

T H E S I S

Submitted to the University of Glasgow
for the Degree of Doctor of Philosophy.

*

"Some Investigations on the Sesquiterpenes
Caryophyllene and Cedrene".

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—oOo—

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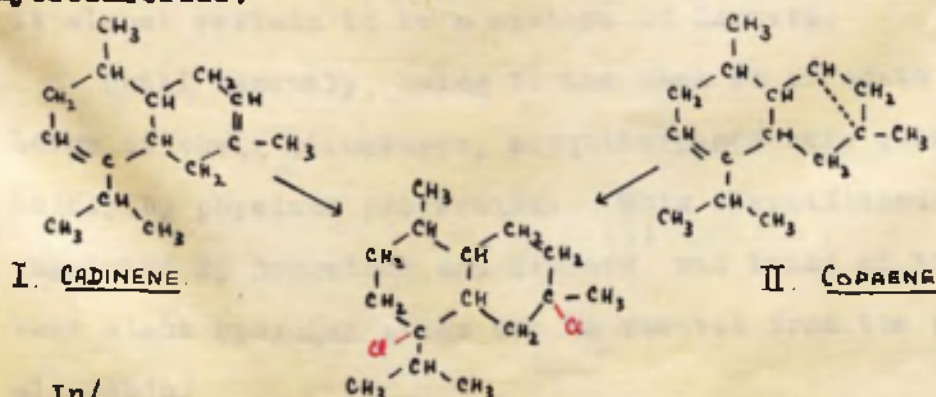
I. Introduction: The Sesquiterpenes.

The essential oils have been found to contain, in addition to the ordinary terpenes $C_{10}H_{16}$, hydrocarbons having the same percentage composition but of molecular weight 204. They have thus the formula $C_{15}H_{24}$ and have been termed Sesquiterpenes. As in the case of the terpenes, hydrocarbons are not the only bodies containing fifteen carbon atoms which are found in essential oils; sesquiterpene alcohols $C_{15}H_{24}O$ and $C_{15}H_{26}O$ have been found as well as other oxy-compounds.

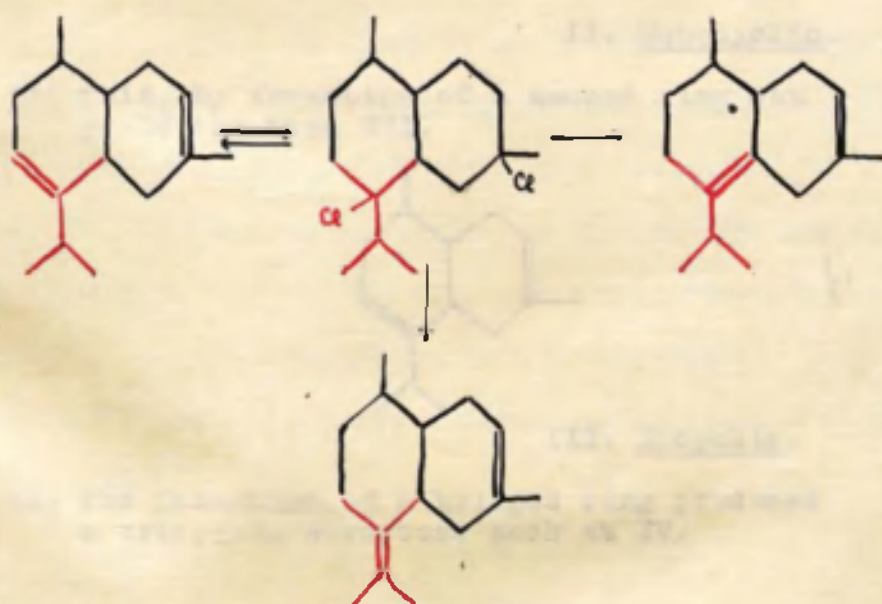
The sesquiterpene content of the essential oil is in the first place, separated by distillation, the boiling point being some $100^{\circ}C$. higher than that of the terpene fraction.

The crude sesquiterpene may contain several distinct sesquiterpenes whose boiling points lie so close together that it may be impossible to separate them by distillation. For this reason the earlier investigators attempted to isolate and characterise them by the formation of crystalline derivatives such as hydrochlorides, nitrosites and nitrosochlorides.

Later work has shown that this method is not always dependable as two hydrocarbons may yield the same derivative. For example, it has been found that Cadiene (I) and Copaene (II) on treatment with hydrochloric acid, gives the same dihydrochloride:



In such cases as crystalline derivatives were obtained, the next step was, obviously, to regenerate the hydrocarbon, but here again difficulties abounded, for it was found that in certain cases a different sesquiterpene was obtained on regeneration. In a compound containing 15 carbon atoms the opportunities for intramolecular changes are very great, the addition and subsequent removal of, say, the elements of hydrochloric acid, introducing possibility of wandering of double bonds, of fission of rings, or of formation of new rings. The following scheme illustrates this in the case of Cadinene, considering only one of the double bonds. For the sake of clearness, the carbon skeletons are given in preference to the full formulae.



Thus the oil regenerated from an additive compound is almost certain to be a mixture of isomers.

Until recently, owing to the lack of accurate knowledge of their structures, sesquiterpenes were classified mainly by physical properties. This classification, suggested by Schreiner and Kremers ⁽¹⁾ was based on the fact that eight hydrogen atoms can be removed from the saturated aliphatic/

aliphatic hydrocarbon $C_{15}H_{32}$ in the following ways:

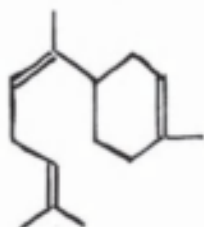
- (a) The removal of 8 hydrogen atoms by the production of 4 double bonds gives a structure such as I.



Saturated $C_{15}H_{32}$

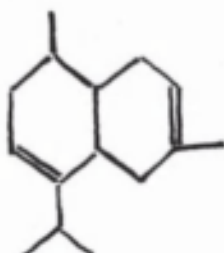
I. Aliphatic.

- (b) The closing of one ring in I causes the disappearance of one double bond giving a structure of type II.



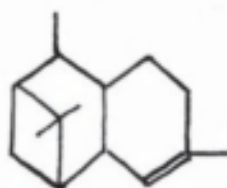
II. Monocyclic.

- (c) This, by formation of a second ring can yield the type III.



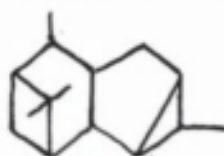
III. Dicyclic.

- (d) The formation of a bridged ring produces a tricyclic structure such as IV.



IV. Tricyclic.

- (e) A fifth type V is theoretically possible: a saturated tetracyclic hydrocarbon containing two bridged rings



V. Tetracyclic.

The formulae shown above do not indicate definite structures: they are intended to illustrate the relationship between the number of rings and the degree of unsaturation.

The following table shows the physical constants of typical hydrocarbons belonging to these classes.

Structure	No. of Double Bonds.	Density	Molecular Weight Found	Refractivity Calc.
1. Aliphatic	4	.864	71.43	69.57
2. Monocyclic	3	.873 - .891	67.35 - 67.87	67.86
3. Dicyclic	2	.898 - .918	65.82 - 66.93	66.15
4. Tricyclic	1	.93 - .939	64.02 - 64.77	64.45
5. Tetracyclic	0	No Members known		

Formerly this physical classification was supported by absorptive capacity for bromine or hydrochloric acid, but, as has been mentioned, this treatment is likely to cause molecular rearrangements. The method now in use is to estimate the amount of hydrogen which is added on in presence of a platinum or palladium catalyst. This converts the sesquiterpene into the corresponding saturated hydrocarbon, thus:

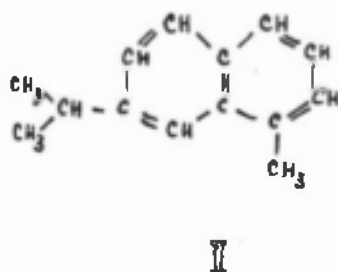
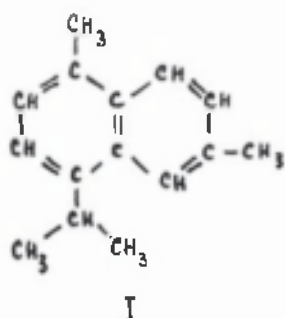
<u>Class</u>	<u>Double Bonds.</u>	<u>Product of Hydrogenation.</u>
1	4	$C_{15}H_{32}$
2.	3	$C_{15}H_{30}$
3	2	$C_{15}H_{28}$
4	1	$C_{15}H_{26}$

Beyond this there was no constitutional knowledge, and up to 1921 the chemistry of the sesquiterpenes was comparable with that of the sugars before the work of Fischer. This was due to the fact that the methods, in particular oxidation, so/

so successful, in the terpene series, were apparently of little value when applied to the sesquiterpenes.

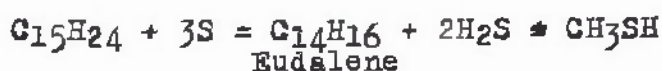
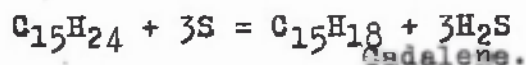
(2)

As early as 1887, Wallach suggested that sesquiterpenes might be partially hydrogenated naphthalene derivatives; Semmler also held this view though without experimental evidence of any kind. This evidence has now been supplied by Ruzicka who by dehydrogenation with sulphur at 180-250°C succeeded in obtaining naphthalene derivatives from a number of sesquiterpenes. So far the derivatives so obtained have been either Cadalene (I) or Eudalene (II).



These constitutions have been proved by degradation and by synthesis.

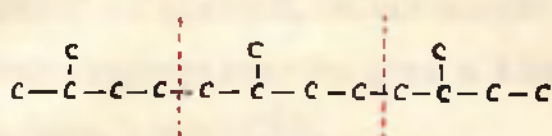
According to Ruzicka, these derivatives are produced from sesquiterpenes thus:



In a few cases the products of dehydrogenation have been indefinite, due to complete disruption of the molecule. The present thesis deals with two such sesquiterpenes, cedrene and caryophyllene, neither of which yields any definite dehydrogenation product, and consequently we have little certain knowledge of their structures.

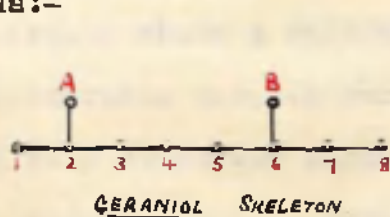
The formula of the aliphatic sesquiterpene, farnesene, the only sesquiterpene whose structure has been elucidated by the methods used for the terpenes, has been shown by Ruzicka/

Ruzicka to be divisible into three isoprene nuclei

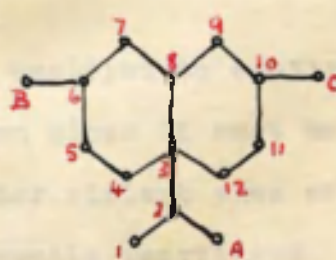
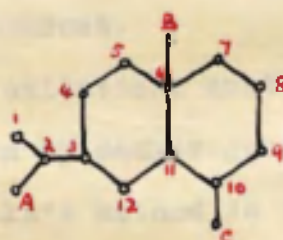
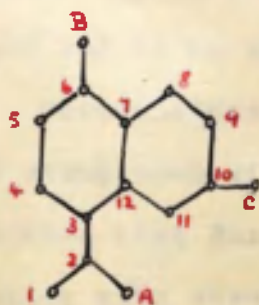


As all the ordinary terpenes are divisible into two isoprene nuclei (C_5H_8), Ruzicka made the bold suggestion that sesquiterpene structures could be considered as built up from three such groups, and to this no exception has been found.

