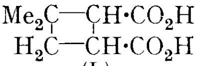
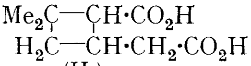
372. *The Caryophyllenes. Part III.*

By G. R. Ramage and J. L. Simonsen.

In previous communications (J., 1934, 1806; this vol., p. 532) we have shown that *d-cis*-norcaryophyllenic acid has the structure (I), and this has been confirmed by Rydon's synthesis of *dl*-norcaryophyllenic acid and of dehydronorcaryophyllenic acid (*J. Soc. Chem. Ind.*, 1935, **54**, 557). It has been shown also that *d-cis*-caryophyllenic acid must be either (II) or (III).


(I.)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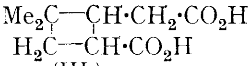
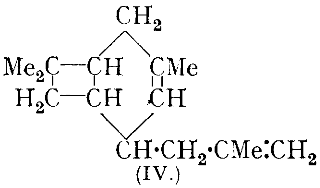

(III.)

A final determination of the constitution of caryophyllenic acid must await its synthesis, and experiments in this direction are in progress, but it is now possible to consider formulæ for the parent hydrocarbons, the caryophyllenes.

In the course of their extensive study of the degradation of these sesquiterpenes Semmler and Mayer (*Ber.*, 1911, **44**, 3657) isolated as the two main products of ozonolysis a diketo-monocarboxylic acid, $C_{14}H_{22}O_4$, and a keto-monocarboxylic acid, $C_{11}H_{18}O_3$. These two acids have been obtained also by Ruzicka and Wind (*Helv. Chim. Acta*, 1931, **14**, 410), and Ruzicka (*J. Soc. Chem. Ind.*, 1935, **54**, 509) has suggested that the two acids, which he represents by (VI) and (VII) respectively, originate from the two hydrocarbons (IV) and (V). In this communication he summarises the evidence on which these formulæ are based.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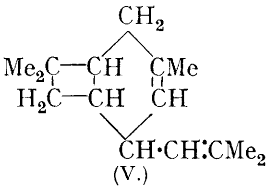
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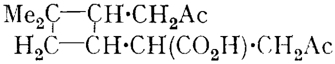
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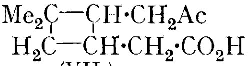
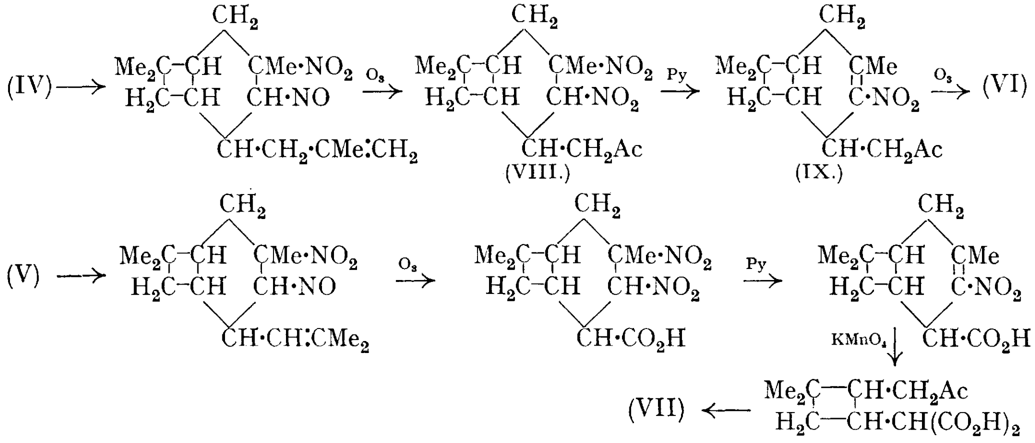

(VII.)

