745. *The Caryophyllenes. Part IX.* Homocaryophyllenic Acid.*

By T. L. Dawson and G. R. Ramage.

2-Carboxymethyl-3 : 3-dimethyl*cyclo*butylacetic acid (3 : 3-dimethyl*cyclo*butane-1 : 2-diacetic acid) (III) and β-(4-carboxy-2 : 2-dimethyl*cyclo*butyl)-propionic acid (IV) have been prepared, and the latter is shown to be identical with homocaryophyllenic acid by reference to the corresponding amides, anilides, and *p*-toluidides. A proposed synthesis of caryophyllenic acid (II; R = H) has been prevented by an anionotropic change; a new route to norcaryophyllenic acid is described.

Dawson and Ramage (*J.*, 1950, 3523) showed that 2-carboxy-3 : 3-dimethyl*cyclo*butylacetic acid (I) was not identical with caryophyllenic acid, which was therefore (II) by exclusion. Campbell and Rydon (*Chem. and Ind.*, 1951, 312) have since reported the synthesis of the racemic form of (II) which is considered to be identical with caryophyllenic acid on the evidence of infra-red spectra.

The next step in establishing the structure of caryophyllene necessitates consideration of homocaryophyllenic acid, which is available by the sodium hypobromite oxidation of a $C_{11}H_{18}O_3$ keto-acid, one of the principal and most characteristic degradation products. Homo-

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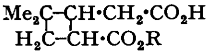
* Part VIII, *J.*, 1950, 3523.

caryophyllenic acid has now been isolated from the acids obtained by oxidation of γ-caryophyllene. Homocaryophyllenic acid must be represented by either (III) or (IV) although earlier work by Ramage and Simonsen (*J.*, 1937, 73) had failed to relate it to products derived from norcaryophyllenic or caryophyllenic acid. The substance (III) was then prepared from norcaryophyllenic acid and characterised by *cis*- and *trans*-dianilides, m. p. 170° and m. p. 280°. These were taken to correspond to the *cis*- and *trans*-dianilides, m. p. 180° and m. p. 282°, obtained from homocaryophyllenic acid and, though they were shown to be different by *X*-ray powder photographs, this was attributed to complication by the possibility of racemisation.


(I)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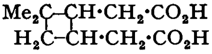
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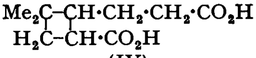

(IV)

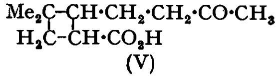
A re-examination of the synthesis of (III) from norcaryophyllenic acid has been possible by using the more convenient Arndt–Eistert reaction, and the resulting dianilides, now optically active, had m. p. 170° and m. p. 282—283°. It was found that the new anilide of m. p. 170° was dextrorotatory, whilst *cis*-homocaryophyllenic acid dianilide, m. p. 180°, was lævorotatory. The dianilides of m. p. 282° gave no depression of the melting point on admixture, but this is not proof of identity since the *trans*-dianilides of norcaryophyllenic and caryophyllenic acid also have the same melting point and give no depression on admixture. The dianilides thus appeared to be unsatisfactory as a means of identification, and the *p*-toluidides have been prepared. Only the *trans*-di-*p*-toluidides were obtained crystalline, and products from substance (III) and homocaryophyllenic acid had m. p. 182° and 227° respectively. On this basis homocaryophyllenic acid must be represented by (IV) and this is confirmed by a new route to this structure which utilises the half ester of caryophyllenic acid previously described by Ruzicka, Bardhan, and Wind (*Helv. Chim. Acta*, 1931, **14**, 423). Mild hydrolysis of methyl caryophyllenate will almost certainly give (II; R = Me); after conversion of this into the corresponding acid chloride and application of the Arndt–Eistert reaction, the resulting ester corresponding to (IV) was shown to be identical with ethyl homocaryophyllenate by the derived *cis*- and *trans*-dianilides and the *trans*-di-*p*-toluidide. Preliminary treatment of the acid with concentrated hydrochloric acid in a sealed tube at 150° increased the proportion of the *trans*-forms of the dianilide and the di-*p*-toluidide, m. p. 282—283° and 227° respectively, thus providing evidence for the configurations of these compounds.