This statement is generally interpreted in its stricter sense, and sesquiterpene skeletons are considered to be derived from the farnesene structure by cyclisation, just as the terpenes are derived by cyclisation of geraniol, thus:-



The farnesene skeleton by cyclisation can yield the following types of naphthalene nucleus:



Sesquiterpenes having skeleton A yield cadalene on dehydrogenation, while type B yields eudalene - a methyl group (common to both rings) being lost in the process.

No/

No member of class C, which should lose three carbon atoms on dehydrogenation, to give a dimethyl naphthalene has as yet been identified.

The general structure of sesquiterpenes having been thus established, it is now necessary to turn to oxidation methods to fix the positions of the double bonds. The success of oxidation in the terpene series lay in the fact that when 3 or 4 carbon atoms had been removed, the residue (containing 7 or 6 carbon atoms) was either synthesised or identified with some substance of known structure. Similar degradation of a sesquiterpene, however, leaves us with a C_{12} or C_{11} compound, which is not so easily identified. Generally where a well-defined oxidation product is obtained considerable work is necessary to establish its constitution and very often the amount of the product at the disposal of the worker does not permit this. As an instance it may be mentioned that in the present work attempts were made to oxidise bisabolene with hydrogen peroxide. A well-defined crystalline acid $C_{12}H_{15}O_2$ was obtained but as it was different from any known acid of this empirical formula, and as the supply of the original sesquiterpene was limited, elucidation of the structure of this acid by systematic means had to be abandoned.

Nevertheless, oxidations must be employed to confirm the structures given by dehydrogenation since it must be admitted that Ruzicka's method is rather violent when we are dealing with structures which are so easily rearranged.

No less important is the work which is necessary to establish the relationships of various derivatives to the parent sesquiterpenes. The examination of the structural changes involved in the conversion of one sesquiterpene into another is of equal importance.

II. The Relationships of Some Derivatives of Caryophyllene and Clovene.

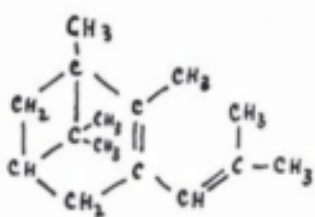
(a) Historical and Theoretical.

Caryophyllene was the name given by Wallach in 1892 to the sesquiterpene content of Oil of Cloves. The same hydrocarbon has since been found in many other oils such as Copaiba Balsam Oil and Ceylon Cinnamon Oil. From consideration of its physical properties, it appeared that caryophyllene possessed a dicyclic structure.

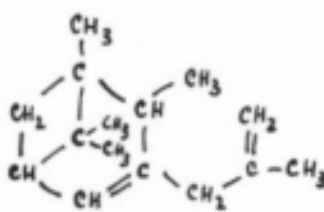
(4)
The work of Deussen since 1907 has shown that caryophyllene probably consists of three hydrocarbons, α -, β - and γ -caryophyllene. The first of these yields derivatives (5) which are optically inactive. Deussen, however, claimed that he was able to separate these three caryophyllenes by distillation, but, while natural caryophyllene is almost certainly a mixture, reference to the tables in the experimental section (p.28) will show that this claim is based on very slender evidence, the boiling points of the fractions not being given at the same pressure.

Although many investigators have interested themselves in caryophyllene, its structure remains doubtful, as it is one of the few sesquiterpenes which do not give a naphthalene derivative on dehydrogenation.

(6)
In 1926, Busse proposed formulae I and II for β - and γ -caryophyllene respectively:



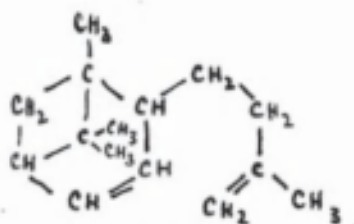
I



II

(7)

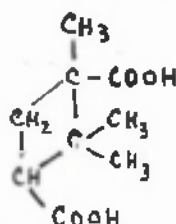
Recently Deussen on reconsideration of the ozonisation products of caryophyllene suggested the following, III, for the γ -form:



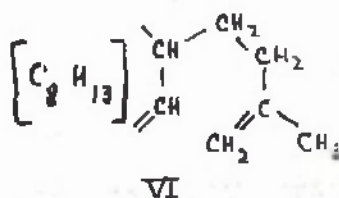
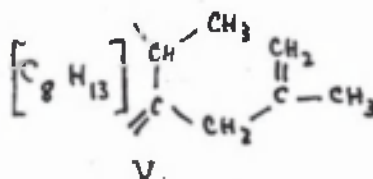
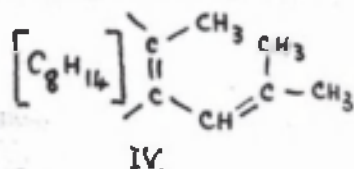
III

While these formulae are divisible into three isoprene nuclei, they cannot be formed from the farnesene skeleton, which is a serious objection to their adoption.

The evidence for the presence of the four-membered ring hangs on the production of an acid $C_9H_{14}O_4$, believed to have the constitution:



As this acid has never been synthesised or obtained crystalline, one does not feel justified at present in using any more definite expressions than IV, V and VI for the caryophyllene structures.



VI

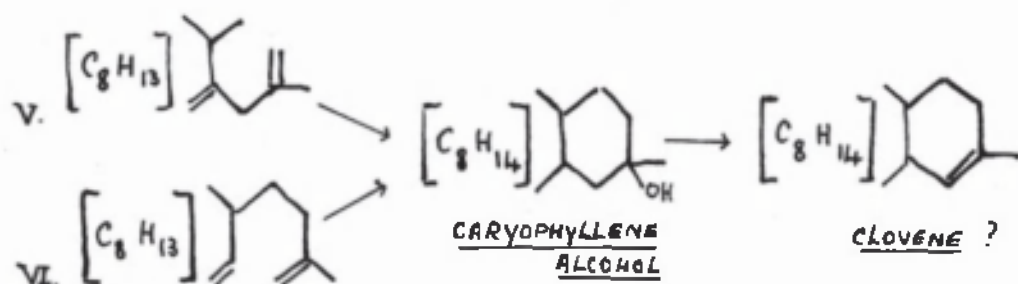
(9)

Wallach and Walker showed that caryophyllene forms a crystalline hydrate $C_{15}H_{25}OH$ on hydration with a mixture of sulphuric and acetic acids. Moreover, they found that this hydrate, known as caryophyllene alcohol, when dehydrated by heating with phosphoric anhydride, did not yield caryophyllene but an isomeric hydrocarbon, clovene, which was apparently of tricyclic structure.

Caryophyllene alcohol has been shown by Henderson, Robertson/

(10)

Robertson and Kerr to be a remarkably stable compound. It is not affected by prolonged treatment with hydrogen peroxide or potassium permanganate. An investigation by the same workers, of the refractivities of the formic and acetic esters indicated that the alcohol possessed a tricyclic structure. This was confirmed by the fact that the alcohol was formed from caryophyllene by the action of formic acid which is a recognised means of inducing ring-closure. It is therefore not surprising that caryophyllene alcohol on dehydration yields a tricyclic sesquiterpene. Formulae V and VI (p. 9) could readily allow such ring closure to take place.



Recently it has been found by Henderson, McCrone and Robertson (11) that when caryophyllene alcohol is carefully dehydrated at a low temperature with phosphoric anhydride the product consists of two fractions, clovene and isoclovene. The latter has been characterized by the production of a crystalline monohydrochloride $C_{15}H_{25}Cl$.

In investigations of the hydration of caryophyllene, Asahina and Tsukamoto (12) developed an improved method for the preparation of caryophyllene alcohol. In addition, they showed that by treating caryophyllene with a mixture of sulphuric acid monohydrate and ether, it was possible to obtain two crystalline hydrates. The first of these was identical with Wallach's caryophyllene alcohol melting at 96° while the second was an isomeric alcohol melting at/

at 117° . The name β -caryophyllene alcohol was given to the former, while the latter was termed α -caryophyllene alcohol.

In Asahina and Tsukamoto's hydration a liquid by-product is obtained. This oil, produced in about 25-30% yield, is tricyclic in structure, and was thought to be identical with clovene.

As the conditions of the Wallach hydration of caryophyllene do not permit the separation of the two isomeric alcohols, a careful examination of the products of this hydration was carried out in the course of the present work, but no α -caryophyllene alcohol was found even after the necessary modifications had been introduced.

Dehydration of the α -alcohol seemed to offer possibilities, the view being held that on dehydration it might yield the characterisable hydrocarbon iso-clovene. For the dehydration a considerable quantity of the α -alcohol was required and this work was hindered by the exceptionally poor yields obtained from the hydrations. In no case was the yield of α -caryophyllene alcohol greater than 4%.

Consideration of Deussen's views on the heterogeneous nature of caryophyllene suggested fractionation as a means of improving the yield, but this met with no success.

Difficulty was also experienced in the preparation of a pure specimen of the α -alcohol. It was found that the best treatment was to re-steam-distil the crude product and to crystallise it from aqueous alcohol, finally subjecting it to repeated crystallisations from petroleum ether or acetone.

On dehydration of the α -alcohol with phosphorus pentoxide, a sesquiterpene $C_{15}H_{24}$ was obtained. It was unsaturated towards bromine in chloroform and appeared to absorb/

absorb hydrochloric acid, but no solid hydrochloride could be isolated, the product being a dark brown oil, smelling strongly of hydrochloric acid. This hydrocarbon, since it yielded no solid hydrochloride, was therefore not iso-clovene.

Another sample of α -caryophyllene alcohol was dehydrated by means of anhydrous oxalic acid according to the method described by Henderson and Smeaton.⁽¹³⁾ The product was similar to that obtained by dehydration with phosphorus pentoxide and behaved in like manner when treated with hydrochloric acid.

From their physical constants it seemed probable that these two products were identical with the clovene prepared from β -caryophyllene alcohol.

	<u>Boiling Point</u>	d_4^{17}	n_D^{17}	<u>Molecular Refractivity.</u>
1. By P_2O_5	118-123/12 m.m.	.9252	1.5000	64.8
2. By $(COOH)_2$	116-122/12 m.m.	.9308	1.4950	64.1
3. Clovene from β -Alcohol	111-114/10 m.m.	.9240	1.4980	64.7

The values for the molecular refractivity show these hydrocarbons to be of tricyclic structure.