In Part I attention was directed to the difficulty in interpreting the results obtained on degradation owing to the fact that the sesquiterpene fraction of oil of cloves consists of a mixture of at least three hydrocarbons and we stated that we proposed to use as the starting point for our investigations a dihydro-β-caryophyllene prepared from β-caryophyllene nitrosite. We now find that the crystalline nitrosite itself can be readily oxidised by ozone. In ethyl acetate–carbon tetrachloride solution it yields, in addition to formaldehyde, a colourless *ketone*, $C_{14}H_{22}O_5N_2$, m. p. 161·5°. The second oxygen atom presumably enters the molecule by converting the nitroso-group into a nitro-group. An isomeric blue ketone is obtained if the oxidation is carried out in acetic acid solution. We shall refer to them as the α- and the β-dinitro-ketone. The blue β-ketone is converted into the colourless form on warming and probably represents, therefore, a unimolecular form, but direct proof of this relationship has not been obtained. When either of these ketones is warmed with pyridine, elimination of nitrous acid occurs with the formation of a crystalline unsaturated *mononitro-ketone*, $C_{14}H_{21}O_3N$, m. p. 69°; this can, however, only be obtained in good yield from the α-ketone. The unsaturated ketone is slowly oxidised by ozone, yielding as the main product a diketo-monocarboxylic acid, $C_{14}H_{21}O_4$, a small quantity of formaldehyde being formed also. The methyl ester of this acid has constants agreeing closely with those of the diketo-ester prepared by Semmler and Mayer to which reference was made above, and the identity of the two esters was proved by the preparation from each of them of a crystalline *bis*-2 : 4-*dinitrophenylhydrazone*, decomp. 108—110°. It follows, therefore, that this diketo-acid must originate from β-caryophyllene.

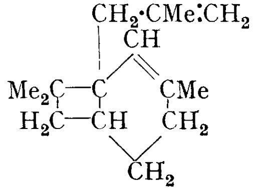
By the ozonolysis of β-caryophyllene nitrosite a small quantity of an acid also was obtained, which contained nitrogen. After treatment with pyridine and oxidation of the resulting unsaturated acid with potassium permanganate a keto-acid was isolated; this lost carbon dioxide at 180°, yielding a liquid keto-acid, which was shown to have the composition $C_{11}H_{18}O_3$ by analysis of the crystalline semicarbazone, m. p. 183°. This acid was identical with the acid of this composition obtained by Semmler and Mayer (*loc. cit.*, p. 3662). The formation of this acid from the nitrosite is explained most readily if we assume that β-caryophyllene contains an *iso*propenyl group, which reacts to some extent as an *iso*propylidene group (compare Bradfield, Penfold, and Simonsen, this vol., p. 309). These two forms would represent the β- and the γ-caryophyllene, which are stated to yield the same dihydrochloride.

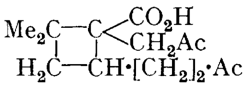
On the basis of Ruzicka's formulæ (IV) and (V), which must now be assigned to these hydrocarbons, the reactions outlined above may be represented by the two following schemes :



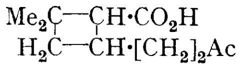
Although these formulæ, subject to certain difficulties to which reference is made below, are in satisfactory agreement with the reactions discussed, it appears to us that formula (X) (for β-caryophyllene) is equally satisfactory. Formula (VI) for the diketo-acid would then be replaced by (XI), and (VII) for the keto-acid by (XII).

(X.)



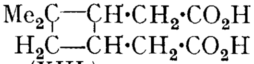


(XI.)



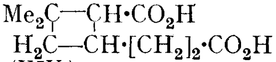
(XII.)

It would be anticipated that the oxidation of the latter acid (VII) or (XII) with sodium hypobromite would yield a homocaryophyllenic acid, either (XIII) or (XIV), but according to Semmler and Mayer (*loc. cit.*, p. 3666) this reaction proceeds abnormally with the formation of *as.*-dimethylsuccinic acid and caryophyllenic acid. Owing to its fundamental importance as a means of deciding between formulæ (IV) and (X) we propose to subject this acid to further study, since it should be readily accessible by the degradation of γ-caryophyllene nitrosochloride. On the basis of either (IV) or (X) caryophyllenic acid must be represented by (II).

(VII) ⟶ 

$$\begin{array}{l}\mathrm{Me_2\underset{|}{C}-\underset{|}{C}H\cdot CH_2\cdot CO_2H}\\ \mathrm{H_2C-CH\cdot CH_2\cdot CO_2H}\end{array}$$

(XIII.)

(XII) ⟶ 

$$\begin{array}{l}\mathrm{Me_2\underset{|}{C}-\underset{|}{C}H\cdot CO_2H}\\ \mathrm{H_2C-CH\cdot [CH_2]_2\cdot CO_2H}\end{array}$$

(XIV.)

