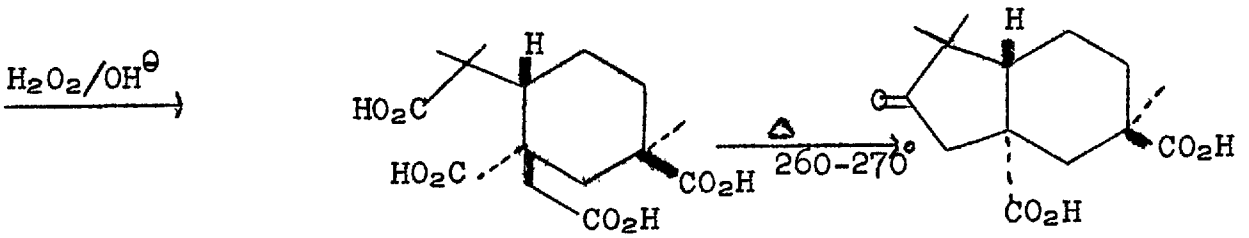
Clovene.

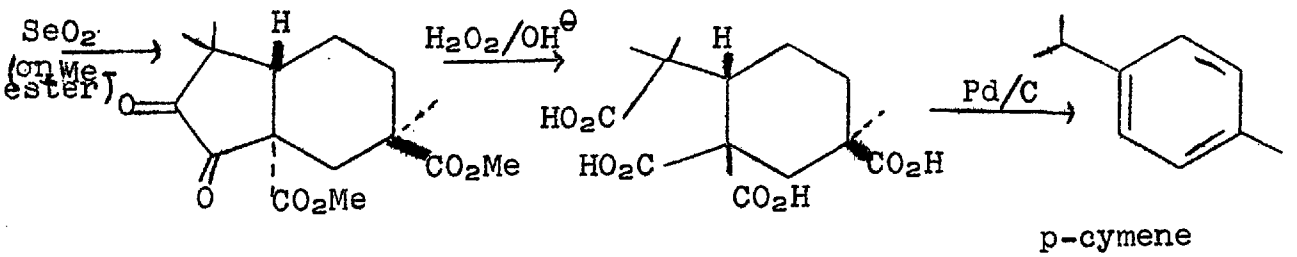
The hydrocarbon clovene (28) is obtained on acid catalysed cyclisation of caryophyllene.[24] It has been shown to be tricyclic and to contain one ethylenic linkage. On oxidation it affords the crystalline clovenic acid, $C_{15}H_{24}O_4$ (30), which readily forms an anhydride but resists bromination and ketonisation.[27] The structure of clovenic acid (30) has been rigidly proven by Barton and his collaborators[26] by relating it to the diol (20). The constitution of the latter has also been established by these workers by a degradation leading to p-cymene according to the following scheme.


H
H
H–OH
H⊕ H+
OH
OH
CrO3
O
OH

(20)


CrO3
H
O
O
CrO3
H
CO2H
CO2H
SeO2
H
O
O
CO2H
CO2H


H2O2/OH⊖
HO2C
HO2C
CO2H
CO2H
H
Δ
260-270°
O
CO2H
CO2H

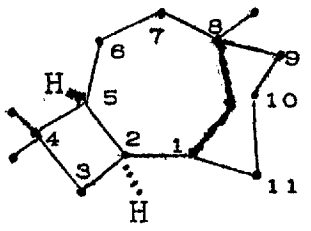

SeO2
(on Me ester)
H
O
O
CO2Me
CO2Me
H2O2/OH⊖
H
HO2C
HO2C
CO2H
CO2H
Pd/C

p-cymene

Caryolan-1-ol.

Caryolan-1-ol has been obtained from caryophyllene under a variety of acid hydrating conditions.[20,29,30] Barton, Bruun and Lindsey (loc. cit.) reported the isolation of a crystalline, saturated tricyclic diol, $C_{15}H_{26}O_2$ (31), from the epoxidation reaction of caryophyllene with hydrogen peroxide.[16] Furthermore this has been shown to be a secondary-tertiary diol, which on oxidation furnishes a ketol (32). Wolff Kishner reduction of this ketol affords caryolan-1-ol. Structure (29; R=OH) was proposed for caryolan-1-ol by these workers and supported by the following sequence of reactions. Oxidation of the ketol (32) with selenium dioxide afforded a diosphenol (33), $\lambda_{max.}$ 278 mμ which was cleaved by hydrogen peroxide to the dicarboxylic acid (34). This could be dehydrated with phosphorous oxychloride in pyridine and when ozonized gave the keto acid (35). This keto acid was also obtained by heating the dicarboxylic acid (34) with 50% aqueous potassium hydroxide, whereby acetic acid was eliminated by dealdolisation. The formation of the keto acid (35) suggested the presence of the grouping $>\overset{OH}{\overset{|}{C}} - CH_2 - CH_2-CH(OH)-$ in diol (31) and hence of the grouping $>\overset{OH}{\overset{|}{C}} - (CH_2)_3 -$ in caryolan-1-ol (29; R=OH). Wallach and Walker[25] were

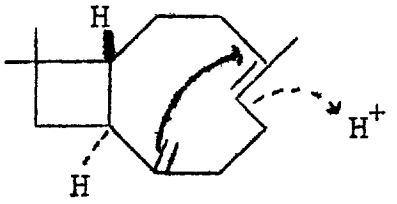
the first to report that caryolan-1-ol (29; R=OH), on treatment with Phosphorous pentachloride, gave a highly crystalline chloride, $C_{15}H_{25}Cl$ (29; R=Cl). Later Henderson, Robertson and Kerr,[30] observed that this chloride was resistant to nucleophilic reagents, although it reacted with sodium acetate in acetic acid to furnish the corresponding acetate (29; R=OAc). These replacement reactions are of great mechanistic interest,[31] because they represent substitution at a bridge-head, where inversion of configuration is impossible and an intermediate carbonium ion must be postulated. Presumably the ion with its required flattened (trigonal) geometry is not seriously impeded in the 4:3:1 system (29; R=OH). The structure for caryolan-1-ol proposed by Barton and co-workers (loc. cit.) was finally confirmed by the brilliant X-ray investigations of Robertson and Todd.[32] Their analyses also demonstrated the trans-fusion of the two rings in caryolanyl halide and, therefore, in caryophyllene itself and have shown that the hydrogen atom at C_5 lies on the same side of the molecule as does the methylene bridge as indicated in (36).



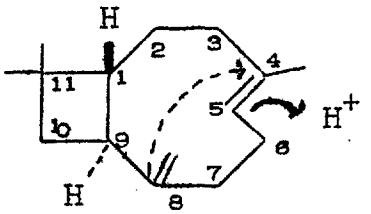
(36)

The stereochemistry of caryolan-1-ol (29; R=OH) having been fully established by these workers, the stereochemistry of other tricyclic derivatives were elucidated by Barton and his collaborators.[26] Lutz and Reid[28] had made the important observation that acid-catalysed dehydration of caryolan-1-ol (29; R=OH) does not afford clovene (28) as would be expected if the methylene bridge had the same configuration in both compounds. This evidence suggests that caryolan-1-ol (29; R=OH) and clovene (28) belong to two different stereochemical families with reference to the configuration of methylene bridge, which is β- in the former and α- in the latter. Supporting evidence is provided by Barton's group[26] from a conformational analysis of the cyclisation reactions. Since four-membered ring is fused trans- to the nine-membered ring, the endocyclic ethylene linkage must lie with its plane perpendicular to that of the four-membered ring. If the C_4-methyl group projects upwards (relative to the upwards β-hydrogen atom at C_1) only α-attack is possible leading to caryolane-type cyclisation (A), whilst if it projects downwards, then only β-attack is possible, which will lead to a clovene-type cyclisation (B). Barton and co-workers[22] have also shown that the diol (31) can

not be an intermediate in the formation of diol (20).



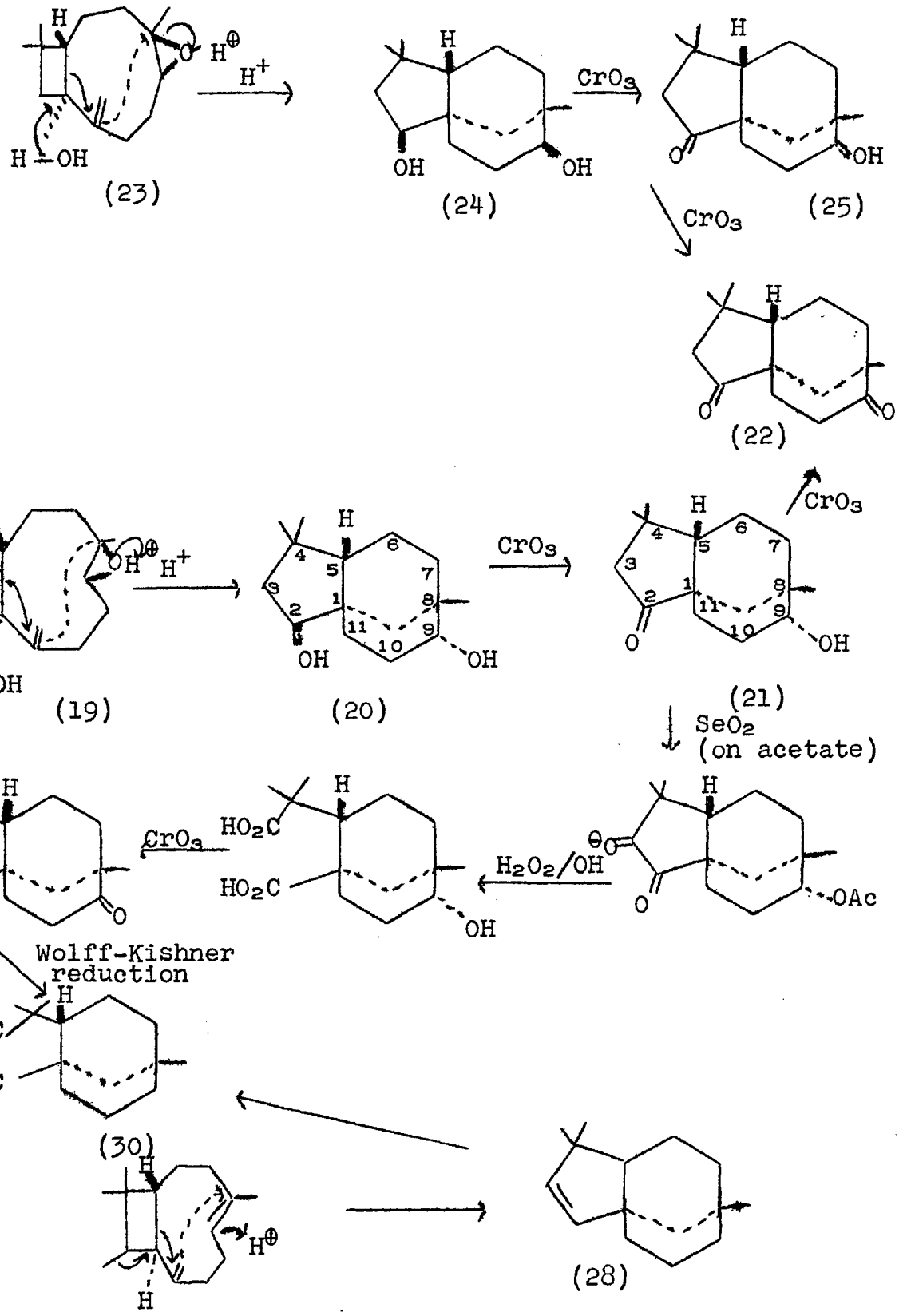
(A)