Wallach found that β -caryophyllene alcohol when treated with phosphorus pentachloride yielded a chloro-derivative $C_{15}H_{25}Cl$ which melted at 63° , and was extraordinarily stable, attempts to remove hydrogen chloride only resulting in regeneration of the parent alcohol. This chloride is isomeric with the monohydrochloride of iso-clovene melting at $87^\circ C$.

In the course of the present work it was thought that the corresponding chloro-derivative of α -caryophyllene alcohol might be identical with iso-clovene hydrochloride, but treatment of the α -alcohol with phosphorus pentachloride yielded/

yielded no crystalline derivative, the products in all cases being easily decomposing oils or oils containing no chlorine. It is, therefore, extremely likely that α -caryophyllene alcohol yields an unstable chloro-derivative, probably a liquid.

It has been mentioned that fractionation of caryophyllene was carried out in attempts to improve the yield of α -caryophyllene alcohol. Deussen, to substantiate the claim that he had separated caryophyllene into two hydrocarbons, stated that he obtained different yields of derivatives, such as the nitrosite, from his fractions.

In the present work, by careful fractionation of crude caryophyllene under reduced pressure a number of fractions was obtained. Of these, the two lowest were rejected, as it was quite possible that they did not consist of caryophyllene, their boiling points being much lower than that of the main fraction. While the other fractions showed slight differences in physical constants, there was no appreciable difference in the yields of the α - and β -alcohols obtained on hydration of these fractions. The yields of the crystalline caryophyllene dihydrochloride reached a maximum in the fraction which constituted the main bulk of the hydrocarbon. This, therefore, does not confirm the theory of the presence of two distinct hydrocarbons, separable by distillation.

(14)

Chapman in a paper on the question of the identity of one of Deussen's fractions with Humulene (a constituent of Oil of Hops) stated that he was unable to repeat Deussen's work on the separation of the two caryophyllenes. Chapman distilled caryophyllene at very low pressures and obtained two main fractions differing slightly in physical properties. He was able to prepare the same derivatives from both fractions.

16.

The fact that the yield of the crystalline dihydrochloride from caryophyllene was never greater than 35% led us to examine the mother liquors from this preparation. Analysis of these mother liquors from the preparation of the dihydrochloride from several fractions of caryophyllene showed the chlorine content to be of the order of 20%. If this chlorine is entirely due to the presence of dihydrochloride dissolved in unattacked hydrocarbon, then the dihydrochloride must be present to the extent of 80% ($C_{15}H_{26}Cl_2$ contains 26% chlorine). This seems untenable as the liquor is allowed to stand for 24-40 hours at $0^{\circ}C$ to allow the dihydrochloride to crystallise out.

The mother liquors were carefully purified from mechanically held hydrochloric acid and freed as completely as possible from dissolved dihydrochloride, but subsequent analysis showed that in no case was the chlorine content lower than 18%. This leads to the conclusion that, by the action of the hydrochloric acid, some of the dicyclic caryophyllene was converted into a tricyclic hydrocarbon, capable of giving a liquid mono-hydrochloride $C_{15}H_{25}Cl$. In support of this, it is well known that acid reagents cause ring closure in the sesquiterpenes.

Such a liquid monohydrochloride $C_{15}H_{25}Cl$ should contain 14.6% chlorine, and the excess (to make up to 18%, the value found) is probably due to a quantity of caryophyllene dihydrochloride remaining dissolved in the oil.

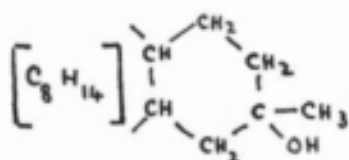
It was found impossible to obtain a separation by distillation.

Now, by slow and careful treatment with sodium methoxide, Semmler⁽¹⁵⁾ was able to regenerate from caryophyllene dihydrochloride an oil consisting largely of dicyclic hydrocarbon, other methods of removing hydrogen chloride yielding a tricyclic sesquiterpene. When treated in this way/

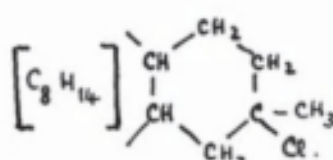
way there should be no possibility of obtaining a bicyclic sesquiterpene from the liquid (tricyclic) monohydrochloride. This experiment was therefore carried out, and for comparison a control experiment was performed, simultaneously, under the same conditions, using the crystalline caryophyllene dihydrochloride. The molecular refractivities of the products showed that while the oil from the solid dihydrochloride consisted largely of a bicyclic sesquiterpene, that from the liquid monohydrochloride appeared to be almost entirely tricyclic, and, as far as could be judged from physical properties, identical with clovene.

There are thus three isomers of the formula $C_{15}H_{25}Cl$. These are (1) the chloro-derivative of β -caryophyllene alcohol melting at $63^{\circ}C$., (2) iso-clovene hydrochloride melting at $87^{\circ}C$., and (3) the liquid monohydrochloride of clovene.

The structure VII is generally adopted for β -caryophyllene alcohol, and its chloro-derivative is shown as VIII.

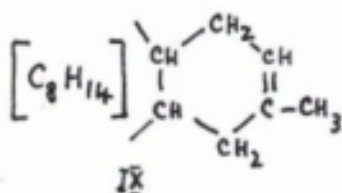


VII.

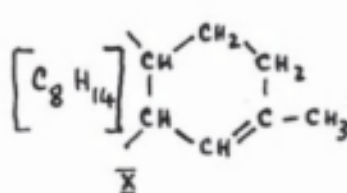


VIII.

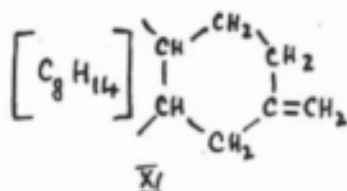
From formula VII by elimination of the elements of water in the simplest ways we obtain three possible formulae for clovene or iso-clovene:



IX.



X.



XI.

It would be expected from these structures that the hydrochlorides/

hydrochlorides from clovene and iso-clovene would be identical with the chloro-derivative (VIII) of β -caryophyllene alcohol, but this is not the case.

It is, therefore, very probable that the dehydration of β -caryophyllene alcohol does not take place in the simple way indicated above, and that some intramolecular rearrangement occurs in the transformation to clovene.

No chemical evidence of the tricyclic nature of clovene is chronicled in the literature, such a structure being assigned on the value for the molecular refractivity alone.

By hydrogenation of clovene, prepared by dehydration of β -caryophyllene alcohol with phosphorus pentoxide, we found that the absorption of hydrogen in presence of palladium black was almost the theoretical quantity calculated for a tricyclic sesquiterpene (containing one ethylenic linkage). The hydrogenated product, extracted in the usual manner gave on analysis results indicating the composition $C_{15}H_{26}$. This is therefore dihydro-clovene and its production confirms the tricyclic nature of clovene.

Since it was indicated that α -caryophyllene alcohol yielded an unstable liquid chloro-derivative (p. 13) the question of the identity of this derivative with the liquid clovene monohydrochloride was considered.

By treatment of the liquid clovene hydrochloride (from the caryophyllene dihydrochloride mother liquors) with silver acetate an oil was obtained. After hydrolysis and steam-distillation, the steam volatile portion on distillation in vacuo yielded two main fractions; (a) 118-124/11 m.m., and (b) 139-147/11 m.m. The first of these proved on examination to consist mainly of regenerated tricyclic clovene. This furnishes additional evidence of ring-closure having taken place by the action of the hydrochloric acid on some of the original (dicyclic) caryophyllene.

The/

The second fraction (b) consisted of an alcohol $C_{15}H_{26}O$. This alcohol was saturated and measurement of its molecular refractivity indicated its tricyclic nature. It could not be induced to crystallise and hence must be regarded as a new isomer of α - and β -caryophyllene alcohols.

Confirmation of the relationship of this alcohol to clovene was obtained by saturating clovene, from β -caryophyllene alcohol, with hydrogen chloride. This yielded a liquid containing 12.4% chlorine and similar to the purified clovene monohydrochloride obtained from the mother liquors as previously described. This oil was treated with silver acetate as before, and a quantity of a similar alcoholic fraction was separated. This alcohol appeared almost identical with that produced in the preceding experiments, although no evidence other than physical constants was obtainable.

The relationships discussed are shown in the accompanying diagram (p.20).

In this paper, it has been proved almost conclusively (though unfortunately by negative results alone) that the dehydration of β -caryophyllene alcohol is not a simple loss of the elements of water, since the tricyclic clovene produced cannot be re-transformed into the parent solid alcohol by any series of reactions such as treatment with hydrogen chloride and subsequently with silver acetate. The nature of the intramolecular change which must take place is at present unknown.

The question whether the α - and β -caryophyllene alcohols differ in structure or are stereo-isomers is of importance. The α -alcohol on dehydration yields a sesquiterpene, which, from physical properties, appears identical with the clovene from the β -alcohol. The action of phosphorus pentachloride on/

on the α -alcohol, however, indicates that the hydroxyl group is in a different environment than in the β -caryophyllene alcohol which on similar treatment yields a very stable chloro-derivative. This has now been confirmed by oxidation of the two alcohols.

(10)
As has been mentioned, Henderson, Robertson and Kerr found that β -caryophyllene alcohol was unattacked by potassium permanganate or by prolonged treatment with hydrogen peroxide.

The use of Beckmann's Chromic Acid Mixture by Henry (16) and Paget for the oxidation of the simpler aliphatic and monocyclic terpenes, and later, the successful application (17) of the same reagent by Gibson and Simonsen to the bicyclic terpenes, suggested it as a suitable oxidising agent for the caryophyllene alcohols.

The oxidation of β -caryophyllene alcohol with Beckmann's Chromic Acid Mixture yielded a liquid acid product, about 50% of the alcohol being recovered unchanged. This acid, which could not be obtained crystalline, was purified by distillation of the methyl ester. Analysis of the methyl ester and of the silver salt of the acid indicated the formula $C_{11}H_{13}O_3$.

A similar oxidation of α -caryophyllene alcohol yielded as main product a crystalline acid which was found to be identical with a dicarboxylic acid $C_{15}H_{24}O_4$ obtained in Professor Ruzicka's laboratory by the chromic acid oxidation of the liquid by-product produced in the hydration of caryophyllene (p.11).

