596. *The Synthesis of Caryophyllenic Acid.*

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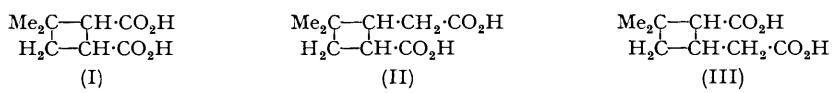
4-Carboxy-2 : 2-dimethyl*cyclo*butylacetic acid (II) has been synthesised, separated into *cis*- and *trans*-forms, and resolved. The synthetic *trans*-(+)-acid is identical with *trans*-caryophyllenic acid, prepared from caryophyllene, the structure of which is thus finally established, as also is the orientation of the dimethyl*cyclo*butane ring of caryophyllene with respect to the second ring.

2-Carboxy*cyclo*butylacetic acid has also been synthesised, separated into *cis*- and *trans*-forms, and resolved.

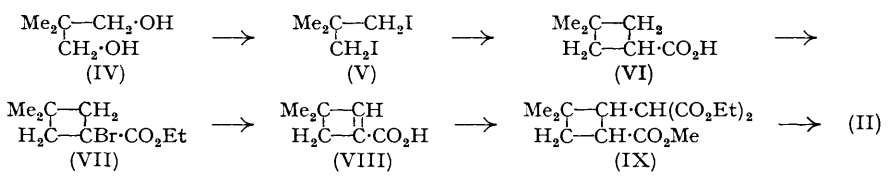
THE synthesis and resolution of norcaryophyllenic acid (I) (Rydon, *J.*, 1936, 593; 1937, 1340) established the presence of a *gem*-dimethyl*cyclo*butane ring in β-caryophyllene but left uncertain the orientation of this ring with respect to the second, larger ring in the sesquiterpene. The final solution of this problem clearly required a synthesis of the higher homologue, caryophyllenic acid, which accompanies norcaryophyllenic acid in the oxidation products of β-caryophyllene (Evans, Ramage, and Simonsen, *J.*, 1934, 1806; Ruzicka and Zimmermann, *Helv. Chim. Acta*, 1935, **18**, 219). The work now reported, which was started in 1947 (cf. Campbell and Rydon, *Chem. and Ind.*, 1951, 312), had as its objective the synthesis of 4-carboxy-2 : 2-dimethyl*cyclo*butylacetic acid (II), which is one of the possible structures for caryophyllenic acid, the other being 2-carboxy-3 : 3-dimethyl*cyclo*butylacetic acid (III) (Ruzicka, *Chem. and Ind.*, 1935, **54**, 509; Ramage and Simonsen, *J.*,



(I) (II) (III)

1935, 532). During the course of our work, (III) was synthesised and resolved by Dawson and Ramage (*J.*, 1950, 3523) and shown to differ from caryophyllenic acid, while strong degradative evidence for preferring structure (II) to structure (III) was advanced by Barton (*J. Org. Chem.*, 1950, **16**, 457) and by Eschenmoser and Fürst (*Experientia*, 1951, **7**, 290).

Our synthesis was carried out by the following route :



(IV) (V) (VI)

(VII) (VIII) (IX) (II)

A similar synthesis was attempted by Owen, Ramage, and Simonsen (*J.*, 1938, 1211) but was taken only as far as the bromo-ester (VII). Like these authors, we had difficulty in preparing pure 2 : 2-dimethylpropane-1 : 3-diol (IV) from formaldehyde and *iso*butyraldehyde (Wessely, *Monatsh.*, 1900, **21**, 216, 232; Franke, *ibid.*, 1913, **34**, 1904; Bincer and Hess, *Ber.*, 1928, **61**, 541); a modified method, which gives consistent yields and was used in most of our work, is described in the Experimental section, but the most satisfactory

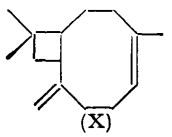
procedure is undoubtedly the lithium aluminium hydride reduction of ethyl dimethylmalonate. The glycol (IV) was converted into the di-iodide (V) in good yield by heating it with triphenyl phosphite and methyl iodide (cf. Landauer and Rydon, *J.*, 1953, 2224); this reaction contributed much to the success of our synthesis since, not only is this preparation much more convenient than that of the dibromide (Gustavson and Popper, *J. pr. Chem.*, 1898, **58**, 458; Owen, Ramage, and Simonsen, *loc. cit.*), but the di-iodide is more reactive than the dibromide and gives a very satisfactory yield of 3 : 3-dimethyl*cyclo*butanecarboxylic acid (VI) by condensation with ethyl malonate, followed by hydrolysis and decarboxylation.