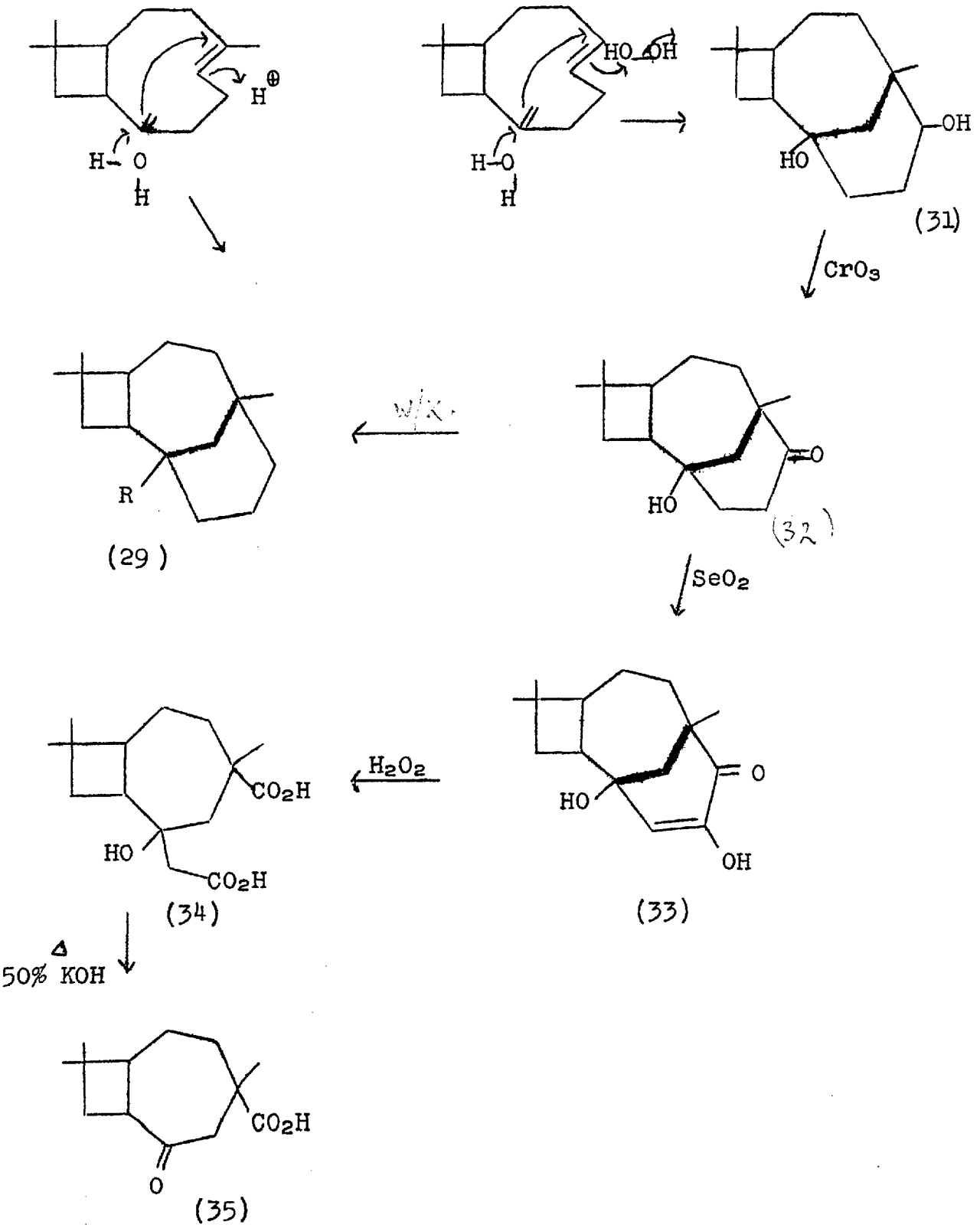


(B)

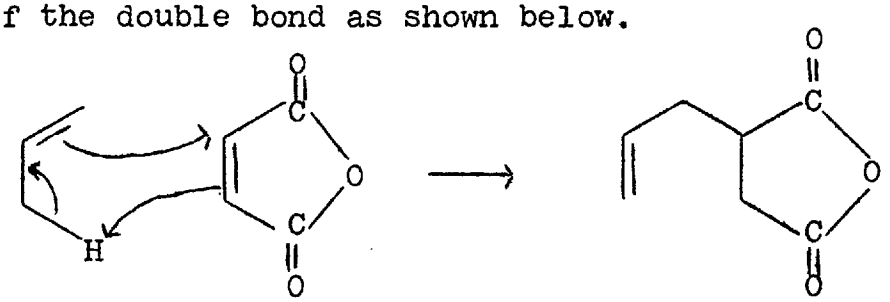
The latter has been shown to be related in constitution to clovene by degrading it to clovenic acid (30). The configuration of the methylene bridge must be α- as in clovene (28) and the 9-hydroxyl must be α- in the diol (20) and β in the epimeric diol (24), derived from iso-caryophyllene.

Diol (31), isolated as a by-product in the preparation of caryophyllene oxide, could be transformed into caryolan-1-ol (29; R=OH) of established stereochemistry. From this it follows that diol (31) should also have β-methylene bridge. In order to have a trans-electrophyllic addition, it must be produced by α-attack by OH^+ on the endocyclic ethylenic linkage. The configuration of the secondary hydroxyl group must therefore be β (note inversion).

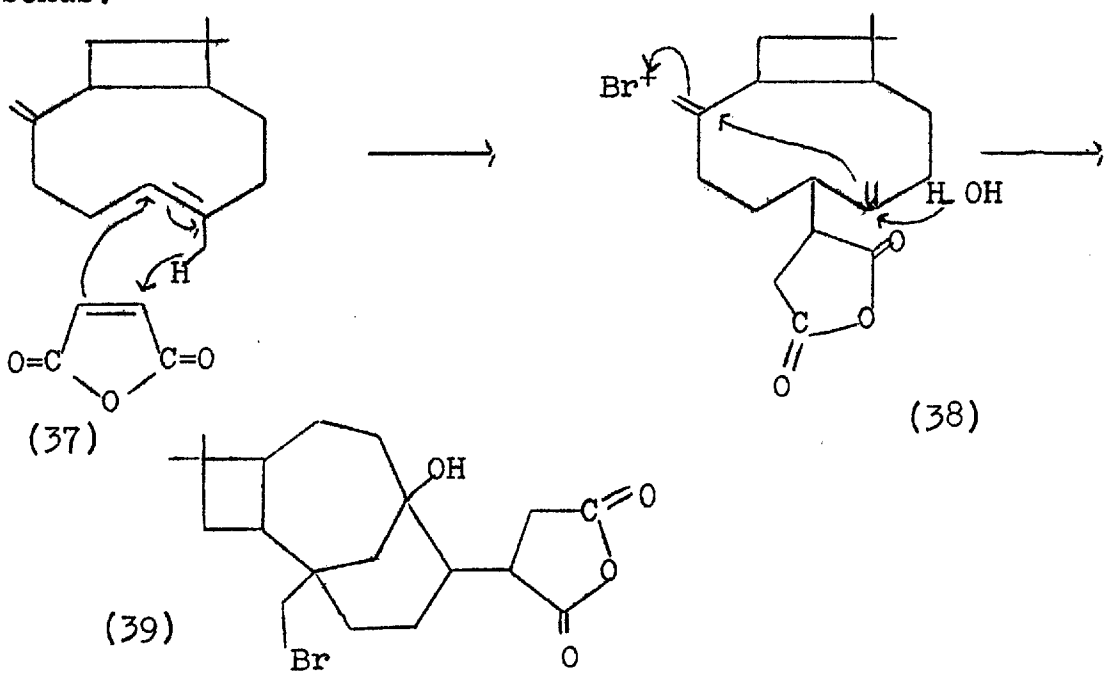

H
H⊕
H+
H—OH
(23)
OH
OH
(24)
CrO3
OH
(25)
CrO3
(22)
(19)
(20)
CrO3
(21)
CrO3
SeO2
(on acetate)
HO2C
HO2C
CrO3
H2O2/OH
OAc
Wolff-Kishner
reduction
(30)
(28)


H⊕
H–O
H
HO OH
H–O
H
OH
HO
(31)
CrO3
R
(29)
w/k.
O
HO
(32)
SeO2
CO2H
HO
CO2H
(34)
H2O2
O
HO
OH
(33)
Δ
50% KOH
CO2H
O
(35)

A particularly interesting reaction of caryophyllene is its formation of an adduct with maleic anhydride[33](38). The adduct is not of the usual Diels-Alder type, but is formed by attachment to an allylic system with migration of the double bond as shown below.

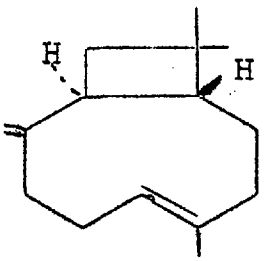


A number of similar reactions are known in the literature,[34] and a cyclic transition state has been proposed. It has been shown that caryophyllene undergoes this reaction at 80°, whereas other cases require temperatures in the range of 200°. The increased reactivity of caryophyllene has been attributed to the strain of endocyclic double bonds.



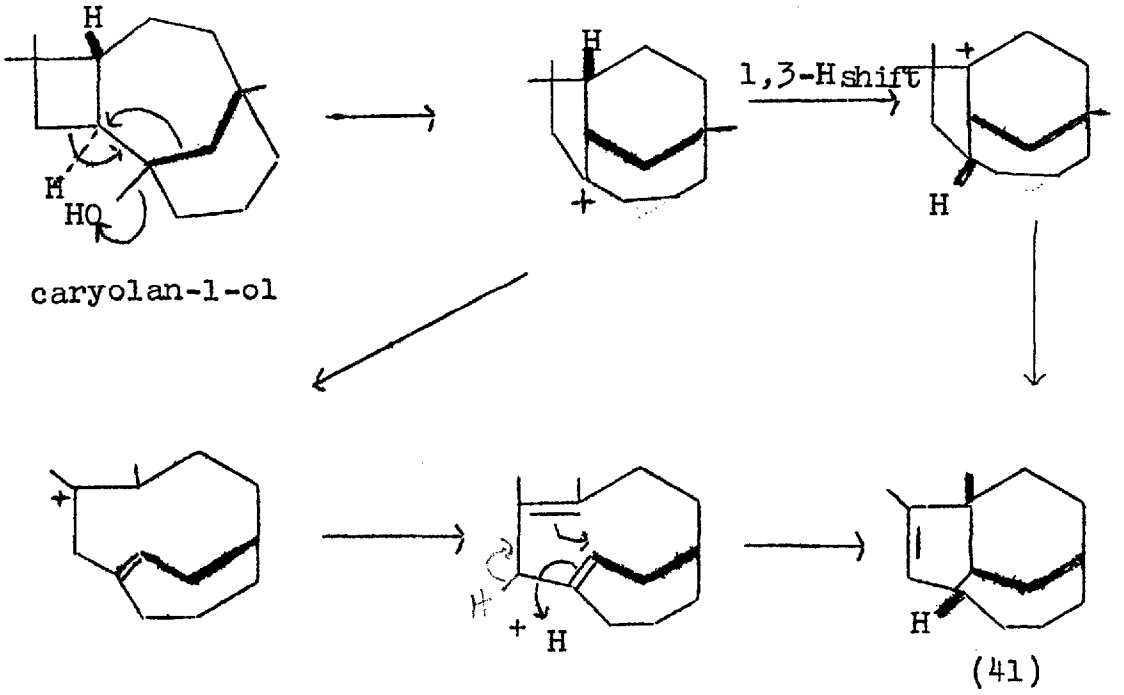
The adduct (38), in the presence of N-bromo-succinimide (electrophilic reagents), adds a molecule of HOBr to form another type of tricyclic caryophyllene derivative (39).

Barton and Nickon,[35] on the basis of their molecular rotation investigations of the tricyclic derivatives of caryophyllene, demonstrated that caryophyllene has the absolute configuration as shown in (40).



(40)

Another rearrangement product in the caryophyllene series is <u>iso</u>clovene, which is prepared by the action of dehydrating agents on caryolan-1-ol (29; R=OH) and was thought first to be clovene and then a double bond isomer of clovene.[28] The structure of <u>iso</u>clovene remained obscure till 1960 when Clunie and Robertson[36] on the basis of their X-ray investigations assigned structure (41) to it. A possible mechanism for the transformation of caryolan-1-ol (29; R=OH) into <u>iso</u>clovene has been suggested by Barton, which is shown below.

