

CLXXVIII.—*The Chemistry of the Caryophyllene Series. Part II. Clovene and isoClovene.*

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WALLACH and WALKER (*Annalen*, 1892, **271**, 283) showed that when caryophyllene alcohol is heated with phosphoric oxide caryophyllene is not regenerated but instead the tricyclic sesquiterpene clovene is produced. We have now ascertained that when other methods of dehydrating the alcohol, *e.g.*, heating with anhydrous oxalic acid, are employed, the result is the same; in no case has caryophyllene been obtained. Moreover, the liquid hydrocarbon which is formed as a by-product when caryophyllene is hydrated by Wallach and Walker's method is closely similar to, if not identical with, clovene. Caryophyllene can be regenerated from its crystalline dihydrochloride by treatment of the latter with a saturated methyl-alcoholic solution of potassium hydroxide or with a concentrated solution of sodium methoxide (Semmler and Mayer, *Ber.*, 1910, **43**, 3451), but when the dihydrochloride is heated with dilute alcoholic alkalis, or with sodium acetate and acetic acid, or with pyridine or quinoline, the product is again a liquid tricyclic sesquiterpene instead of dicyclic caryophyllene. Further, a liquid by-product is obtained in varying quantities during the preparation of caryophyllene dihydrochloride, and we have found that this liquid is capable of dissolving the dihydrochloride, which is not completely separated even if the solution is strongly cooled. At the same time, when allowance is made for the quantity of the dihydrochloride retained in solution after cooling, analysis indicates that the liquid is largely composed of a rather unstable mono-hydrochloride of a sesquiterpene. The hydrocarbon regenerated from this liquid by the usual methods and purified by fractional distillation closely resembles clovene in its physical properties and in the fact that it does not yield a crystalline hydrochloride, as is also the case with the sesquiterpene obtained as a by-product in the hydration of caryophyllene. The physical constants of these hydrocarbons are as follows :

(1) B. p. 111—113°/10 mm., d_4^{20} 0.924, n_D^{20} 1.4980, $[R_L]_D$ 64.7.

(2) B. p. 110—114°/10 mm., d_4^{17} 0.933, n_D^{17} 1.5020, $[R_L]_D$ 64.5.

(3) B. p. 110—114°/9 mm., d_4^{10} 0.926, n_D^{10} 1.5010, $[R_L]_D$ 64.8.

(1) Clovene, (2) sesquiterpene obtained by heating caryophyllene dihydrochloride with quinoline, (3) sesquiterpene obtained in hydration of caryophyllene : $[R_L]_D$ calculated for tricyclic sesquiterpene, 64.4. It is evident that under the influence of mineral acids and

some other reagents, caryophyllene readily undergoes ring closure with formation of clovene or of another tricyclic sesquiterpene which is very similar to clovene in its physical properties.

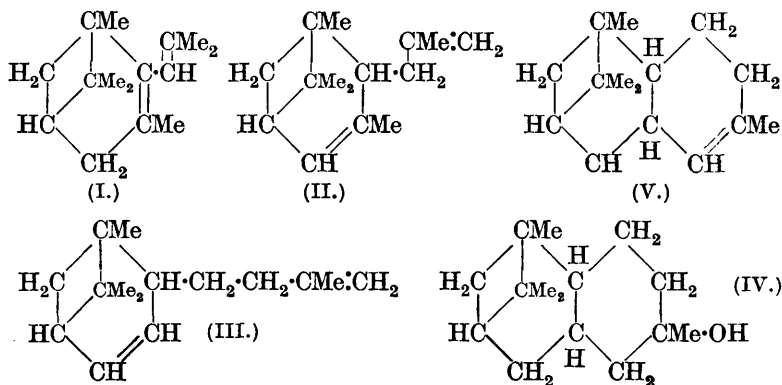
Clovene is attacked by potassium permanganate, but so far no definite oxidation products have been isolated, and all attempts to prepare an alcohol from it by hydration have been unsuccessful. It does not appear to yield either eudalene or cadalene when heated with sulphur, and therefore does not belong to either the eudesmene or the cadinene group of sesquiterpenes.