We mentioned above that we had encountered certain facts which were difficult to reconcile with Ruzicka's formula for β-caryophyllene and equally with our modification. The dinitro-ketone (VIII) should contain a reactive acetyl group, but with Fuson's reagent (*Chem. Rev.*, 1934, **15**, 275) it gives no iodoform; further, in spite of the fact that it is thought to contain the group $CH\cdot NO_2$, it is insoluble in alkali. The mononitro-ketone (IX) does, however, gives traces of iodoform with Fuson's reagent. A somewhat similar anomaly has been observed by Ruzicka and Wind, who find that only one of the two acyl groups in the diketo-acid is oxidised by sodium hypobromite. Further, either formula (IV) or (X) allows of ready cyclisation to the tricyclic hydrocarbon, clovene, although a molecular rearrangement must occur at some stage to account for the facile oxidation of this hydrocarbon to clovenic acid. Subsequent to the preparation of this paper Blair (this vol., p. 1257) has discussed the cyclisation of the caryophyllenes to clovene and has suggested a modification of Ruzicka's formula (IV). Blair's formula leads to a structure for clovene which allows of its oxidation to clovenic acid without loss of carbon, but it does not permit of the formation of the fundamental caryophyllene degradation products.

To indicate the difficulties attending an interpretation of the results of previous investigators, who have worked with mixtures of the sesquiterpene hydrocarbons in varying proportions, it is of interest to note that of the three acid and three neutral primary oxidation products obtained by Semmler and Mayer only the formation of two acid and one neutral product can be explained on the above formulæ as originating from β- and γ-caryophyllenes.

EXPERIMENTAL.

Ozonolysis of β-Caryophyllene Nitrosite.—(i) *In ethyl acetate–carbon tetrachloride.* Ozone was passed through the nitrosite (5 g.) in ethyl acetate (10 c.c.) and carbon tetrachloride (20 c.c.) at 0° until the solution was pale green and ozone had been present in the issuing gases for 1 hour. (This precaution was necessary to prevent the formation of dark-coloured decomposition products.) During the oxidation formaldehyde was liberated (dimedone derivative, m. p. 187°). After removal of the solvents under diminished pressure, water was added, and the ozonide slowly decomposed by heating on the water-bath; a brown oil was then obtained, which partly crystallised on keeping. After decantation of the water, ether was added, and the solid (2 g.) collected. The *α-dinitro-ketone* crystallised from alcohol in long colourless needles, m. p. 161·5°; in chloroform (c, 2·620), $[\alpha]_{5461}$ $-$ 33·6° (Found: C, 56·6; H, 7·3; N, 9·4. $C_{14}H_{22}O_5N_2$ requires C, 56·6; H, 7·4; N, 9·4%). It gave no colour with ferric chloride, was insoluble in water and sodium hydroxide solution, very sparingly soluble in ether, but readily in chloroform. The *phenylsemicarbazone* crystallised from butyl alcohol in needles, decomp. 224° (Found: C, 58·4; H, 6·6. $C_{21}H_{29}O_5N_5$ requires C, 58·4; H, 6·7%); the 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol–ethyl acetate in yellow needles, decomp. 225° (Found: C, 49·9; H, 5·5. $C_{20}H_{26}O_8N_6$ requires C, 50·2; H, 5·4%).

The ethereal solution from which the crystalline ketone had been separated was shaken with sodium carbonate solution and concentrated; a further quantity of the ketone, m. p. 161°, was very slowly deposited. A viscid neutral product (2 g.) remained on complete removal of the ether. This could not be purified and gave no crystalline derivatives. From the sodium carbonate solution a gummy acid (0·4 g.) was isolated, the further oxidation of which is described on p. 1584.

(ii) *In acetic acid.* Ozone was passed through a suspension of the nitrosite (15 g.) in acetic acid (30 c.c.) and water (3 c.c.), formaldehyde being detected in the issuing gases. After remaining for 12 hours at 0°, the light blue product (9·5 g.) which had separated was collected and dried over sodium hydroxide in a vacuum. The β-*dinitro-ketone* crystallised from alcohol (excessive boiling must be avoided) in pale blue needles (Found : C, 56·5; H, 7·4; N, 9·9%), which became colourless at about 146° and decomposed at 155° corresponding to conversion into the α-form. When the β-ketone was heated alone, vigorous decomposition occurred, but this was moderated by boiling in acetic acid for 2 minutes; the solution then became yellow and addition of water precipitated the α-form, m. p. 161°.

Action of Pyridine on the α-Dinitro-ketone.—The ketone (10 g.) in pyridine (25 c.c.) was heated on the water-bath, vigorous evolution of nitric oxide occurring. After 1 hour an excess of dilute hydrochloric acid was added and the brown oil which separated was collected in ether. The dried ethereal extract gave on removal of the solvent an oil which crystallised with difficulty from alcohol, but much more readily after distillation in a low vacuum. Considerable decomposition occurred, but the distillate (5 g.), the *nitro-ketone*, then crystallised readily from alcohol (60%) in long needles (4·5 g.), m. p. 67°, raised to 69° by recrystallisation; in chloroform (*c*, 2·224), $[\alpha]_{5461}$ − 114° (Found : C, 66·8; H, 8·3; N, 5·8. $C_{14}H_{21}O_3N$ requires C, 66·9; H, 8·4; N, 5·6%). The *semicarbazone* crystallised from dilute alcohol in fine needles, m. p. 186—187° (Found : C, 58·6; H, 7·8. $C_{15}H_{24}O_3N_4$ requires C, 58·4; H, 7·8%).