The bromo-ester (VII) was readily obtained from the acid (VI) by the usual Hell–Volhard–Zelinsky procedure but its dehydrobromination was a matter of great difficulty; more conventional methods failing, this was finally brought about, in excellent yield, by treatment with potassium hydroxide under vigorously refluxing toluene. Diazomethane esterification of the resulting unsaturated acid (VIII), followed by a Michael reaction with ethyl malonate (ethyl cyanoacetate was unsatisfactory) yielded the tricarboxylic ester (IX) which, on hydrolysis and decarboxylation, gave a mixture of geometrical isomerides of the derived acid (II). This was converted into *trans*-(±)-4-carboxy-2 : 2-dimethyl*cyclo*butylacetic acid, m. p. 81—82°, by hydrochloric acid at 180°; the *cis*-(±)-acid, m. p. 120°, was obtained from the *trans*-acid by heating it with acetic anhydride at 220° and hydrolysing the resulting anhydride.

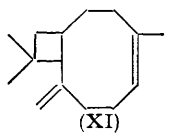
Structural identity of our synthetic *trans*-(±)-acid with *trans*-(+)-caryophyllenic acid prepared from caryophyllene was established by the identity of their infra-red absorption spectra in carbon disulphide solution. Although this evidence is conclusive, comparison of optically active and optically inactive substances in this way has rarely, if ever, been used to establish identity, and it seemed desirable to confirm the conclusion by a more conventional method.

The usual type of base (quinine, brucine, strychnine, morphine, cinchonine, cinchonidine, 2-amino-1-*p*-nitrophenylpropane-1 : 3-diol) having failed, the synthetic *trans*-(±)-acid was successfully resolved with the aid of quinine methohydroxide (Major and Finkelstein, *J. Amer. Chem. Soc.*, 1941, **63**, 1368). The (+)- and (−)-*trans*-4-carboxy-2 : 2-dimethyl*cyclo*butylacetic acids so obtained had m. p. 81—82° and $[\alpha]_D^{20}$ +28·5° and −28·0°, respectively. Both acids crystallised from *cyclo*hexane in needles similar in appearance to *trans*-(+)-caryophyllenic acid, m. p. 81—82°, $[\alpha]_D^{20}$ +28·0°, prepared from caryophyllene; a mixture of the naturally derived and the synthetic acid melted at 81—82°. The identity was further confirmed by converting the synthetic *trans*-acids and that from caryophyllene into the *cis*-isomerides by the usual acetic anhydride procedure; the synthetic *cis*-(+)- and *cis*-(−)-acids [obtained from the *trans*-(−)- and *trans*-(+)-acids, respectively], had m. p. 77—78° and $[\alpha]_D^{20}$ +41·0° and −41·0°, while the *cis*-(−)-acid from caryophyllene had m. p. 77—78° and $[\alpha]_D^{20}$ −43°; a mixture of the last-named acid with the synthetic *cis*-(−)-acid melted at 77—78°. The identity of the synthetic acids with those from caryophyllene is thus completely established and it follows that caryophyllenic acid has the structure (II).

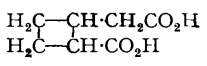
This proof of the structure of caryophyllenic acid establishes beyond doubt the orientation of the dimethyl*cyclo*butane ring in caryophyllene with respect to the nearest oxidisable centres in the larger ring; in terms of the currently accepted structure of β-caryophyllene (Dawson, Ramage, and Wilson, *Chem. and Ind.*, 1951, 464; Barton, Bruun, and Lindsay, *J.*, 1952, 2210), it follows from our work that, of the two alternative possibilities, (X) and (XI), the former is correct.



(X)



(XI)



(XII)

Our synthesis of caryophyllenic acid was guided by model experiments on the synthesis of 2-carboxy*cyclo*butylacetic acid (XII) from the readily accessible *cyclo*butanecarboxylic acid (Cason and Allen, *J. Org. Chem.*, 1949, **14**, 1036), which was carried out by a similar

series of reactions described in the Experimental section. The only noteworthy point which arises from this part of our work is the great difference in stability between *cyclo*but-1-enecarboxylic acid and the 3 : 3-dimethyl compound, the former absorbing oxygen so rapidly from the air as to make it almost impossible to obtain a satisfactory analysis for carbon and hydrogen. All six stereoisomerides of 2-carboxy*cyclo*butylacetic acid were obtained (see Table) :

	trans			*cis*		
Acid	(±)	(+)	(−)	(±)	(+)	(−)
M. p.	64·5°	Oil	Oil	110—111°	110—111°	110—111°
$[\alpha]_D^{20}$	—	+73°	−71°	—	+43°	−45°