We have recently discovered that modification of the conditions under which Wallach and Walker's method of dehydrating caryophyllene alcohol is carried out results in the production of a mixture of clovene and another tricyclic sesquiterpene, which can be separated by fractional distillation. The new sesquiterpene, for which we propose the name *isoclovene*, is a colourless, somewhat viscous liquid, b. p. 130—131°/12 mm., d_4^{20} 0.943, n_D^{20} 1.5039, $[\alpha]_D^{25}$ -56.6°, $[R_L]_D$ 64.11. It is characterised by the formation of a crystalline *monohydrochloride*, $C_{15}H_{25}Cl$, m. p. 87°, and *monohydrobromide*, $C_{15}H_{25}Br$, m. p. 75°, from which the hydrocarbon may be regenerated in a pure state. These compounds are quite different from the remarkably stable substances of the same composition which are obtained by the action of phosphorus pentachloride and pentabromide on caryophyllene alcohol, which melt at 62° and 63°. *iso*Clovene is much more unstable than clovene, resinifying quickly when exposed to air and becoming sticky and resinous even when enclosed. When heated to its boiling point with phosphoric oxide, it is completely decomposed, and thus the possibility of obtaining it from caryophyllene alcohol might easily escape notice. It unites with 1 mol. of bromine, but the dibromide is also very unstable.

On treatment of a solution of *isoclovene* hydrochloride in glacial acetic acid with silver acetate a good yield of the acetate of *isoclovene* alcohol was obtained. The *alcohol*, $C_{15}H_{25}\cdot OH$, purified by recrystallisation from ethyl acetate, is a colourless crystalline solid, m. p. 98°, $[\alpha]_D^{20} = 227^\circ$. It is saturated towards bromine, and presumably tertiary, because attempts to prepare esters were unsuccessful, the alcohol undergoing dehydration in the process; it does not react with phenylcarbimide. The melting point lies near to that of caryophyllene alcohol, but a mixture of the two melts about 20° lower; it is also more sparingly soluble in alcohol and in ethyl acetate than caryophyllene alcohol.

The formulæ suggested by Semmler for β - and γ -caryophyllene (I and II) have been criticised on the ground that they are not in conformity with the now generally accepted view that the carbon nuclei of sesquiterpenes are built up of three isoprene nuclei.

Moreover, as Deussen has pointed out (*J. pr. Chem.*, 1926, **114**, 63), neither hydrocarbon yields a dihydro-compound on treatment with sodium and alcohol, and therefore presumably neither contains a conjugated double linkage. In a later paper (*J. pr. Chem.*, 1927, **117**, 273) Deussen suggests formula (III) for γ -caryophyllene, in consideration of the fact that he obtained succinic acid, along with other products, by the action of steam on its ozonide. If this is the constitution of γ -caryophyllene, formula (IV) may be tentatively assigned to β -caryophyllene alcohol (compare Henderson, Robertson, and Kerr, J., 1926, 62) and formula (V) to clovene. The relation of *isoclovene* to clovene remains for the present unsettled.



EXPERIMENTAL.

Preparation of β -Caryophyllene Alcohol and its Dehydration Products.—Caryophyllene was repeatedly distilled at 13 mm. pressure, and four fractions, b. p. 109—115°, 115—120°, 120—123°, and 123—127°, were collected. Each fraction was hydrated by the method of Asahina and Tsukamoto (*J. Pharm. Soc. Japan*, 1922, 463), which yields the α - as well as the β -alcohol; there was very little difference in the quantities of the latter obtained from the several fractions. 100 C.c. of caryophyllene were added drop by drop to a mixture of 80 c.c. of absolute ether and 30 c.c. of sulphuric acid monohydrate cooled to 0°, the temperature of the reaction mixture being maintained below 10°. After the reaction mixture (kept in the cooling mixture) had reached room temperature, it was poured into a mixture of ice and sodium carbonate, and the alkaline liquid distilled in steam until nothing more passed over. The first portion of the distillate consisted mainly of a hydrocarbon: from the other portion the β -alcohol crystallised on cooling; it was redistilled in steam and crystallised from acetone until its melting

