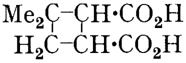
122. *The Caryophyllenes. Part II.*

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

In Part I (J., 1934, 1806) we showed Semmler's liquid "caryophyllenic acid" to be a mixture of two crystalline acids, *d-cis*-caryophyllenic acid, $C_9H_{14}O_4$, m. p. 80—81°, and *d-cis*-norcaryophyllenic acid, $C_8H_{12}O_4$, m. p. 125—127°, the latter acid being converted by appropriate reactions into an unsaturated acid, dehydronorcaryophyllenic acid, $C_8H_{10}O_4$, m. p. 193°. These observations have been fully confirmed by the recent investigations of Ruzicka and Zimmermann (*Helv. Chim. Acta*, 1935, **18**, 219). Our anticipation that an examination of the oxidation products of dehydronorcaryophyllenic acid would throw light on the structure of the parent acid has been realised.

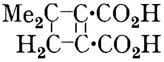
When the unsaturated acid is oxidised with ozone in ethyl acetate or in sodium carbonate solution, it yields a keto-acid, which is extremely hygroscopic and cannot be purified. Analyses of four crystalline derivatives, the *phenylsemicarbazone*, decomp. 165°, the p-*nitrophenylhydrazone*, decomp. 192°, and two 2 : 4-*dinitrophenylhydrazones*, decomp. 243° and 215—217°, show it to have the composition $C_7H_{10}O_5$. On further oxidation with hydrogen peroxide in alkaline solution it gives *as.*-dimethylsuccinic acid.

These results receive their simplest interpretation if *d-cis*-norcaryophyllenic acid is *d-cis*-3 : 3-dimethyl*cyclo*butane-1 : 2-dicarboxylic acid (I); dehydronorcaryophyllenic acid will then be 3 : 3-dimethyl-Δ^1-*cyclo*butene-1 : 2-dicarboxylic acid (II), and the keto-acid * either α-keto-ββ-dimethylglutaric acid (IV) or α′-keto-αα-dimethylglutaric acid (V) formed from the primary oxidation product, αδ-diketo-ββ-dimethyladipic acid (III) by the action of the hydrogen peroxide generated during the decomposition of the ozonide.



$\begin{array}{l}Me_2C{-}CH\cdot CO_2H\\ H_2C{-}CH\cdot CO_2H\end{array}$

(I.)



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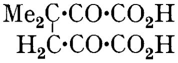
(II.)



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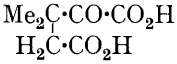
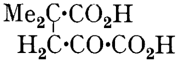
(III.)



$\begin{array}{l}Me_2C\cdot CO\cdot CO_2H\\ H_2C\cdot CO_2H\end{array}$

(IV.)



$\begin{array}{l}Me_2C\cdot CO_2H\\ H_2C\cdot CO\cdot CO_2H\end{array}$

(V.)

An attempt was made to isolate the diketo-acid (III) by decomposing the ozonide with

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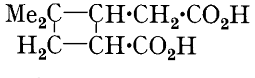
* [Note added, April 1st.] By the courtesy of Dr. E. H. Farmer we have been able to compare this acid with α-keto-ββ-dimethylglutaric acid. The *p*-nitrophenylhydrazone of the latter, decomp. 158°, is not identical with the *p*-nitrophenylhydrazone, decomp. 192°, of the oxidation acid, which must therefore be (V).

hydrogen in the presence of palladium–norit (compare Fischer, Düll, and Ertel, *Ber.*, 1932, **65**, 1467), but only derivatives of the monoketo-acid could be obtained.

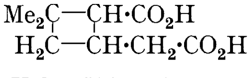
The constitution of norcaryophyllenic acid suggested tentatively by Ruzicka and Zimmermann (*loc. cit.*) is thus confirmed.

Our previous tacit assumption that caryophyllenic and norcaryophyllenic acids belong to a homologous series has now been proved experimentally. Bromocaryophyllenic acid was converted by silver oxide in aqueous solution into hydroxycaryophyllenic acid or, more probably, the lactonic acid, and this, without purification, was oxidised successively with lead peroxide and potassium permanganate (compare Baeyer, *Ber.*, 1896, **29**, 1907), *d-cis*-norcaryophyllenic acid being obtained. It follows, therefore, that caryophyllenic acid must be either (VI) or (VII).

