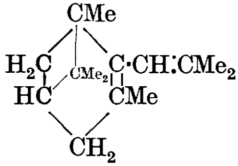
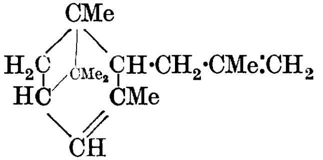
XIII.—*The Chemistry of the Caryophyllene Series. Part I.*

By GEORGE GERALD HENDERSON, JOHN MONTEATH ROBERTSON, and (in part) CARL ALOYSIUS KERR.

β-CARYOPHYLLENE belongs to the dicyclic series of sesquiterpenes, but as no naphthalene or benzenoid derivative can be obtained from it by the sulphur method (Ruzicka and Stoll, *Helv. Chim. Acta*, 1923, **6**, 854), it cannot be assigned to either of the known cadinene or eudesmol types. Its structure is therefore largely a matter of conjecture, although Semmler and Mayer (*Ber.*, 1911, **44**, 3657) consider that it consists of a mixture of two forms, for which, from a study of the ozonide products, they have advanced formulæ I and II. The existence of the bridge ring system is, however, based upon the supposed identity of caryophyllenic acid with *cis*-2 : 2 : 3-trimethyl*cyclo*butane-1 : 3-dicarboxylic acid, and until this is definitely established these formulæ must be regarded as tentative.

(I.)





(II.)

Wallach and Walker (*Annalen*, 1892, **271**, 285) showed that caryophyllene forms a crystalline hydrate known as caryophyllene alcohol, $C_{15}H_{25}\cdot OH$, upon hydration with a mixture of sulphuric and acetic acids. The properties of this alcohol and in particular its relation to the hydrocarbon have not previously been fully examined. As there is some evidence that certain of its derivatives possess a different molecular configuration from that assigned to β-caryophyllene, experiments were carried out with a view to obtain more information in this connexion.

The alcohol prepared by the hydration method was found to be remarkably stable in certain respects. Thus, after heating with hydrogen peroxide for 52 hours, practically the whole of the alcohol was recovered unchanged. On treatment with permanganate the alcohol was again recovered unchanged. Towards bromine in chloroform solution it behaved as a fully saturated substance.

All dicyclic sesquiterpene alcohols of the formula $C_{15}H_{25}\cdot OH$ are unsaturated, uniting additively with bromine and being readily oxidised. It is evident that caryophyllene alcohol does not belong to this class, and therefore cannot be regarded as a direct hydrate of the hydrocarbon, as previously supposed. Apparently the hydrating agents have induced ring closure with the formation of a new tricyclic structure. Confirmation of this view is found in the fact that the alcohol can be formed through the agency of formic acid, which is a well-known means of effecting ring closure in the sesquiterpenes (Robertson, Kerr, and Henderson, J., 1925, **127**, 1944). Moreover, it has long been known that caryophyllene alcohol upon dehydration yields a hydrocarbon, clovene, which is not identical with caryophyllene, but which appears to be tricyclic from its physical properties (Wallach and Walker, *loc. cit.*).

Although it is not feasible to determine the molecular refractivity of caryophyllene alcohol directly owing to its high melting point (compare Semmler, *Ber.*, 1903, **36**, 1037), it appeared probable that the necessary information might be obtained from the physical properties of certain of its esters, which were prepared in the course of this work. The following figures were therefore determined for the formate and the acetate, and they clearly indicate the tricyclic nature of the caryophyllene radical.

				$[R_L]_D$.			
Ester.	t.	$d^{t°}_{4°}$.	$n^{t°}_D$.	Found.	Calc. for $C_{15}H_{25}\cdot R$. Tricyclic.	Typical * $C_{15}H_{25}\cdot R$. Dicyclic.	Calc. for $C_{15}H_{25}\cdot R$. Dicyclic.
Formate, $C_{16}H_{26}O_2$†	7°	1·024	1·4998	71·78	71·02	—	72·75
Acetate, $C_{17}H_{28}O_2$‡	17°	1·003	1·4919	76·37	75 64	78·13	77·37

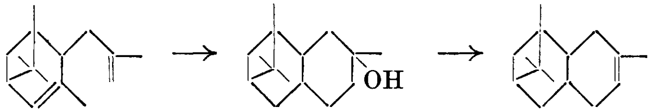
* Semmler and Jonas, *Ber.*, 1914, **47**, 2068, 2072.