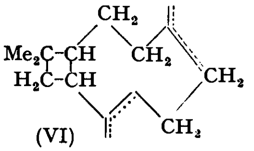
A previous preparation which should have given the dimethyl ester of (IV) (Ramage and Simonsen, *loc. cit.*) led to a dianilide of m. p. 206° and is considered to have involved racemisation of one asymmetric centre; this would undoubtedly occur in the formation of caryophyllenic anhydride by treatment with acetic anhydride at 220°, since complete racemisation occurs under these conditions in the formation of norcaryophyllenic acid anhydride (on hydrolysis this gives inactive norcaryophyllenic acid).

Although the issue is complicated by *cis-trans*- and optical isomerism, it is considered to be established that homocaryophyllenic acid is correctly represented by (IV) and its relation to the $C_{11}H_{18}O_3$ keto-acid has been further examined. The keto-acid is very readily oxidised by potassium permanganate at 50° to yield, by loss of two carbon atoms, a mixture of *cis*- and *trans*-forms of caryophyllenic acid. This, taken in conjunction with the structure (IV) for homocaryophyllenic acid, necessitates structure (V) for the keto-acid.

The present work, coupled with previous degradative experiments on caryophyllene, justifies the caryophyllene formula based on (VI) reported by Dawson, Ramage, and Wilson (*Chem. and Ind.*, 1951, 464). A nine-membered ring formula (VII) for caryophyllene was first suggested by Sŏrm, Dolejš, and Plíva (*Coll. Czech. Chem. Comm.*, 1950, **15**, 186) and this view was subsequently confirmed by Barton and Lindsey (*Chem. and Ind.*, 1951, 313) who provided evidence of the grouping $-C(:CH_2)\cdot CH_2\cdot CH_2\cdot CH:CMe-$. Barton (*J. Org. Chem.*, 1950, **15**, 457) favoured (IV) for homocaryophyllenic acid without advancing additional experimental evidence but the above publication with Lindsey appears to indicate acceptance of (III) and not (IV).

Further experiments have been possible on 7 : 7-dimethyl*bicyclo*[3 : 2 : 0]hept-2-ene (VIII; X = H) (Dawson and Ramage, *loc. cit.*). On treatment with *N*-bromosuccinimide the hydrocarbon was smoothly converted into a bromo-derivative (VIII; X = Br) which, with dimethylamine, gave a basic product subsequently shown to have structure (IX; X = NMe_2) and not (VIII; X = NMe_2). This was proved by reduction of the basic product to the saturated amine, which after Hofmann degradation and oxidation gave (I) and not (II). It appears that the rearrangement making this result possible must have occurred during the treatment of (VIII; X = Br) with dimethylamine. Similar rearrangements have been observed on treatment of allylic bromides with amines (Jones, Lacey, and Smith, *J.*, 1946, 940) and this provides a further example of three-carbon anionotropy (Braude, *Quart. Reviews*, 1950, **4**, 404). Attempts to convert (IX; X = NMe_2) into (IX; X = H) by Emde reduction have not yet been successful and oxidation with potassium permanganate either in acetone or aqueous solution gave norcaryophyllenic acid and not an amino-acid as expected.


(V)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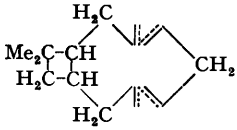
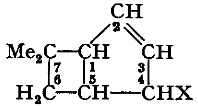
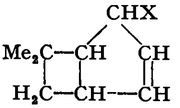

(VII)

(VIII)




(IX)

A new synthesis of norcaryophyllenic acid has been accomplished from the bromo-compound (VIII; X = Br). Treatment with silver oxide produced an unstable unsaturated alcohol, which, the rearrangement being assumed, would have structure (IX; X = OH). Oxidation gave (±)-norcaryophyllenic acid, and the *cis*-form was identical with the product prepared by Ruzicka and Zimmermann (*Helv. Chim. Acta*, 1935, **18**, 219) by a method involving conversion of an active *trans*-acid by acetic anhydride into the (±)-*cis*-anhydride.