(VI.)



$$\begin{matrix} Me_2C\text{—}CH{\cdot}CH_2{\cdot}CO_2H \\ H_2C\text{—}CH{\cdot}CO_2H \end{matrix}$$



$$\begin{matrix} Me_2C\text{—}CH{\cdot}CO_2H \\ H_2C\text{—}CH{\cdot}CH_2{\cdot}CO_2H \end{matrix}$$

(VII.)

The observation of Ruzicka, Bardhan, and Wind (*Helv. Chim. Acta*, 1931, **14**, 423), that the tetramethylglycol prepared from methyl caryophyllenate by the action of methylmagnesium iodide yields αα$\alpha'\alpha'$-tetramethylglutaric acid on oxidation, obviously involves a molecular rearrangement which is more readily explicable on the basis of (VII) than of (VI). It does not, however, appear possible to decide between these two formulæ by analytical methods and we are undertaking the synthesis of this acid and also of norcaryophyllenic acid.

During the purification of dehydronorcaryophyllenic acid (see below) we isolated in small quantity an optically inactive *acid*, $C_8H_{12}O_4$, m. p. 148—149°, which is in all probability *dl-cis*-norcaryophyllenic acid, the active acid having racemised during the treatment with bromine. This acid is identical possibly with the acid having a similar melting point described by Ruzicka and Zimmermann (*loc. cit.*).

Considerable evidence regarding the structure of the caryophyllenes is now available, although interpretation is difficult, and we prefer to defer discussion until we have completed our experiments on the oxidation of dihydro-β-caryophyllene (*loc. cit.*, p. 1808).

It was thought at first that the oxidation product of dehydronorcaryophyllenic acid had the composition $C_5H_8O_3$, and a number of new derivatives of dimethylpyruvic acid were prepared. Dimethylpyruvic acid is obtained most conveniently by the method briefly described by Perkin and Simonsen (*Proc.*, 1909, **25**, 164).

EXPERIMENTAL.

Dehydronorcaryophyllenic Acid and dl-cis-*Norcaryophyllenic Acid.*—For the preparation of the former acid the conditions previously described were followed, except that it was found more convenient to effect the bromination at 140° instead of 120°. After hydrolysis with alcoholic potassium hydroxide and removal of the alcohol, acidification deposited dehydronorcaryophyllenic acid (0·9 g. from 2 g. of norcaryophyllenic acid); the filtrate was extracted with ether and after removal of the solvent an oil was obtained which on treatment with concentrated hydrochloric acid gave a further quantity (0·2 g.) of the unsaturated acid. The methyl ester was an oil which crystallised when cooled in a freezing mixture. The hydrochloric acid mother-liquors gave on concentration an acid (0·5 g.), m. p. 140°, raised to 145—147° by crystallisation from water. Since the acid was not stable to permanganate, it was dissolved in alkali and treated with this reagent until the colour was permanent (ice). The recovered *acid* (0·3 g.) now crystallised from water in rosettes of needles, m. p. 148—149°, and was optically inactive in acetone solution (Found : C, 56·0; H, 7·1; *M*, 171. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%; *M*, 172). By treatment with acetyl chloride a liquid anhydride was obtained which was readily hydrolysed by hot water to the parent acid, m. p. 148—149°.