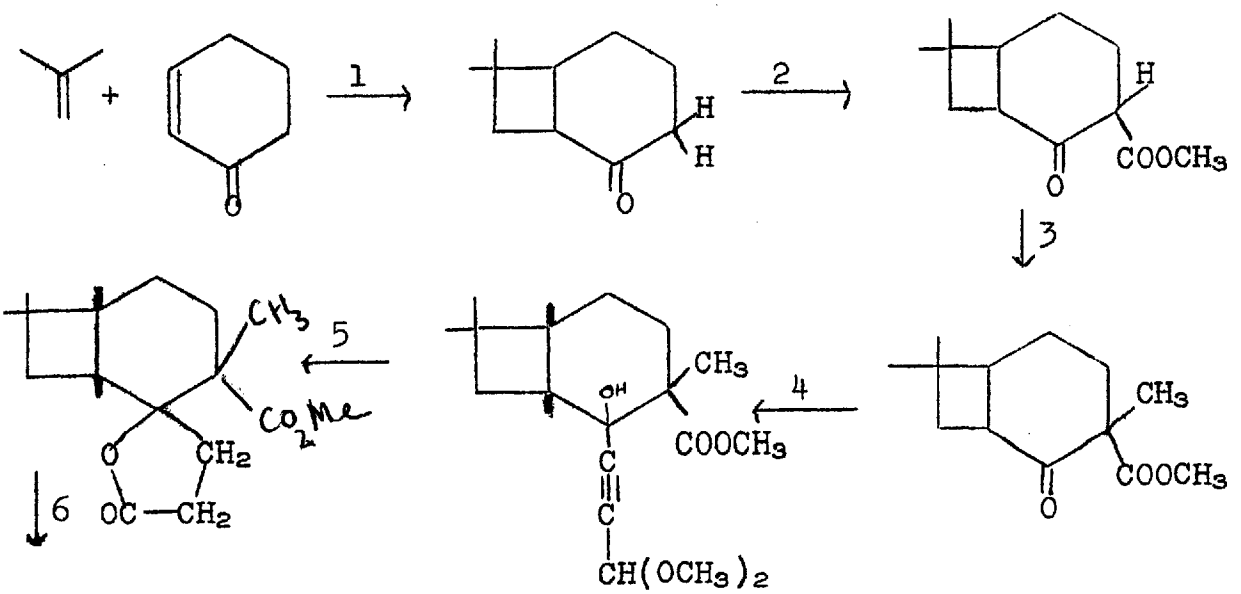


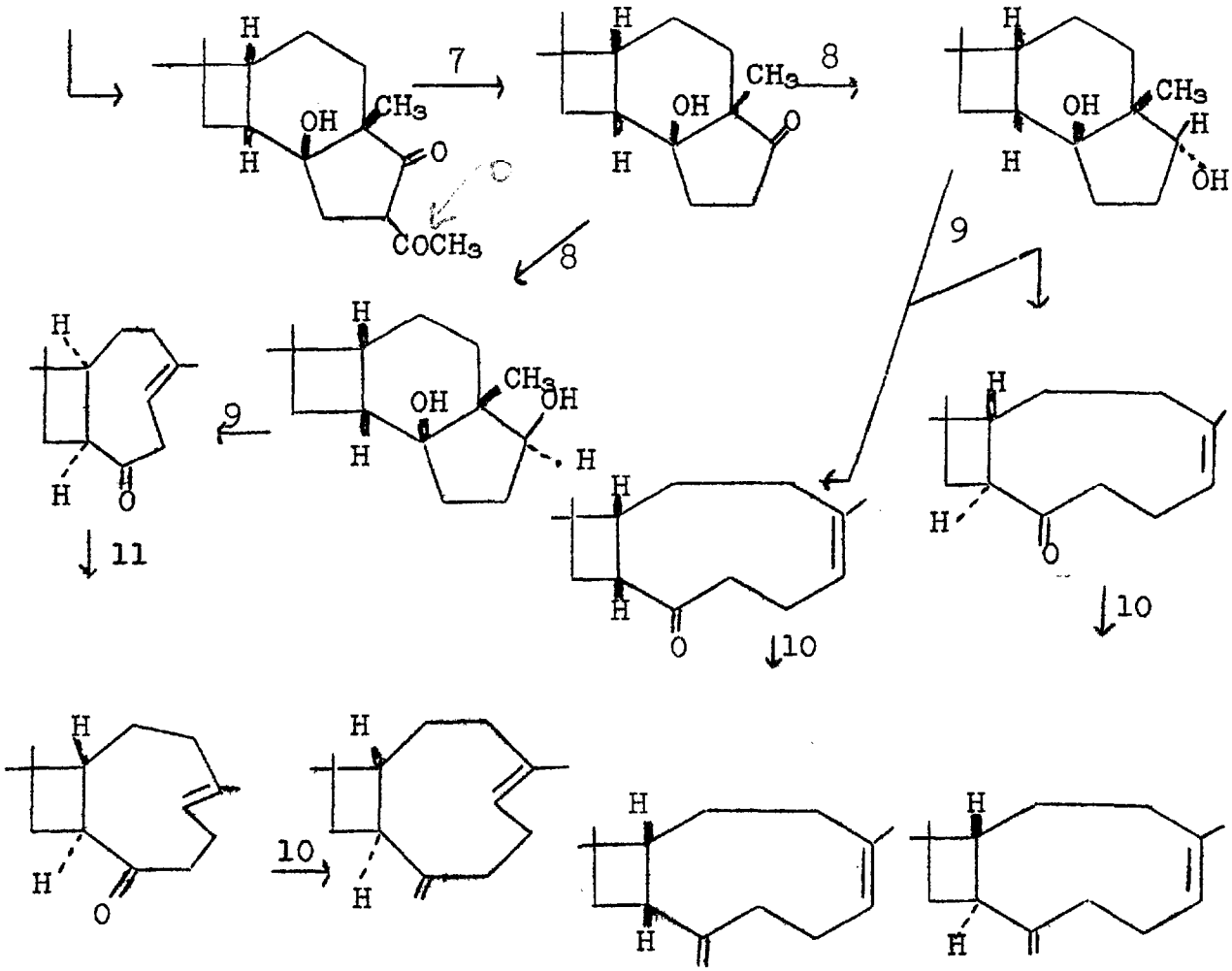
caryolan-1-ol

(41)

isoclovene

Recently Corey and co-workers[37] described the total synthesis of dl-caryophyllene and dl-isocaryophyllene. Their scheme is briefly outlined below.



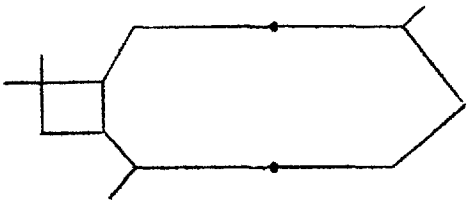


(1) hν; (2) methyl carbonate-sodium hydride-dioxane; (3) methyl iodide-base; (4) Propargyl aldehyde dimethyl acetal lithio derivative in tetrahydrofuran; (5) H_2(Pd/C), CrO_3/AcOH (6) Methyl sulfinyl carbanion in dimethyl sulfoxide (7) $OH^{\ominus}$; $-CO_2$; (8) reduction (9) Tosylation and treatment with methylsulfinylcarbanion in dimethyl sulfoxide; (10) Wittigs reagent (11) Sodium t-butoxide-dimethyl sulfoxide.

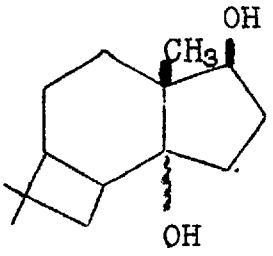
DISCUSSION

"The discovery of rings of medium size in common plant constituents, such as caryophyllene, came as a surprise since earlier larger carbon rings had been found in nature only in the macrocyclic fragrant ketones. Moreover the difficulty of synthetic access to alicyclic compounds with nine- to eleven-membered carbon rings, which has been overcome only fairly recently by the use of the acyloin condensation[49-51] favoured the view that compounds of this type were purely products of human thought and labour."[48]

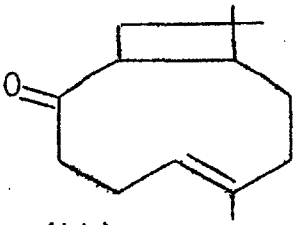
It is, however, conceivable to synthesise the carbocyclic system of caryophyllene by using the conventional synthetic tools and in fact Sorm and his collaborators[52] have achieved the synthesis of caryophyllane (42), the saturated hydrocarbon. These methods could not be applied to the stereospecific synthesis of caryophyllene (40) owing to the two double bonds present, one of them the thermodynamically less stable trans-endocyclic double bond.



(42)



(43)



(44)

The intrinsic nature of caryophyllene (40) to undergo trans-annular cyclisation, which is now well appreciated through the elegant investigations of Barton and co-workers, warned us of the dangers of working with nine membered ring intermediates and suggested that the large ring should be formed as late as possible in the synthesis. An appropriate derivative chosen for this purpose was diol, (43) because on tosylation, followed by base-catalysed ring fission, it might furnish unsaturated ketone (44) with the generation of the double bond with a trans stereochemistry. The latter on Wittig's transformation would then afford caryophyllene (40). Our approach to the synthesis of the diol (43) consisted in making the hexahydroindane system with appropriate functions first and then fusing on the cyclobutane ring to it.

Following the directions of Diels, Sielisch and Müller[43] and also Orchin and Butz[44], ethyl 4-methyl-2,3,5-triketocyclopentylglyoxalate (45) was prepared and hydrolysed to 2-Methylcyclopentane-1,3,4-trione (46). Boyce and Whitehurst[45] had demonstrated that the semicarbazone of the latter on Wolff-Kishner reduction afforded 2-methylcyclopentane-1,3-dione (47). We, however, found this method difficult to reproduce and a very low yield was obtained

in our hands. Based on the mechanistic principle involved in the reduction of α,β-epoxy ketones to allylic alcohols with hydrazine by Wharton and Bohlen,[39] we treated the trione (46) with hydrazine hydrate with a hope of getting the dione (47) straight away, but instead got the mono-hydrazone which when subjected to Wolff-Kishner reduction furnished the dione (47) in considerably better yield and, moreover, gave reproducible results. The dione (47) when condensed with methyl vinyl ketone in the presence of base, according to the method described by Boyce and Whitehurst[45] furnished 5,6,7,8-tetrahydro-8-methylindane-1,5-dione (48) which on reduction with one equivalent of recrystallised sodium borohydride, after the method of Boyce and White-hurst,[46] yielded the corresponding hydroxy compound (49).

Epoxidation of the ketol (49) was attempted under varied conditions as tabulated below:

Reagent	Base	Temp.	Product
H_2O_2 (28%)	NaOH (4N)	Room temp. (12 hr.)	acid
"	"	0° (12 hr.)	acid
"	NaOH (2N)	"	(mixture of acid (and unreacted (product

Reagent	Base	Temp.	Product
H_2O_2 (28%)	NaOH ($^N/_{10}$)	0° (12hr.)	mostly unreacted material
"	Pyridine	Room temp. (12 hr.)	unreacted material
"	"	80° (12 hr.)	mixture of acid and unreacted product
H_2O_2 (80%)	NaOH (4N)	0° (12 hr.)	acid
"	Pyridine	"	acid
Trifluoro peracetic acid	x	"	acid
t-butyl perbenzoate	x	80° (12 hr.)	starting material

It will be seen from the tabulated results that under the conditions used, epoxidation of the ketol (49) apparently occurred but the product was immediately transformed further. In most cases an acidic product was obtained, $\nu_{max.}$ 3400, 1710 cm.$^{-1}$, which was soluble in alkali and gave effervescence with sodium bicarbonate. This acid, however, could not be crystallised even by chromatography nor could a solid derivative be obtained.

Ketol (49) when treated with sodium hydroxide (4N), under the conditions used for epoxidation, gave back the

starting material but when treated with hydrogen peroxide (28%) and sodium hydroxide (4N) at 0° and worked up after one hour, a mixture of an acid and the starting material was obtained. These results coupled with those tabulated, suggest that ketol (49) on treatment with alkaline hydrogen peroxide does form the epoxide and the latter, undergoes a Favorskii type of rearrangement.

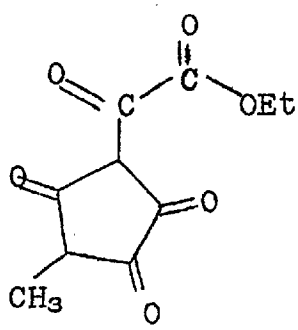
While these experiments were in progress, there appeared a notable publication by Wharton,[41] who accomplished the synthesis of 6-methyl-trans-5-cyclodecenone through the same sequence of reactions which we proposed to follow. In this connection he reported the epoxidation of 8β-benzoyloxy-9β-methyl-Δ^4-3-octalone (50) with alkaline hydrogen peroxide. We, therefore, also converted the ketol (49) into its benzoyl derivative and attempted its epoxidation by treatment with alkaline hydrogen peroxide at room temperature for 12 hr. The results are tabulated below.

Reagent	Base	Product
H_2O_2 (28%)	NaOH (2N)	(starting material; $\nu_{max.}$ (1670, 1710 cm.$^{-1}$ (no change in U.V.absorption
"	NaOH (4N)	" "

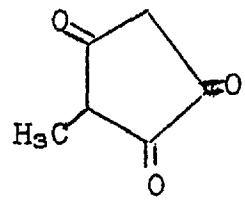
Reagent	Base	Product		
H_2O_2 (28%)	NaOH (6N)	"	"	"
H_2O_2 (80%)	Pyridine	"	"	"
"	NaOH (4N)	"	"	"

The above results show that benzoyl derivative of ketol (49) is highly resistant to epoxidation even under drastic conditions. We can offer no satisfactory explanation for this startling difference.

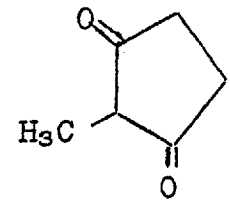
All our efforts to epoxidise the ketol (49) being unsuccessful, we looked for an alternative route. Following the directions of Stork et al.[54], the pyrrolidine enamine from cyclohexanone (52) when heated with acrylonitrile in dioxane afforded 2-cyanoethyl cyclohexanone (53). The latter on reduction with sodiumborohydride gave a mixture of 2-cyanoethyl cyclohexanol (54), 20% and $\gamma\delta$-cyclohexano-δ-valero lactone (55), 80%. The lactone (55), after separation from the mixture, when treated with polyphosphoric acid after the method of Sukh Dev[55] afforded 4,5,6,7-tetrahydro indan-1-one (56). The ketone (56) was also prepared in the low yield of 12% after the method of Sukh Dev[47] by condensing cyclohexene and acrylic



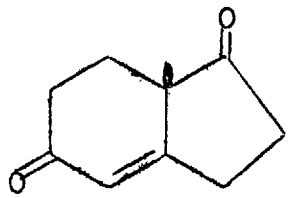
(45)



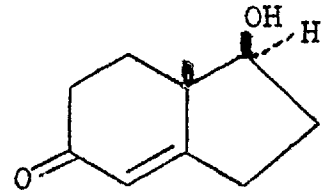
(46)



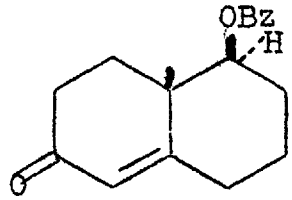
(47)



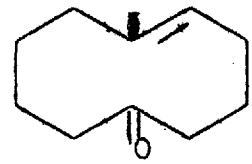
(48)



(49)



(50)