point was 96°. 90 G. of phosphoric oxide were added in small portions to 70 g. of the alcohol heated to its melting point. The vigorous reaction was controlled by cooling and, when completed, the product was neutralised with sodium carbonate and distilled in steam. The oily liquid which passed over was extracted and dried (with anhydrous sodium sulphate) in ether and then distilled several times under diminished pressure. Two fractions were obtained: (1) a mobile oil, b. p. 111—113°/10 mm., which proved to be clovene, and (2) a slightly more viscous oil, b. p. 115—118°/10 mm. The latter was dissolved in twice its volume of absolute ether, cooled to 0°, and slowly saturated with hydrogen chloride. After standing for 3 days at that temperature, the ether was evaporated under diminished pressure and the dark oily residue cooled to -60°, with constant stirring. After some time the *monohydrochloride* of *isoclovene* solidified; after draining on a porous plate, it crystallised from ethyl acetate in hard colourless needles, m. p. 87° (Found: C, 74·6; H, 10·4; Cl, 14·6. $C_{15}H_{25}Cl$ requires C, 74·8; H, 10·5; Cl, 14·7%). Unlike the parent hydrocarbon, this is a stable compound when pure. The *monohydrobromide* of *isoclovene* was prepared in a similar manner. It begins to crystallise from the cooled ethereal solution as saturation approaches, and when purified by recrystallisation from ethyl acetate forms colourless prisms, m. p. 75°. When impure it is apt to decompose on exposure to moist air (Found: Br, 28·2. $C_{15}H_{25}Br$ requires Br, 28·2%).

The fraction of lower boiling point (111—113°/10 mm.) obtained along with *isoclovene* by the dehydration of caryophyllene alcohol as described above was treated in a similar manner with hydrogen chloride, but only a trace of the solid hydrochloride was formed. The great bulk of the product was a dark liquid, which after standing over soda-lime in a vacuum desiccator was found to contain 9·3% of chlorine. A similar liquid was obtained when the hydrocarbon formed as a by-product in the hydration of caryophyllene was purified by distillation over sodium and treated as above with hydrogen chloride.

In another experiment β -caryophyllene alcohol was dehydrated according to Wallach and Walker's method by treatment with phosphoric oxide at its boiling point and heating the liquid thus obtained a second time with the pentoxide. The final product in this case consisted solely of clovene, b. p. 110—113°/10 mm., and gave no crystalline hydrochloride. This result was to be expected, because we have found that *isoclovene* is completely decomposed when heated with phosphoric oxide even at temperatures below its boiling point.

Pure *isoclovene* was obtained from the monohydrochloride as

follows: 3 g. of the hydrochloride and 3.5 g. of anhydrous sodium acetate were boiled under reflux with 25 c.c. of glacial acetic acid for 4 hours; the acid was then neutralised with sodium carbonate, the product extracted with ether, and the ethereal solution washed and dried. After evaporation of the ether the liquid which remained was distilled over sodium under diminished pressure, and *isoclovene* finally obtained as a colourless, somewhat viscous liquid, with the physical constants quoted above (Found: C, 87.8; H, 11.7. $C_{15}H_{24}$ requires C, 88.2; H, 11.8%). When a solution of the hydrocarbon in two volumes of anhydrous ether is treated with hydrogen chloride and then concentrated, a quantitative yield of *isoclovene* monohydrochloride separates quickly.

Preparation of isoclovene Alcohol.—10.5 G. of silver acetate were added to a solution of 15 g. of *isoclovene* hydrochloride in 200 c.c. of glacial acetic acid, and the mixture was agitated in the dark for 4 days. After dilution with ice-water the acid was neutralised with sodium carbonate, and the crude ester extracted with light petroleum. The solution was dried over anhydrous sodium sulphate, the solvent distilled off, and the oily residue mixed with a little ethyl acetate and strongly cooled; about 10 g. of the ester then crystallised. When recrystallised from ethyl acetate it was quite colourless and melted at 25–26°. It was hydrolysed by warming with methyl-alcoholic potassium hydroxide, and also by leaving a solution in ethyl acetate exposed to moist air for some weeks; the *alcohol* then slowly separated. After several crystallisations from ethyl acetate the alcohol melted sharply at 98°. It is optically active: $\alpha_D^{20} = 0.65^\circ$ (in alcohol, $c = 0.5714$, $l = 0.5$); $[\alpha]_D^{20} = 227^\circ$ (Found: C, 80.5; H, 11.2. $C_{15}H_{26}O$ requires C, 81.1; H, 11.7%). It does not unite additively with bromine, and does not yield esters when treated with acetic anhydride, phthalic anhydride and *p*-nitrobenzoyl chloride, but is dehydrated when warmed with acetic anhydride.

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