The first step in these oxidations almost certainly consists of dehydration of the alcohol, hence it may be assumed that the clovene obtained by dehydration of α -caryophyllene alcohol is identical with the clovene obtained/

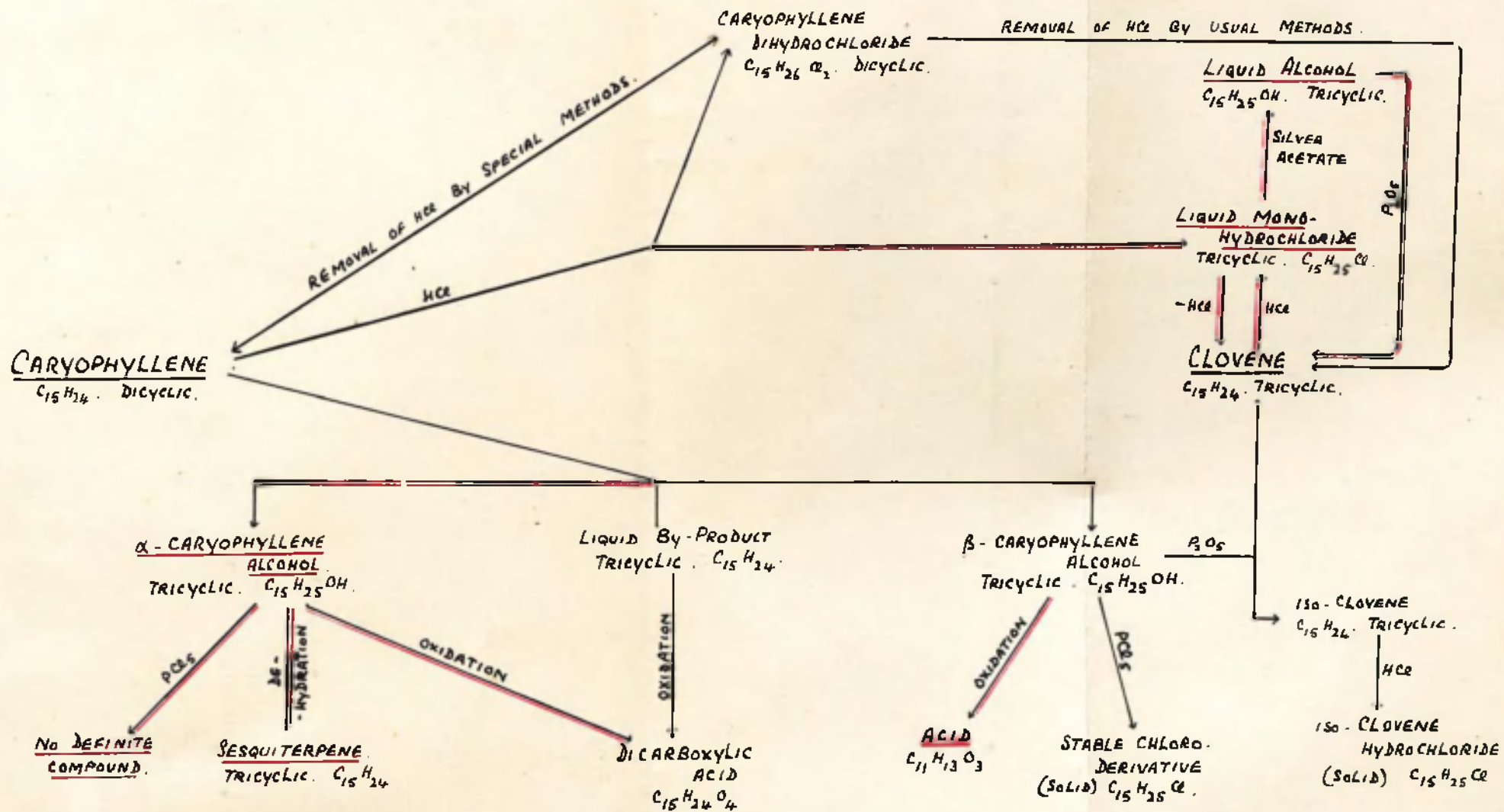
obtained as by-product in the hydration of caryophyllene.

It is indeed, possible that the production of this tricyclic liquid by-product may be due to the dehydration of the α -caryophyllene alcohol as soon as it is formed, the dehydration being effected by the sulphuric acid used in the preparation.

The results of these oxidations show the two caryophyllene alcohols to be structural isomers. The examination of the clovene dicarboxylic acid $C_{15}H_{24}O_4$, which it is understood is in progress, should lead to conclusions which may help to fix the position of the hydroxyl group in α -caryophyllene alcohol. The further oxidation of the liquid acid from β -caryophyllene alcohol may also yield results of importance in solving the problem of the structures of compounds of the clovene group.

DIAGRAM SHOWING RELATIONSHIPS DISCUSSED.

REACTIONS INVESTIGATED ARE UNDERLINED IN RED.



(b) Experimental.

The Caryophyllene used in these experiments was supplied by Messrs Bush and Co. The crude sesquiterpene was of a yellowish colour and boiled over a considerable range of temperature. It was, therefore, generally found necessary to fractionate the oil before use. For ordinary purposes a fraction boiling at 118-126°/10 m.m. was quite satisfactory.

In the careful fractionation of caryophyllene which was carried out in attempting to increase the yield of α -caryophyllene alcohol, a large quantity (about 2½ litres) of the crude sesquiterpene was repeatedly distilled under reduced pressure. Six fractions were ultimately obtained, but of these the two lowest probably do not consist of caryophyllene.

Deussen, as mentioned in the theoretical section, claimed to have separated caryophyllene into its component hydrocarbons by distillation alone. His values were:

B.P.	d.	n_D	Molecular Refractivity	$[\alpha]_D$
132 - 134/16 m.m.	.9035 ₂₀	1.4997	66.45	-4.67
128 - 128.5/17m.m.	.9103 ₁₇	1.4989	65.86	-23.57
123 - 124/14.5mm.	.8990 ₂₀	1.4962	66.31	-

Chapman being unable to repeat this work gave the following constants for the two main fractions of caryophyllene.

B.P./3 m.m.	d_{15}^{20}	n_D^{25}	$[\alpha]_D$
95-97	.9028	1.4987	-8.2
98-102	.9035	1.4990	-9.3

The physical properties of the fractions obtained by

us are given in the next table, together with the yields of the crystalline caryophyllene dihydrochloride.

Fraction	B.P./10 m.m.	n_D^{20}	d_4^{20}	Molec. Refract.	Yield Dihydrochloride. %
A	up to 100	1.4690			-
B	100 - 115	1.4923			3.4
C	116 - 119	1.5000	.9105	65.86	26.
D	120 - 122	1.5000	.9064	66.24	35.1
E	123 - 127	1.5010	.9062	66.31	26.5
F	128 - 134	1.5018	.9058	66.46	19.7

The yield of the dihydrochloride reached a maximum in the fraction constituting the main bulk of the hydrocarbon. Little or no difference was obtained in the yields of the hydration products from different fractions.

Preparation of Caryophyllene Dihydrochloride.

The oil was dissolved in twice its volume of anhydrous ether (dried over sodium) and cooled to 0°C. Dry hydrochloric acid gas was passed in slowly until absorption was complete. During absorption the colour of the solution changed to red, and finally to a deep purple, probably due to the presence of azulene in the commercial oil.

After absorption, the flask containing the solution was tightly stoppered and allowed to remain at 0°C for a further 24 hours. The ether was then removed at room temperature by drawing a current of dried air over the surface of the solution. The residue was once more cooled in a freezing mixture when it set to a semi-solid mass of crystals. These were drained, pressed and recrystallised from ethyl acetate. M.P. 69°.

Hydration of Caryophyllene.

(a) Preparation of β -Caryophyllene Alcohol.

The/

The hydrations were carried out according to the method of Asahina and Tsukamoto.⁽¹²⁾

Caryophyllene (100 cc) was added drop by drop to a mixture of absolute ether (80 cc) and concentrated sulphuric acid (30 cc), the temperature of the mixture being kept below 10°C during the addition of the oil. Shaking at intervals promoted the reaction. The viscous red liquid so produced was allowed to stand at room temperature for 1½-2 hours and then poured quickly on to ice mixed with sufficient sodium carbonate to neutralise the acid. This alkaline mixture was steam-distilled. A quantity of oil distilled first but latterly the oil solidified on cooling and was filtered from the aqueous distillate. Distillation was continued until no more oil volatilised. The crude solid product (β -caryophyllene alcohol) was freed from oil by pressing and recrystallised from petroleum ether. Better crystals were obtained from acetone. Yield 30 g. M.Pt. 94-95°C.

The oil which distilled over first consisted of the by-product tricyclic hydrocarbon together with some unattacked caryophyllene.

(b) α -Caryophyllene Alcohol.

The alkaline aqueous liquor left in the flask after removal of the β -alcohol was made acid with dilute sulphuric acid and steam-distilled once more. Some oily distillate was also obtained at this stage, but later the α -alcohol solidified on cooling. Yield crude product, 4 g.

For purification it was necessary to re-steam-distil the crude product in order to free it from oil which hindered crystallisation. It was then dissolved in ethyl alcohol and reprecipitated by the addition of water, the solution being cooled in ice. Further purification was then/

then possible by repeated crystallisation from petroleum ether, the melting point rising to 117°C .

Modification of Wallach's Hydration.

The method used by Wallach for the preparation of β -caryophyllene alcohol does not permit the separation of α -caryophyllene alcohol if any is formed, since the β -alcohol is obtained by steam-distillation of the acid reaction mixture. The following modification was used: caryophyllene (150 g.) was added to acetic acid (1 litre) containing sulphuric acid (12 cc) and water (40 cc) and the whole maintained at 80 – 100°C for about 30 hours. The mixture was made alkaline with sodium carbonate and steam-distilled, the β -caryophyllene alcohol being obtained in the distillate. The residue was acidified with sulphuric acid and steam-distilled again, but no α -caryophyllene alcohol was obtained.

Dehydration of α -Caryophyllene Alcohol.

(a) By Phosphorus Pentoxide.

α -Caryophyllene alcohol (10 g.) was added in the molten state to an equal weight of phosphorus pentoxide. Reaction took place at once and precautions were taken to keep the temperature as low as possible without stopping the reaction. (This precaution is necessary in the dehydration of β -caryophyllene alcohol since if the dehydration takes place at too high a temperature, no isoclovene is obtained). When the reaction seemed complete, sodium carbonate was added to neutralise, and the oil steam-distilled. A yellowish mobile oil was obtained, and was extracted from the aqueous distillate by ether. After drying over anhydrous sodium sulphate, the solvent was removed by distillation and the resulting oil distilled in *vacuo*. The product consisted of a colourless mobile oil having the following constants:

B.P. 118 – $123^{\circ}/12$ m.m., d_4 .9252, n_D 1.5000.

Molecular/

Molecular Refractivity 64.8 (calculated for a
tricyclic sesquiterpene 64.4)

.1119 gave .3584 g. CO₂ and .1171 g. H₂O

Calculated for

	C ₁₅ H ₂₄	Found
C	88.23	87.8
H	11.70	11.63

The oil (2 g.) was dissolved in twice its volume of anhydrous ether, cooled to 0° and dry hydrogen chloride passed in slowly. When absorption was complete, the mixture was allowed to stand 24 hours at the end of which time the ether was removed by drawing a current of dried air over the surface of the liquid. After the ether had been removed, the product consisted of a dark reddish brown oil which could not be induced to crystallise. It contained approximately 9% chlorine. After standing some days the oil turned to a green colour, hydrochloric acid being evolved, showing that decomposition had taken place.

(b) By-Oxalic Acid.