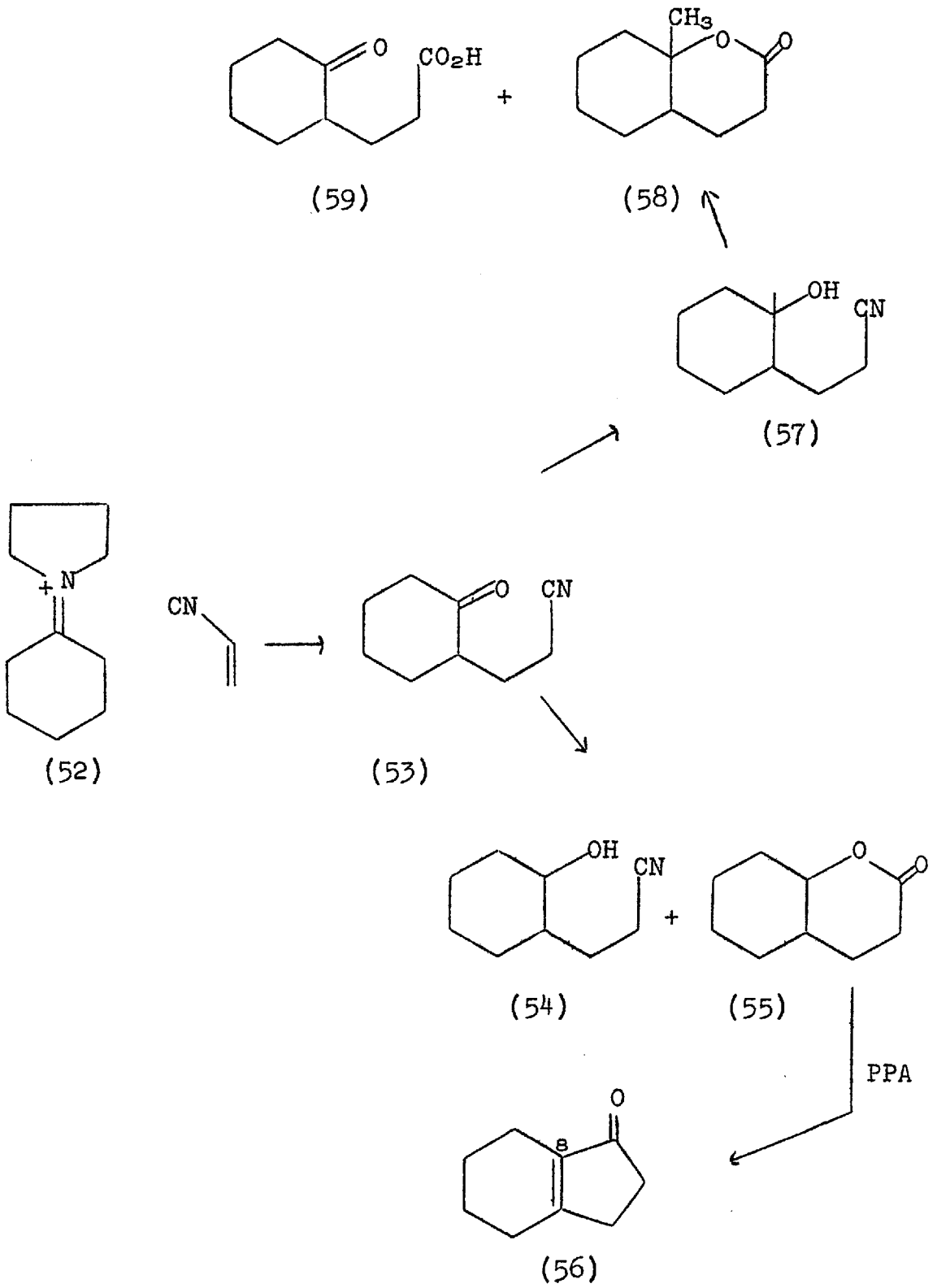


(51)

acid in the presence of polyphosphoric acid.

The next step according to our proposed scheme was the methylation of the ketone (56) at C_8. Following the method of Woodward *et al.*[56], the ketone (56) was treated with methyl iodide (*ca* 70 mols.) and potassium *tert.*-butoxide (*ca* 56 moles), but instead of getting the desired methylated ketone, we got a polymerised product. When methyl iodide and potassium-*tert.*-butoxide were used in molar ratios, no reaction took place and unchanged starting material was recovered. By increasing the quantities of the reactants up to 10 mols, some methylation took place as was observed by the shift in the carbonyl frequency in I.R. spectrum. Comparatively better results were obtained when methylation was carried out by using methyl-*p*-toluene sulphonate in dry dimethyl sulphoxide in nitrogen atmosphere. Even in this case the product was not homogeneous and the yield was very poor.

Since direct methylation at C_8 of the ketone (56) could not be effected, we thought it worth while to methylate a suitable precursor at an earlier stage. 2-Cyanoethylcyclohexanone (53) when reacted with methyl magnesium iodide and worked up in the usual way after 24 hr. gave an oil, $\nu_{max.}$ (liquid film) 3500, 2250, 1720, 1690 $cm.^{-1}$ The infra-red spectrum result suggest it to

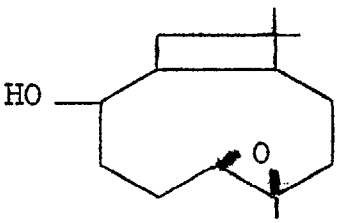

O
CO2H
+
CH3
O
O
(59)
(58)
OH
CN
(57)
+ N
CN
O
CN
(52)
(53)
OH
CN
+
O
O
(54)
(55)
PPA
O
8
(56)

be a mixture of the unreacted ketone (53), 2-cyanoethyl--1-methyl cyclohexanol (57) and γδ-cyclohexano-δ-caprolactone (58). The mixture was resolved via alkaline hydrolysis and pure samples of the lactone (58) and the keto acid (59) were obtained. All efforts to convert the lactone (58) into 5,6,7,8tetrahydro-8-methyl-indan -1-one by the treatment of polyphosphoric acid after the method of Sukh Dev[55] were without success.

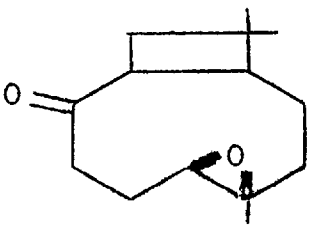
Since our synthetic experiments were held up due to unforeseen difficulties in the epoxidation of the ketol (49) and in the angular methylation of the ketone (56), we turned our efforts to degrade caryophyllene to the tricyclic diol (43) and to the keto-olefin (44), which under suitable conditions might cyclise to (43).

Cornforth and his collaborators[38] have reported a new procedure for the stereospecific conversion of an epoxide into an olefin by first forming the iodohydrin with sodium iodide and sodium acetate in acetic acid and then reducing the adduct with stannous chloride in hydrochloric acid. We, therefore, thought that caryophyllene oxidoketone (61) under similar treatment would give the iodohydrin (62) and then the trans-olefin (44). The latter compound should, on reaction with Wittig's

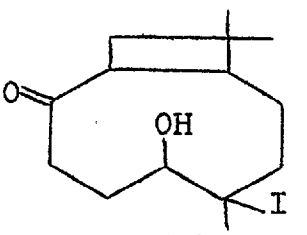
Reagent, produce caryophyllene (40). Attempts to prepare the iodohydrin (62) from the oxidoketone (61) by Cornforth's procedure (loc. cit.), however, were not successful, as unreacted starting material was recovered. We have, however, observed that oxidoketone (61) on modification of Cornforth's procedure - viz. using a mixture of acetic acid and propionic acid as solvent, instead of giving the expected iodohydrin (62) furnished a new compound, $C_{14}H_{22}O_2$, m.p. 110-111°. In the infra red spectrum it showed absorption at 3450 and 1690 $cm.^{-1}$, suggesting it to be a hydroxy ketone which we have called the S-ketol. The latter on treatment with acetic anhydride and pyridine at room temperature afforded a crystalline acetate, $C_{16}H_{24}O_3$, m.p. 125°, dictating that the hydroxyl is secondary. On the basis of available chemical and spectral evidence, we assigned structure (63; R=H) to the S-ketol. This formulation is further supported by the fact that, on ozonolysis, formaldehyde was produced; thus the presence of an exocyclic methylene group was confirmed. Attempts to oxidise the allylic alcohol with manganese dioxide, however, were not successful. The S-ketol (63; R=H) on catalytic hydrogenation (Adam's catalyst) absorbs one mole of hydrogen, though the product could not be obtained in the crystalline form. In agreement with its being



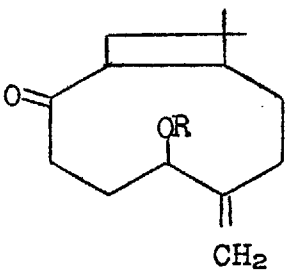
(60)



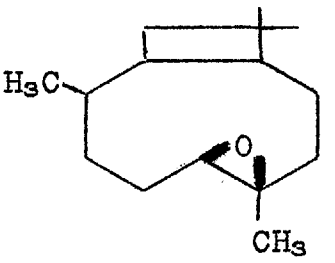
(61)



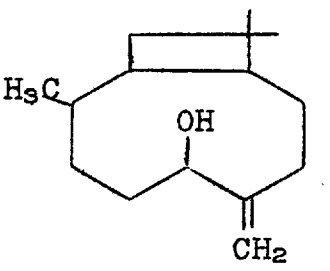
(62)



(63)



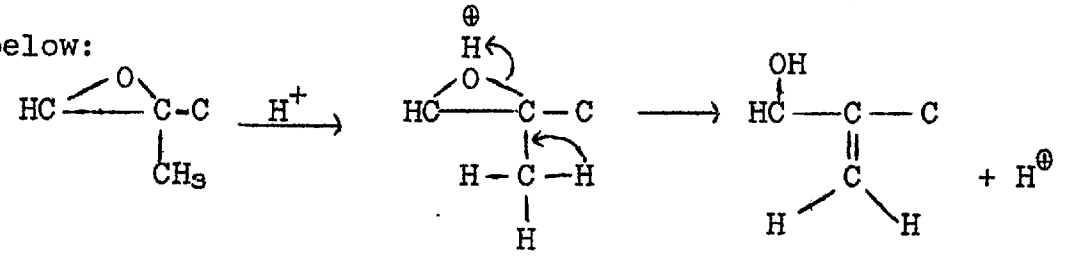
(64)



(65)

an allylic alcohol, (63; R=H) gave a positive test with ceric ammonium nitrate and negative one with tetranitromethane. An attempt to bring the double bond back into the ring by allylic rearrangement with thionyl chloride and pyridine gave intractable material.

Our experiments have proven that propionic acid is an essential ingredient for the conversion of oxidoketone (61) into S-ketol (63; R=H) yet its specific role in the transformation is not clear. It also appears that the transformation does not take place through the intermediate iodohydrin (62), but rather it occurs directly as shown below:



There are a number of precedents in the literature for the isomerisation of epoxides to allylic alcohols[40] and a particularly apt analogy is Sorm's conversion of dihydrocaryophyllene oxide (64) to allylic alcohol (65) with refluxing pyridine hydrobromide.[17]

Since the desired trans-olefin (44) could not be obtained from the oxidoketone (61) by Cornforth's procedure (loc. cit.), we looked for some other suitable

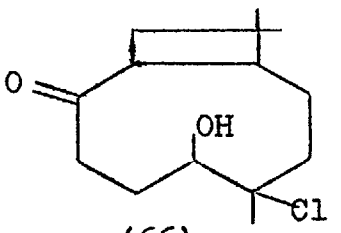
derivative of caryophyllene to transform. Barton and Lindsey[18], by treating oxidoketone with dry hydrogen chloride in chloroform, obtained a highly crystalline compound, $C_{14}H_{23}O_2Cl$, m.p. 145-147°, which they called the 'chlorohydrin' and its oxidation product, $C_{14}H_{21}O_2Cl$, the 'chlorodiketone'. These authors, however, did not assign any structure to either of the two compounds. Since these are nicely crystalline compounds and we wanted to use them as starting material for our degradative studies, we, in accordance with the theoretical considerations, assigned structure (66) to the chlorohydrin and (67) to the chlorodiketone.

If chlorodiketone is correctly formulated as (67), it would be expected that on reduction with zinc or chromous chloride, it would give, with the elimination of chloride, the enol (68) which might cyclise to form the Ketal (72) and then reduced to tricyclic diol (43), which would in fact be the compound, we were planning to synthesise. With this view in mind, the chlorodiketone was prepared after the method described by Barton and Lindsey[18] and its infra red spectrum was measured showing bands at 3337 and 1724 cm.$^{-1}$ The anomalous spectrum of the chlorodiketone (67) showing hydroxyl absorption (3337 cm.$^{-1}$), may be explained by

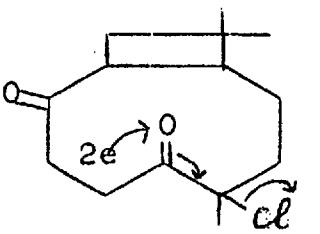
the assumption that during chromatographic purification over alumina, it has undergone base-catalysed cyclisation, giving a hydroxy ketone, probably having the structure (69), though the carbonyl absorption (1724 $cm.^{-1}$) is a bit low for a five-membered ring ketone. On the basis of new formulation (69) for the oxidation product of chlorohydrin (66), it is difficult to see how it could be transformed to the desired diol (43) and hence these studies were not pursued further.

