CCLV.—*The Chemistry of the Caryophyllene Series. Part III. Clovene Alcohol and α-Caryophyllene Alcohol.*

By JAMES BELL and GEORGE GERALD HENDERSON.

IN a previous paper (Henderson, McCrone, and Robertson, J., 1929, 1368) it was recorded that analysis of the liquid by-product obtained during the preparation of caryophyllene dihydrochloride indicated the presence of a liquid monohydrochloride of a tricyclic sesquiterpene, presumably clovene, ring closure of some of the caryophyllene having been effected by the hydrochloric acid. We have now confirmed the presence of this monohydrochloride, $C_{15}H_{25}Cl$, by preparing from it a saturated tricyclic *alcohol*, $C_{15}H_{25}{\cdot}OH$, through the action of silver acetate and subsequent hydrolysis of the product. Moreover, confirmation of the view that this alcohol is a derivative of clovene has been obtained by the observation that an apparently identical alcohol is produced by saturating Wallach's clovene, prepared from β-caryophyllene alcohol, with hydrogen chloride and treating the product with silver acetate. The alcohol is a colourless, viscous liquid, b. p. 146—150°/10 mm., $d_{4^\circ}^{17^\circ}$ 0·9934, $n_{D}^{17^\circ}$ 1·5039, $[R_L]_D$ 66·15. It yields no crystalline derivatives on treatment with phenylcarbimide or *p*-nitrobenzoyl chloride. When dehydrated in the usual manner with phosphoric oxide it is converted into a sesquiterpene closely similar in physical properties to clovene. It must therefore be regarded as a new isomeride of α- and β-caryophyllene alcohols.

No systematic examination of α-caryophyllene alcohol has apparently been carried out since it was first prepared by Asahina and Tsukamoto (*J. Pharm. Soc. Japan*, 1922, 463). We have now investigated its behaviour towards certain reagents with a view to establish its relationship to β-caryophyllene alcohol. Wallach and Walker (*Annalen*, 1892, **271**, 285) showed that the latter alcohol on treatment with phosphorus pentachloride gives a crystalline chloro-derivative, $C_{15}H_{25}Cl$. This compound has been found by Henderson, Robertson, and Kerr (J., 1926, 62) to be remarkably stable towards reagents for the elimination of hydrogen chloride. We find that α-caryophyllene alcohol when treated under exactly similar conditions yields no corresponding derivative, the product being a hydrocarbon resembling clovene in physical properties. It is therefore evident that the constitution of the α-alcohol is different from that of β-caryophyllene alcohol.

Dehydration of α-caryophyllene alcohol with phosphoric oxide or anhydrous oxalic acid yields a sesquiterpene whose physical constants indicate a close resemblance to, if not identity with, clovene, as shown by the following table. Sesquiterpenes (1) and (2) were obtained by dehydration of α-caryophyllene alcohol with phosphoric oxide and with anhydrous oxalic acid, respectively, and (3) is clovene. The calculated $[R_L]_D$ for a tricyclic sesquiterpene is 64·4.

(1) B. p. 118—123°/12 mm., $d_{4°}^{17°}$ 0·9252, $n_D^{17°}$ 1·5000, $[R_L]_D$ 64·8,
(2) b. p. 116—122°/12 mm., $d_{4°}^{17°}$ 0·9308, $n_D^{17°}$ 1·4950, $[R_L]_D$ 64·1,
(3) b. p. 111—114°/10 mm., $d_{4°}^{20°}$ 0·9240, $n_D^{20°}$ 1·4980, $[R_L]_D$ 64·7.

The hydrocarbon from the α-alcohol gives no crystalline hydrochloride, thus showing the absence of *iso*clovene (compare Henderson, McCrone, and Robertson, *loc. cit.*).

β-Caryophyllene alcohol is not attacked by potassium permanganate and is stable even after prolonged treatment with hydrogen peroxide (Henderson, Robertson, and Kerr, *loc. cit.*). We have recently found, however, that it does not resist oxidation by means of Beckmann's chromic acid mixture, and that comparison of the oxidation products of α- and β-caryophyllene alcohols shows that these alcohols are structural isomerides. β-Caryophyllene alcohol on oxidation with this reagent yields as main product a viscous acid which cannot be induced to crystallise, but analyses of its *silver* salt and *methyl* ester indicate that it has the formula $C_{10}H_{12}O_3$. It is evident that oxidation in this manner results in considerable degradation of the original nucleus.