EXPERIMENTAL.

(Analyses by Drs. Weiler and Strauss, Oxford.)

The dianilides and di-*p*-toluidides described in this paper were prepared by Hardy's method (*J.*, 1936, 398) from the appropriate ester and Grignard reagent, though better yields were obtained by way of the acid chlorides.

Oxidation of γ-Caryophyllene.—The γ-caryophyllene used for the oxidation was obtained from the mother-liquors remaining after the preparation of β-caryophyllene nitrosite (Deussen and Lewinsohn, *Annalen*, 1907, **356**, 13) and had b. p. 120°/12 mm., n_D^{19} 1·4965, d_{18}^{18} 0·8964, and $[\alpha]_D^{19}$ −23·95°. Oxidation with nitric acid (Ramage and Simonsen, *loc. cit.*) gave a mixture of acids, the esters from which on one fractionation through a Towers unit (see Vogel, " A Textbook of Practical Organic Chemistry," Longmans, Green & Co., 1948, p. 100) gave : (i) dimethyl *as*-dimethylsuccinate (47·0 g.), b. p. 82—85°/12 mm., n_D^{18} 1·4238 ; (ii) dimethyl norcaryophyllenate (14·5 g.), b. p. 110—114°/15 mm., n_D^{18} 1·4410 ; (iii) dimethyl caryophyllenate (25·0 g.), b. p. 129—133°/15 mm., n_D^{18} 1·4452 ; and (iv) dimethyl homocaryophyllenate (10·2 g.), b. p. 141—145°/15 mm., n_D^{18} 1·4489. The acids from fractions (iii) and (iv) were used below without preliminary separation of the *cis*- and *trans*-forms. Fraction (iv) was identified by preparation of the *cis*- and *trans*-dianilides, m. p. 180° and 282—283° respectively, alone or admixed with the corresponding dianilides of authentic homocaryophyllenic acid.

*2-Carboxymethyl-3 : 3-dimethyl*cyclo*butylacetic (3 : 3-Dimethyl*cyclo*butane-1 : 2-diacetic) Acid* (III).—Norcaryophyllenic acid (17·4 g.) was set aside with thionyl chloride (30 c.c.) at room temperature for 4 hours before the excess of thionyl chloride was removed under reduced pressure. Fractionation of the product gave norcaryophyllenoyl dichloride (15·1 g.), b. p. 103—105°/12 mm. This acid chloride (5·6 g.), dissolved in dry ether, was added in small portions to an ethereal solution of diazomethane (containing *ca.* 6 g. of diazomethane) at 0—5°, and the mixture allowed to attain room temperature overnight. The ether and excess of diazomethane were removed under reduced pressure at room temperature, giving the bisdiazoketone (6·0 g.) as a viscous gum. This was dissolved in methyl alcohol (75 c.c.) and kept at 50—60° whilst silver oxide (2·0 g.) was added in small portions during 2 hours, by which time the evolution of nitrogen had almost ceased. The reaction was completed on the water-bath (15 minutes). The cooled mixture was filtered, the filtrate was evaporated, and the residue on fractionation gave methyl 2-carbomethoxymethyl-3 : 3-dimethyl*cyclo*butylacetate (4·2 g.), b. p. 140—144°/12 mm., n_D^{18} 1·4520, d_{18}^{18} 1·052, $[\alpha]_D^{17}$ +21·3°. The trans-*dianilide*, which was insoluble in ether, crystallised from *cyclo*hexanone in small needles, m. p. 282—283° (Found : C, 75·1 ; H, 7·2. $C_{22}H_{26}O_2N_2$ requires C, 75·4 ; H, 7·5%). The cis-*dianilide*, which was soluble in ether, crystallised from aqueous ethyl alcohol (60%) in shining plates, m. p. 170°, $[\alpha]_D^{18}$ +42·9° (*c*, 1·706 in chloroform) (Found : C, 75·0 ; H, 7·2%). The *diamide*, prepared by keeping the above ester in ammonia solution (*d* 0·880) in a sealed tube for several weeks, crystallised from dioxan in small needles, m. p. 154° (Found : C, 60·1 ; H, 9·2. $C_{10}H_{18}O_2N_2$ requires C, 60·6 ; H, 9·1%). The trans-*di*-p-*toluidide*, which was sparingly soluble in ether, crystallised from ethyl alcohol in flat needles, m. p. 182°, $[\alpha]_D^{20}$ +68·7° (*c*, 0·5825 in acetone) (Found : C, 76·0 ; H, 8·0. $C_{24}H_{30}O_2N_2$ requires C, 76·2 ; H, 8·0%). Homocaryophyllenic acid prepared from the $C_{11}H_{18}O_3$ keto-acid (Ramage and Simonsen, *J.*, 1937, 73) gave a trans-*di*-p-*toluidide*, m. p. 227° (Found : C, 76·2 ; H, 7·9%), but the diamide prepared as above could only be obtained as an oil.