Another nicely crystalline compound, which could be degraded to the diol (43) was chlorohydrin (66), described by Barton and Lindsey (loc. cit.). It was interesting to note that whereas in the infra red spectrum, chlorohydrin (66) showed carbonyl absorption in chloroform solution, there was no absorption in the carbonyl region when the spectrum was measured in nujol mull. This observation led us to believe that in the solid state, the chlorohydrin exists as its hemi-acetal (70), which opens up in solution to give (66) which shows carbonyl absorption.

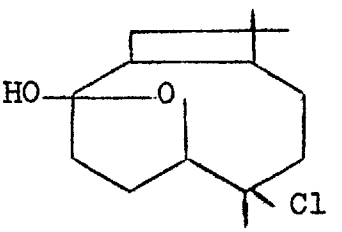
Reduction of organic compounds by metal-ammonia solutions is well known in the literature.[58] Barton and Robinson,[59] observed that the reduction of α,β-unsaturated



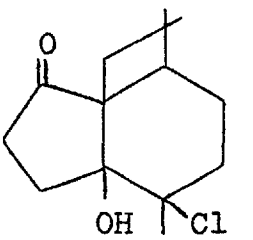
(66)



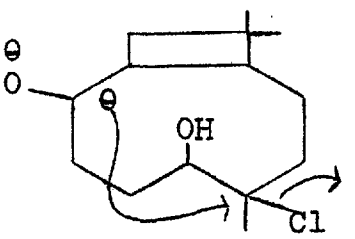
(67)



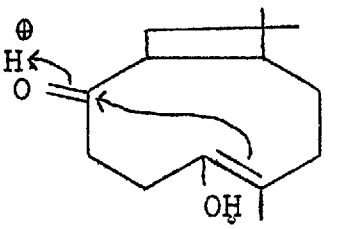
(70)



(69)

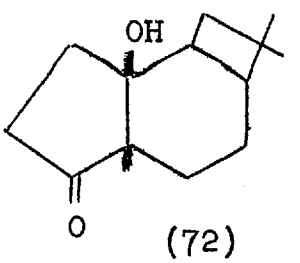


(71)



(68)

(43)



(72)

ketones by dissolving metals in liquid ammonia may be regarded as a carbanion reduction process which can be conveniently represented by the following scheme:

$$\text{>C:C.C:O} \longrightarrow \text{>C}^{-}\text{.C:C.O}^{-} \longrightarrow \text{CH.C:C.OH} \longrightarrow \text{CH.CH.C:O}$$

An extension of this carbanion reduction process to the carbonyl systems in general, would necessarily result in the formation of a dianion as shown below and in particular

$$2e + O = C \longrightarrow {}^{-}O - C^{-}$$

~~and in particular~~ in the case of chlorohydrin (66) the dianion (71) would be formed, and it might cyclise with the elimination of chlorine giving the required diol (43). The chlorohydrin (66) on treatment with lithium dissolved in ammonia after the method of Barton and Robinson (loc. cit.) afforded a crystalline compound, $C_{14}H_{24}O_2$, m.p. 192°, $\nu_{max.}$ 3670, 3500 cm.$^{-1}$. It gives a negative Beilstein test and on treatment with acetic anhydride and pyridine furnished a gummy monoacetate. The foregoing chemical and spectral evidence suggest that the compound m.p. 192°, is a diol, in which one of the hydroxyl groups is tertiary. Oxidation of the diol with chromium trioxide and pyridine[60,61] afforded a crystalline compound, $C_{14}H_{22}O_2$, m.p. 125°, $\nu_{max.}$ (nujol) 3509 and 1681 cm.$^{-1}$,

$\nu_{max.}$ (chloroform) 1708 cm.$^{-1}$ The analytical and spectral evidence suggest that the compound m.p. 125° is a ketol. Since it resists acetylation and further oxidation, it may be concluded that the hydroxyl is tertiary. All these facts could be accommodated if ketol be formulated as (72) and the diol from which it is derived, therefore, should be (43), the compound we were planning to obtain. However, an insurmountable objection to accepting the formulation (72) for the ketol is that it shows carbonyl absorption (1708 cm.$^{-1}$) which is too low for a five membered ring ketone.

While more detailed studies of the reduction product of chlorohydrin were being made, we also thought it worth while to investigate its reduction with lithium aluminium hydride and compare the reduction products obtained in the two cases which in accordance with theoretical consideration might be the same.

The chlorohydrin (66) when treated with lithium aluminium hydride afforded after chromatography, two products:

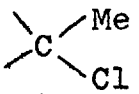
(a) m.p. 160-161°, $\nu_{max.}$ 3570 and 3400 cm.$^{-1}$ It gives negative Beilstein test and analyses for $C_{14}H_{24}O_2$. The spectral and analytical evidence suggest it to be

a diol, containing one double bond and two rings.

(b) m.p. 140-141°, $\nu_{max.}$ 3650 and 3500 cm.$^{-1}$ This also gives a negative Beilstein test and its elemental analysis agrees with the molecular formula, $C_{14}H_{24}O_2$. It appears to be a saturated tricyclic diol on the basis of its spectral characteristics.

At this stage we were able to get the n.m.r. spectra of the above degradation products of caryophyllene measured and as will be seen below the tentative structural assignments made, have to be altered in some cases.

The S-ketol (63; R = H), in the n.m.r., shows a single peak at τ = 8.99 (6 protons) ascribed to the gem dimethyl group and a pair of doublets at τ = 5.02, 4.94 which correspond to the two protons of the exocyclic methylene grouping. The CHOH proton absorbs at τ = 5.84 with a multiplicity of 4. These results confirmed the structure (63; R = H) for the S-ketol.

However, the chlorohydrin (66) shows two partly resolved peaks at τ = 8.94 and 8.96 (gem dimethyl) and at τ = 6.07 (a single proton of multiplicity 4 which must be a CHO type). It does not show the presence of the  grouping as expected on the basis of structure (66) for it, nor does it show the presence of -CH_2Cl or

>CHCl grouping. Nor do the degradation products of the chlorohydrin show the expected >C - Me grouping in their n.m.r. spectra and so that the proposed structures for the chlorohydrin and its degradation products must be reformulated.

While these studies were in progress, Corey and his collaborators[37] published their total synthesis of caryophyllene and isocaryophyllene. In this publication, these workers described the preparation of the diol (43) and the ketol (72), which we were trying to make. A comparison of the physical constants of Corey's diol and the diol, m.p. 192°, obtained from the chlorohydrin by reduction with lithium in ammonia, disclosed that they are different chemical compounds. Since the synthesis of caryophyllene and isocaryophyllene had been achieved by Corey, we turned our efforts to the chemistry of the degradation products of caryophyllene with a view to ascertaining their structures.

We embarked on a fresh re-investigation starting from the chlorohydrin. When the chlorohydrin was prepared as described, material of the same m.p. was obtained but this time it did not show any carbonyl absorption in the infra red, either in chloroform solution or in

nujol; only hydroxyl absorptions, $\nu_{max.}$ 3600, 3450 cm.$^{-1}$ were observed. For this we have no satisfactory explanation at present. The carbonyl absorption was initially observed on three different samples and the band was the strongest in the whole spectrum. We do know that it was not due to either starting material or elimination product. The chlorohydrin must now be formulated as a tricyclic compound containing two hydroxyl groups. Treatment of the chlorohydrin with acetic anhydride and pyridine at room temperature, afforded a crystalline monoacetate, $C_{16}H_{25}O_3Cl$, m.p. 150-151°, $\nu_{max.}$ 3550 (-OH) and 1720 (ester $\rangle$C=O) cm.$^{-1}$, indicating that out of two hydroxyls one is tertiary.

Firstly we decided to attempt to prove that the four membered ring was still present in the chlorohydrin. Vigorous oxidation of the caryophyllene, with potassium permanganate followed by nitric acid gives a mixture of carboxylic acids, from which Semmler and Mayer[3] isolated three dicarboxylic acids - viz: as-dimethyl succinic acid, nor-caryophyllenic acid and caryophyllenic acid. We were able to resolve the crude oxidation mixture of caryophyllene into its components by silica gel thin plates chromatography, using the ethanol: water: ammonia

(d = 0.88) ::80:15:5 system as the moving phase. The indicator used was methyl red-bromothymol blue as described by Duncan and Porteus.[62] Three different spots were obtained which represent the three acids described by Semmler and Mayer (loc. cit.) and were identified by comparing the R_f values with those of the authentic samples of the components. The crude oxidation mixture of caryophyllene was also resolved into its components by vapour phase chromatography after methylation with diazomethane.

Chlorohydrin, when likewise oxidized after the method of Semmler and Mayer (loc. cit.) furnished a mixture of carboxylic acids. The latter, after methylation, was resolved by vapour phase chromatography into three components which were identical in retention times to the three components present in the oxidation mixture of caryophyllene after methylation. The crude oxidation mixture obtained from the chlorohydrin could not, however, be detected on paper or silica gel thin plates using the indicator described above. The presence of as-dimethyl succinic, nor-caryophyllenic and caryophyllenic acids in the oxidation mixture of chlorohydrin clearly proves the presence of a gem-dimethyl cyclobutane ring in the chlorohydrin molecule.

Another important observation made during these studies was the facile transformation of chlorohydrin into the S-ketol (63; R = H) with the elimination of HCl. Thus it was found that the chlorohydrin merely on passing through a column of alumina in benzene solution, undergoes dehydrochlorination with the formation of the S-ketol (63; R = H). Similarly chlorohydrin on treatment with 1N alcoholic potassium hydroxide at room temperature or with zinc dust and acetic acid at room temperature, afforded S-ketol (63; R = H) in quantitative yield. The latter reaction is interesting since it does not occur in the absence of the zinc and the zinc surface instead of acting in its usual role as a reducing agent appears to bring about dehydrohalogenation. However, the possibility remains that zinc acetate is the active agent.

In agreement with the above observations, the chlorohydrin acetate when passed over alumina in benzene solution furnished S-ketol acetate (63; R = Ac) but on mild alkaline hydrolysis, it gave the S-ketol (63; R = H). Later reaction probably proceeds firstly with elimination of HCl to form the S-ketol acetate (63; R = Ac) which is then hydrolysed to the S-ketol (63; R = H).

The first real clue as to the mode of formation of the chlorohydrin came from its synthesis from S-ketol by treatment with hydrogen chloride in chloroform. This suggests that the chlorohydrin was not formed directly from the epoxyketone (61) but that the latter was first isomerised to S-ketol and then added hydrogen chloride. These interconversions further suggest the presence of the HO—C—CH_2—C—Cl grouping in chlorohydrin.

Any attempt at formulating a structure for the chlorohydrin, must necessarily take into consideration the facts summarised below:

(i) the elemental analysis of chlorohydrin corresponds with the molecular formula $C_{14}H_{23}O_2Cl$.

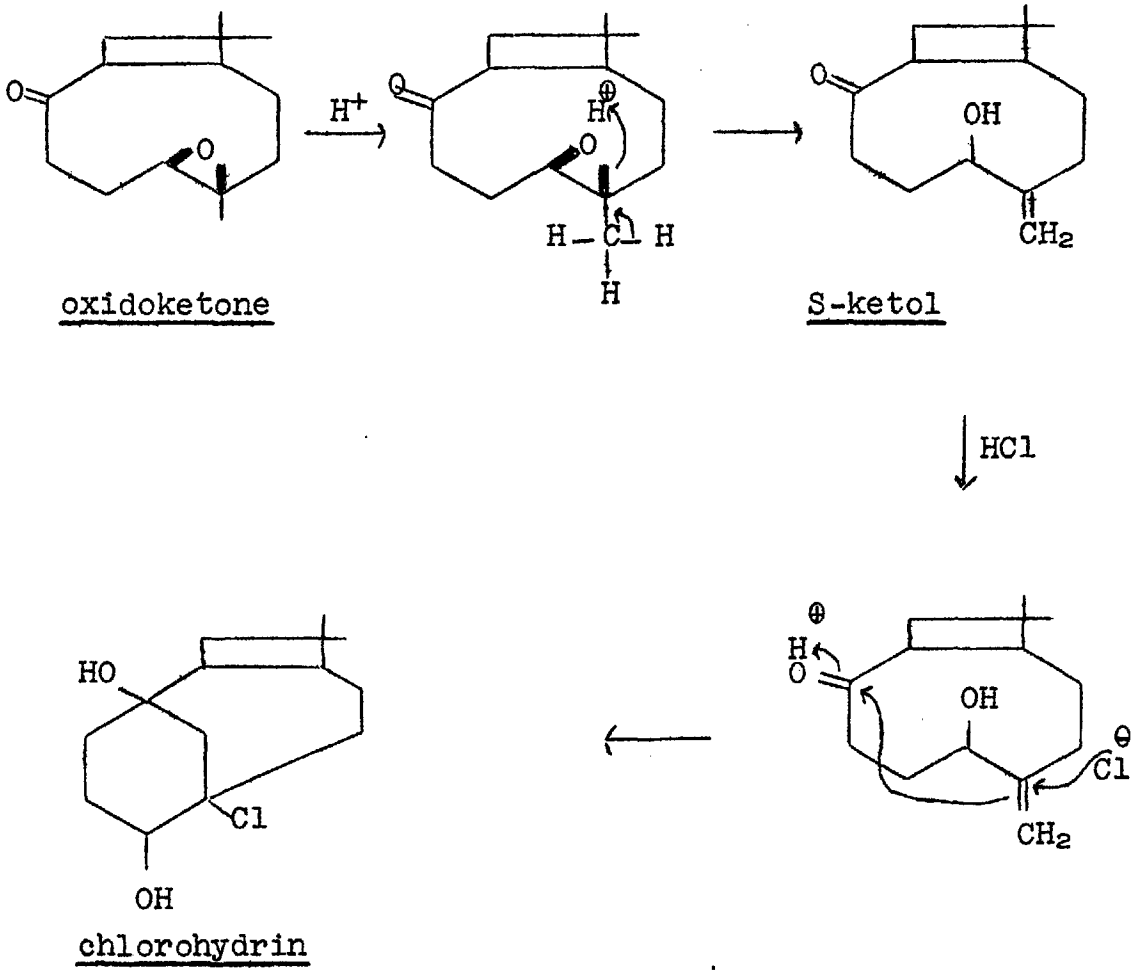
(ii) the n.m.r. spectrum shows the presence of >CHOH grouping and absence of —C(Me)—Cl, $-CH_2Cl$ or >CHCl groupings.

