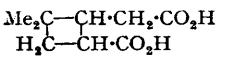
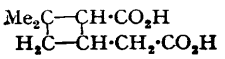
# 695. *The Caryophyllenes. Part VIII. The Synthesis of 2-Carboxy-3 : 3-dimethylcyclobutylacetic Acid.*

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

Caryophyllenic acid is either 4-carboxy-2 : 2-dimethyl- or 2-carboxy-3 : 3-dimethyl-*cyclo*-butylacetic acid (I or II, respectively) since it has been degraded to norcaryophyllenic acid (III). The acid (II) has now been synthesised; on resolution it failed to give caryophyllenic acid. It is concluded therefore that caryophyllenic acid must be (I).

It has long been realised that the structure of β-caryophyllene requires proof of the constitution of caryophyllenic acid, and this appeared to be possible only by synthesis. Caryophyllenic acid has been shown to be the next higher homologue of norcaryophyllenic acid (III) and can therefore be represented by either (I) or (II) (Owen, Ramage, and Simonsen, *J.*, 1938, 1211). A possible


(I.)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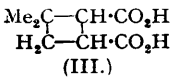
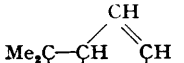

(III.)

method of synthesis of (II) arose from a consideration of the condensation of diphenylketen and *cyclo*pentadiene which was shown to proceed by 1 : 2-addition (Lewis, Ramage, and Simonsen, *J.*, 1937, 1837). This led to an examination of an adduct from dimethylketen and *cyclo*-pentadiene, which on oxidation gave a stable keto-dicarboxylic acid (IV) (Ramage and Simonsen, *Chem. and Ind.*, 1939, **58**, 447). At that time it was only possible to reduce the acid to the corresponding hydroxy-acid and no further, but the examination has been recently resumed since Farmer and Farooq (*J.*, 1938, 1925) have also established other condensation products of ketens and conjugated dienes as arising by 1 : 2-addition. In our experiments the unsaturated ketone was purified through its semicarbazone before oxidation with potassium permanganate, and the resulting keto-dicarboxylic acid isolated by esterification, fractionation, and subsequent hydrolysis. The crystalline *cis*-acid showed no tendency to lose carbon dioxide and must therefore be (IV), derived from (V), and not the alternative (VI), derived from (VII).


(IV.)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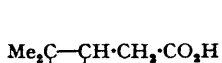
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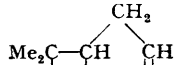
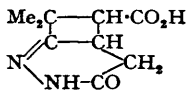
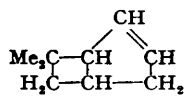

(VII.)

The carbonyl group was reduced by Huang-Minlon's procedure (*J. Amer. Chem. Soc.*, 1946, **68**, 2487), and the resulting acid (II) isolated as its dimethyl ester. A small quantity of an acid product, sparingly soluble in water, was also obtained and is considered to be (VIII).

(VIII.) 


(IX.)

The dimethyl ester of (II) on hydrolysis with methyl-alcoholic potash gave a sparingly soluble potassium salt from which the (±)-*trans*-acid, m. p. 106—108°, was isolated. From the potassium salt mother-liquor, a liquid acid was recovered and converted, by heating it with acetic anhydride in a sealed tube, into the *cis*-anhydride, which gave the (±)-*cis*-acid, m. p.

120—121°, on digestion with water. This method of separation was analogous to the very similar behaviour of caryophyllenic acid.

The oxidation of (V) allowed only a moderate recovery of (VI) as a crystalline product, and after the above facts had been established the *cis*- and the *trans*-acid were made more readily available by carrying out the reduction of (V) to the hydrocarbon (IX). By a modified Wolff–Kishner reaction, on the semicarbazone of the ketone (V), 7 : 7-dimethyl*bicyclo*[3 : 2 : 0]hept-2-ene (IX) was readily available. That no change of bond position had occurred was evident when the same *cis*- and *trans*-acids were obtained on oxidation as had been prepared from the keto-acid (IV).

The acids had to be resolved for comparison of the active isomers with the (−)-*cis*- and (+)-*trans*-caryophyllenic acids, m. p. 77—78° and 80—81°, respectively. Resolution of (II) was achieved by use of the normal (−)-quinine salts from which the (+)-*trans*-acid, m. p. 144—145°, $[\alpha]_D$ +24·2°, and the (−)-*trans*-acid, m. p. 142—143°, $[\alpha]_D$ −24·6°, were recovered. Similarly available were the (−)-*cis*-acid, m. p. 157°, $[\alpha]_D$ −11·1°, and the (+)-*cis*-acid, m. p. 157—158°, $[\alpha]_D$ +10·9°.