α-Caryophyllene alcohol when similarly treated with chromic acid mixture is oxidised to a crystalline dicarboxylic acid, which is identical with an acid prepared in Professor Ruzicka's laboratories by the chromic acid oxidation of the sesquiterpene obtained as by-product in the hydration of caryophyllene (private communication). Hence it may be assumed that the tricyclic sesquiterpene produced by the dehydration of α-caryophyllene alcohol is identical with this by-product. It is possible that the production of this tricyclic liquid by-product of hydration is 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.

EXPERIMENTAL.

Purification of Liquid By-product obtained during Preparation of Caryophyllene Dihydrochloride.—The mother-liquor from the preparation of the dihydrochloride was a black mobile oil, smelling strongly of hydrogen chloride. After as much as possible of the dihydrochloride had been removed by cooling to 0°, the liquid was kept for 72 hours in a vacuum desiccator containing caustic soda. The oil, which then showed no trace of acid fumes, was shaken repeatedly with dilute sodium bicarbonate solution, extracted with ether, the extract washed and dried, and the solvent removed at room temperature. A small quantity of the solid caryophyllene dihydrochloride crystallised after four days at —10°, leaving a clear yellowish-brown oil, containing Cl, 18·4% (Calc. for $C_{15}H_{25}Cl$: Cl, 14·6%), so it was evident that a small percentage of the dihydrochloride still remained in solution, but decomposition ensued when an attempt was made further to purify the monohydrochloride by distillation under diminished pressure.

Preparation of Hydroxyl Derivative from the Liquid Hydrochloride.—Treatment with moist silver oxide in ether proved useless, the hydrochloride being recovered unchanged after 5 days' heating under reflux. Better results were obtained by using silver acetate.

Finely divided silver acetate (17 g.) was added in small quantities during 6 hours to a solution of the monohydrochloride (20 g.) in glacial acetic acid (200 c.c.); the mixture was then maintained at 50—60° for 3 hours, and, after cooling, the precipitated silver chloride was removed and the acetic acid neutralised with sodium carbonate. The product which separated was extracted with ether, and on removal of the solvent was obtained as a viscous red-brown oil. After hydrolysis with methyl-alcoholic potassium hydroxide (10%), the product was distilled in a current of steam, collected, dried and distilled, yielding finally two main fractions : (*a*) b. p. 118—124°/10 mm., and (*b*) b. p. 146—154°/10 mm. Fraction (*a*) was proved to be clovene by examination of its physical constants; $d_{4°}^{20°}$ 0·9276, $n_D^{20°}$ 1·4992, $[R_L]_D$ 64·6. Fraction (*b*) reacted slowly with metallic sodium and had $d_{4°}^{17°}$ 0·9934, $n_D^{17°}$ 1·5039, $[R_L]_D$ 66·15 (Calc. for a tricyclic sesquiterpene alcohol, 66·4) (Found : C, 81·8; H, 11·5. $C_{15}H_{26}O$ requires C, 81·1; H, 11·7%). The *alcohol* was saturated towards bromine and potassium permanganate. It gave no solid derivative when treated with phenylcarbimide or with *p*-nitrobenzoyl chloride, and therefore appears to be a tertiary alcohol; on dehydration with phosphoric oxide, it yielded clovene, $d_{4°}^{17°}$ 0·9250, $n_D^{17°}$ 1·5004, $[R_L]_D$ 64·8.

Preparation of Hydroxyl Derivative of Clovene.—Clovene, prepared from β-caryophyllene alcohol by dehydration with phosphoric oxide, was dissolved in twice its volume of anhydrous ether, cooled to 0°, 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, and then contained Cl, 12·4% (Calc. for $C_{15}H_{25}Cl$: Cl, 14·6%). It was treated with silver acetate as previously described, and the products were similar to those obtained from the by-product monohydrochloride. In this case, however, the recovered clovene constituted about three-quarters of the total product, consequently purification of the higher fraction was more difficult. This fraction had b. p. 143—152°/10 mm.; $d_{4^\circ}^{17^\circ}$ 0·9860, $n_{D}^{17^\circ}$ 1·5010, $[R_L]_D$ 66·3 (Found, C, 82·6; H, 11·5%). These results indicated the presence of the tricyclic alcohol previously obtained.