(iii) the infra red spectrum shows the presence of two hydroxyl groups, one of which was shown to be tertiary.

(iv) the facile transformation of chlorohydrin into S-ketol (63; R = H) by elimination of HCl, suggests the presence of HO—C—CH_2—C—Cl grouping in it.

(v) there is present a gem-dimethyl cyclobutane ring in chlorohydrin.

To account for all the above mentioned facts, we propose structure (76; R = H) for chlorohydrin and suggest that it is formed by acid catalysed isomerisation of the epoxide to the S-ketol which then undergoes an acid catalysed transannular reaction as shown below.



oxidoketone

S-ketol

chlorohydrin

We then attempted to degrade the S-ketol acetate (63; R = Ac) further in order to prove this structure. As described earlier, the S-ketol (63; R = H) on ozonolysis provided formaldehyde in agreement of its having an exo-cyclic methylene grouping. Similarly S-ketol acetate (63; R = Ac) when ozonized gave formaldehyde and another fragment which was isolated and shown to be an acetoxy dione, $C_{15}H_{22}O_4$, m.p. 78-79° (73), $\nu_{max.}$ 1740, 1720 and 1690 $cm.^{-1}$ It was then decided to attempt to hydrolyse off the acetoxy grouping of (73) to get the corresponding alcohol, which on oxidation should furnish the keto dicarboxylic acid (74) which could be related to the known keto acid (75).

To achieve this aim hydrolysis of (73) was attempted under varied conditions but with no success. The reagents used for hydrolysis were:

(i) alcoholic potassium hydroxide, 0.1N, 1N, 10N.

(ii) aqueous sodium hydroxide solution.

(iii) sodium methoxide in methanol.

(iv) ethanol-ammonia solution.

(v) ethanol-hydrochloric acid solution.

(vi) saturated solution of sodium bicarbonate in 50% aqueous ethanol.

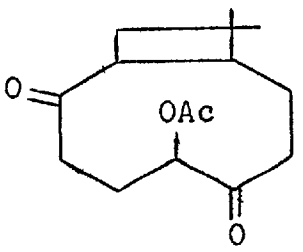
(vii) sodium bicarbonate in tetrahydrofuran.

(viii) liquid ammonia.

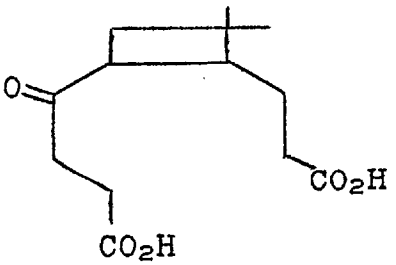
In all cases intractable material was formed and no crystalline products were isolated. Similarly attempts to reduce out the acetoxyl group using zinc and acetic acid or calcium in liquid ammonia gave no useful products.

The readiness with which hydrogen chloride reacts with the oxidoketone (61) prompted us to study this reaction on oxidoalcohol (60). The latter on being treated with hydrogen chloride furnished a yellowish viscous liquid, $\nu_{max.}$ (film) 3400 and 1700 cm.$^{-1}$ The presence of carbonyl absorption (1700 cm.$^{-1}$) in the infra red spectrum suggests that under acid conditions the epoxide group has rearranged to carbonyl grouping.

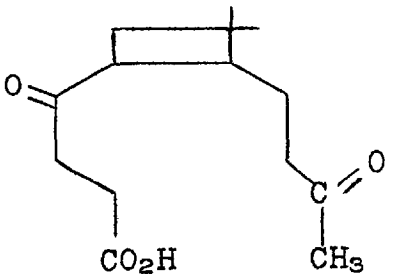
Having assigned structure (76; R = H) to the chlorohydrin, we proceeded to examine the structures of its degradation products. Barton and Lindsey[18] reported that the chlorohydrin on oxidation with chromium trioxide and acetic acid afforded a chlorodiketone, to which we had previously assigned structure (67). On the basis of our new formulation (76; R = H) for the chlorohydrin, the chlorodiketone must be (77) and its n.m.r. and infra red spectra are consistent with this. In particular the carbonyl absorption at 1724 cm.$^{-1}$ fits for an α-chloro carbonyl system in a six membered ring.



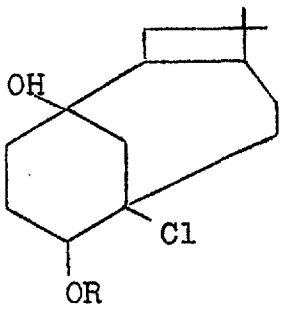
(73)



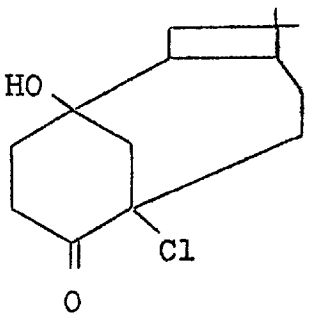
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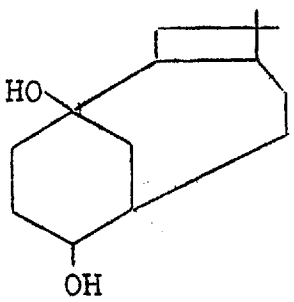
(75)



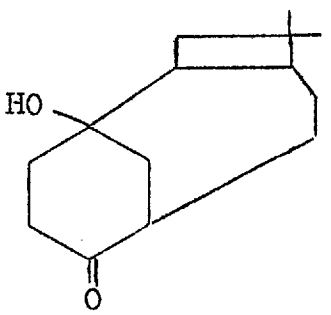
(76)



(77)



(78)



(79)

Earlier we have described the lithium in liquid ammonia reduction of the chlorohydrin to a tricyclic secondary-tertiary diol, m.p. 192°, to which we had previously assigned structure (43). Oxidation of this diol with chromium trioxide and pyridine afforded a tertiary-hydroxy ketone, m.p. 125°, which was earlier represented by structure (72). In light of the new structure for the chlorohydrin the diol is most simply represented as the hydrogenolysis product (78) and the ketol as (79). These structures are consistent with their n.m.r. spectra. The diol (78) shows a peak at τ= 8.97 (6 protons) corresponding to gem-dimethyl grouping and at τ= 6.22 (1 proton) representing the hydrogen attached to a hydroxyl bearing carbon. Similarly the ketol (79) gives a doublet at τ = 9.02, 8.96 (6 protons), which could be assigned to the gem-dimethyl grouping.

However, earlier, we had thought it necessary to prove that the chlorohydrin did not revert to either oxidoketone or S-ketol under the conditions of reaction and that the diol was not a reduction product of either of these compounds.

To prove this, we carried out reduction of the oxidoketone (61) with lithium in ammonia to see whether or not, we could get the same material as obtained in the

case of chlorohydrin. We observed that the oxidoketone (61) on reduction with lithium-ammonia solution afforded two products one of which was identified as the oxido alcohol (60) and the other was shown to be identical to the diol (78), as obtained from the reduction of chlorohydrin (76; R = H). Since the diol, (78), was obtained only in small quantity, the hypothesis that reduction of chlorohydrin might be going through the intermediate formation of oxidoketone had been ruled out. However, the presence of the diol, (78) in the reduction mixture of oxidoketone was puzzling. A possible explanation for this might be that some ammonium salt (an acid in liquid ammonia) present in the medium caused isomerisation of the oxidoketone to S-ketol which, in turn, might form chlorohydrin in the presence of ammonium chloride. Indeed by adding ammonium chloride to the reaction mixture we reduced the ratio of the oxidoalcohol to diol produced in the reduction from 4/1 in the absence of added ammonium chloride to 3/1 in the presence of 2 mols. and 2/1 in the presence of 10 mols.

This marked effect of the added ammonium chloride on the yield of the diol, supported the idea that the S-ketol might be an intermediate in the <u>in situ</u> formation of the

chlorohydrin.

To test this view the S-ketol (63; R = H) was subjected to lithium-ammonia reduction but we obtained no trace of the diol (78). Instead a different compound, $C_{13}H_{22}O_2$, m.p. 175°; $\nu_{max.}$ 3650 and 3550 cm.$^{-1}$ was obtained. The n.m.r. spectrum of this compound shows peaks at τ = 8.95, 8.88 (9 protons) corresponding to the gem-dimethyl grouping and one other $\rangle$C - Me group. At present we can offer no suggestion for its structure; indeed its composition (which has been checked by a M.W. determination using the isothermal method) suggests that a most unusual reaction is taking place. It does, however, effectively dispose of our hypothesis concerning the reduction of the chlorohydrin and we have no further ideas on this at present.

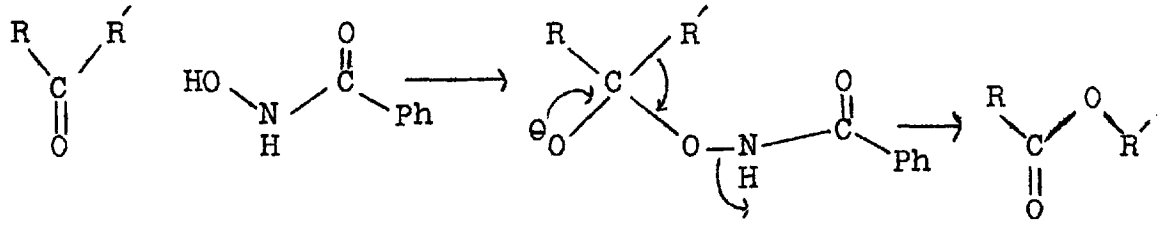
The ketol (79) obtained from (78) which was, in turn, derived from the chlorohydrin by lithium ammonia reduction seemed a likely compound for further degradative work to prove the postulated structures. Firstly we showed that (79) was reduced in excellent yield back to (78) thus precluding any rearrangement in the oxidation step. Further oxidation of the ketol, m.p. 125° with chromium trioxide and acetic acid afforded a gummy product, $\nu_{max.}$

3650, 3500, 1770 and 1700 cm.$^{-1}$ which could not be crystallised. However, the presence of a strong band at 1770 cm.$^{-1}$ indicated the presence of a γ-lactone. Since this lactonic material could not be crystallised, we looked for some other methods to break the ring.

We were particularly interested in the lactonisation as it would indicate the relative position of the hydroxyl and the carbonyl grouping. Another useful tool which could be employed for this purpose is the Baeyer-Villiger oxidation[63] which has found a fairly wide applicability. Oxidation of the ketol, m.p. 125°, with trifluoro peracetic acid under Baeyer-Villiger reaction conditions afforded an uncrystallisable gum, again showing γ-lactone absorption. Similar results were obtained when the ketol, (79) was oxidised with hydrogen peroxide (80%) in tert.-butanol.[64] In both cases the presence of bands at 1760 cm.$^{-1}$ show that some lactone has formed but bands at 1600 cm.$^{-1}$ indicate that the molecule has rearranged. Oxidation of the ketol (79) with m-chloro perbenzoic acid furnished unreacted starting material.

Based on the mechanistic principle involved in the Baeyer-Villiger reaction, we thought that a hydroxamic acid in liquid ammonia solution might act as oxidant

according to the following equation:



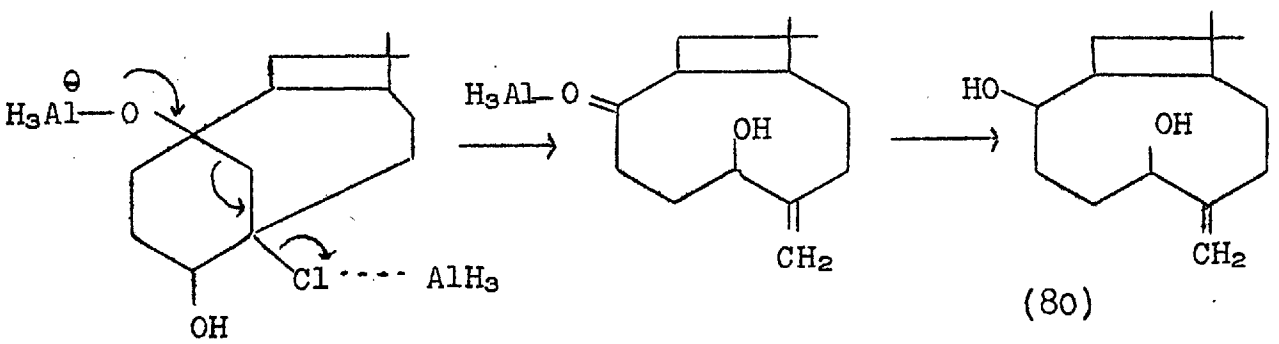
and attempted this reaction on cyclohexanone when a dark red liquid was obtained, $\nu_{max.}$ 3450, 1700 and 1600 cm.$^{-1}$ which seemed to be an amide but none of the expected w--hydroxyhexanoylamide could be isolated. The reaction was also attempted using N-phenyl benzhydroxamic acid and N-phenyl p-toluensulphonyl hydroxamic acid, but in both cases unreacted starting material was recovered. Similarly no reaction occurred when cyclohexanone was treated with a mixture of p-toluene sulphonyl chloride, hydrogen peroxide (30%), sodium hydroxide ($^{N}/10$) and tert.-butanol.

