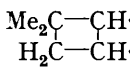
228. *The Caryophyllenes. Part VII. Experiments on the Synthesis of Caryophyllenic Acid.*

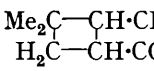
By MORGAN D. OWEN, G. R. RAMAGE, and J. L. SIMONSEN.

3 : 3-*Dimethyl*cyclo*butanecarboxylic acid* (IV) and **3 : 3-*dimethyl*cyclo*butanone*** (VIII) have been synthesised. The former was obtained by the condensation of ethyl potassiomalonate with 1 : 3-dibromo-2 : 2-dimethylpropane, followed by hydrolysis of the resulting ester and elimination of carbon dioxide; the latter by the interaction of diazomethane and dimethylketen. It is proposed to use these two substances for the synthesis of caryophyllenic acid (II or III).

THE degradation of caryophyllenic acid to its lower homologue, norcaryophyllenic acid (I), and the proof provided of the structure of the latter acid (J., 1935, 532), later confirmed by Rydon's synthesis (J., 1936, 593; 1937, 1340), have shown that the former acid must be represented by either (II) or (III). The accepted view, based on Ruzicka's formula for β-caryophyllene, is that (III) is the more probable.



(I.)



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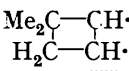


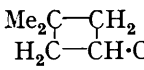
(III.)

We have for some time been engaged in experiments on the synthesis of the acids (II) and (III) and a possible method for the synthesis of (III), recently suggested (Lewis, Ramage, and Simonsen, J., 1937, 1837), is being studied. We now describe the preparation of two *cyclo*butane derivatives which open up other possible routes.

The obvious method for the synthesis of 3 : 3-dimethyl*cyclo*butanecarboxylic acid (IV) follows Perkin's method (J., 1892, **61**, 40) for the synthesis of *cyclo*butanecarboxylic acid by the condensation of 1 : 3-dibromopropane and ethyl sodiomalonate. The necessary 1 : 3-dibromo-2 : 2-dimethylpropane was prepared by Franke (*Monatsh.*, 1913, **34**, 1893) by the action of phosphorus tribromide on 1 : 3-dihydroxy-2 : 2-dimethylpropane at 150°.

He described the dibromide as being extremely stable and he was unable to prepare the corresponding dinitrile by the action of potassium cyanide.

We have found the pure glycol difficult to isolate from the product of the Cannizzaro reaction on the aldol formed by the condensation of formaldehyde and *iso*butaldehyde (Wessely, *Monatsh.*, 1900, **21**, 216, 232). With the crude glycol poor yields of the dibromide, accompanied by much charring, were obtained with phosphorus tribromide and the ordinary hydrobromic–sulphuric acid method was ineffective. By utilising the diacetyl derivative of the glycol and hydrogen bromide in acetic acid (cf. Perkin and Simonsen, J., 1905, **87**, 856), the dibromide, together with the *bromoacetyl* derivative, was, however, readily obtained in good yield by close adherence to the conditions given. In agreement with Franke we found the dibromide to be very unreactive and condensation with ethyl potassiomalonate could only be effected by prolonged heating at 130—140° or by carrying out the reaction in boiling *iso*butyl-alcoholic solution. Under these conditions the reaction proceeded normally and on hydrolysis of the condensation product 3 : 3-*dimethyl*cyclo*butane*-1 : 1-*dicarboxylic acid*, decomp. 162°, was obtained in comparatively good yield. There was no evidence of the formation of the open-chain tetracarboxylic ester. Elimination of carbon dioxide gave 3 : 3-*dimethyl*cyclo*butanecarboxylic acid* (IV), from which *methyl* 1-*bromo*-3 : 3-*dimethyl*cyclo*butane*-1-*carboxylate* (V) was prepared. Attempts to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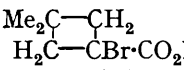
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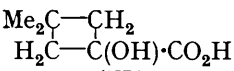
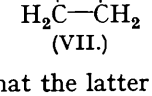

(VI.)

eliminate hydrogen bromide from the ester by the action of diethylaniline were unsuccessful, reduction to the *methyl* ester of the parent acid occurring (cf. Haerdi and Thorpe, J., 1925, **127**, 1242; Gibson and Simonsen, J., 1929, 1076). With methyl-alcoholic potassium hydroxide solution, a similar reduction occurred to some extent, together with simultaneous formation of 1-*hydroxy*-3 : 3-*dimethyl*cyclo*butane*-1-*carboxylic acid* (VI), m. p. 83°. In attempts to prepare the hydroxy-acid by the action of baryta on the bromo-ester, only the unsaturated acid could be isolated. This acid is being further investigated, since it should provide a convenient route to (II).