Action of Phosphorus Pentachloride on α-Caryophyllene Alcohol.—Vigorous reaction took place when α-caryophyllene alcohol was heated with phosphorus pentachloride, hydrogen chloride 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 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 similar to the dehydration product of α-caryophyllene alcohol. It was not further examined.

Dehydration of α-Caryophyllene Alcohol.—(a) *By phosphoric oxide.* α-Caryophyllene alcohol (10 g.) was dehydrated by means of phosphoric oxide according to the method by which *iso*clovene was obtained from β-caryophyllene alcohol (Henderson, Robertson, and Kerr, *loc. cit.*). The product consisted of a colourless mobile oil having b. p. 118—123°/12 mm., $d_{4^\circ}^{17^\circ}$ 0·9252, $n_{D}^{17^\circ}$ 1·5000, $[R_L]_D$ 64·8 (Found : C, 87·8; H, 11·6. Calc for $C_{15}H_{24}$: C, 88·2; H, 11·7%). No solid hydrochloride was obtained on saturation of the oil at 0° with dry hydrogen chloride, and thus the absence of *iso*clovene was proved.

(b) *By oxalic acid.* α-Caryophyllene alcohol (10 g.) was mixed with anhydrous oxalic acid (10 g.) and kept for four days at 150—160°. The product was then distilled in steam; a faintly yellowish oil resulted, similar to that obtained by the previous method of dehydration, and after distillation in a vacuum it showed the following constants: b. p. 116—122°/12 mm., $d_{4^\circ}^{17^\circ}$ 0·9308, $n_{D}^{17^\circ}$ 1·4950, $[R_L]_D$ 64·1 (Found : C, 87·6; H, 11·6%). As before, this sesquiterpene yielded no solid hydrochloride.

Oxidation of β-Caryophyllene Alcohol.—The chromic acid mixture used in this and the following oxidation was made from 60 g. of potassium dichromate (1 mol.), 80 g. of concentrated sulphuric acid (4 mols.), and 27 g. of water. β-Caryophyllene alcohol (10 g.) was dissolved in glacial acetic acid (150 c.c.) and the mixture (100 c.c.) added. The whole was then kept at 60—70° for 35—40 hours; the bulk of the acetic acid was then distilled off under reduced pressure, and the residue repeatedly extracted with ether. The extract was washed and dried, the solvent removed, and the semisolid product heated with aqueous sodium carbonate. The alkaline solution was freed from mechanically suspended neutral products by extraction with ether, and on removal of the ether, the neutral product solidified and was found to consist of unchanged β-caryophyllene alcohol (m. p. and mixed m. p. 96°; recovered, 5 g.). The acid product was obtained by acidifying the alkaline solution in the form of a viscous oil, which was freed from traces of chromium and neutral products by conversion into the sodium salt. For further purification the acid was converted into the *methyl* ester, which was prepared from the insoluble silver salt by the action of methyl iodide in the usual manner. The ester was a colourless, somewhat viscous oil, the main bulk distilling at 170—180°/10 mm. (Found: C, 67·8; H, 7·4. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%). This analysis, indicating $C_{10}H_{12}O_3$ as the formula for the acid, was supported by analysis of the *silver* salt which gave 187 as the molecular weight of the acid (assumed monobasic). The purified methyl ester on hydrolysis yielded the acid as a viscous oil once more.

Oxidation of α-Caryophyllene Alcohol.—α-Caryophyllene alcohol (10 g.) was oxidised by means of chromic acid mixture under the same conditions as described for the β-alcohol, and the products were worked up similarly. Practically no α-caryophyllene alcohol was recovered unchanged, but the neutral products contained a small quantity of an oil which appeared to be a hydrocarbon. The acid product was obtained as 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 anhydride could be extracted (total yield of acid, 4 g.). The acid, recrystallised from ethyl alcohol, melted sharply at 187°. When heated above its m. p. it lost the elements of water, forming an anhydride. The anhydride when recrystallised from light petroleum, in which the acid was insoluble, melted at 49·5°. Mixed melting-point determinations on the acid along with a specimen of Ruzicka's dicarboxylic acid, and also on the anhydride mixed with the anhydride of the same dicarboxylic acid, showed no depression.

We take this opportunity to express grateful thanks to the Directors of Imperial Chemical Industries Ltd. for a grant which helped to defray the cost of this work, and one of us (J. B.) is indebted to the Department of Scientific and Industrial Research for a maintenance allowance.

UNIVERSITY OF GLASGOW. [*Received, June 24th,* 1930.]