The above rearrangement of the bisdiazoketone was also carried out in aqueous solution to give the acid which was converted into the ester, but the yields were considerably lower.

*β-(2-Carboxy-4 : 4-dimethyl*cyclo*butyl)propionic Acid* (IV).—On treatment with thionyl chloride, the half ester (5·4 g.) of caryophyllenic acid gave the ester-chloride (4·0 g.), b. p. 125—128°/14 mm., which in dry ether was added to ethereal diazomethane (*ca.* 2·5 g. of diazomethane) at 0—5° and the mixture allowed to attain room temperature overnight. Removal of the ether and diazomethane under reduced pressure gave the diazoketone (4·3 g.). This was dissolved in dry methyl alcohol (45 c.c.) and kept at 50—60° while silver oxide (2·0 g.) was added in portions during 2 hours. The reaction was completed by refluxing the mixture for ½ hour. The cooled mixture was filtered, the filtrate was evaporated, and the residue on fractionation gave methyl β-(2-carbomethoxy-4 : 4-dimethyl*cyclo*butyl)propionate (2·85 g.), b. p. 140—145°/12 mm., n_D^{19} 1·4498, d_{18}^{18} 1·047, $[\alpha]_D^{20}$ +30·1°. The derived *trans*-dianilide, which was insoluble in ether, crystallised from *cyclo*hexanone in small needles, m. p. 282—283° (Found : C, 75·4; H, 7·4. Calc. for $C_{22}H_{26}O_2N_2$: C, 75·4; H, 7·5%). The *cis*-dianilide, which was soluble in ether, crystallised from aqueous ethyl alcohol (60%) in shining plates, m. p. 180° (alone and admixed with *cis*-homocaryophyllenic dianilide), $[\alpha]_D^{19}$ −34·6° (*c*, 1·737 in chloroform) (Found : C, 75·0; H, 7·2%). The *trans*-di-*p*-toluidide crystallised from ethyl alcohol in balls of needles, m. p. 227° (alone and admixed with homocaryophyllenic di-*p*-toluidide) (Found : C, 76·2; H, 7·9. Calc. for $C_{24}H_{30}O_2N_2$: C, 76·2; H, 8·0%).

Oxidation of the $C_{11}H_{18}O_3$ *Keto-acid* (V).—The keto-acid (2·0 g.) was dissolved in sodium carbonate solution (2N.; 30 c.c.) and oxidised by the addition of aqueous potassium permanganate (3%; 195 c.c.) to the solution at 50° during 5 hours. Acidification of the filtered solution followed by ether-extraction gave an acid (1·6 g.) which was esterified with ethereal diazomethane. Distillation afforded dimethyl caryophyllenate (1·3 g.), b. p. 128—133°/17 mm., n_D^{17} 1·4461. The ester was hydrolysed with potassium hydroxide (1·0 g.) and methyl alcohol (10 c.c.), and the sparingly soluble potassium salt which separated was filtered off from the ice-cold solution. Acidification and extraction of the salt gave (+)-*trans*-caryophyllenic acid (0·6 g.) which crystallised from *cyclo*hexane in long needles, m. p. 80—81° [alone or admixed with authentic (+)-*trans*-caryophyllenic acid]. From the potassium salt filtrate was obtained a liquid acid which after treatment with acetic anhydride in a sealed tube at 220° and hydrolysis of the anhydride formed gave *cis*-caryophyllenic acid (0·3 g.), m. p. 77—78° (alone or in admixture)