It has been shown by Lipp and Köster (*Ber.*, 1931, **64**, 2823) that, by the interaction of diazomethane and keten, *cyclo*butanone and not, as might have been anticipated, *cyclo*propanone, is obtained. By a similar condensation with dimethylketen, either 2 : 2-dimethyl*cyclo*butanone (VII) or 3 : 3-*dimethyl*cyclo*butanone* (VIII) should be formed. We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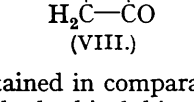
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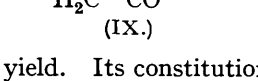
(IX.)

find that the latter ketone is obtained in comparatively good yield. Its constitution was proved by its conversion through the bisulphite compound and hydroxy-nitrile into the hydroxy-acid (VI). We propose to attempt the preparation of the keto-ester (IX) from the ketone, since it is probable that this ester could be used for the synthesis of (III).

The preparation of 3 : 3-dimethyl*cyclo*butanone in quantity requires easy access to dimethylketen and diazomethane. Dimethylmalonic acid had been prepared on a considerable scale by the methylation of ethyl sodiomalonate with methyl sulphate in benzene solution when Bowden (*J. Amer. Chem. Soc.*, 1938, **60**, 131) indicated the general application of alkyl sulphates for the alkylation of reactive methylene groups in alcoholic solution. In the experimental section a procedure for the preparation in quantity of nitrosomethylurea from acetamide is described (cf. Brüning, *Ber.*, 1888, **21**, 1809; *Annalen*, 1889, **253**, 6). We have found this cheaper and more convenient than Arndt's process ("Organic Syntheses," **15**, p. 48) or that of Adamson and Kenner (J., 1937, 1551), the latter process, although economical, involving long and troublesome preparative work.

Experimental.

1 : 3-*Dibromo*-2 : 2-*dimethylpropane*.—Crude 1 : 3-dihydroxy-2 : 2-dimethylpropane (27 g.) (from *iso*butaldehyde, 25 g.), prepared as described by Wessely (*loc. cit.*), was refluxed with

acetic anhydride (100 c.c.) and pyridine (3 drops) for 3 hours. After being poured into water, the mixture was extracted with ether, and the extract washed with sodium carbonate solution, dried, and fractionated, giving the diacetyl derivative (45 g.), b. p. 100°/20 mm.

The diacetate (12 g.) was heated with hydrogen bromide in acetic acid (30 c.c., 50% w/v) at 155—160° for 10 hours (below this temperature there is very little conversion and above considerable charring occurs). The product from 10 tubes was distilled in steam and on fractionation gave the dibromide (60 g.), b. p. 80—82°/26 mm., and slightly impure 1-*bromo*-3-*acetoxy*-2 : 2-*dimethylpropane* (20 g.), b. p. 85—95°/26 mm. (Found : Br, 42·5. $C_7H_{13}O_2Br$ requires Br, 38·3%). The latter fraction was heated again with hydrogen bromide in acetic acid, giving finally an 85% yield of the dibromide.

Condensation of 1 : 3-*Dibromo*-2 : 2-*dimethylpropane and Ethyl Potassiomalonate.*—(i) The dibromide (5 g.) and ethyl malonate (3·5 g.) were added to potassium (1·7 g.) in ethyl alcohol (50 c.c.), and the mixture heated in a sealed tube for 36 hours at 130—140°. Water was added to the products of four similar experiments, and the oil extracted with ether and fractionated. The main product (6·5 g.) had b. p. 118—119°/20 mm. and consisted essentially of *ethyl* 3 : 3-*dimethyl*cyclo*butane*-1 : 1-*dicarboxylate* (Found : C, 61·8; H, 8·8. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%). The ester (19 g.) was refluxed for 3 hours with potassium hydroxide (20 g.) in methyl alcohol (100 c.c.), the alcohol removed on the water-bath, and the aqueous solution acidified and extracted with ether. After removal of the solvent, the residue was dissolved in a little water, and the solution saturated with hydrogen chloride. 3 : 3-*Dimethyl*cyclo*butane*-1 : 1-*dicarboxylic acid* crystallised in irregular plates, decomp. 162° (Found : C, 55·7; H, 7·1. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%). After this acid had been heated for ½ hour at 180° to eliminate carbon dioxide, the resulting 3 : 3-*dimethyl*cyclo*butanecarboxylic acid* was distilled, b. p. 204°/760 mm. (Found : C, 65·3; H, 9·3. $C_7H_{12}O_2$ requires C, 65·5; H, 9·4%). The p-*phenylphenacyl* ester crystallised from dilute alcohol in plates, m. p. 92° (Found : C, 78·0; H, 6·9. $C_{21}H_{22}O_3$ requires C, 78·3; H, 6·8%).

(ii) Potassium (7 g.) was dissolved in dry *iso*butyl alcohol (200 c.c.) and to the solution ethyl malonate (14 g.) and the dibromide (20 g.) were added. After 90 hours' boiling, the solution was not quite neutral, but the ester was then hydrolysed by the addition of potassium hydroxide (20 g.) in alcohol (100 c.c.) and digestion for 5 hours. The ethyl and *iso*butyl alcohols were removed in steam, and the aqueous solution concentrated, acidified, and extracted repeatedly with ether. On removal of the ether, the acid, which was partly crystalline, was heated at 180°, and the product fractionated, giving a little *iso*butyric acid, followed by the *cyclo*butane acid (4·5 g.), b. p. 103—107°/15 mm.

