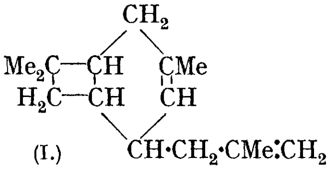
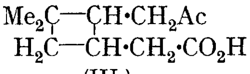
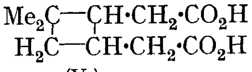
16. *The Caryophyllenes. Part V. The Structure of Homocaryophyllenic Acid.*

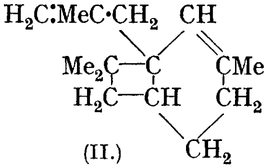
By G. R. Ramage and J. L. Simonsen.

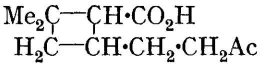
It was pointed out (J., 1935, 1583) that the determination of the structure of the keto-acid $C_{11}H_{18}O_3$ (Semmler and Mayer, *Ber.*, 1911, **44**, 3662) would enable a distinction to be drawn between the formulæ (I) (Ruzicka, *J. Soc. Chem. Ind.*, 1935, **54**, 509) and (II) (Ramage and Simonsen, *loc. cit.*, p. 1581) suggested for β-caryophyllene, since the former would give on oxidation the keto-acid (III), and the latter, (IV), which with sodium hypobromite would yield the homocaryophyllenic acids (V) and (VI) respectively.

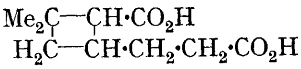

(I.)


$$\begin{array}{l}\mathrm{Me_2C{-}CH{\cdot}CH_2Ac}\\ \mathrm{H_2C{-}CH{\cdot}CH_2{\cdot}CO_2H}\end{array}$$
(III.)


$$\begin{array}{l}\mathrm{Me_2C{-}CH{\cdot}CH_2{\cdot}CO_2H}\\ \mathrm{H_2C{-}CH{\cdot}CH_2{\cdot}CO_2H}\end{array}$$
(V.)


(II.)

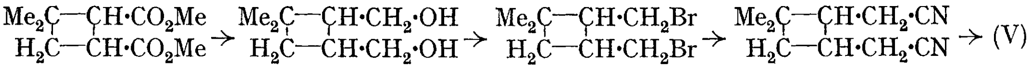

$$\begin{array}{l}\mathrm{Me_2C{-}CH{\cdot}CO_2H}\\ \mathrm{H_2C{-}CH{\cdot}CH_2{\cdot}CH_2Ac}\end{array}$$
(IV.)


$$\begin{array}{l}\mathrm{Me_2C{-}CH{\cdot}CO_2H}\\ \mathrm{H_2C{-}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H}\end{array}$$
(VI.)

Utilising *cis*-norcaryophyllenic and caryophyllenic acids, we have undertaken the synthesis of the dibasic acids, 2-carboxymethyl-1 : 1-dimethyl*cyclo*butane-3-acetic acid (V) and 2-carboxy-1 : 1-dimethyl*cyclo*butane-3-β-propionic acid (VI), in order to compare their dianilides with the dianilide, m. p. 179—180°, prepared from homocaryophyllenic acid (J., 1936, 742).

The considerable quantities of the caryophyllenic acids required for these syntheses were obtained by the direct oxidation of the caryophyllenes with nitric acid and we now find the crude acids, isolated as described in Part I (J., 1934, 1806), to be mixtures of the *cis*- and *trans*-forms, complete purification by crystallisation yielding finally the *trans*-acids. By analogy with the dianilides of *cis*- and *trans*-caryophyllenic acids, we assign to the homocaryophyllenic dianilide, m. p. 179—180°, described previously the *cis*-configuration. A repetition of the preparation of homocaryophyllenic acid, a specimen of the keto-acid regenerated from the semicarbazone, once recrystallised, being used, gave a small quantity of a second, trans-*dianilide*, m. p. 282°.