α -Caryophyllene alcohol (10 g.) was mixed with anhydrous oxalic acid (10 g.) and kept for 4 days at 150-160°C. At the end of that time the product was distilled in steam. A yellowish oil similar to that obtained by the previous method of dehydration resulted and after distillation in vacuo showed the following constants:

B.P. 116-122/12 m.m., d_4 .9308 n_D 1.4950.

Molecular Refractivity 64.1

.1139 g. gave .3656 g. CO₂ and .1183 g. H₂O.

Calculated for

	C ₁₅ H ₂₄	Found
C	88.23	87.6
H	11.70	11.57

When/

When treated with hydrochloric acid as described before, this oil yielded a product similar in all respects to that obtained from the oil from the phosphorus pentoxide dehydration. There is little doubt that these two dehydration products are identical.

Treatment of α -Caryophyllene Alcohol with Phosphorus Penta-chloride.

Vigorous reaction took place when the α -alcohol was heated with phosphorus pentachloride, hydrochloric acid fumes being evolved. The product consisted entirely of a resinous oil, from which it appeared that the reaction had been too violent. To avoid this, the α -alcohol was dissolved in carbon tetrachloride and treated at the ordinary temperature with phosphorus pentachloride suspended in the same solvent. The tetrachloride solution was subsequently washed with dilute ammonia and with water. On removal of the solvent an oil was obtained which contained no chlorine, and appeared to be similar to the dehydration products of α -caryophyllene alcohol, but the quantity did not permit its examination.

Investigation of the Mother Liquors from Preparation of Caryophyllene Dihydrochloride.

The mother liquor from the preparation of caryophyllene dihydrochloride was a mobile oil, almost black, and smelling strongly of hydrochloric acid. As much as possible of the dihydrochloride had been removed by cooling the liquor to 0°C. A sample was kept for 72 hours in a vacuum desiccator containing caustic soda. At the end of that time there was no trace of acid fumes from the liquor, yet analysis showed the chlorine content to be 20.1%. This oil was then shaken repeatedly with dilute sodium bicarbonate solution to remove any dissolved hydrochloric acid. It was finally washed with water and extracted with ether. The solvent was removed at the/

the ordinary temperature. At this stage the product was a clear yellow-brown oil containing 19.17% chlorine. It was kept for 4 days at $-10^{\circ}\text{C}.$, and during that time a small quantity of the solid dihydrochloride crystallised out, and was filtered off in a Buchner funnel surrounded by a freezing mixture. The filtrate contained 18.81% chlorine. A repetition of this process yielded an oil containing 18.4% chlorine.

$\text{C}_{15}\text{H}_{26}\text{Cl}_2$ requires $\text{Cl} = 26.1\%$, and $\text{C}_{15}\text{H}_{25}\text{Cl}$ requires $\text{Cl} = 14.6\%$, hence the conclusion was formed that the oil consisted of a liquid monohydrochloride $\text{C}_{15}\text{H}_{25}\text{Cl}$, together with some dissolved dihydrochloride. This was supported by the fact that a saturated solution of the solid dihydrochloride in caryophyllene or in clovene at $0^{\circ}\text{C}.$ contains only 6.8% chlorine.

It was found impossible to obtain a pure specimen of this liquid monohydrochloride by distillation under reduced pressure of the mother liquors referred to above. Decomposition took place (as shown by the liberation of hydrochloric acid) and the chlorine content of the resulting oils varied from 4-9%.

Similar results were obtained on steam-distillation.

Treatment of the Liquid Hydrochloride with Sodium Methoxide.

The oily liquid hydrochloride (16 g.) was added to 150 cc. of concentrated sodium methoxide solution and allowed to stand at the ordinary temperature for several days. The temperature was then raised by $5-10^{\circ}$ each day till 60° was reached, where it was maintained for 2 days. The solution was poured into water, extracted with ether, and after removing the dried solvent, the resulting oil distilled in vacuo. For comparison a test was carried out simultaneously using the solid (dicyclo) dihydrochloride.

The/

The products had the following constants:

	B.P/20 m.m.	d_4^{25}	n_D^{25}	R_L
1. From Liquid Hydrochloride	138-144	.9328	1.5023	64.53
2. From solid Dihydro- chloride	132-128	.9142	1.5005	65.66

Consideration of the molecular refractivities (last column) showed that the oil from the dihydrochloride was largely dicyclic, while that from the liquid monohydrochloride was tricyclic, thus indicating the tricyclic nature of the monohydrochloride.

On analysis of the oil from the monohydrochloride, .1253 g. gave .4064 g. CO_2 and .1307 g. H_2O .

Calculated for

	$\text{C}_{15}\text{H}_{24}$	Found
C	88.23	88.05
H	11.70	11.59

Preparation of Hydroxyl Derivatives from the Liquid Monohydrochloride.

Treatment of the liquid monohydrochloride in ether with moist silver oxide proved of no value, as after standing 5 days at 30-35°C. the hydrochloride was recovered unchanged. Better results were obtained using silver acetate.

The monohydrochloride (70 g.) was dissolved in a slight excess of glacial acetic acid and finely-divided silver acetate (60 g.) added in small quantities; the addition of the silver acetate occupied about 6 hours. Shaking promoted the reaction. The reaction mixture was then warmed on the water-bath at 50-60°C. for 3 hours to complete the reaction. The precipitated silver chloride was filtered off after cooling, and the acetic acid neutralised/

neutralised with sodium carbonate. The heavy oil thus liberated was extracted with ether, and, on removal of the solvent, was obtained as a rather viscous red-brown oil. It probably consisted of a mixture of acetates, and was therefore hydrolysed by boiling under reflux for 1 hour with dilute (10%) methyl-alcoholic caustic potash. The caustic alkali was neutralised by saturating the solution with carbon dioxide. The solution was then diluted with an equal volume of water, and the methyl alcohol distilled off on the water-bath. The residue was steam distilled, yielding as the steam volatile portion a yellowish oil. The residue from the steam distillation yielded a small amount of a solid which was shown to be the glycol obtained by Henderson, Robertson and Kerr (loc.cit.) by treatment of caryophyllene dihydrochloride with silver acetate. (M.P. and mixed M.P. 173°).

On repeated fractionation under reduced pressure, the steam-volatile oil was separated into two main fractions: (a) 118 - 124/10 m.m. and (b) 146 - 154/10 m.m.

Fraction (a) was suspected of being regenerated clovene and examination of its physical constants confirmed this: d_4^{10} .9276, n_D^{10} 1.4992, R_L 64.6, (calculated for a tricyclic sesquiterpene 64.4)

.1151 g. gave .3656 g. CO₂ and .1164 g. H₂O.
Calculated for

	C ₁₅ H ₂₄	Found
C	88.23	86.6
H	11.7	11.2

The low result for carbon was probably due to incomplete separation of the two fractions, further, Henderson, Robertson and Kerr obtained in their work on caryophyllene dihydrochloride a liquid dicyclic alcohol, and/

and the presence of a small quantity of this, due to some dihydrochloride present in the original liquid monohydrochloride would increase the difficulty of separation.

Fraction (b) reacted slowly with metallic sodium and therefore appeared to be an alcohol. It had the following constants: d_4^{17} .9934 n_D^{17} 1.5039, R_L 66.15 (calculated for a tricyclic sesquiterpene alcohol 66.4). On analysis the following results were obtained:

.1126 g. gave .3380 g. CO_2 and .1159 g. H_2O .

Calculated for

	$C_{15}H_{26}O$	$C_{15}H_{24}O$	Found
C	81.1	81.8	81.8
H	11.7	10.9	11.5

The fact that the analysis of fraction (a) indicated incomplete separation of the two fractions shows the formula $C_{15}H_{26}O$ to be the more likely for this alcohol.

The alcohol was saturated towards bromine in chloroform and this, together with the value obtained for the molecular refractivity clearly indicates its tricyclic nature. It gave no solid phenylurethane when treated with phenylcarbimide, and no ester was obtained with β -nitrobenzoyl chloride; it would therefore appear to be a tertiary alcohol.

This alcohol is therefore a new isomer of α - and β -caryophyllene alcohols.

The alcohol (3 g.) was dehydrated with phosphoric oxide by the method described for caryophyllene alcohol (p.24.).

The product, worked up in the usual way appeared from physical properties to be identical with clovene.

d_4^{17} .9250 n_D^{17} 1.5004 R_L 64.8
.1078/

.1078 g. gave .3505 g. CO_2 and .1132 g. H_2O .

Calculated for

	$\text{C}_{15}\text{H}_{24}$	Found
C	88.23	88.6
H	11.70	11.66

Preparation of Hydroxyl Derivative of Clovene.

The clovene was prepared from β -caryophyllene alcohol by dehydration with phosphorus pentoxide by the method described for α -caryophyllene alcohol (p. 24). It was freed from iso-clovene by fractional distillation, the portion used having B.P. 114 - 120/11 m.m.

The oil was dissolved in twice its volume of anhydrous ether, cooled to 0°C and saturated with dry hydrogen chloride. After standing for 24 hours, the ether was removed at the ordinary temperature. The resulting oil was purified by washing with dilute sodium bicarbonate solution and with water. It then contained 12.4% chlorine ($\text{C}_{15}\text{H}_{25}\text{Cl}$ requires 14.6% Cl) and in appearance resembled the liquid monohydrochloride previously described.

This clovene hydrochloride (20 g.) was treated with silver acetate (16 g.) in exactly the same way as the liquid monohydrochloride, the products being worked up in a similar manner.

The steam volatile oil was fractionated into two portions corresponding to the fractions previously obtained. In this case the lighter fraction constituted about three-quarters of the total product, and its constants showed it to be regenerated clovene: B.P. 118 - 126/10 m.m. d_4^{20} .9290 n_D^{20} 1.4997 R_L 64.57.

.1109 g. gave .3568 g. CO_2 and .1156 g. H_2O

Calculated for

	$\text{C}_{15}\text{H}_{24}$	Found
C	88.23	87.7
H	11.70	11.58

A small amount of an oil resembling the alcohol previously described was obtained as the higher fraction. It had the following constants: B.P. 140 - 150/10.

d_4^{20} .9860 n_D^{20} 1.5010 n_D^{25} 66.3

.1012 g. gave .3064 g. CO₂ and .1047 g. H₂O

Calculated for

	C ₁₅ H ₂₆ O	Found
C	81.1	82.6
H	11.7	11.5

This, therefore, indicates the presence of the tricyclic saturated alcohol previously obtained from the original liquid monohydrochloride from the dihydrochloride mother liquors.

Hydrogenation of Clovene.

Clovene (5 g.) prepared from β -caryophyllene alcohol by dehydration with phosphorus pentoxide was dissolved in purified methyl alcohol (150 cc) and palladinised asbestos (.05 g. Pd) added. Hydrogen generated from zinc and sulphuric acid and purified by passing through potassium permanganate, caustic potash, silver nitrate, and water, was passed into the reduction mixture at slightly greater than atmospheric pressure. Absorption took place rapidly at first, the rate falling off as the reaction neared completion. The total hydrogen absorption was about 510 cc, the theoretical absorption assuming clovene to have one double bond, being 550 cc.