† We wish to take this opportunity of correcting the density for the formate previously given (J., 1925, **127**, 1945), where $d^{17°}_{4°}$ 1·22 should be $d^{7°}_{4°}$ 1·024.

‡ Determined on the super-cooled liquid.

It will be observed that the exaltation found in the case of the caryophyllene derivatives is not greater than the corresponding divergence for a typical dicyclic member.

It is noteworthy that the limonene form (II) of active caryophyllene could readily adapt itself to such ring formation as is indicated by the above results. The course of the reaction and the dehydration of the alcohol to clovene may therefore be represented by the following scheme :



Clovene.

In addition to caryophyllene alcohol, Wallach's hydration method gives rise to a liquid product. We find this substance to consist of an unsaturated *hydrocarbon*, $C_{15}H_{24}$, b. p. 110—114°/9 mm., $d^{10°}_{4°}$ 0·9263, $n^{10°}_D$ 1·5010, $[\alpha]^{16°}_{5790\cdot3}$ —19·56°, which evidently differs from β-caryophyllene and is perhaps identical with the tricyclic caryophyllene obtained from the dihydrochloride by the quinoline method (Semmler and Mayer, *Ber.*, 1910, **43**, 3451) which had b. p. 122—123°/13 mm., $d^{20°}_{4°}$ 0·927, $n^{20°}_D$ 1·50246, $\alpha^{20°}_D$ —57°. Clovene, also regarded as tricyclic, has closely similar properties. The possible identity of these three substances is under examination.

Our experiments were next directed towards the synthesis of hydroxyl derivatives from caryophyllene corresponding to the dicyclic structure of the hydrocarbon, since it has been shown that Wallach and Walker's hydration method leads to ring closure. From caryophyllene dihydrochloride by the action of silver acetate in glacial acetic acid solution we obtained products which upon hydrolysis yielded an unsaturated *alcohol*, $C_{15}H_{25}\cdot OH$, a saturated *glycol*, $C_{15}H_{26}(OH)_2$, and some regenerated hydrocarbon. The alcohol, $C_{15}H_{25}\cdot OH$, which may be termed *caryophyllol*, has properties corresponding closely to those of a dicyclic sesquiterpene alcohol. Although it reacts with sodium, no ester has yet been obtained by any of the usual methods, which indicates that the alcohol is tertiary. By the action of a chloroform solution of bromine in the cold it is converted into a rather unstable *dibromide*, $C_{15}H_{26}OBr_2$.

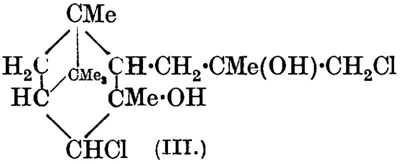
The compound $C_{15}H_{26}(OH)_2$ is quite a stable substance, and is probably a glycol with both hydroxyl groups attached to tertiary carbon atoms. It possesses properties closely similar to those of cadinene glycol (Henderson and Robertson, J., 1924, **125**, 1992). The fact that the hydrocarbon product of the reaction gives a good yield of caryophyllene dihydrochloride on treatment with hydrogen chloride indicates that these hydroxyl derivatives also retain the dicyclic caryophyllene structure.

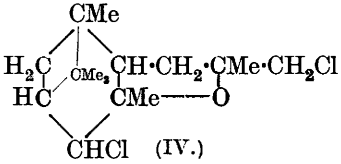
Wallach and Walker (*loc. cit.*) found that caryophyllene alcohol gives a series of halogen derivatives, of which the chloride, $C_{15}H_{25}Cl$, can be readily obtained. We have found that this compound also, as was to be expected from the above results, behaves as a fully saturated substance like the alcohol, and therefore must also be regarded as being tricyclic. It thus becomes of interest to enquire whether hydrogen chloride can be eliminated from this compound by any of the usual methods, because if this proved to be the case, a new type of tricyclic sesquiterpene would be expected, of which the above-mentioned compound would be the hydrochloride.