It was obvious therefore that 2-carboxy-3 : 3-dimethyl*cyclo*butylacetic acid (II) is not identical with caryophyllenic acid, which must therefore be represented by (I) (see also Barton, *J. Org. Chem.*, 1950, **15**, 457). It is not proposed at this stage to discuss the bearing of this formulation on the structure of β-caryophyllene, because of the many conflicting views concerning this sesquiterpene, but to await the completion of further experiments now in progress.

## Experimental.

Analyses by Drs. Weiler and Strauss, Oxford.

7 : 7-*Dimethyl*bicyclo[3 : 2 : 0]*hept*-2-*en*-6-*one* (V).—Dimethylketen (8 g.; from 20 g. of dimethylmalonic acid) and *cyclo*pentadiene (12 c.c.; freshly distilled) were mixed at about −80° and set aside to attain room temperature. Next day unchanged *cyclo*pentadiene was distilled off at atmospheric pressure through a short fractionating column, and the residue gave 7 : 7-dimethyl*bicyclo*[3 : 2 : 0]hept-2-en-6-one (10·0 g.), b. p. 175—178° (cf. Staudinger, *Helv. Chim. Acta*, 1924, **7**, 19).

The semicarbazone (13·0 g.), m. p. 215°, prepared in aqueous alcohol, quickly separated in balls of needles. The pure ketone was recovered almost quantitatively by steam-distillation of the semicarbazone with an equal weight of oxalic acid, followed by ethereal extraction and fractionation; it had b. p. 72°/15 mm.

2-*Carboxy*-4-*keto*-3 : 3-*dimethyl*cyclo*butylacetic Acid* (IV).—The purified ketone (V) (20 g.) in acetone (150 c.c.) was stirred, with ice-cooling, during the addition of finely powdered potassium permanganate (48 g.) during 12 hours. Next morning the sludge was filtered, and unchanged ketone (7 g.) recovered from the filtrate. The precipitate was suspended in water (200 c.c.) and treated with sulphur dioxide to remove manganese dioxide, and the solution exhaustively extracted with ether. Removal of the solvent gave the crude keto-acid (15·7 g.) which was esterified by refluxing it with methanol (20 c.c.) and concentrated sulphuric acid (3 c.c.) for 3 hours. The ester was isolated with ether, and on fractionation gave *methyl* 2-*carbomethoxy*-4-*keto*-3 : 3-*dimethyl*cyclo*butylacetate* (7·5 g.), b. p. 152°/12 mm. (Found : C, 57·5; H, 7·2. $C_{11}H_{16}O_5$ requires C, 57·9; H, 7·1%), together with a high-boiling residue.

The ester (6·5 g.) was hydrolysed by refluxing it with potassium hydroxide (5·0 g.) in methanol (40 c.c.), and the acid (4·5 g.), isolated by ether, crystallised readily. On recrystallisation from concentrated hydrochloric acid, 2-*carboxy*-4-*keto*-3 : 3-*dimethyl*cyclo*butylacetic acid* (IV) was obtained in large rhombohedra, m. p. 124—125° (Found : C, 53·9; H, 5·9%; equiv., 100·2. $C_9H_{12}O_5$ requires C, 54·0; H, 6·0%; equiv., 100). Treatment with acetyl chloride gave a liquid anhydride, b. p. 162—167°/16 mm., which on digestion with water regenerated the original acid, m. p. and mixed m. p. 124—125°.

On treatment of the methyl ester with an aqueous solution of semicarbazide acetate, the semicarbazone separated slowly. Most of this product was insoluble in benzene and was crystallised from water to give the ester *semicarbazone* as prisms, m. p. 167—168° (Found : C, 50·4; H, 6·5; N, 15·1. $C_{12}H_{19}O_5N_3$ requires C, 50·5; H, 6·7; N, 14·7%). There was evidence of an isomeric semicarbazone which was soluble in benzene and crystallised on the addition of light petroleum (b. p. 40—60°) in needles, m. p. 125—127° (Found : C, 50·3; H, 6·7%).

4-*Keto*-8 : 8-*dimethyl*-2 : 3-*diaza*bicyclo[4 : 2 : 0]*oct*-1-*ene*-7-*carboxylic Acid* (VIII).—The semicarbazone, m. p. 167—168°, and sodium ethoxide were heated in ethanol at 180° for 10 hours. Water was added, the alcohol removed on the water-bath, and the residual solution acidified and set aside. The crystalline *acid* which separated was recrystallised from water, giving needles, m. p. 198—200° (Found : C, 55·2; H, 6·1; N, 14·8. $C_9H_{12}O_3N_2$ requires C, 55·1; H, 6·2; N, 14·3%). The product was identical with the substance isolated in the hydrazine experiment described below.

