227. *The Caryophyllenes. Part VI. γ-Caryophyllene.*

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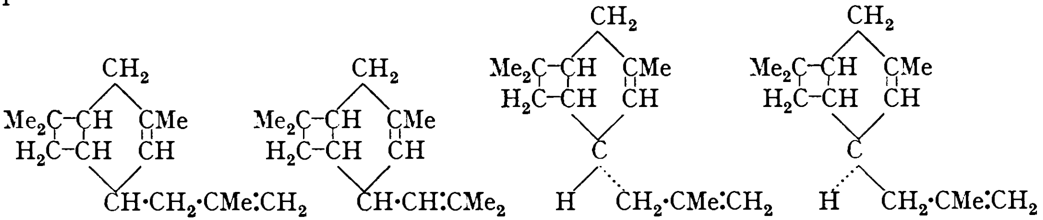
By the ozonolysis of acetamidodihydro-γ-caryophyllene, prepared from γ-caryophyllene α-nitrosochloride, and of acetamidodihydro-β-caryophyllene a crystalline *ketone*, $C_{16}H_{27}O_2N$, m. p. 139—140°, has been obtained. It is suggested that the parent hydrocarbons, β- and γ-caryophyllenes, are stereoisomerides. On the basis of Ruzicka's representation (I) for β-caryophyllene the most probable formulæ would appear to be (III) and (IV).

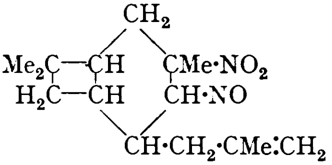
The designation *iso*caryophyllene, later changed to γ-caryophyllene (Deussen, *J. pr. Chem.*, 1914, **90**, 324), was given by Deussen and Lewinsohn (*Annalen*, 1907, **356**, 20) to a hydrocarbon isolated by the distillation in steam of the oil remaining after the preparation of the blue nitrosite of β-caryophyllene. It was obtained later by the same authors (*ibid.*, 1908, **359**, 251) in a purer state by the digestion of β-caryophyllene nitrosite with alcohol. The hydrocarbon was characterised by the preparation of two nitrosochlorides, α-, m. p. 123—124°, and β-, m. p. 147—148°; it did not, however, yield a nitrosite. Deussen considered γ-caryophyllene to be a homogeneous hydrocarbon, but this was questioned by Ruzicka and Wind (*Helv. Chim. Acta*, 1931, **14**, 410). Although there is no evidence that γ-caryophyllene occurs in nature or of its identity with the main hydrocarbon constituent of high rotatory power occurring in oil of cloves, it appeared of interest to investigate its structure, more especially since Deussen and his collaborators have shown that it must be related very closely to β-caryophyllene. They found that γ-caryophyllene α- and β-nitrosochlorides, β-caryophyllene nitrosochloride, and β-caryophyllene nitrosite gave on treatment with benzylamine the same nitrolamine and also that the nitrosochlorides of both hydrocarbons gave with sodium ethoxide the same substance, $C_{17}H_{29}O_2N$, m. p. 163—164° (cf. Deussen, *Annalen*, 1912, **388**, 137). We have confirmed the observation that γ-caryophyllene α-nitrosochloride and β-caryophyllene nitrosite give the same nitrolamine. It therefore appeared to us either that γ-caryophyllene must be the *iso*propylidene isomeride (II) or that the two hydrocarbons must be stereoisomerides, and of the various possibilities (III) and (IV) seem to us to be the most probable.



(I.) (II.) (III.) (IV.)

We now submit evidence which appears to support the latter explanation.

By the action of pyridine on γ-caryophyllene α-nitrosochloride, *oximino-γ-caryophyllene* was obtained as a viscid oil, which on reduction with sodium and alcohol gave *amino-*



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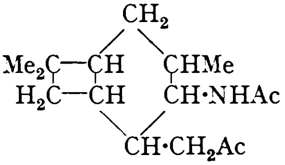
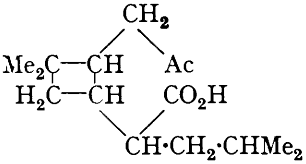


(VI.)



