398. *The Caryophyllenes. Part I.*

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Although the clove oil sesquiterpenes, the so-called caryophyllenes, have been extensively investigated (for references, see Simonsen, " The Terpenes," Vol. 2, pp. 513—527), little progress has been made in the elucidation of their constitutions. This mixture of sesquiterpenes consists essentially of three hydrocarbons, designated respectively α-, β-, and γ-caryophyllene, the first of these being in all probability identical with the hop oil sesquiterpene, humulene (Chapman, J., 1928, 785; 1929, 359). From the hydrocarbons, well-defined crystalline derivatives have been prepared : these we have used for degradative experiments, since the hydrocarbons themselves are inseparable and the proportion of any one present in different samples of clove oil shows considerable variation. Although our experiments are only in a preliminary stage, we place them on record because one of us can no longer participate in the investigation.

Our intention is to prepare from the crystalline nitrosite (or nitrosochloride) the corresponding saturated amine, and convert this through the alcohol into the unsaturated hydrocarbon, from which it is hoped to obtain simple degradation products enabling us to deduce the structure of the parent hydrocarbon.

From the blue β-caryophyllene nitrosite (Deussen and Lewisohn, *Annalen*, 1907, **356**, 13), by vigorous reduction with sodium and alcohol, aminodihydro-β-caryophyllene (Semmler and Mayer, *Ber.*, 1911, **44**, 3678) was prepared. This base does not yield any well-defined derivatives and is probably a mixture of stereoisomerides. On catalytic hydrogenation, *aminotetrahydro-β-caryophyllene* was obtained, from which, by the action of nitrous acid, followed by dehydration, *dihydro-β-caryophyllene* was prepared. This hydrocarbon differs markedly in its physical properties from the two isomeric dihydrocaryophyllenes described by Deussen (*J. pr. Chem.*, 1927, **117**, 273). Preliminary experiments have shown the hydrocarbon to be readily attacked by oxidising agents : the products will be discussed in a future communication.

From humulene (α-caryophyllene) nitrosochloride we have prepared, by the action of pyridine, a mixture of nitrosohumulenes, from which a crystalline nitrosohumulene, m. p. 126—127°, has been separated. This is identical probably with the substance, m. p. 128—129°, obtained by Deussen, Loesche, and Klemm (*Annalen*, 1909, **369**, 47) by the action of sodium ethoxide or propoxide on the nitrosochloride. On mild reduction with sodium and alcohol the crystalline nitrosohumulene yields *aminodihydrohumulene*, characterised by the preparation of an *acetyl* derivative, m. p. 142°. This base differs from aminodihydro-β-caryophyllene in that it is apparently homogeneous.

During the examination of the degradation products of dihydro-β-caryophyllene it soon became apparent that it was of fundamental importance to determine the structure of caryophyllenic acid. This acid, $C_9H_{14}O_4$, first isolated as an oil by Semmler and Mayer (*loc. cit.*, p. 3663), has been shown by Ruzicka, Wind, and Bardhan (*Helv. Chim. Acta*, 1931, **14**, 410, 423) to be not homogeneous, evidence being obtained of the presence of two crystalline acids, m. p. 145—150° and 66—75°, respectively. The two acids were not obtained pure, but analysis suggested that the former acid had the composition $C_8H_{12}O_4$ and the latter $C_9H_{14}O_4$. The composition of the latter acid was confirmed by the preparation from its methyl ester of crystalline tetramethyl and tetraphenyl glycols. Somewhat remarkable results were obtained by the degradation of these glycols, the latter yielding *as.*-dimethylsuccinic acid and the former αα'α'-tetramethylglutaric acid. It is obvious that the latter acid can only result from some profound molecular rearrangement.

By the oxidation of caryophyllene (Deussen's γ-caryophyllene, recovered from the preparation of the nitrosite) with potassium permanganate in acetone solution, followed by nitric acid, we have prepared a considerable quantity of crude caryophyllenic acid. This on purification through its methyl ester (p. 1809) was separated into fractions which gave on hydrolysis (i) *as.*-dimethylsuccinic acid, (ii) a strongly dextrorotatory acid, $C_8H_{12}O_4$, m. p. 125—127°, *norcaryophyllenic acid*, and (iii) caryophyllenic acid, $C_9H_{14}O_4$, m. p. 80—81°. The last acid can be readily separated from the appropriate ester fraction because it yields a potassium salt which is sparingly soluble in methyl alcohol (compare Deussen and Hacker, *J. pr. Chem.*, 1929, **122**, 261).