We have found that this chloride is much more stable than the known hydrochlorides of the sesquiterpene series. Even after prolonged heating in a concentrated alcoholic solution of sodium ethoxide, or with quinoline, practically all the compound was recovered unchanged. On treatment with sodium acetate in glacial acetic acid solution, however, chlorine was removed from the molecule, but the product of the reaction in this case proved to be the *acetate* of caryophyllene alcohol, $C_{15}H_{25}\cdot OAc$. Wallach and Tuttle (*Annalen*, 1894, **279**, 393) mention a caryophyllene acetate, but as no melting point or other data are given, it is impossible to state whether the compound we have obtained is similar to theirs.

Since hypochlorous acid has proved of service in investigating the simpler terpenes (compare Slawinski, *Ber.*, 1899, **32**, 2064; Henderson and Marsh, J., 1921, **119**, 1492; Henderson and Kerr, J., 1924, **125**, 102), we examined the action of this reagent on β-caryophyllene. In this case, however, instead of using a dilute aqueous solution of the acid we adopted Detoeuf's method of preparing chlorohydrins (*Bull. Soc. chim.*, 1922, **31**, 102, 169, 176) through the agency of chlorocarbamide, which in acid solution undergoes hydrolysis with formation of carbamide and hypochlorous acid. In order to regulate the reaction and to diminish the rate of hydrolysis of the chlorocarbamide, the caryophyllene was dissolved in 4—5 times its bulk of acetone. The first product of the reaction was not obtained in a pure state, but appeared to be a *dichlorohydrin* of caryophyllene, $C_{15}H_{24}Cl_2(OH)_2$. On treatment with acetic anhydride it yielded a small quantity of a *monoacetate*, but also in an impure state. When distilled at 1 mm. pressure, it was converted into a *saturated compound* of the formula $C_{15}H_{24}OCl_2$. This substance, a colourless liquid, appears to be the anhydride of the dichlorohydrin. The chlorine in this compound is not easily replaced, and oxidation with hydrogen peroxide yielded no definite product except some succinic acid.

If β-caryophyllene has the constitution (II) given above, the constitution of the dichlorohydrin may be represented by the formula (III) and that of the anhydride by (IV).


(III.)


(IV.)

It is true that the supposed anhydride does not undergo hydration to the corresponding glycol on treatment with dilute sulphuric acid, but Franke and Lieben (*Monatsh.*, 1914, **35**, 431) have shown that the anhydrides of 1 : 4- and 1 : 5-glycols are quite stable in this respect.

EXPERIMENTAL.

Preparation and Properties of Caryophyllene Alcohol.—The β-caryophyllene used in the following experiments was purified by fractional distillation (compare Robertson, Kerr, and Henderson, *loc. cit.*). To 1 litre of acetic acid containing 12 c.c. of sulphuric acid and 40 c.c. of water, 150 g. of caryophyllene were added and the whole was maintained at 80—100° for 30 hours. The product was steam distilled. At first acetic acid and an oil passed over, then the solid alcohol slowly distilled. After crystallisation from light petroleum at a low temperature it melted at 94—96° (yield, about 30%).

The liquid product of the hydration was collected by means of light petroleum and dried. On removing the solvent and allowing the product to remain 24 hours at 0°, a further quantity of the alcohol separated and was removed. The resulting oil was distilled under diminished pressure and the main fraction was finally redistilled over sodium in a vacuum. The product consisted of a colourless oil with a pleasant odour which had b. p. 110—114°/9 mm., $n_D^{10°}$ 1·5010, $d_{4°}^{10°}$ 0·9263, $[\alpha]_{5790}^{16°}$ —19·56°. $[R_L]_D$ found, 64·8; calc. for a tricyclic sesquiterpene, 64·4 (Found: C, 87·7; H, 11·7. $C_{15}H_{24}$ requires C, 88·2; H, 11·8%). This substance was unsaturated towards bromine.

Caryophyllene alcohol (50 g.) in glacial acetic acid (200 c.c.) and 30% hydrogen peroxide (55 c.c.) were heated together at 50—55° for 52 hours. The solution was then neutralised, when practically the whole of the caryophyllene alcohol was recovered unchanged. M. p. 94°. On standing in the cold with 1% permanganate the latter was not decolorised, and the alcohol was recovered unchanged. When the alcohol was gradually treated with bromine, both in chloroform solution at room temperature, no absorption or substitution could be detected.