(VII.)

dihydro-γ-caryophyllene. Ozonolysis of the acetyl derivative of this base gave formaldehyde and a crystalline lævorotatory *ketone*, $C_{16}H_{27}O_2N$, m. p. 139—140°. Since we have shown (J., 1935, 1581) that, Ruzicka's representation (I) for β-caryophyllene being accepted, the blue nitrosite must be (V), there can be no doubt that this ketone must be

(VI) and its formation negatives the possibility that (II) represents the parent hydrocarbon.

In some preliminary experiments we investigated the ozonolysis of oximino-γ-caryophyllene and obtained as the only recognisable products formaldehyde and acetaldehyde. It is difficult on any method of formulation to account for the formation of the latter aldehyde, which we obtained from two distinct preparations of the oximino-compound, and it cannot therefore result from some extraneous impurity. We can at present offer no explanation

Further evidence, although not conclusive, in support of the structure (VI) assigned to the ketone was obtained by the catalytic hydrogenation of aminodihydro-γ-caryophyllene to *aminotetrahydro-γ-caryophyllene*, from which by the action of nitrous acid, followed by dehydration, *dihydro-γ-caryophyllene* was prepared. On ozonolysis the hydrocarbon gave, in addition to a neutral product having aldehydic properties, a liquid keto-acid, analysis of the silver salt indicating that it had the expected composition $C_{15}H_{26}O_3$. Unfortunately no crystalline derivatives could be prepared, but, in agreement with its probable representation (VII), it gave bromoform with sodium hypobromite. The dibasic acid was a gum and it gave a resinous dianilide, so its composition could not be determined. Additional products of the ozonolysis were small quantities of formaldehyde and acetone, originating probably from a trace of the dihydro-base present in the tetrahydro-base used in the preparation of the hydrocarbon.

Three dihydrocaryophyllenes are recorded in the literature. By the catalytic hydrogenation of γ-caryophyllene Deussen (*J. pr. Chem.*, 1914, **90**, 325) obtained a dihydrocaryophyllene, α_D — 29·4°, and from crude caryophyllene (*Annalen*, 1912, **388**, 156) a hydrocarbon, α_D — 25°, whilst we (J., 1934, 1808) prepared from β-caryophyllene nitrosite a hydrocarbon, $[\alpha]_{5461}$ — 47·15°. The hydrocarbon now referred to had α_{5461} — 26·1° in fair agreement with the values recorded by Deussen, but no proof of identity is of course possible.

In view of these results it appeared to be of interest to investigate the ozonolysis of acetamidodihydro-β-caryophyllene prepared by the acetylation of aminodihydro-β-caryophyllene (J., 1934, 1808). This gave as the main products of the ozonolysis formaldehyde and the ketone $C_{16}H_{27}O_2N$, m. p. 139—140°, identical with that derived from the isomeric acetamide prepared from γ-caryophyllene. This result was not unexpected in view of the obviously facile interconversion of β- and γ-caryophyllenes. The fact, however, that the two dihydrocaryophyllenes prepared from the two bases are clearly not identical suggests that the isomerism of the two parent hydrocarbons must have persisted in the two bases.

We consider that these experiments, in conjunction with those of Deussen, leave little doubt of the relationship of β- and γ-caryophyllenes, although the final proof of structure must await the synthesis of caryophyllenic acid. The ketone $C_{16}H_{27}O_2N$, which is comparatively readily accessible, should be of value in elucidating the character of the side chain present in the caryophyllenes, for which direct evidence is lacking, and we propose to extend our investigations in this direction.

EXPERIMENTAL.

The γ-caryophyllene (from β-caryophyllene nitrosite) used in the experiments to be described had b. p. 130—131°/24 mm., $d_{25^\circ}^{25^\circ}$ 0·8923, $n_D^{25^\circ}$ 1·4942, $[\alpha]_{5461}$ — 29·7°.