Oxidation of Dehydronorcaryophyllenic Acid with Ozone.—(i) *In sodium carbonate solution.* The acid (0·6 g.) in sodium carbonate solution (10 c.c.; Na_2CO_3, 0·2 g.) (ice) was treated with ozone until the solution was stable to potassium permanganate. After acidification and saturation with ammonium sulphate, the solution was extracted with ether (10 times), and the dried extract evaporated; an oil (0·42 g.) remained which crystallised when kept over sulphuric acid but liquefied rapidly in the air. The keto-acid (IV or V) gave a faint colour with ferric chloride and did not reduce Fehling's solution. On admixture with an aqueous sulphuric acid solution of 2 : 4-dinitrophenylhydrazine a dinitrophenylhydrazone (A) separated; the filtrate slowly deposited a second dinitrophenylhydrazone (B) in long needles. The 2 : 4-*dinitrophenylhydrazone A* crystallised from alcohol in yellow needles, decomp. 243°, unaltered by two further crystallisations (Found : C, 44·6; H, 4·1. $C_{13}H_{14}O_8N_4,\frac{1}{2}C_2H_5{\cdot}OH$ requires C, 44·5; H, 4·5%). The 2 : 4-*dinitrophenylhydrazone B* crystallised from dilute alcohol in yellow prisms, decomp. 215—217° (Found : C, 44·4; H, 4·2%). In one experiment the acid was kept with a dilute alcoholic solution of the dinitrophenylhydrazine sulphate for some weeks; a third hygroscopic 2 : 4-*dinitrophenylhydrazone C*, m. p. 132°, was then obtained in pale yellow needles [Found : (air-dried) N, 13·2; H_2O, 18·4; (dried in a low vacuum) C, 43·6; H, 4·5. $C_{13}H_{14}O_8N_4,4\frac{1}{2}H_2O$ requires N, 12·9; H_2O, 18·6%. $C_{13}H_{14}O_8N_4$ requires C, 44·1; H, 4·0%].

(ii) *In ethyl acetate.* The acid (0·5 g.) in ethyl acetate (15 c.c.) was ozonised for 2·5 hours at 0°. After removal of the ethyl acetate in a vacuum, the ozonide was kept over-night with water (0·5 c.c.) and then heated on the water-bath for 1 hour. The two dinitrophenylhydrazones A and B referred to above were prepared and the former was analysed (Found : C, 44·3, 44·5; H, 4·2; 4·1; N, 14·6. $C_{13}H_{14}O_8N_4,\frac{1}{2}C_2H_5{\cdot}OH$ requires C, 44·5; H, 4·5; N, 14·8%). The p-*nitrophenylhydrazone* crystallised from dilute alcohol in small yellow needles, decomp. 192° (Found : C, 50·5; H, 4·8; N, 13·3. $C_{13}H_{15}O_6N_3$ requires C, 50·5; H, 4·9; N, 13·6%). The *phenylsemicarbazone* separated from dilute alcohol in prismatic needles, decomp. 165°. This derivative is somewhat difficult to purify, since it tends to separate as an oil (Found : C, 54·5; H, 5·7. $C_{14}H_{17}O_5N_3$ requires C, 54·7; H, 5·5%).

Oxidation of the Keto-acid (IV or V) *with Hydrogen Peroxide.*—To the acid (0·3 g.) in sodium hydroxide solution, hydrogen peroxide (100 vol.; 1 c.c.) was added and after 1 hour the mixture was heated on the water-bath for a further hour. The cooled acidified solution was saturated with ammonium sulphate and extracted with ether; evaporation of the solvent from the extract left a crystalline solid (0·23 g.), decomp. 139°. The acid crystallised from water in prismatic needles, decomp. 139—140°, both alone and after admixture with *as.*-dimethylsuccinic acid (Found : C, 49·6; H, 6·6. Calc. : C, 49·3; H, 6·9%).