Our acid, m. p. 80—81°, is undoubtedly identical with Ruzicka's somewhat impure acid, m. p. 66—75°, but the relationship of norcaryophyllenic acid to Ruzicka's acid, m. p. 145—150°, is obscure. Like the last, our acid is a *cis*-acid, since it yields a liquid anhydride by the action of acetyl chloride, and it is possible that the higher-melting acid is the racemic modification.

Adequate grounds have been given by Ruzicka and his collaborators for rejecting Semmler and Mayer's suggestion that caryophyllenic acid is a methylnorpinic acid, and the isolation of norcaryophyllenic acid affords further support to this view, although we have no evidence at present that norcaryophyllenic and caryophyllenic acids are related to one another as norpinic and pinic acids. Norcaryophyllenic acid resembles very closely in its properties the lævorotatory acid, umbellaric acid, m. p. 121°, obtained by Tutin (J., 1906, **89**, 1115) by the oxidation of umbellulone. By the kindness of Dr. T. A. Henry we have been able to compare norcaryophyllenic acid with a specimen of Tutin's acid, and the comparison leaves no doubt that the two acids are not stereoisomerides. Unlike umbellaric acid, norcaryophyllenic acid does not form a hydrate when crystallised from water, and a mixture of the two acids, in proportions which would yield the *dl*-acid, melts indefinitely from 50—80°. The stability of norcaryophyllenic acid to mineral acids (it is not attacked by hydrochloric acid at 120°) renders it very improbable that it is a *cyclo*propane acid, and on other grounds a *cyclo*butane structure is equally improbable. We suggest, therefore, that it is a methyl*cyclo*pentanedicarboxylic acid. Owing to its stability the determination of its constitution is difficult, but we have found (p. 1809) that bromination, followed by the elimination of hydrogen bromide, yields *dehydronorcaryophyllenic acid*, $C_8H_{10}O_4$, m. p. 193°. This acid is unstable to potassium permanganate and it is hoped, when more material is available, to examine its oxidation products.

EXPERIMENTAL.

Aminodihydro-β-caryophyllene.—β-Caryophyllene nitrosite (16 g. from caryophyllene 50 c.c.) in absolute alcohol (250 c.c.) was added to sodium (24 g.) and at the end of the vigorous reaction the alcohol was removed by steam distillation. The amine was extracted in ether, purified from non-basic material by means of dilute sulphuric acid, and recovered (9 g.), b. p. 138—143°/2 mm., $d_{25°}^{25°}$ 0·9293, $n_D^{17°}$ 1·5030, $[\alpha]_{5461}$ + 13·5° (Found : C, 81·6; H, 12·2. Calc. : C, 81·4; H, 12·2%). Its derivatives would not solidify, except the 3 : 5-dinitrobenzoate, m. p. 172—173° (soft. 163°) after four crystallisations from methyl alcohol.

Aminotetrahydro-β-caryophyllene.—The above-mentioned amine (52 g.) in alcohol (100 c.c.) was shaken at 70° with palladium-norite (5 g., 10%) and hydrogen under pressure (3 atm.). Absorption was complete after 24 hours and the filtered solution on fractionation gave the *amine* (45 g.), b. p. 140—142°/12 mm., $d_{20°}^{20°}$ 0·9194, $n_D^{15°}$ 1·4956, $[\alpha]$ − 29·1° (Found : C, 80·4; H, 12·9. $C_{15}H_{29}N$ requires C, 80·7; H, 13·0%).

Dihydro-β-caryophyllene.—The tetrahydro-amine (10 g.) in acetic acid (100 c.c.; 10%) was cooled in a freezing mixture, and a saturated solution of sodium nitrite (10 c.c.) added slowly with shaking. After standing at room temperature for 1 hour, the liberated oil was collected in ether and twice fractionated, giving an oil (5 g.), b. p. 118—120°/14 mm., and a fraction (2·2 g.), b. p. 157—159°/18 mm. In subsequent experiments dehydration was effected by heating the whole with powdered potassium hydrogen sulphate (12 g.) for 6 hours at 190°. The *hydrocarbon*, steam-distilled and collected in ligroin (b. p. 40—60°) before distillation over sodium, was obtained as a colourless oil (6 g.), b. p. 118—121°/14 mm., $d_{25°}^{25°}$ 0·8833, $n_D^{25°}$ 1·4840, $[\alpha]_{5461}$ − 47·15° (Found : C, 87·4; H, 12·8. $C_{15}H_{26}$ requires C, 87·4; H, 12·6%).