In this series, as with the caryophyllenic acids, geometrical inversion was accompanied by inversion of the sign of rotation. The low melting point of the *trans*-acid, compared with the *cis*-, is an exception to the usually accepted relationship and is paralleled by the only two other fully investigated cases of carboxy*cyclo*butyl acetic acids (caryophyllenic acid, this paper; 2-carboxy-3 : 3-dimethyl*cyclo*butylacetic acid, Dawson and Ramage, *loc. cit.*) and by the inactive 2-carboxy*cyclo*pentylacetic acids (Linstead and Meade, *J.*, 1934, 935; Cook and Linstead, *J.*, 1934, 956); it is clear that melting points are a most unreliable guide to configuration.

Experimental

Synthesis of (±)-*Caryophyllenic Acid.*—2 : 2-*Dimethylpropane*-1 : 3-*diol* (IV). (*a*) The bulk of the material used in the present work was prepared by the following modification of Franke's method (*Monatsh.*, 1913, **34**, 1904).

*iso*Butyraldehyde (50 g.), dissolved in aqueous formaldehyde (35% w/w; 119 g.) and ethanol (25 ml.), was slowly added to a stirred solution of potassium hydroxide (39 g.) in ethanol (290 ml.), cooled to 0° during, and for 1 hr. after, the addition. The golden-yellow solution was set aside for 12 hr. at room temp. (the time is critical) and then neutralised (phenolphthalein) with acetic acid. Removal of the alcohol under reduced pressure, followed by extraction with ether (15 × 100 ml.), yielded the crude glycol (65 g.), which could only be recrystallised with difficulty and was therefore converted into the diacetate by 6 hours' refluxing with acetic anhydride (104 g.), containing fused sodium acetate (2 g.) and pyridine (2 g.). After removal of acetic acid and excess of acetic anhydride by distillation, the residual ester was dissolved in ether (100 ml.) and washed with 5% sodium hydrogen carbonate solution until neutral. Distillation gave 1 : 3-diacetoxy-2 : 2-dimethylpropane (55 g., 42%; average for 8 runs, 44%), b. p. 105—108°/15 mm., n_D^{20} 1·4348.

This ester (56 g.) was refluxed for 1 hr. with 10% alcoholic potassium hydroxide (400 ml.); removal of alcohol under reduced pressure, followed by exhaustive ether-extraction, drying, evaporation, and crystallisation from benzene, afforded 2 : 2-dimethylpropane-1 : 3-diol (27 g., 37%) as large needles, m. p. 126—127° (lit., m. p. 127°).

(*b*) The glycol can also be prepared by reduction of ethyl dimethylmalonate. Ethyl dimethylmalonate (18·8 g.) was added, under reflux, with stirring, to a solution of lithium aluminium hydride (3·8 g.) in anhydrous ether (100 ml.) at such a rate as to maintain gentle refluxing. Ten min. after completion of the addition water (5 ml.) was added and the mixture then poured into 10% sulphuric acid (50 ml.). Working up as in (*a*) gave the diol (8 g., 82%), m. p. 127°.

1 : 3-*Di-iodo*-2 : 2-*dimethylpropane* (V). The glycol (IV) (10 g.), triphenyl phosphite (68 g.), and methyl iodide (42 g.) were heated together under reflux in an oil-bath at 130° for 24 hr.; the internal temperature rose from 68° to 130° during the reaction; occasionally a little methyl iodide had to be distilled off at this stage to raise the internal temperature to 130°. Heating was then continued at 130° for a further 36 hr.; at lower temperatures the reaction is incomplete, whereas higher temperatures cause serious decomposition. After cooling, the product was dissolved in ether (200 ml.), washed with 5% sodium hydroxide solution, dried (K_2CO_3), and twice distilled, yielding 1 : 3-*di-iodo*-2 : 2-*dimethylpropane* (24 g., 75%; average for 6 runs, 76%), b. p. 70—71°/0·1 mm., n_D^{20} 1·5938 (Found : I, 78·6. $C_5H_{10}I_2$ requires I, 78·4%).