2-*Carboxy*-4-*hydroxy*-3 : 3-*dimethyl*cyclo*butylacetic Acid*.—The keto-acid (IV) (2 g.) was neutralised with aqueous sodium carbonate, and the solution (50 c.c.) reduced by stirring it with sodium amalgam (3%; 300 g.) for 6 hours. The alkaline solution was separated, almost neutralised with sulphuric acid, considerably concentrated, and then acidified and exhaustively extracted with ether in a constant-extraction apparatus. A crystalline product separated from the ether during the extraction and gave 2-*carboxy*-4-*hydroxy*-3 : 3-*dimethyl*cyclo*butylacetic acid* (1·1 g.) which recrystallised from benzene–acetone in plates, m. p. 183° (Found : C, 53·2; H, 7·0. $C_9H_{14}O_5$ requires C, 53·5; H, 7·0%). Treatment of the

acid with ethereal diazomethane gave *methyl 2-carbomethoxy-4-hydroxy-3 : 3-dimethyl*cyclo*butylacetate*, b. p. 153—156°/3 mm. (Found : C, 57·1; H, 8·0. $C_{11}H_{18}O_5$ requires C, 57·4; H, 7·8%).

7 : 7-*Dimethyl*bicyclo[3 : 2 : 0]*hept-2-ene* (IX).—To a solution of sodium (5·0 g.) in diethylene glycol (60 c.c.) was added the ketone (V) semicarbazone (10·0 g.), and the mixture was heated at 190—200° for 4 hours, the product being allowed to distil. The resulting mobile liquid (5·4 g.) was washed with water and dilute sulphuric acid and dried before fractionation; it gave 7 : 7-*dimethyl*bicyclo[3 : 2 : 0]*hept-2-ene*, b. p. 131—134°, $n_D^{19}$ 1·4578, $d_{19}^{19}$ 0·8464 (Found : C, 88·7; H, 11·7. $C_9H_{14}$ requires C, 88·5; H, 11·5%).

2-*Carboxy*-3 : 3-*dimethyl*cyclo*butylacetic Acid* (IV).—(*a*) The keto-acid (IV) (5 g.) was refluxed with potassium hydroxide (4·0 g.), hydrazine hydrate (85%; 4·5 c.c.), and diethylene glycol (45 c.c.) for 1 hour. Water and unchanged hydrazine hydrate were distilled off until the temperature reached 190—200°, whereupon refluxing was continued for a further 4 hours. The cooled, acidified solution on being kept deposited a substance (0·5 g.) considered to be (VIII) which crystallised from water in long, flattened needles, m. p. 198—200° (Found : C, 54·8; H, 6·2; N, 14·6%). Extraction of the solution with ether gave an acidic product which was esterified with ethereal diazomethane. The resulting *methyl 2-carbomethoxy-3 : 3-dimethyl*cyclo*butylacetate* (2·2 g.) on distillation had b. p. 128—135°/18 mm., redistilled for analysis, b. p. 129—130°/18 mm. (Found : C, 61·6; H, 8·5. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·5%). When this was hydrolysed with potassium hydroxide (2·0 g.) and methyl alcohol (15 c.c.), a sparingly soluble potassium salt separated from the hot solution and was filtered off after strong cooling. The solid, washed with a little ice-cold methanol, was dissolved in water, and the solution evaporated somewhat to remove alcohol, acidified, and extracted with ether. Removal of the solvent left the acid (1·0 g.) which solidified on being kept and was crystallised from *cyclo*hexane; it gave (±)-trans-2-*carboxy*-3 : 3-*dimethyl*cyclo*butylacetic acid* as prisms, m. p. 106—108° (Found : C, 57·7; H, 7·4%; equiv., 92·8. $C_9H_{14}O_4$ requires C, 58·0; H, 7·6%; equiv., 93·0). The filtrate from the potassium salt was evaporated to remove the alcohol, acidified, and extracted with ether. The acid (0·9 g.), obtained from the extract, failed to crystallise and was heated with acetic anhydride at 220° for 6 hours. Fractionation gave the *cis*-anhydride which on digestion with water followed by ether-extraction gave the (±)-cis-*acid*. On being kept the acid slowly crystallised, and was recrystallised from *cyclo*hexane in rhombs, m. p. 120—121° (Found : C, 57·7; H, 7·5. $C_9H_{14}O_4$ requires C, 58·0; H, 7·6%).