The catalyst was removed by filtration through a Gooch crucible and the methyl alcohol distilled off on the water-bath. The oil was then thoroughly dried by dissolving in anhydrous ether and adding anhydrous sodium sulphate. After removal of the ether the product was distilled under reduced pressure/

pressure. B.P. 121 - 124/11 m.m.

.1427 g. gave .4599 g. CO_2 and .1554 g. H_2O

Calculated for

	$\text{C}_{15}\text{H}_{24}$	$\text{C}_{15}\text{H}_{26}$	Found
C	88.23	87.4	87.9
H	11.7	12.6	12.2

The catalyst for the above reduction was prepared by the following method. Palladium (.05 g.) was dissolved in aqua regia and the nitric acid removed by successive evaporations to small bulk with concentrated hydrochloric acid. Finely divided asbestos was added to the solution and then excess of formaldehyde. The solution was made strongly alkaline with caustic soda and twice raised to the boiling point, the palladium black being precipitated on the asbestos on heating. The palladinised asbestos was filtered off, washed till free from alkali, and dried in a desiccator.

—oOo—

Comparative Oxidations of α - and β -Caryophyllene Alcohols
with Beckmann's Chromic Acid Mixture.

The Chromic Acid Mixture was made up using the following proportions: 60 g. potassium dichromate (1 mol.), 80 g. conc. sulphuric acid (4 mols.) 27(g) water.

100 g. of this solution is equivalent to 2.4 g. active oxygen.

(a) Oxidation of β -Caryophyllene Alcohol.

β -Caryophyllene alcohol (10 g.) was dissolved in glacial acetic acid (150 cc) and 100 cc of Beckmann's Chromic Acid Mixture added. The whole was then kept at 60-70°C for 35-40 hours. At the end of that time the mixture was green, oxidation having proceeded slowly. The acetic acid was then distilled off on the water-bath under reduced pressure. The residue was extracted repeatedly with ether, until the ether removed no more oil, as shown by evaporation of a small quantity of the ethereal layer. The bulk of the ether was then distilled off and the product extracted several times with sodium carbonate solution. The sodium carbonate liquors were carefully freed from any mechanically held neutral product by extraction with ether.

On removal of the ether, the neutral product solidified and was shown to consist of unchanged β -caryophyllene alcohol (Recovered - 5 g. approx.).

The acid products of the oxidation were obtained in the form of a viscous oil by acidification of the sodium carbonate extract. In several experiments it was found that the acid oil was green due to the presence of some chromium compound. It was possible, however, to free the acids from chromium by dissolving in caustic soda solution and reprecipitating after filtration.

The acid product was not obtained crystalline. When freed/

freed from chromium and neutral products by conversion into the sodium salt, as above, it was obtained in the form of a viscous oily acid. It was almost colourless.

For further purification the acid was converted into the methyl ester. This was prepared from the silver salt of the acid by the following method. The acid was dissolved in dilute aqueous ammonia and the solution boiled until neutral. To this solution of the ammonium salt a slight excess of aqueous silver nitrate was added. After cooling, the precipitated silver salt was filtered off, washed and dried.

Analysis of the silver salt indicated that the acid oxidation product consisted largely of a mono-basic acid.

.2915 g. salt gave on ignition .1070 g. silver.

	Molecular Weight of Acid
Monobasic	187
Dibasic	374

The production of a dibasic acid of such a high molecular weight (374) is very improbable as it means that for its production, two partially degraded sesquiterpene molecules must combine.

Preparation of Methyl Ester.

The dried silver salt (25 g.) was mixed with anhydrous ether and an equal weight (25 g.) of methyl iodide added, in small quantities. The reaction took place smoothly, silver iodide being precipitated. After the addition of all the methyl iodide the mixture was boiled under reflux for 2½ hours to complete the reaction. It was then diluted with more ether and the silver iodide filtered off. The ether and excess methyl iodide were removed by distillation. The resulting ester was distilled under reduced pressure. The main bulk distilled over at 165 - 180 / 10 m.m.

The distilled ester on hydrolysis with methyl alcoholic potash gave once more a liquid acid similar to the original crude acid.

Analysis of methyl ester:

.1474 g. oil gave .3661 g. CO_2 and .0984 g. H_2O .

Calculated for

	$\text{C}_{11}\text{H}_{15}\text{O}_3$	Found
C	67.7	67.8
H	7.7	7.41

The close agreement of these results may be purely adventitious as the ester may be a mixture of difficultly separable esters.

No crystalline semi-carbazone was obtained by the action of semi-carbazide acetate, nor did treatment with β -nitro-benzoyl chloride yield a solid β -nitro-benzoate.

The above formula $\text{C}_{11}\text{H}_{15}\text{O}_3$ for the methyl ester thus gives $\text{C}_{10}\text{H}_{13}\text{O}_3$ as the formula of the acid.

(b) Oxidation of α -Caryophyllene Alcohol.

α -Caryophyllene alcohol (10 g.) was subjected to oxidation by means of Bechmann's Chromic Acid Mixture under exactly the same conditions as described for the β -alcohol (p. 34).

Oxidation appeared to take place more rapidly than in the case of the β -alcohol.

The product was worked up in the usual manner, viz. the acetic acid distilled off under reduced pressure, and the residue repeatedly extracted with ether. The acid products were removed by sodium carbonate solution, and on acidification were obtained in the form of a white crystalline solid. A further quantity of the same acid was obtained by boiling the neutral products with aqueous caustic soda; in this way any acid present as an anhydride could/

could be extracted. Total yield of acid 4 g.

The acid product was recrystallised from ethyl alcohol and thereafter it melted sharply at 187°C . When heated above its melting point it lost the elements of water forming an anhydride. The anhydride was recrystallised from petroleum ether, in which the acid was insoluble. M.P. of anhydride 49.5°C .

Mixed melting point determinations on the acid along with clovene dicarboxylic acid $\text{C}_{15}\text{H}_{24}\text{O}_4$ and on the anhydride mixed with the anhydride of clovene dicarboxylic acid, showed no depression.

It is noteworthy that no α -caryophyllene alcohol was recovered from the oxidation, the only neutral product being a small quantity of an oil which appeared to be a hydrocarbon but the quantity obtained did not permit further examination.

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III. The Treatment of Cedrene with Mercuric Acetate.

(a) Historical and Theoretical.

Cedar-wood oil from the wood of Virginian Juniper consists to a large extent of the sesquiterpene Cedrene. Compounds containing oxygen are also found in small quantities the best known being cedrol $C_{15}H_{26}O$, often referred to as "cedar camphor".

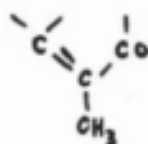
Practically nothing certain is known regarding the structure of cedrene and its related compounds. Application of Ruzicka's method of dehydrogenation with sulphur yielded no naphthalene derivative, complete disruption of the molecule having apparently taken place. (18)

The earlier investigators (19) found that the density and refractive index indicated that cedrene belonged to the class of tricyclic sesquiterpenes.

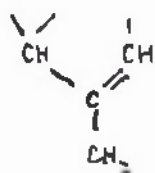
When treated with hydrochloric acid, cedrene gave no definite product but an oil was obtained (20) which might have been a monohydrochloride.

Such investigations as have been carried out have proceeded along the lines of oxidation. By oxidation with chromic acid Rousset (21) converted cedrene into a ketone cedrone $C_{15}H_{24}O$, which gave iodoform on treatment with sodium hypobromite and potassium iodide, whereby he concluded the presence of a $-COCH_3$ group.

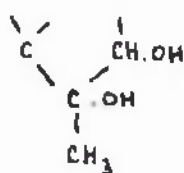
(22)
Semmler in oxidising cedrene with potassium permanganate obtained as chief products a well-defined crystalline glycol $C_{15}H_{26}O_2$ and a keto-acid $C_{15}H_{24}O_3$, the latter yielding on further oxidation cedrene dicarbonic acid $C_{15}H_{22}O_4$. In repeating Rousset's work, Semmler found the composition of the ketone cedrone to be $C_{15}H_{22}O$, this compound on reduction giving an alcohol, dihydro-isocedrol $C_{15}H_{26}O$. From this Semmler concluded that the double bond in cedrone must be in the neighbourhood of the ketonic group:



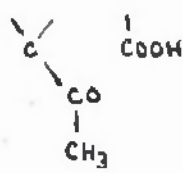
He therefore assumed that the cedrene molecule must contain the grouping I and suggested the partial formulae II, III and IV, for cedrene glycol, cedrene keto-acid and cedrene dicarbonic acid.



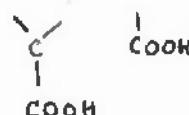
I.



II.



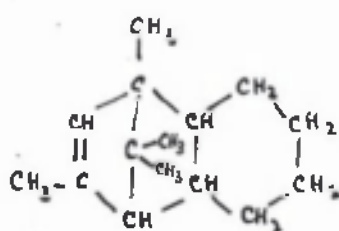
III.



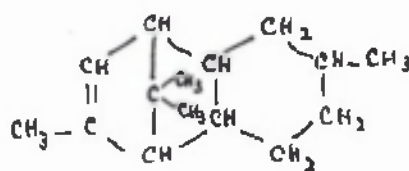
IV.

(23)

Oxidations of cedrene by Deussen with manganese dioxide and sulphuric acid yielded besides small quantities of cedrene keto-acid, an acid of composition $\text{C}_8\text{H}_6\text{O}_4$ which was identified as ortho-phthalic acid. Without other evidence, Deussen suggested the following two formulae for cedrene:



V.



VI.

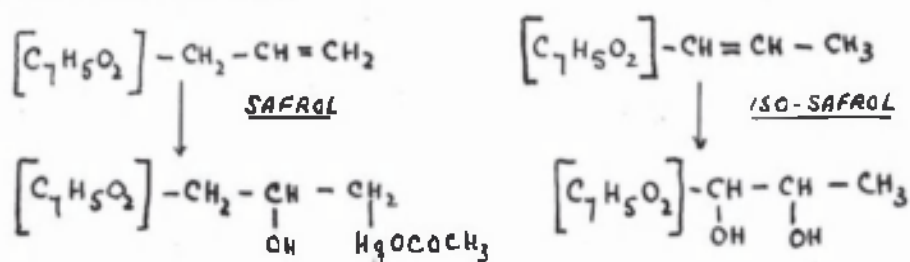
Formula V must be disregarded as it cannot be split up into three isoprene nuclei, VI satisfies this condition, but cannot be produced from the farnesene skeleton.

Cedrene cannot be hydrated by any of the usual methods, and Deussen has shown that it is unaffected by heating with 70% sulphuric acid. In the present work some attempts were made to obtain hydroxyl compounds by oxidation of cedrene with mercuric acetate.