Preparation and Properties of Other Hydroxyl Derivatives of Caryophyllene.—The dihydrochloride of caryophyllene was prepared by gradually treating caryophyllene (100 g.) in anhydrous ether (100 c.c.) with dry hydrogen chloride, the temperature of the reaction being kept at 0°. After remaining a further 24 hours at 0°, the ether was removed by passing a current of dry air over the surface of the liquid. On reducing the temperature to —20°, practically the whole of the liquid crystallised. Recrystallised from ethyl acetate, caryophyllene dihydrochloride had m. p. 69°, $[\alpha]_D^{16°}$ + 67° in 2·5% ethyl-alcoholic solution. Failure to observe the conditions stated, in particular with regard to temperature, results in a greatly diminished yield of the dihydrochloride.

A solution of caryophyllene dihydrochloride (50 g.) in glacial acetic acid (250 g.) was gradually treated with silver acetate (70 g.). The mixture was shaken for 2 to 3 hours at room temperature, and the reaction completed by gently warming on the water-bath. On cooling, the silver chloride was filtered off, and the acetic acid neutralised with sodium carbonate. The resulting product, consisting principally of acetates, was collected by means of ether and hydrolysed by warming with dilute methyl -alcoholic potash for ½ hour. After the alcohol had been distilled off, the product was rendered neutral with carbon dioxide and steam distilled. The portion volatile in steam was collected with ether, dried over anhydrous sodium sulphate, and distilled under reduced pressure. After several distillations, three principal fractions were obtained: (a) b. p. 122—130°/10 mm., (b) b. p. 130—140°/10 mm., and (c) b. p. 140—150°/10 mm. The fraction (a) consisted of regenerated caryophyllene. When treated with hydrogen chloride in the manner described above, an almost theoretical yield of the dihydrochloride,

m. p. 69°, was obtained. The fraction (c), which represented about 20% of the product, on further purification had b. p. 142—150°/10 mm., $d_{4^\circ}^{17^\circ}$ 0·9632, $n_{D}^{17^\circ}$ 1·5015; $[R_L]_D$ found, 68·03; calc. for a dicyclic sesquiterpene alcohol, 68·12 (Found: C, 80·6; H, 11·2. $C_{15}H_{26}O$ requires C, 81·1; H, 11·7%). This substance gave no solid derivative when treated in the usual manner with phthalic anhydride, or with phenylcarbimide, and therefore appears to be a tertiary alcohol. On boiling with acetic anhydride, dehydration occurred yielding a hydrocarbon. The alcohol is unsaturated towards bromine and alkaline permanganate. When slowly treated with bromine at 0°, both in chloroform solution, absorption occurred but no substitution was detected. The chloroform was removed under reduced pressure, leaving a colourless, oily dibromide (Found: Br, 40·1. $C_{15}H_{26}OBr_2$ requires Br, 41·8%) which slowly decomposed on exposure to light. The fraction (b) consisted of a mixture of the above alcohol and the hydrocarbon. A small higher-boiling fraction was also obtained, containing a higher percentage of oxygen, which probably consists of a mixture of the above alcohol with a small amount of the glycol referred to below.

The residue from the steam distillation contained a thick brown oil, which was repeatedly extracted with ether and dried. On removing the ether, most of this substance crystallised and by the addition of a small amount of light petroleum the remainder was deposited in minute, white needles. The substance was recrystallised from ether as a flocculent mass of minute needles, m. p. 173° (yield 3%). The composition corresponds with that of caryophyllene glycol, $C_{15}H_{26}(OH)_2$ (Found: C, 74·5; H, 11·7. $C_{15}H_{28}O_2$ requires C, 75·0; H, 11·7%). The substance is very soluble in alcohol, slightly soluble in ether, and almost insoluble in light petroleum. It does not decolorise bromine or alkaline permanganate solution.

Reactions of Chlorodihydrocaryophyllene.—The chloro-compound, $C_{15}H_{25}Cl$, was prepared by the action of phosphorus pentachloride on the alcohol (Wallach and Walker, *loc. cit.*) and purified by crystallisation from light petroleum. M. p. 63° (Found: Cl, 14·9. Calc., Cl, 14·8%). The yield was almost theoretical.