The nitrosochloride was most conveniently prepared by the following modification of Deussen and Lewinsohn's method. To a mixture of the hydrocarbon (5 c.c.), methyl alcohol (10 c.c.), and ethyl nitrite (10 c.c.), cooled in ice–salt and mechanically stirred, an alcoholic solution of hydrogen chloride (15 c.c.; 0·24 g. HCl per c.c.) was gradually added. The heavy blue oil obtained solidified in the ice-chest after 24 hours. It crystallised from alcohol–acetone in needles, m. p. 122°. No evidence of the formation of the higher-melting β-isomeride was obtained.

Oximino-γ-caryophyllene.—A mixture of the nitrosochloride (8·5 g.) and pyridine (25 c.c.) was heated on the water-bath for 2 hours. The brown solution, which deposited pyridine hydrochloride on cooling, was poured into dilute sulphuric acid, the oil taken up with ether, the ethereal solution washed with dilute sulphuric acid and sodium carbonate solution and dried over potassium carbonate, and the solvent removed. On distillation of the residual oil under diminished pressure (4 mm.), after a small quantity of hydrocarbon had passed over, the remainder had b. p. 160—170°. The extremely viscid, colourless oil was redistilled for analysis, b. p. 162—167°/5 mm. (Found: N, 6·1. $C_{15}H_{23}ON$ requires N, 6·0%). With Brady's reagent *oximino-γ-caryophyllene* reacts immediately, yielding a deep red 2 : 4-dinitrophenylhydrazone, m. p. 155—167°, which could not be crystallised. Ozonolysis of the oximino-derivative in methyl acetate solution gave formaldehyde (dimedone) and acetaldehyde (2 : 4-dinitrophenylhydrazone, m. p. 149°. Found: C, 42·5; H, 3·7. Calc.: C, 42·9; H, 3·6%) together with resinous products.

Aminodihydro-γ-caryophyllene.—To a boiling solution of oximino-γ-caryophyllene (12 g.) in alcohol (400 c.c.), sodium (25 g.) was added as rapidly as possible. After solution was complete the alcohol was removed in steam, and the crude base dissolved in ether and extracted from this with dilute hydrochloric acid. The base was liberated by the addition of sodium hydroxide solution and redissolved in ether, the ethereal extract dried over potassium hydroxide, and the *base*, after removal of the solvent, distilled, being obtained as a colourless viscid oil, b. p. 147°/13 mm. (Found: N, 6·7. $C_{15}H_{27}N$ requires N, 6·3%). The acetyl derivative was obtained as an extremely viscid oil, b. p. 218—220°/17 mm., by digestion of the base with acetic anhydride.

Oxidation of Acetamidodihydro-γ-caryophyllene.—The acetyl derivative (3 g.) in methyl acetate (20 c.c.) was ozonised at 0°; formaldehyde was present in the issuing gases. After removal of the solvent under diminished pressure, water (10 c.c.) was added, and the ozonide decomposed by heating on the water-bath for 1 hour and on the sand-bath for ½ hour. The resulting heavy oil was dissolved in ether, the solution washed with dilute aqueous sodium hydroxide and dried, and the solvent removed. The viscid oil (2 g.) obtained slowly crystallised in rosettes of needles, which, after three crystallisations from ethyl acetate–light petroleum (b. p. 40—60°), had m. p. 139—140°, $[\alpha]_{5461}$ − 58° in ethyl acetate (*c*, 1·643) (Found: C, 72·5; H, 9·9; N, 5·5. $C_{16}H_{27}O_2N$ requires C, 72·5; H, 10·2; N, 5·3%). The *ketone*, which gave no colour with tetranitromethane in alcoholic solution, was readily soluble in the ordinary organic solvents with the exception of ether and ligroin; it reacted with carbonyl reagents, but crystalline derivatives were not obtained. With Fuson's reagent it gave iodoform.

The sodium hydroxide solution (see above) gave on acidification a gummy acid (0·7 g.), which was not further examined.

Aminotetrahydro-γ-caryophyllene.—An alcoholic solution of the dihydro-base (5 g.) was catalytically hydrogenated, a palladium–norit catalyst being used. Reduction was slow and was completed at 3 atms. The *base*, b. p. 147°/11 mm., was a colourless mobile oil, which appeared to take up carbon dioxide somewhat readily (Found: C, 81·1; H, 12·8. $C_{15}H_{29}N$ requires C, 80·7; H, 13·0%). Its alcoholic solution gave a faint yellow colour with tetranitromethane.