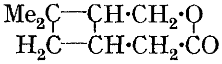
Methyl *d*-*cis*-norcaryophyllenate was converted by the stages outlined below into the methyl ester of (V). Owing to the poor yields and in view of the previous difficulties

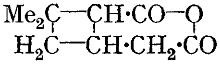

$$\begin{array}{lllllllll}\mathrm{Me_2C{-}CH{\cdot}CO_2Me} & & \mathrm{Me_2C{-}CH{\cdot}CH_2{\cdot}OH} & & \mathrm{Me_2C{-}CH{\cdot}CH_2Br} & & \mathrm{Me_2C{-}CH{\cdot}CH_2{\cdot}CN} & & \\ \mathrm{H_2C{-}CH{\cdot}CO_2Me} & \rightarrow & \mathrm{H_2C{-}CH{\cdot}CH_2{\cdot}OH} & \rightarrow & \mathrm{H_2C{-}CH{\cdot}CH_2Br} & \rightarrow & \mathrm{H_2C{-}CH{\cdot}CH_2{\cdot}CN} & \rightarrow & \mathrm{(V)}\end{array}$$

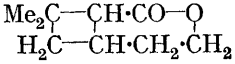
encountered in the preparation of glycols and bromides of this type (Bradfield, Jones, and Simonsen, J., 1936, 1136), no attempt was made to purify the intermediate products. The *methyl* ester was faintly optically active, but analysis showed it to be not quite pure. Preparation of the crystalline dianilide indicated that a partial conversion of this *cis*- into the *trans*-configuration had occurred, since two *dianilides*, m. p. 170° and 280°, were obtained. The former was optically inactive in chloroform solution. The latter did not depress the melting point of the *trans*-dianilide of homocaryophyllenic acid, but this cannot be regarded as a proof of identity, since no depression results in admixture with the *trans*-dianilide of caryophyllenic acid. It is probable that the racemisation of methyl *d*-*cis*-norcaryophyllenate occurs during the reduction to the glycol, which, if it proceeds through the di-enolic form of the ester, must result in the loss of optical activity.

The *methyl* ester of (VI) was prepared by the reduction with sodium and alcohol of caryophyllenic anhydride, the resulting lactone being converted into the dibasic acid by

Blanc's method. Although the reduction of the anhydride (VII) can result theoretically in the formation of the two isomeric lactones (VIII) and (IX), a consideration of previous work on the reduction of the anhydrides of unsymmetrical acids (*inter al.*, Blanc, *Bull. Soc. chim.*, 1905, **33**, 879) suggests that (VIII) would form the main, if not the sole product. Reduction to (IX) would probably be accompanied by ring fission, as was observed in the case of sodium methyl caronate (Hariharan, Menon, and Simonsen, J., 1928, 438). This view receives support from the fact that the yield of the lactone is very poor and little unchanged caryophyllenic acid can be recovered.


(IX.)


(VII.)


(VIII.)

The *dianilide*, prepared from the methyl ester of the acid, was optically active and melted at 206°; another specimen prepared in small quantity in a preliminary experiment melted at 212°. The slight difference in melting point may be due to a difference in optical purity, but the higher-melting anilide was insufficient in quantity for its rotatory power to be determined. There was no evidence of the presence of a *trans*-modification of the dianilide.

Whilst the racemisation which occurred in the synthesis of 2-carboxymethyl-1 : 1-dimethyl*cyclo*butane-3-acetic acid has precluded a rigid proof of its identity with homocaryophyllenic acid, we consider the dianilide, m. p. 179–180°, prepared from the latter acid to be the lævorotatory form (not necessarily optically pure) of the synthetic dianilide, m. p. 170°, and this view, in our opinion, receives support from the fact that each of these dianilides is accompanied by a higher-melting *trans*-dianilide. The difficulty involved in the preparation of the synthetic acid makes it improbable that it will be available in quantity sufficient for its resolution.

We referred previously (*loc. cit.*, p. 742) to the suggestion made by Treibs (*Ber.*, 1936, **69**, 41) that methyl betulolate was identical with methyl homocaryophyllenate. By the kindness of Dr. Treibs we have now had the opportunity of preparing the dianilide of his acid. Like homocaryophyllenic acid, it yields two dianilides, m. p. 180° and 279°, identical in all respects with the dianilides of this acid. Details of this work will be published by Dr. Treibs.