7 : 7-*Dimethyl*-2-*dimethylamino*bicyclo[3 : 2 : 0]*hept*-3-*ene* (IX; X = NMe_2).—The hydrocarbon (VIII) (4·5 g.) in carbon tetrachloride (30 c.c.) was refluxed for 5 minutes with *N*-bromosuccinimide (6·5 g.). The filtrate was poured into dimethylamine in carbon tetrachloride (13% w/v; 28 c.c.) and refluxed for ½ hour. Dimethylamine hydrobromide was filtered off and the solvent removed under reduced pressure. The residue was treated with ether, and the base extracted with dilute sulphuric acid. The acid extract was made alkaline with sodium hydroxide solution and extracted with ether. Removal of the solvent from the dried extract and fractionation gave 7 : 7-*dimethyl*-2-*dimethylamino*bicyclo[3 : 2 : 0]*hept*-3-*ene* (3·7 g.), b. p. 80—81°/17 mm., n_D^{20} 1·4568, d_{21}^{21} 0·8846 (Found : C, 79·9; H, 11·9. $C_{11}H_{19}N$ requires C, 79·9; H, 11·6%). The amine *picrate* crystallised from ethyl alcohol in balls of flat yellow needles, m. p. 177° (Found : C, 51·3; H, 5·5. $C_{17}H_{22}O_7N_4$ requires C, 51·8; H, 5·6%).

7 : 7-*Dimethyl*-2-*dimethylamino*bicyclo[3 : 2 : 0]*heptane*.—The above amine (7·3 g.) was hydrogenated at atmospheric pressure in methyl alcohol using palladium–charcoal (2 g.) as catalyst. Intake of hydrogen was 1104 c.c. (theoretical intake at room pressure and temperature = 1090 c.c.). The solution was filtered, the methyl alcohol was removed, and the residue on fractionation gave 7 : 7-*dimethyl*-2-*dimethylamino*bicyclo[3 : 2 : 0]*heptane* (6·6 g.), b. p. 79—80°/14 mm., n_D^{20} 1·4638 (Found : C, 78·3; H, 12·6. $C_{11}H_{21}N$ requires C, 79·0; H, 12·7%). The saturated amine *picrate* crystallised from ethyl alcohol in clusters of yellow prisms, m. p. 161° (Found: C, 51·6; H, 5·8. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1%).

Hofmann Degradation of the Saturated Amine.—The above saturated amine (3·6 g.) in ethyl acetate was treated with a slight excess of methyl iodide, the solution warmed for 5 minutes after the initial spontaneous reaction, and the methiodide which separated filtered off. The methiodide, m. p. 258° (decomp.), was dissolved in methyl alcohol and shaken for ½ hour with excess of moist silver oxide, and the solution filtered. The methyl alcohol was removed from the filtrate, and the residue heated in an oil-bath until nothing further distilled. The oily distillate was shaken with dilute sulphuric acid and the oil collected in a little ether. Removal of the ether from the dried extract and fractionation gave 7 : 7-dimethyl*bicyclo*[3 : 2 : 0]hept-2-ene (1·5 g.), b. p. 131—134°, n_D^{22} 1·4570. The sulphuric acid extract was made alkaline and the original saturated amine (0·5 g.) recovered.

Oxidation of the Hydrocarbon from the Above Reaction.—The above hydrocarbon (1·8 g.) was oxidised with potassium permanganate (7·0 g.) in acetone (50 c.c.) at 0°. The acid isolated from the sludge did not give a sparingly soluble potassium salt with alcoholic potassium hydroxide and on storage solidified completely. Crystallisation from *cyclo*hexane gave (±)-*cis*-2-carboxy-3 : 3-dimethyl*cyclo*butylacetic acid, in prisms, m. p. 120—121° alone or mixed with the *cis*-acid obtained from (IX; X = H).