3 : 3-*Dimethyl*cyclo*butanecarboxylic acid* (VI). Ethyl malonate (45 g.), followed by 1 : 3-di-iodo-2 : 2-dimethylpropane (90 g.), was added to a solution of potassium *iso*butoxide prepared from potassium (22 g.) and anhydrous *iso*butyl alcohol (600 ml.), and the mixture refluxed, with stirring, for 100 hr. Potassium hydroxide (40 g.) in 50% v/v aqueous ethanol (200 ml.)

was then added and refluxing continued for a further 8 hr. *iso*Butyl alcohol was then removed by steam-distillation and the residual solution acidified with hydrochloric acid and extracted with ether. Evaporation of the dried extract gave crude 3 : 3-dimethyl*cyclo*butane-1 : 1-dicarboxylic acid (38 g.) [a specimen crystallised from ethyl acetate in stout needles, m. p. 162° (decomp.), in agreement with Owen, Ramage, and Simonsen, *loc. cit.*], which was decarboxylated at 180° for 1 hr. and then distilled, yielding 3 : 3-dimethyl*cyclo*butanecarboxylic acid (27 g., 73%; average for 4 runs, 61%), b. p. 105—106°/15 mm., n_D^{20} 1·4317, characterised as the p-*bromophenacyl* ester, plates (from ethanol), m. p. 93° (Found : C, 55·7; H, 5·3; Br, 24·5. $C_{15}H_{17}O_3Br$ requires C, 55·4; H, 5·2; Br, 24·6%). Substitution of *tert.*-butyl alcohol for *iso*butyl alcohol reduced the yield to 11%.

Ethyl 1-*bromo*-3 : 3-*dimethyl*cyclo*butanecarboxylate* (VII). The acid (VI) (90 g.) was heated under reflux at 100° for 1 hr. with purified thionyl chloride (90 g.). Red phosphorus (1 g.) and bromine (120 g.; dried under concentrated sulphuric acid) were then added and heating continued at 110—120° for a further 3 hr. The cooled product was poured into absolute ethanol (100 ml.), diluted with water (200 ml.), and extracted with ether. Distillation of the dried extract gave *ethyl* 1-*bromo*-3 : 3-*dimethyl*cyclo*butanecarboxylate* (114 g., 69%), b. p. 46—47°/0·7 mm., n_D^{20} 1·4550 (Found : C, 46·1; H, 6·7; Br, 32·2. $C_9H_{15}O_2Br$ requires C, 45·9; H, 6·4; Br, 34·0%).

3 : 3-*Dimethyl*cyclo*but*-1-*enecarboxylic acid* (VIII). Molten potassium hydroxide (10 g.) was stirred vigorously under refluxing toluene (150 ml.) while ethyl 1-bromo-3 : 3-dimethyl-*cyclo*butanecarboxylate (10 g.) was added dropwise; a vigorous exothermic reaction set in and the source of heat was removed during the addition; solid potassium salts separated. After completion of the addition, heating was resumed for a further 40 min. and the mixture was then cooled before addition of water (100 ml.). The aqueous solution was separated, washed with light petroleum (b. p. 40—60°) (50 ml.), acidified with 30% w/w sulphuric acid and extracted with ether (4 × 50 ml.); evaporation of the dried extract gave the crude acid as a viscous yellow oil (5·2 g., 97%) which crystallised. Distillation gave 3 : 3-*dimethyl*cyclo*but*-1-*enecarboxylic acid*, b. p. 76—77°/1 mm., which crystallised from light petroleum (b. p. 40—60°) at −30° in plates, m. p. 54—55° [Found : C, 66·4; H, 7·8%; Equiv. (by titration), 126. $C_7H_{10}O_2$ requires C, 66·7; H, 7·9%; Equiv., 126]. Addition of bromine in carbon tetrachloride, followed by evaporation and crystallisation from light petroleum (b. p. 40—60°), afforded 1 : 2-*dibromo*-3 : 3-*dimethyl*cyclo*butanecarboxylic acid* in prisms, m. p. 88—89° [Found : C, 29·2; H, 3·2%; Equiv. (by titration), 284. $C_7H_{10}O_2Br_2$ requires C, 29·4; H, 3·5%; Equiv., 286].

Methyl 3 : 3-*dimethyl*cyclo*but*-1-*enecarboxylate*. The crude acid (VIII) (5·2 g.) was added to a solution of diazomethane (1·8 g.) in ether (50 ml.). Distillation through a short column packed with Fenske helices gave *methyl* 3 : 3-*dimethyl*cyclo*but*-1-*enecarboxylate* (4·8 g., 82%) as a mobile liquid with a penetrating pineapple odour, b. p. 52°/14 mm., n_D^{20} 1·4360 (Found : C, 68·7; H, 8·7. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%).