Nitrosohumulene.—Fractionation of the total terpene content of clove oil closely followed Henderson's results (J., 1929, 1370). For the preparation of humulene nitrosochloride, the fraction, b. p. 118—122°/12 mm., gave the best yield (12—15%) with ethyl nitrite in ethyl-alcoholic solution.

The nitrosochloride (15 g.) and pyridine (25 c.c.) were gently boiled for 5 minutes and the cooled acidified solution was extracted with ether. The solvent was removed; the residue distilled as a viscid colourless oil (10·5 g.), b. p. 138—143°/2 mm., which deposited plates (5 g.) from ethyl alcohol (25 c.c.; 80% by volume), m. p. 126—127° after recrystallisation (Found : C, 77·0; H, 10·1. $C_{15}H_{23}ON$ requires C, 77·3; H, 9·9%).

Aminodihydrohumulene.—Sodium (16 g.) was added in two pieces to nitrosohumulene (8 g.) in alcohol (150 c.c.), no attempt being made to ensure a vigorous reaction. After completion of the reaction water was added, and the separated oil collected in a little ether. With dilute hydrochloric acid the ethereal extract gave a solid *hydrochloride*, which was washed with ether, dried (8·5 g., m. p. 255°), and crystallised from very dilute hydrochloric acid, long needles being obtained, m. p. 257° (Found : Cl, 13·7. $C_{15}H_{27}N,HCl$ requires Cl, 13·8%). The *base* was recovered by shaking the hydrochloride (8 g.) with excess of dilute sodium hydroxide solution and ligroin; the colourless oil had b. p. 141—142°/11 mm., $d_{25°}^{25°}$ 0·9202, $n_D^{25°}$ 1·5039, $[\alpha]_{5461}$ − 0·64° (Found: C, 80·7; H, 12·2. $C_{15}H_{27}N$ requires C, 81·4; H, 12·2%); it was practically insoluble in water and gave a solid sulphate and nitrate. The *acetyl* derivative formed readily from the base (0·2 g.) and acetic anhydride (0·3 g.) on warming and solidified on cautious addition of water. It crystallised from ligroin (b. p. 60—80°) in needles, m. p. 142° (Found : C, 77·5;

H, 11·1. $C_{17}H_{29}ON$ requires C, 77·6; H, 11·0%). The *picrolonate* crystallised in yellow plates, m. p. 232° (Found : C, 62·1; H, 7·3. $C_{15}H_{27}N,C_{10}H_8O_5N_4$ requires C, 61·9; H, 7·2%).

Norcaryophyllenic and Caryophyllenic Acids.—γ-Caryophyllene (50 g.; b. p. 115—118°/11 mm.) in acetone (300 c.c.) (ice) was stirred, and finely powdered potassium permanganate (170 g.) added during one day. The filtered sludge was repeatedly digested with water and the combined washings were concentrated. After extraction with ether to remove neutral products, the acidified solution was repeatedly extracted with ether, evaporation of the dried solution yielding a brown gum (38 g.). This was further vigorously oxidised by cautious addition of nitric acid (*d* 1·165), followed by heating on the water-bath. In all, 400 c.c. of acid were added and the heating was continued for 48 hours before the excess of mineral acid was completely removed. The residue (23 g.) was refluxed (20 hours) with methyl alcohol (125 c.c.) and sulphuric acid (25 c.c.) : the crude ester (56 g.; b. p. 100—150°/20 mm.) from six similar experiments was systematically fractionated under diminished pressure (20 mm.) and after four distillations the following fractions boiling below 140° were obtained : (i) up to 100°; (ii) 100—115° (7·2 g.); (iii) 115—125° (15 g.); (iv) 125—130° (5 g.); (v) 130—135° (12·8 g.); (vi) 135—140° (7 g.).