A portion was refluxed at 100° with a concentrated solution of sodium ethoxide for 12 hours. No action took place and the chloride was recovered unchanged. Another portion was heated at 210° in quinoline solution for 3 hours, but again the compound was recovered unchanged. A third portion (20 g.) was dissolved in glacial acetic acid (150 c.c.), and anhydrous sodium acetate (19 g.) gradually added. The solution was boiled for 3 hours. After 1 hour, sodium chloride began to be deposited. On cooling, the product was diluted with water and extracted with light petroleum. After removing the solvent from the dried extracts, the product was distilled under reduced pressure, when a colourless oil was obtained, b. p. 149—152°/10 mm., which was saturated towards bromine. When mixed with light petroleum and cooled to —20°, a solid mass of small, white crystals separated, which on purification melted at 40°. The yield was nearly theoretical. This substance is fairly soluble in alcohol and in petroleum. Acid ethyl-alcoholic hydrolysis yielded ethyl acetate, and by hydrolysis with methyl-alcoholic potash a theoretical yield of caryophyllene alcohol, m. p. and mixed m. p. 95°, was obtained. The substance is therefore caryophyllene acetate, $C_{15}H_{25}O{\cdot}CO{\cdot}CH_3$ (Found: C, 76·8; H, 10·6. $C_{17}H_{28}O_2$ requires C, 77·2; H, 10·6%).

The Action of Hypochlorous Acid on β-Caryophyllene.—A solution of 108 g. of chlorocarbamide (2 mols.) in 300 c.c. of water was added slowly to a cooled solution of 120 c.c. of β-caryophyllene (1 mol.) and 10 c.c. of acetic acid in about 500 c.c. of acetone, and the mixture shaken for several hours until all the hypochlorous acid had disappeared. The acetone was then distilled off, the residual liquid extracted with ether, and the extract dried and distilled. The product, which presumably was the dichlorohydrin of β-caryophyllene, $C_{15}H_{24}(OH)_2Cl_2$, was a yellow, oily liquid, which could not be obtained in crystalline form, was not volatile in a current of steam, and could not be distilled without partial decomposition. The compound did not give a semicarbazone nor a nitrobenzoate, but when a portion was warmed with acetic anhydride (2 mols.) after addition of a drop of sulphuric acid reaction took place quickly. The product was extracted and after repeated distillation under diminished pressure yielded a colourless liquid, b. p. 190—200° of which the composition approximated to that of a monoacetate of the dichlorohydrin (Found: C, 57·1; H, 6·9; Cl, 19·9. $C_{17}H_{28}O_3Cl_2$ requires C, 58·1; H, 7·1; Cl, 20·2%). The supposed dichlorohydrin distilled at 1 mm. with little decomposition. Repeated fractionation finally yielded a colourless liquid, b. p. 125—140°/1 mm., which was essentially the anhydride of the dichlorohydrin (Found: C, 62·3; H, 7·9; Cl, 23·4. $C_{15}H_{24}OCl_2$ requires C, 61·8; H, 8·3; Cl, 24·3%).

This compound is saturated towards both bromine and potassium permanganate. It does not react with *p*-nitrobenzoyl chloride, with semicarbazide acetate, or with ammoniacal silver nitrate. It is not attacked by boiling aqueous 2% sulphuric acid or by dilute aqueous potassium hydroxide, but when heated with an aqueous alcoholic solution of the last reagent yielded an oily liquid which contained only a trace of chlorine, was unsaturated, and did not give the reactions of an alcohol.

Attempts to replace the chlorine in this compound by hydrogen were not successful. Addition of successive quantities of sodium amalgam to an alcoholic solution containing a trace of water resulted in the production of a yellow, oily liquid, which distilled for the greater part at 120—130°/1 mm., and still contained 14·20% of chlorine. Thus by this treatment approximately one atom of Cl was replaced ($C_{15}H_{25}OCl$ requires Cl, 13·8%). Prolonged heating of the compound with zinc dust and alcohol failed to yield a substance free from chlorine.

On oxidation with 30% hydrogen peroxide in glacial acetic acid solution the chloroanhydride yielded a small quantity of a viscous neutral product, some succinic acid, and another acid, in the form of a brown oily liquid, which has not been identified.

We are grateful to the Carnegie Trust for the award of grants which assisted us to prosecute this work.

UNIVERSITY OF GLASGOW. [*Received, November 14th*, 1925.]