Distillation of the combined residues from several preparations gave methyl 1-hydroxy-3 : 3-dimethyl*cyclo*butanecarboxylate, b. p. 68—70°/7 mm., n_D^{20} 1·4185, identified by hydrolysis to the acid, m. p. and mixed m. p. 83°.

Ethyl (4-*carbomethoxy*-2 : 2-*dimethyl*cyclo*butyl*)*malonate* (IX). Methyl 3 : 3-dimethyl*cyclo*but-1-enecarboxylate (4·8 g.) was added to a solution of ethyl potassiomalonate, prepared from potassium (0·5 g.), anhydrous *tert.*-butyl alochol (25 ml.), and ethyl malonate (5 g.), and the mixture refluxed for 2 hr. After addition of acetic acid (1 ml.), the mixture was cooled and dissolved in ether (100 ml.). After being washed with 5% w/w sodium hydrogen carbonate solution until neutral and dried (Na_2SO_4), the product was distilled, yielding *ethyl* (4-*carbomethoxy*-2 : 2-*dimethyl*cyclo*butyl*)*malonate* (6 g., 58%; average in 4 runs, 57%), b. p. 103°/0·1 mm., n_D^{20} 1·4492 (Found : C, 59·8; H, 8·1. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·0%).

A similar preparation, using ethyl cyanoacetate (4 g.) in place of ethyl malonate, yielded *ethyl* α-(4-*carbomethoxy*-2 : 2-*dimethyl*cyclo*butyl*)-α-*cyanoacetate* (0·75 g., 8·6%), b. p. 144—145°/0·5 mm., n_D^{20} 1·4626 (Found : C, 61·6; H, 7·4; N, 5·7. $C_{13}H_{19}O_4N$ requires C, 61·7; H, 7·5; N, 5·5%); the yield was not improved by varying the proportion of the reactants or by longer heating.

(±)-*Caryophyllenic acids*. Ethyl (4-carbomethoxy-2 : 2-dimethyl*cyclobutyl*)*malonate* (25 g.) was heated under reflux with constant-boiling hydrochloric acid (50 ml.) for 20 hr. Dilution with an equal volume of water, followed by extraction with ether (10 × 100 ml.), drying, and evaporation, yielded a mixture of the *cis*- and the *trans*-(±)-acid (14·5 g., 93·5%) as an oil which slowly crystallised in a vacuum-desiccator. This mixture (14 g.) was heated with concentrated hydrochloric acid (50 ml.) in a sealed tube at 180° for 5 hr. The solution, diluted with two volumes

of water, was extracted with light petroleum (b. p. 40—60°; 2 × 100 ml.), to remove a dark, oily decomposition product (5 g.), and then boiled with decolorising charcoal, filtered, and evaporated to dryness under reduced pressure. The crude *trans*-(±)-acid so obtained (7·5 g., 53%) was neutralised with a solution of potassium hydroxide (5·5 g.) in absolute methanol (25 ml.); after 1 hr. at 0° the insoluble potassium salt was filtered off and dissolved in water; acidification, followed by extraction with ether (10 × 100 ml.), evaporation of the dried extract, and crystallisation from *cyclo*hexane yielded trans-(±)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butyl-acetic acid* [*trans*-(±)-caryophyllenic acid] (II) as rosettes of short, curved needles, m. p. 81—82° [Found : C, 58·5; H, 7·7%; Equiv. (by titration), 93. $C_9H_{14}O_4$ requires C, 58·0; H, 7·5%; Equiv., 93]. The infra-red absorption spectrum of a carbon disulphide solution of this compound in the 1350—1900- and 850—665-cm.$^{-1}$ regions was kindly determined by Mr. S. F. D. Orr, of the Chester Beatty Research Institute, Royal Cancer Hospital, who found it indistinguishable from that of authentic *trans*-(+)-caryophyllenic acid prepared from caryophyllene.

The *trans*-(±)-acid (0·5 g.) was heated with acetic anhydride (5 ml.) in a sealed tube at 220° for 6 hr. Distillation gave the *cis*-anhydride as an oil, b. p. 110—112°/0·5 mm. Digestion with water, followed by crystallisation from *cyclo*hexane, in which the acid is difficultly soluble, yielded cis-(±)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butylacetic acid* [*cis*-(±)-carophyllenic acid] in small prisms, m. p. 120° [Found : C, 58·2; H, 7·7%; Equiv. (by titration), 93].