The action of mercuric acetate in aqueous solution as a mild oxidising agent has long been known. Balbiano and Paolini/

(24)

Paolini found that unsaturated compounds with the double bond in the terminal position yielded organo-mercuric derivatives when treated with mercuric acetate, while the corresponding isomeric compounds with the double bond in the penultimate position underwent oxidation to glycols. This can be illustrated by consideration of the behaviour of safrol and iso-safrol.



True acetoxy-mercuri-derivatives of the type shown are generally easily soluble in alcohol and other organic solvents, and though they may not be crystalline, crystallisable derivatives can be obtained by replacing the acetoxy-group by halogen, this substitution taking place smoothly in alcoholic solution on the addition of alkali halides.

This principle was applied by Balbiano to members of the terpene series, with a view to establishing the positions of double bonds. In most cases oxidation products were obtained.

(25)

Deussen has investigated the action of aqueous mercuric acetate on the sesquiterpene caryophyllene, and was able to prepare a mercury derivative. This appeared to be an acetoxy-mercuri-hydroxyl compound of the formula $C_{15}H_{24}(OH)Hg.O.CO.CH_3$ although it was not isolated owing to its gummy nature. The fact, however, that the acetoxy group could be readily replaced by halogen to give crystalline compounds of the type $C_{15}H_{24}(OH)Hg.Cl$ would appear to justify the formula for the primary product.

In the present research therefore the action of mercuric acetate/

44
acetate on cedrene was investigated in the hope that hydroxy or oxy-compounds would be obtained without the possibility of rearrangements in the molecule.

It was found that cedrene reacted slowly at the ordinary temperature with mercuric acetate in aqueous solution, mercurous acetate being precipitated. After the reaction had proceeded for 4-6 weeks, the aqueous solution contained a solid amorphous organo-mercury product. It appeared probable that both oxidation and mercuration had taken place, since the precipitation of mercurous acetate indicated oxidation.

This mercury compound was soluble to a very slight extent in alcohol and was insoluble in most other organic solvents with the exception of chloroform and glacial acetic acid. It was not obtained in crystalline form, but purification was possible by precipitation from its solution in chloroform by the addition of ether.

Investigation having indicated the presence of the acetoxy grouping, various attempts were made to replace this by halogen, but these met with no success. Addition of an alkali halide to a solution of the compound in alcohol containing a little acetic acid only reprecipitated the original compound.

It appeared at this stage, therefore, that this compound was not a true acetoxy-mercury derivative of cedrene, but was possibly a mercurated oxidation product. Attempts to elucidate its structure by the removal of mercury with hydrogen sulphide, caustic alkali, acids or halogens, were unsuccessful, since the products were in most cases resinous, though occasionally traces of cedrene were found.

When purified by repeated reprecipitation, the mercury compound melted at 193-195° (decomp.). In attempting to purify it by sublimation under a high vacuum it was found that/

that it remained solid to much higher temperatures. At 250° it showed no signs of melting. No. sublimation took place, but some decomposition was evident, mercury being produced, and on opening the tube, the characteristic smell of cedrene was perceptible.

Analysis, in which carbon, hydrogen and mercury were estimated indicated $C_{16}H_{27}Hg_2O_6$ as the most probable formula for this compound.

This curious result suggests that the compound is a mixture of two or more derivatives which might have been separated if crystallisation had been possible.

Treatment of cedrene with mercuric acetate in other solvents such as methyl alcohol and chloroform, yielded mainly unattacked hydrocarbon together with small amounts of the same organo-mercury compound.

In investigating the oxidation of pinene with mercuric acetate, Henderson and Agnew⁽²⁶⁾ found it possible to obtain the same oxidation products by the action of mercuric oxide in glacial acetic acid. This method was now applied to cedrene and was successful in that a mercury-free oxidation product was obtained although there was much resinification during the oxidation.

The product obtained was fractionated into two portions, the first consisting largely of unattacked cedrene while the second appeared to be a hydroxy compound.

This alcohol which boiled at 140-150/10 m.m. appeared on analysis to have the formula $C_{15}H_{24}O$, but a tricyclic alcohol of this formula would be unsaturated, while this product was saturated towards bromine in chloroform.

Identical results were obtained by Henderson and Sword in unpublished work on the oxidation of cedrene with hydrogen peroxide.

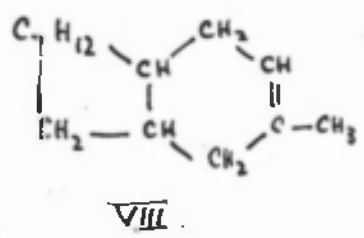
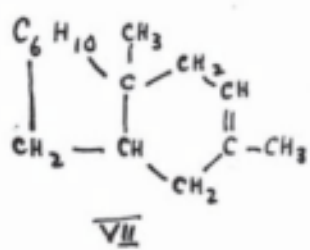
(27)

Semmler isolated from cedar wood oil a saturated, tertiary alcohol, pseudo-cedrol, having the composition $C_{15}H_{26}O$. This alcohol gave no solid derivatives, and had the constants: d .9964; n_D 1.5131. These physical $C_{15}H_{26}O$'s are not far removed from those of the product of the oxidation with mercuric oxide which had d .9872; n 1.5071, so that possibly this alcohol is identical with the naturally-occurring pseudo-cedrol, although the absence of solid derivatives of either alcohol enhances the difficulty of proving their identity.

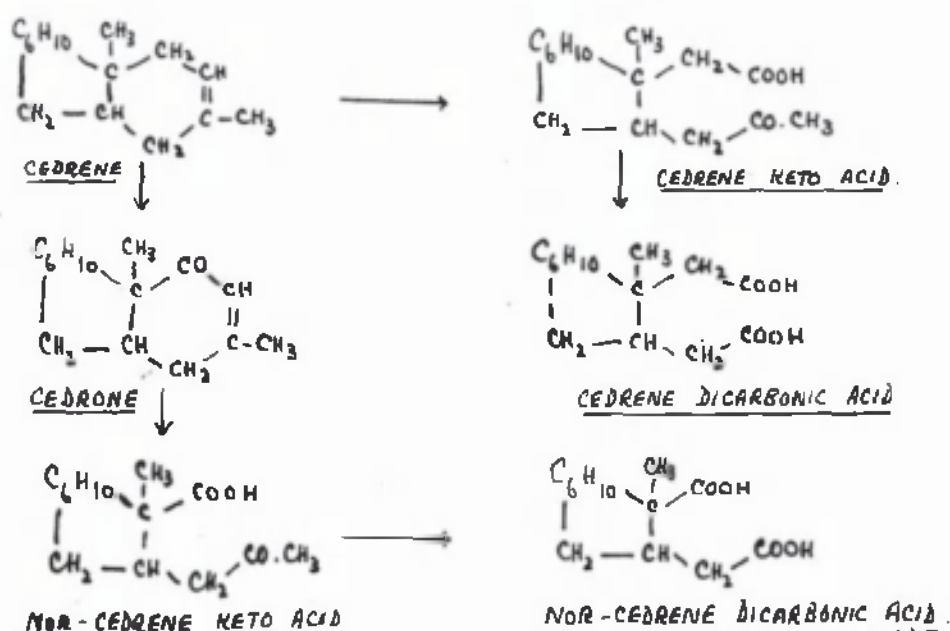
(28)

While the work described in this paper was in progress, Ruzicka and Van Melsen have made a comprehensive study of the oxidation products of cedrene. The most interesting part of their work deals with the oxidation of the ketone cedrene, from which were obtained nor-cedrene keto acid $C_{14}H_{22}O_3$ and nor-cedrene dicarbonic acid $C_{13}H_{20}O_4$.

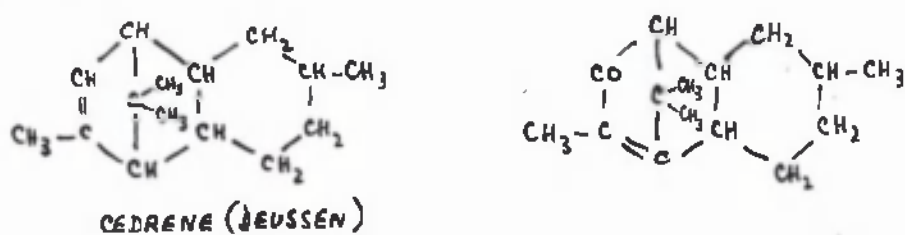
According to Ruzicka the production of these compounds excludes both Deussen's and Semmler's formulae and he suggests the following alternatives:



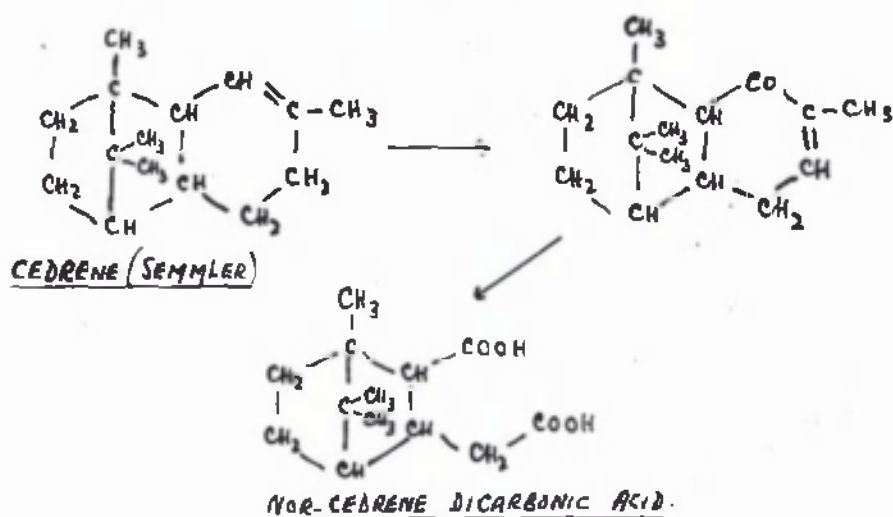
Since Ruzicka is of the opinion that the carbonyl group in cedrene is derived from the $-CH_2$ adjacent to the $-CH=$ group, we might illustrate the oxidations thus:



If now we examine the structure of cedrone as derived from Deussen's formula for cedrene, it is obvious that the production of oxidation products $C_{14}H_{22}O_3$ and $C_{13}H_{20}O_4$ is impossible.



Semmler's formula, we consider, allows for the production of nor-cedrene dicarboxylic acid $C_{13}H_{20}O_4$ but not for the intermediate keto acid $C_{14}H_{22}O_3$.

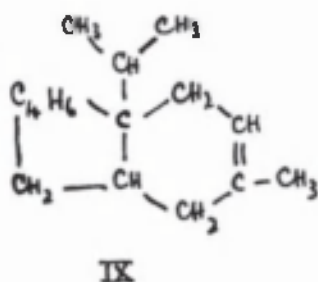
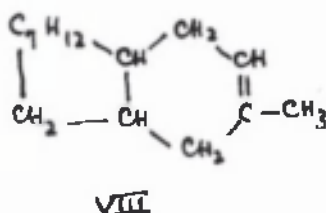
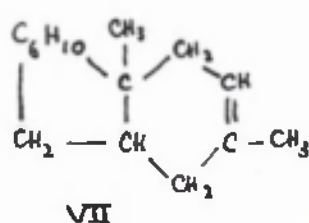


The formulae given by Deussen and Semmler are not inadmissible if the production of the better known oxidation products, cedrene keto acid and cedrene dicarboxylic acid only are considered.