(*b*) The hydrocarbon (IX) (17·8 g.) in acetone (150 c.c.) was stirred and maintained at 0—4° by external cooling during the addition of finely-divided potassium permanganate (63·0 g.) for 12 hours. Next day the sludge was filtered off and suspended in water (200 c.c.), and sulphur dioxide passed in to remove manganese dioxide. The acidified solution was extracted with ether to give, on removal of the solvent, the crude acid (17·5 g.), which was esterified with diazomethane. On fractionation, methyl 4-carbomethoxy-3 : 3-dimethyl*cyclo*butylacetate (14·4 g.), b. p. 119—126°/12 mm., $n_D^{20}$ 1·4450, was obtained. The ester was hydrolysed by refluxing it with potassium hydroxide (13 g.) and methanol (60 c.c.), and, by the procedure of separating the insoluble potassium salt described above, gave the (±)-*trans*-acid (4·7 g.) (crystallised from *cyclo*hexane), m. p. 106—108° alone or mixed with the *trans*-acid from the keto-acid. The crude *cis*-acid (6·9 g.) yielded the *anhydride* of (±)-*cis*-2-carboxy-3 : 3-dimethyl*cyclo*butylacetic acid, b. p. 140—144°/3 mm. (Found : C, 63·9; H, 7·0. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%). Digestion with water gave the *cis*-acid, m. p. 120—121° alone or mixed with the corresponding acid from the keto-acid.

*Resolution of* (±)-trans-2-*Carboxy*-3 : 3-*dimethyl*cyclo*butylacetic Acid*.—The (±)-*trans*-acid (1·000 g.) and anhydrous (−)-quinine (1·742 g.) were dissolved in ethanol (16 c.c.) and water (26 c.c.). The solution was filtered and on being kept deposited the salt (1·56 g.) as needles. Three crystallisations from aqueous ethanol (2 : 1 by vol.) gave the neutral (+)-acid–(−)-quinine salt in large rosettes of fine needles, m. p. 121°, $[\alpha]_D^{21}$ −114·4° (in ethanol; *c*, 4·036). The salt was dissolved in aqueous methanol and decomposed by addition of ammonia. The precipitated quinine was filtered off and the alcohol distilled from the filtrate which was then acidified and extracted with ether. Removal of the solvent gave the (+)-trans-*acid* (0·26 g.) which crystallised from *cyclo*hexane in prisms, m. p. 144—145°, $[\alpha]_D^{21}$ +24·2° (in acetone; *c*, 1·115) (Found : C, 57·8; H, 7·6. $C_9H_{14}O_4$ requires C, 58·0; H, 7·6%).

The acid recovered from the more soluble quinine salt fractions (0·71 g.), m. p. 123—125°, $[\alpha]_D^{21}$ −17·4°, was again treated with quinine (1·24 g.) in alcohol (5 c.c.) and water (10 c.c.). After one further crystallisation from alcohol the less soluble salt (0·77 g.) was collected, and the combined filtrates containing the more soluble salt were decomposed as above and gave the (−)-trans-*acid*, m. p. 142—143°, $[\alpha]_D^{21}$ −24·6° (in acetone; *c*, 1·084) (Found : C, 57·7; H, 7·7%).

*Resolution of* (±)-cis-2-*Carboxy*-3 : 3-*dimethyl*cyclo*butylacetic Acid*.—The (±)-*cis*-acid (1·000 g.) and anhydrous (−)-quinine (1·742 g.) were dissolved in ethanol (30 c.c.) and water (50 c.c.), and on being kept the filtered solution deposited the salt (1·48 g.) as needles. Two crystallisations from aqueous ethanol gave this (−)-acid–(−)-quinine salt (0·76 g.) in large clusters of fine needles, m. p. 202°. Decomposition of the salt with ammonia gave finally the (−)-cis-*acid* (0·25 g.) which crystallised from *cyclo*hexane in prisms, m. p. 157°, $[\alpha]_D^{19}$ −11·1° (in acetone; *c*, 3·650) (Found : C, 58·0; H, 7·3. $C_9H_{14}O_4$ requires C, 58·0; H, 7·6%). Treatment of the more soluble salt fractions in the manner described for the *trans*-acid, gave the (+)-cis-*acid* (0·35 g.) which crystallised from *cyclo*hexane in prisms, m. p. 157—158°, $[\alpha]_D^{20}$ +10·9° (in acetone; *c*, 3·960) (Found : equiv., 92·9. $C_9H_{14}O_4$ requires equiv., 93·0).

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