Resolution of Caryophyllenic Acid.—Quinine methohydroxide solution (0·41N; 79 ml.) (Major and Finkelstein, *J. Amer. Chem. Soc.*, 1941, **63**, 1368) was exactly neutralised by the addition of *trans*-(±)-caryophyllenic acid (3 g.). The salt (16·9 g.), obtained by evaporating the solution to dryness, was dissolved in absolute ethanol (15 ml.) and the solution diluted with pure dioxan (150 ml.). The salt which crystallised out in small balls of fine needles (9·5 g.), $[\alpha]_D^{20}$ −134° (*c* = 1·121 in EtOH) was thrice recrystallised similarly, giving the pure quinine metho-salt of *trans*-(−)-caryophyllenic acid in rosettes of fine needles (3·5 g.), m. p. 202—203°, $[\alpha]_D^{20}$ −148° (*c* = 1·421 in EtOH). This salt was dissolved in 10% w/w sulphuric acid, and the organic acid removed by extraction with ether (10 × 100 ml.) as a yellow oil, which rapidly crystallised. Purification through the sparingly soluble potassium salt, followed by crystallisation from *cyclo*hexane, yielded trans-(−)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butylacetic acid* [*trans*-(−)-caryophyllenic acid] as rosettes of long needles, m. p. 81—82°, $[\alpha]_D^{20}$ −28° (*c* = 2·125 in C_6H_6) (Found : C, 58·3; H, 7·3%; Equiv. (by titration), 93].

Recovery of the acid from the more soluble metho-salt of the *cis*-acid, contained in the filtrate from the original crude *trans*-salt, gave an oil (2·3 g.) which, on fractional crystallisation from *cyclo*hexane, yielded pure trans-(+)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butylacetic acid* [*trans*-(+)-caryophyllenic acid] (0·15 g.) as long needles, m. p. 81—82°, $[\alpha]_D^{20}$ +28·5° (*c* = 1·452 in C_6H_6) [Found : C, 57·9; H, 7·4%; Equiv. (by titration), 93]. A 50% mixture of this acid with authentic *trans*-(+)-caryophyllenic acid, m. p. 81—82°, $[\alpha]_D^{20}$ +28° (*c* = 1·468 in C_6H_6), prepared from caryophyllene essentially by the method of Evans, Ramage, and Simonsen (*J.*, 1934, 1807), but omitting the preliminary permanganate oxidation, melted at 81—82°.

Synthetic *trans*-(+)-caryophyllenic acid (300 mg.) was heated with acetic anhydride (3 ml.) in a sealed tube at 220° for 6 hr. Distillation yielded the *cis*-anhydride (180 mg.), b. p. 110—111°/0·5 mm., which, on digestion with water, gave the *cis*-(−)-acid (190 mg.). Two crystallisations from *cyclo*hexane yielded pure cis-(−)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butylacetic acid* [*cis*-(−)-caryophyllenic acid] as long needles, m. p. 77—78°, $[\alpha]_D^{20}$ −42° (*c* = 1·314 in C_6H_6) [Found : C, 57·9; H, 7·4%; Equiv. (by titration), 93]. A 50% mixture of this acid with authentic *cis*-(−)-caryophyllenic acid, m. p. 77—78°, $[\alpha]_D^{20}$ −43° (*c* = 2·421 in C_6H_6), from caryophyllene, melted at 77—78°.

Similar treatment of synthetic *trans*-(−)-caryophyllenic acid yielded cis-(+)-4-*carboxy*-2 : 2-*dimethyl*cyclo*butylacetic acid* in long silky needles, m. p. 77—78°, $[\alpha]_D^{20}$ +41° (*c* = 1·482 in C_6H_6) [Found : C, 58·3; H, 7·2%; Equiv. (by titration), 93].

Synthesis and Resolution of 2-*Carboxy*cyclo*butylacetic Acid.*—cyclo*But*-1-*enecarboxylic acid. cyclo*Butanecarboxylic acid (50 g.) (Cason and Allen, *J. Org. Chem.*, 1949, **14**, 1036) and pure thionyl chloride (65·5 g.) were heated under reflux at 110° for 1 hr., and then with red phosphorus (0·5 g.), bromine (88 g.), and later ethanol, etc., as in the preparation of (VII), gave ethyl 1-bromo-*cyclo*butanecarboxylate (61·5 g., 77·5%; average for 8 runs, 71%), b. p. 67—68°/5 mm., n_D^{20} 1·4691.

