CVI.—*On the Chemical Individuality of Humulene.*

By A. Chaston Chapman.

In the course of a study of the constituents of the essential oil of hops I discovered that this oil contained a considerable proportion (usually from one-third to one-half) of a sesquiterpene, to which I gave the name *humulene*. The properties of this hydrocarbon and of a number of its derivatives were described (J., 1895, **67**, 54, 780). Struck chiefly by the fact that Wallach had shortly before this obtained from caryophyllene a nitrosochloride melting at very nearly the same temperature as humulene nitrosochloride, I examined the new sesquiterpene very closely in order to ascertain whether it might not be an inactive form of caryophyllene. For reasons which seemed to me adequate I came very definitely to the conclusion that these two sesquiterpenes were not identical. Three years later Kremer, Schreiner, and James prepared a number of caryophyllene and humulene derivatives, and as a result of a careful comparison of these arrived at the same conclusion (*Pharm. Arch.*, 1898, **1**, 209). So far as I am aware, no further work on this subject was carried out until 1911, when a paper by Deussen appeared (*J. pr. Chem.*, 1911, **83**, 483) in which he stated that he had identified humulene with " inactive α-caryophyllene."

In 1907, Deussen and Lewinsohn (*Annalen*, **356**, 1), in continuation of some work by Kremer and Schreiner (*Pharm. Arch.*, 1899, **2**, 273), had devoted their attention to a study of certain caryophyllene derivatives, and found that by a process of crystallisation some of these could be resolved into isomeric substances which they designated by the prefixes α- and β-, respectively.

The same authors (*ibid.*, 1908, **359**. 245) also stated that caryophyllene on repeated distillation under reduced pressure yields two lævorotatory hydrocarbons, one having b. p. 132—134°/16 mm., $d^{20°}$ 0·90346, and $[\alpha]_D^{20°} - 4{\cdot}67°$, and the other b. p. 128—128·5°/17 mm., $d^{17°}$ 0·91034, and $[\alpha]_D^{17°} - 23{\cdot}57°$. The hydrocarbon of lower boiling point yielded 20·8% of a nitrosochloride and over 8% of blue nitrosite, whereas the higher-boiling hydrocarbon yielded little more than traces of a nitrosochloride or of a nitrosite. They concluded that caryophyllene as usually known is a mixture of inactive caryophyllene with a considerable amount of a lævorotatory hydrocarbon.

In that paper the expression " inactive caryophyllene " appears to have been used for the first time, but in support of the existence of such a hydrocarbon no proof is given. In a subsequent paper, Deussen (*ibid.*, 1909, **369**, 41) assigned a structural formula to the so-called β-caryophyllene, and in collaboration with Loesche and Klemm described a number of derivatives obtained from three hydrocarbons, referred to as α-, β-, and *iso*-caryophyllene respectively, although what the relationship between these was is not very clear. Deussen also states (*loc. cit.*, 1911) that it is the " inactive " caryophyllene with which humulene was considered to be identical, that is to say, the caryophyllene fraction boiling at the higher temperature, and this statement appears to have been accepted by many chemists and to have passed into the literature. In that paper Deussen directed attention to the resemblance between the properties of humulene as described by me, and confirmed by other observers, and those of the higher, or α-caryophyllene fraction, but he gave very little information in regard to the physical constants of the so-called " α-caryophyllene " ; he again referred to it as being inactive, and again without adducing any evidence of its actual existence. Certain of the better known derivatives of this hydrocarbon were compared with those of humulene, but the results were of an indefinite character and certainly were not such as to justify the statement that these two hydrocarbons were identical. In this connexion it may be pointed out that whereas humulene yields a nitrosite with great readiness, no such compound could apparently be prepared from the higher caryophyllene fraction, and no attempt appears to have been made to prepare the very characteristic caryophyllene alcohol.

In the following year Deussen (*Annalen*, 1912, **388**, 136) claimed to have devised a method by which β-caryophyllene could be estimated, and by the application of this method reached the conclusion that the hydrocarbon from hop oil which I had described as humulene contained 4% of β-caryophyllene.

In 1914 Deussen in collaboration with Vielitz and Mayer instanced a case in which two quite different halogen derivatives of α-caryophyllene having the same melting point, gave no depression when mixed, whereas this property was in the 1911 paper relied upon as establishing the identity of humulene and the so-called α-caryophyllene, and in 1923 Deussen (*Z. angew. Chem.*, **36**, 348) recapitulated some of the results obtained in the comparison of certain compounds of humulene with those of α-caryophyllene.

EXPERIMENTAL.

Inasmuch as Deussen and his colleagues have assigned the expression α- or inactive caryophyllene to that portion of the crude sesquiterpenes boiling at the higher temperature and having the lower lævorotation, I thought it would be desirable in the first place to repeat their experiments. Five lb. of crude caryophyllene, representing a batch of 40 lb. prepared by the British Drug Houses from clove oil, were submitted to fractional distillation under a pressure of about 3 mm. from a long-necked flask with bulbs. Boiling commenced at 50°, the temperature rose rapidly to 90°, at which the hydrocarbon began to distil in quantity, and then slowly to 105°. Between 105° and 125°—at which point the distillation was stopped—the amount distilling was very small. The densities ($d_{20^\circ}^{20^\circ}$) of the various fractions rose gradually from 0·9024 to 0·9047, and the optical rotations ($\alpha_D^{20^\circ}$; $l = 1$) increased more or less uniformly from $-$ 7·3° to $-$ 9·3°. The final small fraction referred to above (105—125°) had *d* 0·9138 and α $-$ 11·6°.