3 : 3-*Dimethyl*cyclo*butane*-1 : 2-*dicarboxylic Acid*.—*N*-Bromosuccinimide (5·4 g.) was added to the hydrocarbon (VIII; X = H) (3·7 g.) in carbon tetrachloride (15 c.c.), and the mixture warmed on the water-bath for 5 minutes. The precipitated succinimide was filtered off from the cooled solution, and the filtrate shaken with moist silver oxide (8·0 g.) for 1 hour. The silver oxide and bromide were filtered off and the dried solution on evaporation under reduced pressure gave the unsaturated alcohol, which, like the bromo-compound, decomposed on distillation, and without further purification was dissolved in acetone and oxidised by the slow addition of potassium permanganate (11·6 g.) to the solution at 0°. The sludge was filtered off, suspended in water, and decolorised with sulphur dioxide. The acidified solution was extracted with ether, and the acid component isolated with sodium carbonate solution. The alkaline extract was further oxidised by the addition of aqueous potassium permanganate solution (3%) until the colour was permanent. The filtered and acidified solution was extracted with ether. Removal of the solvent from the dried extract gave an acid (1·4 g.). Crystallisation from *cyclo*hexane afforded a crude acid, m. p. 146—148°, which was heated with acetic anhydride in a sealed tube at 220° for 6 hours. Distillation gave the anhydride which on digestion with water and evaporation gave pure

(±)-*cis*-3 : 3-dimethyl*cyclo*butane-1 : 2-dicarboxylic acid, which crystallised from benzene in prisms, m. p. 149—150° [alone or admixed with (±)-*cis*-norcaryophyllenic acid described below] (Found: C, 56·1; H, 6·8. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%). The *cis*-dianilide, which was insoluble in ether, crystallised from ethyl alcohol in balls of needles, m. p. 267° (alone or admixed with *cis*-norcaryophyllenic dianilide) (Found: C, 74·2; H, 6·7. $C_{20}H_{22}O_2N_2$ requires C, 74·5; H, 6·9%). The *cis*-acid was heated with concentrated hydrochloric acid in a sealed tube at 180° overnight, and the solution was treated with charcoal and evaporated. Crystallisation of the residual acid from *cyclo*hexane gave (±)-*trans*-3 : 3-dimethyl*cyclo*butane-1 : 2-dicarboxylic acid in prisms, m. p. 148—149° [alone or admixed with (±)-*trans*-norcaryophyllenic acid described below] (Found: C, 55·6; H, 7·1. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%). The trans-*dianilide*, which was soluble in ether, crystallised from aqueous ethyl alcohol (60%) in flat needles, m. p. 238° (alone or admixed with *trans*-norcaryophyllenic dianilide) (Found: N, 8·8. $C_{20}H_{22}O_2N_2$ requires N, 8·7%).

Racemisation of (+)-trans-*Norcaryophyllenic Acid.*—(+)-*trans*-Norcaryophyllenic acid (0·65 g.) was heated with acetic anhydride (6 c.c.) in a sealed tube at 220° for 6 hours. Distillation of the product afforded an anhydride (0·4 g.) which on digestion with water and evaporation gave (±)-*cis*-norcaryophyllenic acid, which crystallised from benzene in prisms, m. p. 149—150°. The (±)-*cis*-acid was heated with concentrated hydrochloric acid in a sealed tube at 150° for 15 hours. The solution, after treatment with charcoal, was evaporated and gave (±)-*trans*-norcaryophyllenic acid, which crystallised from *cyclo*hexane in prisms, m. p. 148—149°. The (±)-*trans*-dianilide crystallised from aqueous ethyl alcohol (60%) in flat needles, m. p. 238°, and the (±)-*cis*-dianilide crystallised from ethyl alcohol in balls of needles, m. p. 267°.

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