This bromo-ester (20 g.) was treated with potassium hydroxide (20 g.) in toluene (250 ml.) as in the previous case and worked up similarly. The aqueous layer was extracted once with light petroleum (b. p. 40—60°; 100 ml.), acidified with 30% w/w sulphuric acid and extracted with ether (5 × 50 ml.). Quinol (200 mg.) was added to the dried extract, from which the ether

was then removed under reduced pressure. The partly crystalline residue was warmed to 40° with light petroleum (b. p. 40—60°; 80 ml.), and the extract decanted and cooled to −20°; the needles which separated were filtered off and stored at 0°. This extraction process was repeated until no more crystals were obtained; the total yield of crystalline acid was 6·8 g. (72%). One recrystallisation from light petroleum (b. p. 40—60°) at −20° yielded cyclo*but*-1-*enecarboxylic acid* in needles, m. p. 72° [Found: Equiv. (by titration), 98. $C_5H_6O_2$ requires Equiv., 98]. A satisfactory analysis for carbon and hydrogen could not be obtained owing to rapid polymerisation and absorption of atmospheric oxygen (Found, 12 hr. after preparation: C, 60·2; H, 6·0. 36 hr. after preparation: C, 58·1; H, 5·9. Calc. for $C_5H_6O_2$: C, 61·2; H, 6·1%).

cis- *and* trans-(±)-2-*Carboxy*cyclo*butylacetic acids.* Freshly prepared *cyclo*but-1-enecarboxylic acid (6 g.) in ether (25 ml.) containing quinol (200 mg.) was treated at 0° with an excess of ethereal diazomethane. Distillation gave methyl *cyclo*but-1-enecarboxylate (6·8 g., 87·5%) as a mobile liquid, with a penetrating pineapple-like odour, b. p. 42—43°/25 mm., n_D^{20} 1·4492, which rapidly polymerised to a hard resin.

This ester (6·8 g.) was added, with shaking, to a solution of ethyl potassiomalonate (from potassium 0·5 g., *tert.*-butyl alcohol 150 ml., and ethyl malonate 15 g.) at 10°. After 3 hr. at room temperature, glacial acetic acid (1 ml.) was added and the mixture diluted with water (100 ml.) and extracted with ether (2 × 100 ml.). Distillation gave *ethyl* (2-*carbomethoxy*-cyclo*butyl*)*malonate* (5·6 g., 54%), b. p. 105—106°/0·3 mm., n_D^{20} 1·4993 (Found: C, 57·05; H, 7·4. $C_{13}H_{20}O_6$ requires C, 57·4; H, 7·4%). The experimental conditions for this condensation are critical; unsatisfactory results are obtained by increasing the time of standing or the amount of potassium *tert.*-butoxide or by heating the reaction mixture.

Ethyl (2-carbomethoxy*cyclo*butyl)malonate (20 g.) was refluxed for 1 hr. with potassium hydroxide (10 g.) in 50% aqueous ethanol (100 ml.), and the ethanol then removed by distillation. The cooled residue was diluted with an equal volume of water, acidified with 30% w/w sulphuric acid and extracted with ether (20 × 200 ml.). Evaporation of the dried extract left a gum (13·8 g.) which was heated at 180° for 1 hr. One crystallisation from benzene gave crude *cis*-(±)-2-carboxy*cyclo*butylacetic acid in needles, m. p. 110—111° [Found: Equiv. (by titration), 79. $C_7H_{10}O_4$ requires Equiv., 79]. This material (5 g.) was heated with acetic anhydride (20 ml.) to 220° in a sealed tube for 6 hr. Distillation yielded cis-(±)-2-*carboxy*-cyclo*butylacetic anhydride* (4·8 g., 97%) as an oil, b. p. 102—103°/0·5 mm., n_D^{20} 1·4868 (Found: C, 59·9; H, 5·8. $C_7H_8O_3$ requires C, 60·0; H, 5·7%). Digestion of this anhydride with water and evaporation of the resulting solution gave cis-(±)-2-*carboxy*cyclo*butylacetic acid* (4·9 g., 90%) which crystallised from benzene in needles, m. p. 110—111° [Found: C, 53·3; H, 6·5%; Equiv. (by titration), 79. $C_7H_{10}O_4$ requires C, 53·2; H, 6·3%; Equiv., 79].