Conversion of d-cis-*Caryophyllenic Acid into* d-cis-*Norcaryophyllenic Acid.*—Caryophyllenic acid (10 g.) and phosphorus pentachloride (22 g.) were heated on the water-bath and after ½ hour bromine (12 g.) was gradually added. After completion of the reaction the acid chloride was poured on ice, and the bromo-acid extracted with ether. Removal of the solvent gave an oil (14·2 g.), which was dissolved in water (150 c.c.) and, after the addition of silver oxide (25 g.), kept at 80° for 3 hours. The dried silver salt was suspended in ether and warmed with methyl iodide (25 g.) for 1 hour. The filtered solution gave, after the removal of the ether, an oil, which yielded on distillation a fraction (*A*), b. p. 138—142°/17 mm. (1·8 g.), and a high-boiling residue (*B*) (2 g.). From the original aqueous filtrate from the silver salt, an acid (*C*) (5 g.) was isolated by extraction of the acidified solution with ether. For the preparation of norcaryophyllenic acid, (*B*) was dissolved in warm aqueous sodium hydroxide, and the solution acidified and extracted with ether; after removal of the solvent the residual oil was dissolved in water (20 c.c.) and acetic acid (5 c.c.) and warmed on the water-bath, and lead peroxide (6 g.) added. When effervescence had ceased, the solution was filtered, the excess of lead removed with sulphuric acid, and the filtered solution made alkaline with aqueous sodium carbonate. Potassium permanganate solution (2·5%) was added (mechanical stirring) until the colour was permanent; the boiled and filtered solution was made acid to Congo-paper with hydrochloric acid and evaporated to dryness. The residual salts were extracted with ether, which left on evaporation a gum (1·5 g.). This was dissolved in cold water (charcoal), and a little insoluble resin thus removed. After removal of the water, the residue was dissolved in hot benzene and decanted from the insoluble gum, and the benzene evaporated; an oil remained which crystallised on being stirred with hydrochloric acid. The solid, m. p. 123—125°, was crystallised from benzene and then had m. p. 125—127°, both alone and after admixture with *d-cis*-norcaryophyllenic acid (Found : C, 55·7; H, 6·8. Calc. : C, 55·8; H, 7·0%). This acid was obtained also from the ester (*A*) after hydrolysis. In this case lead tetra-acetate was used in place of lead peroxide and the yield was inferior. The acid (*C*) contained much unchanged caryophyllenic acid, and norcaryophyllenic acid could not be isolated from it after oxidation.

2-*Phenyl*-4-iso*propylideneoxazolone.*—A mixture of hippuric acid (powdered to pass a 40-mesh sieve; 48 g.), acetone (120 g.), acetic anhydride (90 g.), and freshly fused sodium acetate (24 g.) was heated under reflux at 110° for 6 hours. In the early stages of the reaction a pasty solid separated, which slowly redissolved, yielding a pink solution. The solid which separated when the cooled solution was poured into a large volume of water was collected, washed with aqueous sodium carbonate to remove benzoic acid, and recrystallised from alcohol, the *oxazolone* being obtained in needles, m. p. 99—100° (Found : C, 71·4; H, 5·4. $C_{12}H_{11}O_2N$ requires C, 71·6; H, 5·5%).

*α-Benzamido-*ββ*-dimethylacrylic Acid.*—The oxazolone (1 g.) was mixed with aqueous potassium hydroxide solution (KOH, 0·5 g.) and heated on the water-bath for 1 hour. The sparingly soluble potassium salt that separated was decomposed with hydrochloric acid. The *acrylic acid* obtained crystallised from ethyl acetate–ether in fine needles, decomp. 217° (Found : C, 65·7; H, 5·8; N, 6·8; *M*, 218. $C_{12}H_{13}O_3N$ requires C, 65·7; H, 5·9; N, 6·4%; *M*, 219). The acrylic acid results also when the oxazolone is hydrolysed with baryta or cold concentrated hydrochloric acid.

Dimethylpyruvic Acid.—The oxazolone (18 g.), dissolved in concentrated hydrochloric acid (100 c.c.), was heated on the water-bath for 6 hours. In the early stages of the reaction a granular precipitate separated, which redissolved, crystallisation of benzoic acid following. The cooled solution was filtered, and the filtrate extracted with ether. Evaporation of the solvent left dimethylpyruvic acid, b. p. 65°/14 mm. (Found : C, 51·9; H, 7·3. Calc. : C, 51·7; H, 6·9%). In agreement with Craig (*J. Amer. Chem. Soc.*, 1934, **56**, 2008; compare Perkin and Simonsen, *loc. cit.*) the phenylhydrazone was found to have m. p. 152°. The *phenylsemicarbazone*, long needles from dilute alcohol, had m. p. 137° (Found : N, 17·0. $C_{12}H_{15}O_3N_3$ requires N, 16·9%); the p*-nitrophenylhydrazone* crystallised from dilute alcohol in bright yellow needles, which became buff-coloured when dried at 100°; m. p. 155° (Found : N, 16·8. $C_{11}H_{13}O_4N_3$ requires N, 16·7%); the 2 : 4*-dinitrophenylhydrazone* separated from dilute alcohol in yellow needles, m. p. 194—195° (Found : C, 44·3; H, 4·3. $C_{11}H_{12}O_6N_4$ requires C, 44·6; H, 4·1%).

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UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, March 7th,* 1935.]