An attempt was made to utilise *X*-ray powder photographs to compare the synthetic dianilides with those derived from homocaryophyllenic and betulolic acids. We are much indebted to Professor E. A. Owen, Sc.D., and Mr. I. G. Edmunds, B.Sc., for carrying out this work. The identity of the dianilides of homocaryophyllenic and betulolic acids was confirmed and they differed from the dianilides of the two synthetic acids. Since the dianilides of the degradation acids were both optically active, identity with the dianilide of the optically inactive synthetic acid would not be expected.

These experiments lead us to conclude that, assuming caryophyllenic acid has been correctly formulated (synthetic proof of which has not yet been obtained), Ruzicka's formula (I) provides, so far as the present evidence goes, the most satisfactory representation of β-caryophyllene.

EXPERIMENTAL.

Nitric Acid Oxidation of Caryophyllene.—Caryophyllene (30 c.c.) and nitric acid (100 c.c.; *d* 1·14) were gently heated on the water-bath for 36 hours, a further quantity of acid (300 c.c.) being added at intervals. The mixture was concentrated on the water-bath, and the residual gummy acid freed from water and esterified with methyl-alcoholic sulphuric acid in the presence of benzene. In all, 3000 g. of caryophyllene were oxidised and the ester on fractionating (4 times) with a short column gave (i) b. p. up to 105°/18 mm., chiefly methyl dimethylsuccinate (250 g.), (ii) b. p. 108–116°/18 mm., methyl norcaryophyllenate (106 g.), and (iii) b. p. 122–132°/18 mm., methyl caryophyllenate (150 g.).

Methyl cis-*Norcaryophyllenate.*—The fraction (ii) was hydrolysed, and crude norcaryophyllenic acid (45 g.), m. p. 120°, isolated. A portion (12 g.) was gently refluxed with acetyl chloride: the anhydride (6 g.), b. p. 138–139°/15 mm., solidified almost completely. The remainder of the acid (33 g.) was treated with acetic anhydride at 220° for 6 hours and gave the anhydride (25 g.), b. p. 139–142°/15 mm. The combined anhydrides were refluxed with methyl alcohol (100 c.c.), benzene (100 c.c.), and sulphuric acid (25 c.c.) for 9 hours, and the ester (31 g.) purified by distillation, b. p. 117–120°/16 mm.

Methyl dl-2-*Carbomethoxymethyl*-1 : 1-*dimethyl*cyclo*butane*-3-*acetate*.—The above ester (10 g.) in ethyl alcohol (150 c.c., distilled over sodium) was poured on clean sodium (20 g.) and when the vigorous reaction had subsided the mixture was heated at 130° until the sodium dissolved. The cooled solution was acidified with concentrated hydrochloric acid, with the addition of sufficient water to dissolve the sodium chloride, and extracted repeatedly with chloroform. Removal of the solvent left a mobile oil (3 g.), which was gently heated with phosphorus tribromide (5 g.) on the water-bath for 1 hour. Ice was added, the precipitated oil collected in ether, the ethereal extract shaken with sodium carbonate solution and dried, and the ether evaporated. The liquid *dibromo*-compound (3·2 g.), after keeping in a vacuum, was reasonably pure (Found : Br, 52·5. $C_8H_{14}Br_2$ requires Br, 59·3%). It was refluxed with methyl alcohol (20 c.c.) and finely powdered potassium cyanide (2·0 g.) for 18 hours and the resulting nitrile, isolated with ether, was heated for 3 hours with methyl-alcoholic hydrogen chloride (20 c.c.). Ammonium chloride separated from the cooled solution, water was added, and the *methyl* ester after extraction with ether was distilled, b. p. 140–160°/20 mm. (1·7 g.). The ester obtained from three such experiments, on refractionation, gave an oil (3·5 g.), b. p. 145–155°/19 mm., $n_D^{20°}$ 1·4480, α_{5461} + 0·56°, which was not quite pure (Found : C, 61·4; H, 9·3. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%).