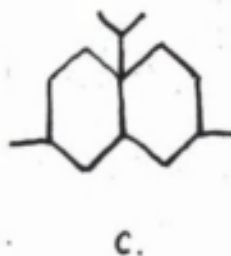
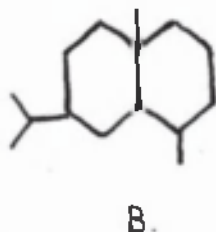
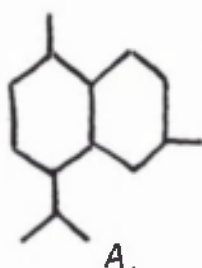
Discussing/

Discussing their suggested formulae Ruzicka and Van Melsen say, "The group C_6H_{10} or C_7H_{12} of these formulae must contain the third ring of cedrene, and following the general regularity of terpene and sesquiterpene structures, this group must contain an iso-propyl group or two methyl groups in the ring, and if we make the very probable assumption that the second ring in cedrene is a six-membered ring, the only possibility for the third ring is that it should be three or four-membered."

Consideration shows that Ruzicka's experimental evidence would be satisfied by a formula such as IX in which the methyl group (in formula VII) common to both rings is replaced by an iso-propyl group.



It has already been shown that the cyclisation of farnesene leads to only three possible carbon skeletons (p. 6).



Now, in Ruzicka's formulae for cedrene (VII and VIII) the position of the methyl group in the right-hand ring has been definitely established, so that skeleton B cannot apply, and since this is the only one having a methyl group common to both rings we consider that formula VII must therefore be rejected.

Formula VIII may correspond to the carbon skeleton A, and as this would have a tendency to yield cadalene on dehydrogenation, it may be rejected in favour of a structure such as IX which is derived from carbon skeleton C.

The iso-propyl group is almost certainly contained in a third ring which according to Ruzicka must be three or four-membered, but there is no experimental evidence on which to base speculation as to its position.

(b) Experimental.

The cedrene used was supplied by the British Drug Houses Ltd.; it was entirely free from colour and had the following physical constants: B.P. 127-128/11 m.m. $d_{20} 0.9378$, $n_D^{20} 1.5052$ whence $R_D = 64.52$.

Treatment of Cedrene with Mercuric Acetate.

Preliminary experiments were performed to ascertain the most suitable proportions of cedrene and mercuric acetate. These showed that it was convenient to use two molecules of mercuric acetate for each molecule of cedrene.

Mercuric acetate (86 g.) was dissolved in 400 cc water at room temperature and cedrene (28 g.) added. The mixture was allowed to stand with occasional shaking. After 24 hours the precipitation of mercurous acetate began, and proceeded slowly. The reaction was allowed to proceed for 5-6 weeks. It is noteworthy that there was no indication of the mercurous acetate being further reduced as even after standing for 12 weeks, there was no evidence of separation of metallic mercury. The cedrene, after 4 weeks had all passed into solution, the clear liquid from which the mercurous acetate settled being brownish yellow. The liquid was filtered from mercurous acetate and then extracted repeatedly with chloroform. As this aqueous liquor contains acetic acid, owing to the reduction of the mercuric acetate, it was in one experiment neutralised with sodium carbonate before extraction, but this made no appreciable difference in the yield of organo-mercury products and had the disadvantage of making filtration much more difficult owing to the precipitation of mercuric oxide. The chloroform extract was dried over anhydrous sodium sulphate and evaporated to small bulk. After cooling, anhydrous ether was added and the product was precipitated as a fine yellow powder. It was allowed to settle, filtered off, and dried on/

on porous pot. Removal of the whole of the chloroform gave the compound in the form of a brown oil which set on cooling to a hard resin.

The crude mercury compound was soluble to a very slight extent in alcohol, easily soluble in chloroform and in glacial acetic acid, and insoluble in the usual other organic solvents and in water. All attempts to obtain it in a crystalline state met with no success, hence precipitation was resorted to as a means of purification. The crude product was dissolved in chloroform and reprecipitated by anhydrous ether. After several applications of this treatment it was obtained as a pale yellow powder melting at $193-195^{\circ}$ (decomp.).

Under a pressure of 1-2 m.m. the mercury compound could be heated to about 280° without melting, though slight darkening occurred in the region of 240° . Some decomposition took place, as beads of metallic mercury were observed and the characteristic smell of cedrene was noticed on opening the tube.

Slight decomposition took place on boiling with water, the smell of cedrene being once more apparent, although the bulk of the compound was unchanged.

The substance gave the cacodyl test, showing the presence of the acetoxy group.

On analysis, the following results were obtained:

$$C = 26.5; \quad H = 3.55; \quad Hg = 57.5$$

From these results it appears that the most probable formula is $C_{16}H_{27}Hg_2O_6$ which requires $C = 26.8; H = 3.78; Hg = 56.0$.

Preparation of Mercury-free Products.

(1) Hydrogen Sulphide.

Cedrene and aqueous mercuric acetate in the same proportions/

40

proportions as above were allowed to react for 5 weeks. After filtration from mercurous acetate, the clear liquid was saturated with hydrogen sulphide to precipitate the mercury in solution. The mercuric sulphide was removed by filtration and the filtrate freed from hydrogen sulphide by warming on the water-bath for 3 hours. After cooling, it was extracted with ether, the precipitated mercuric sulphide being also washed with the same solvent. The ethereal solution was then dried with anhydrous sodium sulphate. On removal of the solvent a yellowish residue smelling strongly of acetic acid was obtained. This product was therefore treated with sodium carbonate and extraction with ether then yielded a quantity of a very viscous yellow oil which on subsequent examination was found to contain mercury. It was then dissolved in acetic acid (containing some water) and subjected to the action of sulphuretted hydrogen once more, but the product was a similar oil containing mercury. It was not further examined

(2) Sodium Sulphide.

The solid mercury product (2 g.) was dissolved in a hot concentrated aqueous solution of sodium sulphide, and the solution boiled under reflux for half an hour. On cooling excess of ammonium chloride was added, this causing the precipitation of the mercury as sulphide. After filtration the residue (mercuric sulphide) was washed with ether, and the filtrate extracted with the same solvent. Removal of the solvent, after drying, left as product a dark brown viscous oil which still contained mercury and could not be distilled without decomposition. Even on standing at the ordinary temperature this oil gradually resinified, with deposition of metallic mercury.

(3) Halogens.

The mercury compound (3 g.) was dissolved in chloroform and iodine added in small quantities until an excess was present as shown by the colour of the solution. Some mercuric iodide was precipitated and the solution was heated under reflux for one hour. After cooling, the mercuric iodide was filtered off, and the deep red solution treated with dilute sulphurous acid to remove the excess iodine. It was subsequently washed with sodium bicarbonate solution and with water, dried over anhydrous sodium sulphate and the solvent distilled off. A small quantity of a viscous dark oil containing no mercury was obtained. As it contained halogen, it was dissolved in alcohol and treated with excess sodium. When the precipitation of sodium iodide was complete, an equal volume of water was added, the alcohol distilled off, and the residue extracted with ether. Removal of the ether yielded only a small quantity of a brown resin which was not further examined.

Treatment of the mercury compound with bromine under similar conditions yielded a like product.

Attempts to Prepare Halogen Derivatives of the Solid Mercury Compound.

(25)

Since Deussen was able to prepare crystalline halogen derivatives from the primary acetoxy-mercuri-compound of caryophyllene, attempts were made to replace the acetoxy grouping in the compound from cedrene by halogen.

Treatment of a solution of the solid mercury compound in alcohol (in which it was unfortunately only sparingly soluble) with 10% aqueous potassium iodide only caused reprecipitation of the starting product. Potassium iodide in alcohol also produced this result.

In order to increase the solubility of the primary mercury/

mercury compound, 5% of glacial acetic acid was added to the alcohol, but although it was possible in this way to work with larger quantities, the results were the same as in the previous experiments. Potassium bromide and chloride yielded similar results.

Oxidation of Cedrene with Mercuric Oxide.

Cedrene (20 g.) was dissolved in 150-200 cc. of glacial acetic acid and heated to 60-70° on the water-bath. Mercuric oxide (24 g.) was then added in small quantities. After a short time metallic mercury began to be precipitated showing that oxidation was taking place. When all the mercuric oxide had been added, the solution was kept at the above temperature for 4-5 hours by which time most of the mercury appeared to be precipitated. The amount of mercury precipitated was almost theoretical. The mercury was separated by filtration, and the acetic acid filtrate was diluted with an equal volume of water. The acetic acid was then neutralised with sodium carbonate and extracted with ether. The ether solution was washed with water and dried over anhydrous sodium sulphate. Removal of the ether gave a brown mobile oil with the odour of cedrene. This oil was distilled under reduced pressure when two main fractions were obtained. About one third of the oil distilled at 125-130/10 m.m. and consisted mainly of unchanged cedrene. The second fraction boiling at 140-150/10 m.m. was yellowish and was roughly of the same bulk as the first. There was a good deal of resinification during the distillation.

The constants of these two fractions were:

- (1) B.P. 125-130/10 m.m. d_4^{20} .9504 n_D^{20} 1.5020
 .1240 g. gave .3941 g. CO₂ and .1282 g. H₂O.

Calculated for

	C ₁₅ H ₂₄	Found
C	88.23	86.7
H	11.70	11.5

The conclusion is that this fraction consisted largely of unattacked cedrene, contaminated, in all probability, with a little of the second fraction.

(2) B.P.140-150/10 m.m. d_4^{20} .9872 n_D^{20} 1.5071 R_L (calculated as $C_{15}H_{26}O$) 66.9 (R_L calculated for a typical tricyclic sesquiterpene alcohol 66.4)

.1412 g. gave .4220 g. CO_2 and .1352 g. H_2O .

Calculated for

	$C_{15}H_{24}O$	$C_{15}H_{26}O$	Found
C	81.9	81.3	81.5
H	10.9	11.7	10.7

The alcohol was saturated, and this appears to cut out the possibility of this alcohol having the formula $C_{15}H_{24}O$ which is indicated by the combustion results.

The alcohol did not yield an acetate when heated with acetic anhydride, the product giving on analysis the same results as the starting product. No solid *p*-nitrobenzoate or phenylurethane was obtained which, as would be expected from the proposed structures for cedrene, would indicate the tertiary nature of this alcohol.

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In conclusion, I desire to offer my best thanks to my Chief and Supervisor, Professor G.G.Henderson, F.R.S., for his continued encouragement and advice during the progress of this work.

My thanks are also due to the Department of Scientific and Industrial Research for a Maintenance Allowance, during the tenure of which the earlier part of this work was carried out, and to the Imperial Chemical Industries, Ltd. for a grant towards the cost of materials.

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