Dihydro-γ-caryophyllene.—To a solution of the above-mentioned base (5 g.) in acetic acid (2 c.c.) and water (20 c.c.), a concentrated solution of sodium nitrite (1·8 g.) was very slowly added, nitrogen being evolved. After 1½ hours the mixture was heated on the water-bath until the evolution of nitrogen ceased; excess of alkali was then added, and the heating continued for 15 minutes. The oil extracted from the cooled solution with ether was washed with dilute sulphuric acid (to remove a little unchanged base) and sodium carbonate solution, dried, and the solvent removed. Without further purification the residual oil (4 g.) was mixed with finely powdered potassium hydrogen sulphate (3 g.) and heated at 180—200° for 3 hours. The deep brown oil was dissolved in ether, washed with sodium carbonate solution, which removed a brown resin, dried, and the ether evaporated. The *hydrocarbon* had b. p. 127°/13 mm. and was a colourless oil, the last few drops having a faint blue colour. After distillation over potassium it had b. p. 140°/24 mm., $n_D^{16°}$ 1·4921, α_{5461} − 26·1° (Found: C, 87·0; H, 12·2. $C_{15}H_{26}$ requires C, 87·4; H, 12·6%).

Oxidation of Dihydro-γ-caryophyllene.—The hydrocarbon (1·8 g.) in methyl acetate (10 c.c.) was ozonised at 0° until ozone passed freely through the solution (2 hours), the issuing gases being passed through water (*A*). After removal of the methyl acetate under diminished pressure, water (10 c.c.) was added, and the ozonide decomposed by warming on the water-bath for ½ hour and finally boiled under reflux for 15 minutes under conditions such that any readily volatile ketone (or aldehyde) could be trapped in a solution of Brady's reagent (*B*). The aqueous solution was extracted with ether, the extract washed with sodium hydroxide solution (*C*) and dried, and the solvent evaporated. The residual neutral oil (0·8 g.) reacted readily with carbonyl reagents, but no crystalline derivatives could be prepared; it reduced ammoniacal silver nitrate solution with the formation of a silver mirror. The alkaline solution (*C*) was acidified and the oil which separated was extracted with ether; removal of the solvent left a viscid gum (1 g.), which reacted slowly with carbonyl reagents and gave a liquid *p*-phenylphenacyl ester. The amorphous *silver* salt, which was readily soluble in alcohol, was analysed (Found: Ag, 30·3. $C_{15}H_{25}O_3Ag$ requires Ag, 29·8%).

The aqueous solution (*A*) was mixed with Brady's reagent, a yellow 2 : 4-dinitrophenylhydrazone (2 mg.) separating. This crystallised from light petroleum (b. p. 60—80°) in yellow needles, m. p. 153—155°, both alone and in admixture with formaldehyde-2 : 4-dinitrophenylhydrazone. The solution (*B*) gave on addition of dilute sulphuric acid a yellow precipitate (50 mg.). This had m. p. 110—115°, raised by three crystallisations from alcohol to 128°, both alone and in admixture with acetone-2 : 4-dinitrophenylhydrazone.

Oxidation of Acetamidodihydro-β-caryophyllene.—The acetyl derivative (8 g.), b. p. 220—222°/18 mm., obtained as a viscid gum by digestion of the base (J., 1934, 1808) with acetic anhydride, was ozonised in methyl acetate (35 c.c.) at 0°; formaldehyde was present in the issuing gases. The ethereal solution of the neutral product of the ozonolysis was concentrated, a small quantity of light petroleum (b. p. 40—60°) added, and the solution kept in the ice-box for 2 days; a crystalline solid had then separated, m. p. 132—135°, raised to 139—140° by crystallisation from ethyl acetate–ligroin. The ketone, $[\alpha]_{5461}$ — 59° in ethyl acetate (*c*, 2·174), was identical in all respects with that described above (Found: C, 72·3; H, 10·1%).

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