Barton and co-workers[65] have described a general method for introducing an α-hydroperoxy group into ketones using dry oxygen in the presence of a tert.-alkoxide in the corresponding alcohol. The ketol, (79) when treated with oxygen in the presence of potassium-tert.-butoxide and tert.-butanol, readily absorbs one mole of oxygen, but the product could not be obtained in crystalline form and did not appear to be a diosphenol or hydroperoxide.

Similarly attempts to degrade the ketol (79) by oxidation with selenium dioxide or by oximination with amylnitrite[67] were not successful and in both cases intractable material was obtained which showed γ-lactone absorption. Reaction of the ketol (79) with N-bromo succinimide,[57] apparently proceeds smoothly but the final product does not contain any bromine suggesting that elimination has occurred. However, this product did not show the U.V. absorption expected for an α, β-unsaturated ketone. To explain the almost invariable appearance of γ-lactone absorption in the reaction mixtures we suggest that the electrophillic reagents, instead of attacking the methylene group α to the carbonyl, attack at the bridgehead and then ready elimination occurs, as with the chlorohydrin, to give sensitive products which undergo further degradation to intractable materials.

Mention has already been made that the chlorohydrin (76; R = H) on reduction with lithium aluminium hydride furnished two products (a) m.p. 160-161° and (b) m.p. 140-141° but neither of them corresponds to the lithium ammonia reduction products of either the chlorohydrin (76; R = H), oxidoketone (61) or S-ketol (63; R = H).

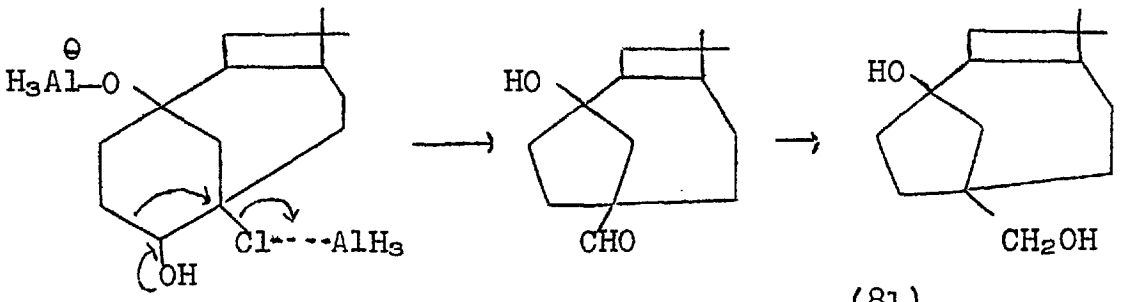
We then examined the n.m.r. spectra of these products and found that the diol, m.p. 160-161° shows a doublet at τ = 9.03, 9.0 (6 protons) corresponding to the gem--dimethyl grouping, a partially resolved peak at τ = 4.95, 4.94 (2 protons) representing the exocyclic methylene grouping and á rather broad peak at τ = 5.8 (2 protons), which may be ascribed to protons attached to a hydroxyl bearing carbon and thus suggest the presence of two secondary hydroxyls. The presence of exocyclic methylene grouping was confirmed by ozonolysis whereby formaldehyde was produced and identified as its dimedone derivative. In view of the evidence obtained so far, we propose structure (80) for the diol, m.p. 160-161°. Since it has been well established in the course of our investigations that chlorohydrin readily eliminates HCl to form S-ketol, it is postulated that a trivalent aluminium derivative acts as a Lewis acid causing elimination to S-ketol, as shown below, and this is then reduced further to (80).



(80)

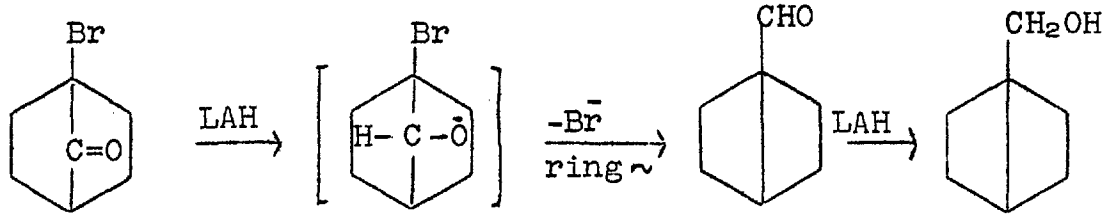
We tried to reduce the S-ketol (63; R = H) with lithium aluminium hydride as well as with sodium borohydride but both reactions failed to give the diol (80). However, this is being investigated under modified conditions as the intermediates might not be identical starting from the two different compounds.

The n.m.r. spectrum of the other diol, m.p. 140-141° obtained by lithium aluminium hydride reduction of chlorohydrin shows a singlet at τ = 8.97 (6 protons) representing the gem-dimethyl grouping and a singlet at τ = 6.64 (1 proton) which may be assigned to the two protons of a CH_2OH group, attached to a quaternary carbon atom. No other -CHO- proton was detected in this region. Thus the molecule must be tricarbocyclic. On the basis of the spectral evidence we assigned structure (81) to the diol, m.p. 140-141°. The genesis of (81) from chlorohydrin may again be explained by a trivalent aluminium derivative acting as a Lewis acid to give the previous intermediate which can eliminate chloride by the alternate ring contraction, as shown below, to give the aldehyde which is then reduced to (81).



(81)

There are a few isolated examples in the literature whereby reduction of halohydrins resulted in the contraction of a ring. For example the bicyclic bromoketone (82), as shown below, on reduction with lithium aluminium hydride undergoes ring contraction to form the aldehyde (83) which is then reduced to the alcohol[66] (84). In our case ring contraction cannot occur by the



(82) (83) (84)

normal mechanism involving inversion at the receptor carbon atom since this is prohibited at the bridgehead.

EXPERIMENTAL

M.p.'s were determined on a Kofler block and are uncorrected. Except when otherwise stated, rotations and infrared spectra were measured in chloroform and the latter spectra were determined on a Unicam SP 200 Spectrometer.

Ultraviolet absorption spectra were determined in ethanol using a Perkin Elmer 4000 Spectrophotometer.

Nuclear magnetic resonance spectra were measured by Mrs. I. Boston on a Varian A-60 spectrometer using deuterochloroform as solvent and tetramethylsilane as internal standard.

Analyses were carried out by Miss J. Cuckney (Imperial College) and her associates.

Zanzibar Clove Oil sesquiterpene mixture was kindly supplied by Messrs. White, Tomkins, and Courage Ltd., Reigate, to whom we offer our best thanks.

Light petroleum refers throughout to the fraction of b.p. 60-80°. The caryophyllene used was obtained by fractionation of clove-bud sesquiterpenes. A typical specimen has b.p. 74-76°/0.5 mm. n_D^{25} 1.4987.

Caryophyllene oxide.

Treibs[16] reported the preparation of caryophyllene oxide by treating caryophyllene with perbenzoic acid. We have, however, prepared it by the action of peracetic acid in chloroform on caryophyllene in 40% yield. The advantage in using peracetic acid is that it avoids the cumbersome job of preparing perbenzoic acid. Caryophyllene oxide so obtained on crystallisation from methanol had m.p. 61-62°.

Oxido Ketone[16]

To a well stirred solution of caryophyllene epoxide (15 g.) in acetone (150 ml.) and water (37 ml.), potassium permanganate (30 g.) was added with water cooling over 8 hr. After the addition was completed, cooling was stopped but stirring was continued for another 16 hr. at room temperature. Manganese dioxide was filtered off and from the pink filtrate, solvent was removed in vacuo. The residue

was taken up in benzene, treated with charcoal and filtered to give a colourless solution. The benzene was distilled off *in vacuo* and the liquid residue (9 g.) on crystallisation from light petroleum at low temperature, afforded crystalline oxidoketone (4.2 g.), m.p. 62-63°.

Chlorohydrin (76; R=H)

Following the directions of Barton and co-workers,[18] the oxidoketone in chloroform was treated with dry hydrogen chloride for 15 minutes. Removal of the solvent *in vacuo* and recrystallisation from chloroform-light petroleum afforded the highly crystalline chlorohydrin, m.p. 146-47°. $\nu_{max.}$ 3600 cm. 3450 cm.$^{-1}$

Chlorodiketone (77)

The chlorohydrin was oxidised with chromium trioxide in acetic acid according to the method described by Barton and Lindsey (*loc. cit.*). Working up the reaction mixture in the usual way and passing the product through a column of alumina in benzene solution gave, after recrystallisation from chloroform-light petroleum, the chlorodiketone, m.p. 90°. $\nu_{max.}$ 1724 cm.$^{-1}$

Ethyl 4-methyl-2,3,5-triketo cyclopentylglyoxylate.[43,44]

This compound was prepared as described by condensation of two moles of ethyl oxalate with one mole of butan-2-one, m.p. 160-3°.

2-Methylcyclopentane-1,3,4-trione.[43,44]

Hydrolysis of the previous compound with 50% phosphoric acid gave the trione, m.p. 118-119°.

2-Methylcyclopentane-1:3 dione, (47)

To a well stirred solution of 2-methylcyclopentane-1:3:4-trione monohydrate (7 g.) in methanol (50 c.c.) was added dropwise a 64% solution of hydrazine hydrate (15 ml.) during 30 min. The precipitated yellow monohydrazone was collected, washed with aqueous methanol and dried in vacuo, (yield 97%). The hydrazone (4.5 g.) was added to potassium hydroxide (4.5 g.), dissolved in ethylene glycol (45 ml.) at 130°. The solution was heated at 150° for 30 min. and at 180° for 1 hr., and then all solvent was removed under reduced pressure (0.1 mm.). The residue, in water (200 ml.), was acidified to pH 3 with hydrochloric acid and the precipitate on crystallisation from water afforded 2-methylcyclopentane-1:3 dione (yield 1.1 g.;

30%), m.p. 208-209°.

In the literature[45] this dione has been prepared by the Wolff Kishner reduction of the semicarbazone of the trione, and an average yield of 51% has been recorded. We, however, found this method difficult to reproduce and in our hands an average yield of 10-12% was obtained. The above method we have found to be reproducible.

5,6,7,8-Tetrahydro-8-methylindane-1,5-dione.[45]

Condensation of the 2-methylcyclopentane-1,3-dione with methyl vinyl ketone in the presence of methanolic potassium hydroxide gave the dione as described.

The 1-hydroxy compound was prepared by the literature method,[46] *viz* reduction of the dione with one equivalent of recrystallised sodium borohydride in ethanol.

4,5,6,7-Tetrahydroindan-1-one.[47]

The ketone was prepared by the action of polyphosphoric acid on a mixture of acrylic acid and cyclohexene. Yield 12%.

S-Ketol. (63; R=H)

a) The oxidoketone (250 mg.) in acetic acid (0.2 ml.), and propionic acid (0.5 ml.) was treated with sodium

iodide (230 mg.) and sodium acetate (20 mg.). The yellowish solution so obtained turned red and completely homogeneous on standing overnight at room temperature. This was poured into cold dilute sodium bicarbonate solution and extracted with ether. The reddish organic layer was treated with a dilute solution of sodium metabisulphite to reduce the iodine and finally washed with distilled water and dried over anhydrous magnesium sulphate. Removal of the solvent in vacuo and crystallisation of the residue from ether-light petroleum gave a crystalline product, m.p. 100-105°. Recrystallisation of this product from chloroform-light petroleum afforded highly crystalline hydroxy ketone (240 mg.), m.p. 110°-111°, $[\alpha]_D$ -41° (c, 1.05); $\lambda_{max.}$ 287 mμ (ε = 27); $\nu_{max.}$ 3450 and 1690 cm.$^{-1}$ (Found: C, 75.30; H, 9.97. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%). 3:5-dinitrobenzoate, prepared after the method of Brewster and Ciotti,[42] on crystallisation from aqueous methanol had m.p. 133-34°. (Found: C, 60.16; H, 6.12; N, 6.81. $C_{21}H_{26}O_7N_2$ requires C, 60.29; H, 6.22; N, 6.70%).

(b) The chlorohydrin (100 mg.) in ethanol (1 ml.) was treated with aqueous potassium hydroxide solution (2N, 1 ml.). The mixture was slightly warmed on the water bath and left for 16 hr. at room temperature. The reaction mixture,

after dilution with water, was extracted with ether and the combined ethereal extracts were dried over anhydrous magnesium sulphate. Removal of the solvent *in vacuo* and recrystallisation from chloroform-light petroleum furnished crystalline *hydroxy ketone* (80 mg.), m.p. 109-110°C. Its identity was further confirmed by mixed melting point and comparing its spectrum with that of the sample made in (a) above. It can also be prepared by passing the chlorohydrin in benzene over Grade 'H' alumina.