Fraction (ii). Hydrolysis of this fraction with methyl-alcoholic potassium hydroxide solution (KOH, 8 g.) gave an acid (isolated by ether) which crystallised on scratching. It was dissolved in aqueous ammonia, addition of calcium chloride precipitating a sparingly soluble calcium salt on boiling. This was collected and decomposed with hydrochloric acid; the acid recovered by ether was identified as *as.*-dimethylsuccinic acid, m. p. and mixed m. p. 139—140°. The filtrate from the insoluble calcium salt was acidified; the recovered acid (1·7 g.) slowly partly crystallised. After trituration with concentrated hydrochloric acid the crystalline acid was collected, m. p. 80—100°. It was combined with the crude norcaryophyllenic acid from later fractions.

Fraction (iii). The acid from the hydrolysis of this ester fraction, treated as described above, gave *as.*-dimethylsuccinic acid (2·4 g.) and crude norcaryophyllenic acid (7·7 g.).

Fraction (iv). This fraction gave on hydrolysis norcaryophyllenic acid (2·4 g.). The hydrochloric acid from which this separated left, on evaporation in a vacuum over potassium hydroxide, a gum which on solution in methyl-alcoholic potassium hydroxide gave a quantity of the sparingly soluble potassium salt of caryophyllenic acid.

Fraction (v). On hydrolysis of this fraction with methyl-alcoholic potassium hydroxide a sparingly soluble potassium salt separated in needles from the hot solution. After digestion for 1 hour the well-cooled solution (ice) was filtered, the potassium salt washed rapidly with cold methyl alcohol and dissolved in water, and after removal of methyl alcohol by evaporation the acidified solution was repeatedly extracted with ether. Evaporation of the ether left an oil, which rapidly set to a hard crystalline cake (6 g.), m. p. 66—75°. The filtrate from the sparingly soluble salt gave a liquid acid, from which caryophyllenic acid and norcaryophyllenic acid were separated by renewed treatment with methyl-alcoholic potassium hydroxide.

Fraction (vi). Caryophyllenic acid (4 g.) was separated from this fraction through the potassium salt.

cis-*Norcaryophyllenic acid* was purified by repeated crystallisation from benzene, in which it was somewhat sparingly soluble, separating in hard conglomerates consisting of rosettes of thin prisms, m. p. 125—127° (sint. 118°). It was very readily soluble in water and in the usual organic solvents except benzene, *cyclo*hexane, and ligroin. It crystallised well from hydrochloric acid. In chloroform (*c*, 1·885) $[\alpha]_{5461} + 137°$; $[\alpha]_{5780} + 118·6°$ (Found : C, 56·1; H, 7·1; *M*, 171·1. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%; *M*, 172). An aqueous solution of the acid gave no precipitate with copper acetate in the cold, but a sparingly soluble copper salt separated on warming. When the acid was digested with acetyl chloride, a liquid anhydride was obtained which was only slowly decomposed by hot water. The acid regenerated from the anhydride had m. p. 125—127°.

cis-*Caryophyllenic acid* crystallised from *cyclo*hexane, in which it was not readily soluble and from which it tended to separate as an oil, in rosettes of fine needles, m. p. 80—81° (sint. 76°). It was extremely soluble in water and the ordinary organic media except ligroin and *cyclo*hexane. In chloroform (*c*, 1·902) $[\alpha]_{5461} + 13·56°$. With copper acetate it behaved in a similar manner to the nor-acid (Found : C, 58·2; H, 7·7; *M*, 187·2. $C_9H_{14}O_4$ requires C, 58·0; H, 7·5%; *M*, 186).

Dehydronorcaryophyllenic Acid.—Norcaryophyllenic acid (1 g.) and phosphorus pentachloride (2·3 g.) were warmed on the water-bath for 10 minutes and to the cooled solution bromine (1 g.) was added. No reaction was apparent after 6 hours on the water-bath in a sealed tube, but the bromine had disappeared after 6 hours' heating at 120°. The product was esterified by gentle refluxing for 30 minutes with methyl alcohol (20 c.c.), and the bromo-ester isolated with ether. Without further purification it was refluxed (2 hours) with ethyl-alcoholic potassium hydroxide (2 g. in 4 c.c.), potassium bromide being immediately precipitated. Water was added, the alcohol evaporated, and the acidified solution extracted with ether. On removal of the solvent the residue solidified; *dehydronorcaryophyllenic acid* (0·3 g.) crystallised from water in plates, m. p. 193° (Found : C, 56·5, 56·4; H, 5·9, 6·0. $C_8H_{10}O_4$ requires C, 56·4; H, 5·9%). The acid is readily soluble in hot water and acetone and in the latter solvent rapidly decolorises potassium permanganate. It is probably optically inactive.

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