As the result of further fractional distillation the caryophyllene was obtained in two main fractions: (1) b. p. 95—97°/3 mm., $d_{20^\circ}^{20^\circ}$ 0·9028, $n_D^{20^\circ}$ 1·4987, $[\alpha]_D$ $-$ 8·2°; (2) b. p. 98—102°/3 mm., $d_{20^\circ}^{20^\circ}$ 0·9035, $n_D^{20^\circ}$ 1·4990, $[\alpha]_D$ $-$ 9·3°.

Continued fractionation failed to effect any further separation and it became clear, therefore, that even when working on large quantities of the crude hydrocarbon, fractional distillation could not be relied upon to effect any further separation than is indicated by the above results. This, it will be seen, is very different from the experience of Deussen and his colleagues, who stated that there had been a separation into two forms of caryophyllene, that one of these, namely, that corresponding with the higher boiling range, was nearly inactive, and consisted mainly of the so-called α-caryophyllene, and further that this was identical with humulene.

The experiments recorded above show, on the contrary, that with rising boiling point the lævorotation showed a small but steady increase. At no point was any fraction obtained which was inactive, or which did not show approximately the steady rise referred to.

Fractional distillation having failed to effect any satisfactory separation so far as this could be judged by reference to the physical properties, recourse was had to the preparation of derivatives for purposes of comparison. Fraction No. 2 was used in the preparation of these derivatives as presumably containing the higher proportion of the so-called α-caryophyllene, although there was in reality no material difference between the two fractions. The humulene used was freshly prepared from 1¼ lb. of fresh hop oil distilled from green hops, and had the following characteristics : b. p. 99—100°/ 3 mm., $d_{20^\circ}^{20^\circ}$ 0·8923, $n_D^{20^\circ}$ 1·5001, $[\alpha]_D$ + 1·7°.

Dihydrochloride. Humulene does not appear to form a solid compound with hydrogen chloride, whereas caryophyllene readily forms the crystalline dihydrochloride. When dry hydrogen chloride was passed into the No. 2 caryophyllene fraction an amount of crystalline hydrochloride corresponding with at least 80% of ordinary caryophyllene was obtained. This melted at 69° and had the usual properties of the caryophyllene compound.

Caryophyllene alcohol. A portion of the second fraction, when treated by Bertram and Walbaum's method, gave a large yield of the solid alcohol, which was steam-distilled and purified in the usual way. Humulene, when treated in the same manner, gave no solid product.

Nitrosite. Both the No. 1 and the No. 2 caryophyllene fraction gave substantial yields of the blue nitrosite, which melted, after two recrystallisations from cold dilute acetone, at 115°. The corresponding compound from humulene melted at 114°. The addition of the humulene to the caryophyllene compound depressed the melting point by about 20°.

Nitrosate. Caryophyllene nitrosate was prepared by the usual method and after several recrystallisations melted at 163°. The yield was small. The yield of the corresponding compound from humulene was very much larger, but the melting point was the same, and there was no depression when this was mixed with the compound obtained from crude caryophyllene.

Nitrosochloride. The caryophyllene fraction gave a very small yield of the nitrosochloride as compared with humulene from hop oil, the latter giving at least eight times as much. The melting point in each case after recrystallisation was 176° and no depression was observed when a mixed melting-point determination was made. The conditions adopted for the preparation of the nitrosochloride were those under which the β-caryophyllene compound is not obtained in crystal form.

Nitrolbenzylamine. This compound, when prepared from the nitrosochloride, was found after a second recrystallisation to melt at 136°, which is the same temperature as that at which the humulene derivative melted. A mixture of the crystals showed no depression of melting point.

Nitrolpiperidide. This compound also was prepared from the nitrosochloride and after several recrystallisations melted at 153°. The corresponding humulene compound also melts at this temperature and a mixed melting point showed no depression.

The above results appear to show that the crude sesquiterpene obtained from clove oil consists substantially of caryophyllene with a rotation of about $[\alpha]_D - 8°$, and that this crude hydrocarbon contains a small proportion—say 5—10%—of humulene.

Working on a very large quantity of crude caryophyllene, I have in fact been unable to obtain an inactive form of this hydrocarbon,* and it is obvious that the hydrocarbon to which Deussen refers as the α- or inactive caryophyllene is neither more nor less than humulene. Probably crude caryophyllene is subject to slight variations depending on the source from which it has been obtained, and other sesquiterpenes than humulene may at times be present.

I have to offer my best thanks to Messrs. The British Drug Houses, Ltd., for having placed at my disposal a large quantity of crude caryophyllene, and to Messrs. White, Tomkins, and Courage, Ltd., for the higher fractions of some freshly distilled hop oil from which a new specimen of humulene was prepared. I have also great pleasure in acknowledging the valuable assistance rendered to me by Mr. Gerald Bishop, M.Sc., A.I.C.

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