The dianilide was prepared by Hardy's method (J., 1936, 398). To a Grignard solution prepared from magnesium (0·5 g.) and ethyl bromide (2·5 g.), aniline (2·0 g.) was added, followed by the methyl ester (1 g.) in ether (10 c.c.), and the mixture was gently refluxed. Excess of dilute hydrochloric acid was added and after shaking the mixture was allowed to stand. The trans-*dianilide* (0·2 g.), which was insoluble in ether, separated and was collected. It crystallised from *cyclo*hexanone in long colourless needles, m. p. 280° (Found : C, 75·4; H, 7·4. $C_{22}H_{26}O_2N_2$ requires C, 75·4; H, 7·4%). The ether, from which this dianilide had separated, was dried and yielded on evaporation an oil (1 g.), which partly crystallised when mixed with dilute alcohol. Recrystallised from this solvent, the cis-*dianilide* (0·3 g.) separated in long needles, m. p. 170° (Found : C, 75·3; H, 7·5%).

Methyl 2-*Carbomethoxy*-1 : 1-*dimethyl*cyclo*butane*-3-β-*propionate*.—The crude methyl caryophyllenate (150 g.) (see above) was hydrolysed, and the acid (90 g.) recovered from the insoluble potassium salt. After treatment with acetyl chloride the anhydride (35 g.) was distilled, and the residual *trans*-acid converted into the anhydride by treatment with acetic anhydride at 220°. The combined caryophyllenic anhydride was fractionated, b. p. 165–172°/20 mm. (54 g.).

The anhydride (10 g.) in alcohol (100 c.c., distilled from sodium) was added to clean sodium (15 g.) and finally heated at 130° to complete the reduction. Water was added, the alcohol removed in steam, and the residue, after being strongly acidified with hydrochloric acid, distilled in steam. The distillate (1000 c.c.), saturated with salt, was repeatedly extracted with ether, and the total product (8·5 g.) from caryophyllenic anhydride (44 g.) was distilled, b. p. 142—146°/20 mm., $n_D^{20°}$ 1·4728, α_{5461} + 40·3°.

The lactone (8·2 g.) was heated with powdered potassium cyanide (5 g., dried at 250° under reduced pressure) for 6 hours at 250°, water added, and the filtered solution acidified and extracted with ether. The cyano-acid remaining after removal of the solvent was esterified with methyl-alcoholic hydrogen chloride (40 c.c.) and the *methyl* ester (5·5 g.), b. p. 145–150°/18 mm., isolated. The analysed sample had b.p. 145–146°/18 mm., $n_D^{20°}$ 1·4502, α_{5461}–4·8° (Found: C, 63·1; H, 9·1. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%). The *dianilide*, prepared as described above (0·7 g. from the ester, 1 g.), crystallised from alcohol (80%) in long thin plates, m. p. 206°, $[\alpha]_{5461}$ –28·3° in pyridine (*c*, 3·217) (Found : C, 75·1; H, 7·7%).

d-*Homocaryophyllenic Acid*.—The semicarbazone (6 g.) of the keto-acid was converted into homocaryophyllenic acid as previously described (*loc. cit.*, p. 742), and the latter esterified with diazomethane giving *methyl homocaryophyllenate* (3·5 g.), b. p. 144–150°/18 mm. The analysed fraction had b. p. 145–147°/18 mm., $n_D^{20°}$ 1·4492, $[\alpha]_{5461}$ + 56·9° (Found : C, 62·9; H, 8·8. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%). The ester (1 g.) was converted into the dianilide as described; the small quantity of product, insoluble in ether, crystallised from *cyclo*hexanone in small colourless needles, m. p. 282° (Found : C, 75·4; H, 7·4%). From the product soluble in ether, the *cis*-dianilide (0·8 g.), m. p. 179°, $[\alpha]_{5461}$ –57·5°, in chloroform (*c* 3·360), was obtained; it crystallised readily from alcohol (60%) in shining plates.

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