Alternatively, methyl *cyclo*but-1-enecarboxylate (8·3 g.) was added, with cooling and shaking, to a solution of ethyl potassiocyanoacetate prepared from potassium (2·9 g.), *tert.*-butyl alcohol (100 ml.) and ethyl cyanoacetate (10 g.). After 3 hr. at room temperature, the mixture was acidified with acetic acid (4 g.), diluted with water, and extracted with ether (2 × 100 ml.). Distillation afforded *ethyl* α-(-2-*carbomethoxy*cyclo*butyl*)-α-*cyanoacetate* (7·1 g., 52%) as an oil, b. p. 144—155°/0·1 mm., n_D^{20} 1·4678 (Found: C, 58·6; H, 6·7; N, 6·3. $C_{11}H_{15}O_4N$ requires C, 58·7; H, 6·6; N, 6·2%). This ester (10 g.) was refluxed for 20 hr. with constant-boiling hydrochloric acid (50 ml.). The resulting dark solution was diluted with an equal volume of water, boiled with charcoal (2 g.), filtered, cooled, and extracted with ether (10 × 100 ml.). Evaporation of the dried extract yielded a brown oil (7 g.) which deposited crystals during 6 weeks in a vacuum-desiccator. The crystals (1 g.) were recrystallised from benzene, affording *cis*-(±)-2-carboxy*cyclo*butylacetic acid, m. p. 110—112° [Found: Equiv. (by titration), 79].

The *cis*-(±)-acid (5 g.) was heated in a sealed tube at 180° for 5 hr. with concentrated hydrochloric acid (20 ml.). Evaporation gave an oil (5 g.) which crystallised when rubbed; two recrystallisations from anhydrous ether–*cyclo*hexane (1 : 10) afforded trans-(±)-2-*carboxy*cyclo*butylacetic acid* in rhombohedra, m. p. 64—65° [Found: C, 53·1; H, 6·1%; Equiv. (by titration), 78. $C_7H_{10}O_4$ requires C, 53·2; H, 6·3%; Equiv., 79].

Resolution of 2-*carboxy*cyclo*butylacetic acid.* Quinine methohydroxide solution (0·39N; 97·4 ml.) (Major and Finkelstein, *loc. cit.*) was exactly neutralised by the addition of the *cis*-(±)-acid (3 g.). The salt, recovered by evaporation under reduced pressure, was dissolved in absolute ethanol (20 ml.) and the resulting solution diluted with pure dioxan (200 ml.). The salt which separated rapidly in fluffy needles (8 g.), m. p. 220—224° (decomp.), $[\alpha]_D^{20}$ −140° (c = 2·105 in EtOH), was recrystallised six times by a similar procedure. The final product (3·5 g.), which had m. p. 225—226°, $[\alpha]_D^{20}$ −154° (c = 1·024 in EtOH), was decomposed with

10% w/w sulphuric acid; extraction with ether (15 × 100 ml.) yielded the crude *cis*-(−)-acid (350 mg.), m. p. 105—106°, $[\alpha]_D^{20}$ −34° (*c* = 1·216 in EtOH). Fractional crystallisation from benzene afforded cis-(−)-2-*carboxy*cyclo*butylacetic acid* (190 mg.) in clusters of long needles, m. p. 110—111°, $[\alpha]_D^{20}$ −45° (*c* = 1·254 in EtOH) [Found: C, 53·1; H, 6·4%; Equiv. (by titration), 79]. Fractional crystallisation of the acid recovered from the more soluble quinine metho-salt yielded cis-(+)-2-*carboxy*cyclo*butylacetic acid* (140 mg.) in rosettes of thin needles, m. p. 110—111°, $[\alpha]_D^{20}$ +43° (*c* = 2·15 in EtOH) [Found: C, 53·3; H, 6·2%; Equiv. (by titration), 79].

The pure *cis*-(+)-acid (500 mg.) was heated in a sealed tube at 180° for 5 hr. with concentrated hydrochloric acid (5 ml.). Evaporation, followed by dissolution in ether, treatment with charcoal (300 mg.), and re-evaporation afforded trans-(−)-2-*carboxy*cyclo*butylacetic acid* as an oil, $[\alpha]_D^{20}$ −71° (*c* = 0·92 in EtOH), which resisted all attempts at crystallisation [Found: C, 52·9; H, 6·1%; Equiv. (by titration), 78]. Similar treatment of the pure *cis*-(−)-acid yielded trans-(+)-2-*carboxy*cyclo*butylacetic acid* as an uncrystallisable oil, $[\alpha]_D^{20}$ +73° (*c* = 0·84 in EtOH) [Found: C, 52·9; H, 6·4%; Equiv. (by titration), 79·5].

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