(c) To chlorohydrin (130 mg.) was added zinc dust (50 mg.) and glacial acetic acid (3 ml.), and the mixture was then shaken for 18 hr. at room temperature. Unreacted zinc was filtered off and the filtrate was diluted with water and extracted thrice with ether. The combined ethereal solution was successively washed with water, sodium bicarbonate solution and water and finally dried over anhydrous sodium sulphate. Removal of the solvent and recrystallisation of the residue from chloroform-light petroleum afforded the crystalline *hydroxy ketone* (85 mg.) m.p. 108-109°, confirmed by mixed m.p. and by comparing the I.R. spectrum of the authentic sample.

Similar treatment omitting the zinc dust gave back starting material.

Ozonolysis of the S-Ketol.

The S-Ketol (100 mg.) in dry methylene dichloride (25 ml.) at 0° was treated with a stream of ozonized oxygen for one hour. The ozonide was decomposed, by warming (5 min.) with water (10 ml.) and then steam distilled.

The distillate, which was neutral to litmus was treated with a solution of dimedon (0.5 g.) in 50% aqueous ethanol (10 ml.). After 20 minutes a crystalline solid (80%), m.p. 180-185° separated out, and was identified as the formaldehyde-dimedon derivative. It shows no depression in m.p. on admixture with an authentic sample of formaldehyde-dimedon derivative (m.p. 187-190°).

Isolation of the non-volatile portion gave an uncrystallisable gum.

Reduction of S-Ketol with Lithium in Ammonia.

The S-Ketol (136 mg.) in dry ether (10 ml.) was added dropwise during 10 min. to a well stirred blue solution obtained by dissolving lithium metal (0.15 g.) in liquid ammonia (250 ml.). Stirring was continued for another hour after the addition was complete. The excess of lithium was destroyed by the addition of solid ammonium

chloride followed by few drops of ethanol. After evaporation of the ammonia the white pasty residue was diluted with water and extracted with ether. The ethereal layer was freed of ammonia by washing it with water, a saturated solution of ammonium chloride and finally with water, and dried over anhydrous sodium sulphate. Removal of the solvent in vacuo and crystallisation from ethyl acetate afforded a crystalline diol, m.p. 175° C, $[\alpha]_D$ + 33.3° (c, 1.26); $\nu_{max.}$ 3650 and 3550 cm.$^{-1}$ (Found: C, 74.27; H, 10.35; M.W.209. $C_{13}H_{22}O_2$ requires C, 74.25; H, 10.54% M.W.210).

The reduction was carried out as above but in the presence of (a) 1 mol. ammonium chloride (b) 10 mol. ammonium chloride but the yield was unaltered (ca 30%).

Reduction of the oxidoketone with Lithium in Ammonia.

Treibs' oxidoketone (1.126 g.) in dry ether (20 ml.) was added dropwise to a well stirred blue solution obtained by dissolving lithium (1 g.) in liquid ammonia (500 ml.). Working up in the usual way furnished a gum which was chromatographed over alumina ('H'-type, 60 g.). Elution with benzene and with benzene-ether (3:1) furnished two crystalline compounds:-

(a) a dihydroxy compound m.p. 192°. This was shown to be identical with the dihydroxy compound obtained on reduction of chlorohydrin with lithium in ammonia by mixed melting point and comparing the I.R. spectra.

(b) oxido alcohol m.p. 140-141° which is identical to the oxido alcohol reported by Barton and Lindsey[18] to be obtained on reduction of the oxidoketone with lithium aluminium hydride. It shows no depression in m.p. on admixture with an authentic sample and has identical infra-red and n.m.r. spectra to the authentic specimen.

The effect of added ammonium chloride on this reduction was investigated. In the above reduction the a/b ratio was $\frac{1}{4}$. In the presence of 2 mol. ammonium chloride this became $\frac{1}{3}$ and $\frac{1}{2}$ when 10 mol. were present.

Reduction of Chlorohydrin with Lithium in Ammonia.

The chlorohydrin (1 g.) in dry tetrahydrofuran (10 ml.) was added dropwise during 20 minutes to a well stirred deep blue solution obtained by dissolving lithium metal (1.0 g.) in liquid ammonia (500 ml.). Stirring was continued for two hours after the addition was completed. Working up in the usual way and recrystallisation of the product from chloroform-light petroleum furnished a highly

crystalline diol, (598 mg.), m.p. 192° $[\alpha]_D$ + 2.28° (c, 1.748); $\nu_{max.}$ 3670, 3500 $cm.^{-1}$ (Found: C, 74.67; H, 10.77. $C_{14}H_{24}O_2$ requires C, 75.0; H, 10.8). It gave a negative Beilstein test.

Tricyclic Hydroxy Ketone, $C_{14}H_{22}O_2$.(79)

The diol from lithium ammonia reduction of the chlorohydrin (400 mg.) in pyridine (1 ml.) was treated with chromium trioxide (600 mg.) suspended in pyridine (5 ml.) and left for 16 hr. at room temperature. The reaction mixture, which turned from yellow to dark green, was poured into an ice-hydrochloric mixture and the solid which separated was filtered off. The dark brown filtrate was extracted thrice with ether and the combined ethereal solution was washed with dilute sodium bicarbonate and then with water and finally dried over anhydrous magnesium sulphate. Removal of the solvent in vacuo and recrystallisation from ether-light petroleum furnished the tricyclic hydroxy ketone (246 mg.) as colourless plates, m.p. 125°C, $[\alpha]_D$ + 49.5° (c, 1.414); $\lambda_{max.}$ 286 mμ (ε = 23); $\nu_{max.}$ (Nujol mull) 3509 and 1681 $cm.^{-1}$, $\nu_{max.}$ 1708 $cm.^{-1}$ (Found: C, 75.71; H, 9.76. $C_{14}H_{22}O_2$ requires C, 75.67; H, 9.9%).

All attempts to degrade this compound further failed. The reagents which gave rise to intractable gums are mentioned in the discussion.

Action of hydrogen chloride on the S-Ketol.

The S-Ketol (66 mg.) in chloroform (20 ml.) was treated with a stream of dry hydrogen chloride at room temperature for 10 minutes. Removal of the solvent *in vacuo* and recrystallisation of the residue from chloroform--light petroleum furnished Barton's chlorohydrin m.p. 147-148° C in quantitative yield. Its' identity was confirmed by mixed melting point and also by comparing the I.R. spectrum with that of the authentic chlorohydrin.

Reduction of Chlorohydrin with Lithium Aluminium Hydride.

The chlorohydrin (2.3 g.) in dry ether (250 ml.) was refluxed with lithium aluminium hydride (1 g.) for one and a half hours and then left overnight. Excess of the reagent was destroyed by the addition of ethyl acetate, followed by saturated aqueous solution of ammonium chloride. The organic layer was separated and the aqueous layer was extracted thrice with ether. The combined ethereal solution was washed with water and dried over anhydrous

magnesium sulphate. Removal of solvent afforded a thick, viscous liquid (1.99 g.) which was carefully chromatographed over alumina (Grade V, 100 g.). Elution with benzene and benzene-ethyl acetate (3:1) furnished two crystalline products.

(a) Diol, m.p. 160-161°, on crystallisation from ethyl acetate. $[\alpha]_D$ + 39.1° (c, 1.15), $\nu_{max.}$ 3570, 3400 and 1640 cm.$^{-1}$ (Found: C, 75.02; H, 11.15. $C_{14}H_{24}O_2$ requires C, 74.98; H, 10.75%). The presence of an exocyclic methylene grouping was shown by its ozonolysis, upon which formaldehyde was produced, and identified as its crystalline dimedon derivative. On treatment with acetic anhydride and pyridine at room temperature the diol afforded an oily monoacetate, $\nu_{max.}$ 3550, 1725 cm.$^{-1}$ which, however, could not be crystallised even after chromatography.

(b) Diol, m.p. 140-141°, on crystallisation from ether-light petroleum, $[\alpha]_D$ + 61° (c, 0.95); $\nu_{max.}$ 3650, 3500 and 1640 cm.$^{-1}$ It shows no absorption in the ultra-violet region (Found: C, 74.40; H, 11.44. $C_{14}H_{24}O_2$ requires C, 74.98; H, 10.75%).

Reduction of the tricyclichydroxyketone (79)

(a) To the tricyclic hydroxyketone (60 mg.) in anhydrous methanol (10 ml.) was added with stirring sodium borohydride (10 mg.). The vigorous reaction subsided in half an hour, but the stirring was continued for another two hours. Alcohol was distilled off *in vacuo* and the solid residue was diluted with water and extracted with ether. The ethereal solution was washed with water and dried over anhydrous sodium sulphate. Removal of the solvent *in vacuo* and recrystallisation of the residue from chloroform-light petroleum afforded the crystalline diol, m.p. 192° (78), confirmed by mixed melting point and comparison of the I.R. spectrum with that of an authentic sample.

(b) The tricyclic hydroxyketone, (79) was also reduced with sodium and alcohol to the diol (78).

(c) Reduction of the hydroxyketone, (79) with lithium-ammonia solution afforded after fractional crystallisation of the reaction product two diols one m.p. 192° (78) and the other m.p. 280°. Perhaps the latter is an epimer of the former.

S-Ketol Acetate, (63; R=Ac).

The S-Ketol (100 mg.) in 'Analar' pyridine (0.8 ml.) was treated with acetic anhydride 'Analar' grade (0.25 ml.) and the homogeneous solution left for 16 hr. at room temperature. Removal of the solvents *in vacuo* and recrystallisation of the solid residue from light petroleum afforded colourless, flat needles of acetate (92 mg.), m.p. 125° $[\alpha]_D$ -17°(c, 1.1); $\nu_{max.}$ 1690, 1720 cm.$^{-1}$ (Found: C, 72.88; H, 9.22. $C_{16}H_{24}O_3$ requires C, 72.75; H, 9.1%).

The acetate is hydrolysed back to starting material with methanolic potassium hydroxide.

Ozonolysis of the S-Ketol Acetate.

The S-Ketol acetate (160 mg.) in dry methylene dichloride (25 ml.) at 0° was subjected to ozonolysis for one hour. The ozonide was decomposed by warming with water (10 ml.) for ten minutes and the solvent removed *in vacuo*. The residue was taken up in ether, dried ($MgSO_4$) and the solvent distilled off. The residue on crystallisation from ether-light petroleum afforded a crystalline acetoxy-dione, (80%), m.p. 78-79°; $\nu_{max.}$ 1690, 1720 and 1740 cm.$^{-1}$ (Found: C, 67.81; H, 8.53.

$C_{15}H_{22}O_4$ requires C, 67.65; H, 8.33%).

Chlorohydrin acetate, (76; R=Ac)

The chlorohydrin (200 mg.) in 'Analar' pyridine (1.5 ml.) was treated with 'Analar' acetic anhydride (0.5 ml.) and the homogeneous mixture was left for 16 hr. at room temperature. Removal of solvents in vacuo afforded a reddish brown solid which was dissolved in chloroform, charcoaled and the solvent distilled off. The residue thus obtained on crystallisation from chloroform-light petroleum furnished the highly crystalline chlorohydrin acetate, (150 mg.), m.p. 150-51° $[\alpha]_D$ -6.39° (c, 1.72) $\nu_{max.}$ (nujol) 3550, 1710 cm.$^{-1}$ (Found: C, 64.01; H, 8.47; Cl, 12.09. $C_{16}H_{25}O_3Cl$ requires C, 63.90; H, 8.32; Cl, 11.81%).

Vigorous oxidation of caryophyllene.

Following the method of Semmler and Mayer,[3] caryophyllene in acetone was oxidised with potassium permanganate. The resulting oxidation product was further oxidised with nitric acid (d = 1.65). After the usual working up the crude oil obtained (a mixture of caryophyllenic, nor-caryophyllenic and as-dimethylsuccinic acids) was

resolved by paper and silica gel thin-plate chromatography, using ethanol:water:ammonia (d = 0.88) ::80:15:5 system as the moving phase. Three different spots were obtained, which were identified as caryophyllenic, norcaryophyllenic and as-dimethyl succinic acid by comparing the R_f values with those of the authentic samples of the components. Samples of the last two named acids were very kindly provided by Professor Owen. The crude oxidation mixture of caryophyllene was also resolved into its components by vapour phase chromatography after methylation with diazomethane.

The chlorohydrin, when, likewise subjected to vigorous oxidation after the method of Semmler and Mayer (loc. cit.) afforded a mixture of carboxylic acids. The latter, after methylation, were resolved into three components by vapour phase chromatography. They were identified to be the three acids present in the oxidation mixture of caryophyllene as the chromatograms obtained in this case were superimposable on the trace obtained from the methylated oxidation products of caryophyllene. The crude acid mixture obtained from the chlorohydrin, however, could not be detected on paper or silica gel chromatography.

The S-ketol, when similarly oxidised and methylated did not show any of the acids obtained previously on vapour phase chromatography.

The vapour phase chromatograms were run on Pye Argon machine using a Celite-Polyester column at 100°.

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