Oxidation of the Nitro-ketone with Ozone.—The ketone (10 g.) in ethyl acetate was cooled to 0° and ozone was passed through the solution for 40 hours, since unchanged ozone was present in the issuing gases from the commencement of the oxidation; only traces of formaldehyde were evolved. After removal of the solvent, water was added, and the ozonide decomposed by heating on the water-bath. No acetone was formed. After addition of sodium carbonate, the neutral products were removed by ether, which on evaporation gave an oil, from which unchanged material (0·9 g.) was recovered. The non-crystalline portion, possibly a diketone, gave no crystalline derivatives. On acidification of the sodium carbonate solution a liquid acid (7·1 g.) separated, which was esterified with diazomethane. The *methyl* ester had b. p. 194—196°/15 mm., 166—167°/4 mm., $d_{25^\circ}^{25^\circ}$ 1·042, $n_D^{19^\circ}$ 1·4632. Analysis showed the ester to be not quite pure (Found : C, 66·0; H, 8·9. $C_{15}H_{24}O_4$ requires C, 67·2; H, 9·0%). The *bis*-2 : 4-*dinitrophenylhydrazone*, prepared in methyl-alcoholic solution, was precipitated immediately as an oil, which quickly hardened. It crystallised from methyl acetate in fine needles, decomp. 108—110° with previous softening (Found : C, 51·4; H, 5·2; N, 17·7. $C_{27}H_{32}O_{10}N_8$ requires C, 51·6; H, 5·1; N, 17·8%).

This ester was prepared also by the ozonolysis of " caryophyllene " (b. p. 116°/12 mm., $d_{25^\circ}^{25^\circ}$ 0·9135, $n_D^{20^\circ}$ 1·5001, $[\alpha]_{5461}$ − 8·54°) by the method described by Semmler and Mayer (*loc. cit.*, p. 3660) except that ethyl acetate was used as the solvent during the ozonolysis and the acid was esterified by diazomethane. The methyl ester so prepared had b. p. 205—210°/25 mm., $d_{25^\circ}^{25^\circ}$ 1·040, $n_D^{25^\circ}$ 1·4668 (Semmler and Mayer give b. p. 184—188°/12 mm., d^{20° 1·047, n_D 1·4680). The bis-2 : 4-dinitrophenylhydrazone prepared from this ester decomposed at 108—110°, both alone and after admixture with the hydrazone referred to above.

Isolation of the Keto-acid, $C_{11}H_{18}O_3$.—The acid (20 g.) obtained by the ozonolysis of β-caryophyllene nitrosite (p. 1583) was heated with pyridine (30 c.c.) for 1 hour on the water-bath, the solution poured into dilute hydrochloric acid, and the unsaturated acid, which separated, was extracted with ether. Evaporation of the ether gave a gum (16 g.), which was dissolved in sodium carbonate solution (50 c.c.; 8%) and stirred whilst potassium permanganate solution (5%) was added until the pink colour persisted (300 c.c.). The manganese dioxide sludge was removed and washed with water and the combined filtrates were concentrated, acidified, and extracted with ether. After extraction the aqueous solution gave the brown ring test indicating the presence of either nitric or nitrous acid. Evaporation of the ether gave an almost colourless oil (12 g.), which was heated at 180° for 30 minutes, carbon dioxide being evolved (identified as barium carbonate). The crude acid was dissolved in ether, which left undissolved a brown tar, and after removal of the solvent fractionation gave an oil (2·8 g.), b. p. 196—200°/22 mm., $n_D^{21^\circ}$ 1·4688 (Semmler and Mayer give b. p. 183—187°/11·5 mm., $n_D^{20^\circ}$ 1·4677 for the keto-acid $C_{11}H_{18}O_3$). The semicarbazone, which was rapidly formed, crystallised from methyl alcohol in rectangular prisms, m. p. 183°, and this m. p. was unchanged after admixture with the semicarbazone prepared by Semmler and Mayer's method (Found : C, 56·7; H, 8·3. Calc. : C, 56·4; H, 8·2%).

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