Methyl 1-*Bromo*-3 : 3-*dimethyl*cyclo*butane*-1-*carboxylate.*—The acid (4·5 g.) and thionyl chloride (4·2 g.) were heated on the water-bath for ½ hour, bromine (6 g.) then slowly added, and the heating continued until bromination was complete. The product was poured into methyl alcohol (30 c.c.) and kept for 12 hours, and an ethereal solution of the ester poured on ice. Evaporation of the dried ethereal extract gave the *bromo*-ester, b. p. 82—83°/14 mm. (Found : Br, 35·8. $C_8H_{13}O_2Br$ requires Br, 36·2%).

In one experiment the bromo-ester was heated with diethylaniline for 8 hours, yielding *methyl* 3 : 3-*dimethyl*cyclo*butanecarboxylate*, b. p. 70—80°/30 mm., which was redistilled and the middle fraction analysed (Found : C, 68·0; H, 9·6. $C_8H_{14}O_2$ requires C, 67·6; H, 9·8%). In a further experiment the bromo-ester was heated with methyl-alcoholic potassium hydroxide solution; the recovered acid was unsaturated, b. p. 125—135°/25 mm., and the undistilled residue partly solidified. 1-*Hydroxy*-3 : 3-*dimethyl*cyclo*butane*-1-*carboxylic acid* crystallised from ligroin (b. p. 80—100°) in flat needles, m. p. 83° (Found : C, 58·2; H, 8·5. $C_7H_{12}O_3$ requires C, 58·3; H, 8·3%).

Dimethylmalonic Acid.—Sodium (23 g.) was finely powdered under xylene, which was decanted and dry benzene (500 c.c.) added, followed by ethyl malonate (160 g.). After 2 hours' heating, methyl sulphate (130 g.) was cautiously added with shaking to the cooled mixture, and the heating then continued for 3 hours. Water was added, and the benzene separated, washed with aqueous ammonia (*d* 0·880) and dilute sulphuric acid, dried, and fractionated, giving ethyl methylmalonate (150 g.), b. p. 90—95°/18 mm. Ethyl dimethylmalonate (135 g.), b. p. 90—96°/18 mm., was obtained by repeating the process. It was not found possible to prepare the disodium derivative in one operation, but the second quantity of sodium could be added after the boiling with methyl sulphate, the isolation of the monomethyl ester thus being avoided without serious diminution of the yield. Hydrolysis of the ester (135 g.) with methyl-alcoholic potassium hydroxide solution in the usual manner gave dimethylmalonic acid (68 g.), m. p. 190°.

Nitrosomethylurea.—Aqueous sodium hydroxide (10%) was added slowly to acetamide

(100 g.) and bromine (45 c.c.) with shaking until the solution was permanently pale yellow, first with ice-cooling and then after heating on the water-bath. After the solution had been cooled, the acetylmethylurea, m. p. 179—180°, was collected; a further quantity was obtained by concentration of the filtrate (total yield, 75 g.). The acetate was hydrolysed by heating for 3 hours with 8% hydrochloric acid (200 c.c.), the solution cooled in ice, and a saturated solution of sodium nitrite (37 g.) slowly added below the level of the liquid. The nitrosomethylurea (52 g.) was collected, washed with a small quantity of cold water, and dried in a vacuum.

3 : 3-*Dimethyl*cyclo*butanone*.—Dimethylketen (*ca.* 22 g., from dimethylmalonic acid, 60 g., prepared as described by Staudinger, *Helv. Chim. Acta*, 1925, **8**, 306) in ether (200 c.c.) was cooled in a good freezing mixture, and diazomethane (from nitrosomethylurea, 150 g.) in ether slowly added until the solution remained permanently yellow. The ether was very slowly distilled through a Widmer column, and the residue fractionated at the ordinary pressure, giving (i) 5 g., b. p. up to 120°, (ii) 14 g., b. p. 120—130°, (iii) a residue (12 g.) which contained no nitrogen. If the keten is added to the diazomethane, the fraction (ii) is slightly less, but it can be increased by decomposing some pyrazolone present in the higher-boiling fraction by digestion with copper bronze. The *semicarbazones* from fractions (i) and (ii) were identical and after crystallisation from alcohol had m. p. 232°, raised to 234° by further crystallisation (Found: C, 54·6; H, 8·4. $C_7H_{13}ON_3$ requires C, 54·2; H, 8·4%).

The pure 3 : 3-*dimethyl*cyclo*butanone*, which is not very soluble in water, was regenerated from the semicarbazone (10 g.) by steam-distillation with oxalic acid (20 g.); the distillate, after saturation with ammonium sulphate, was extracted with ether. Removal of the solvent gave an oil (5·5 g.) having a pleasant, somewhat camphoraceous odour; b. p. 122—124°/770 mm., $d_{25°}^{25°}$ 0·8632, $n_D^{15°}$ 1·4170 (Found: C, 73·6; H, 10·5. $C_6H_{10}O$ requires C, 73·5; H, 10·2%).

1-*Hydroxy*-3 : 3-*dimethyl*cyclo*butane*-1-*carboxylic Acid*.—The ketone (1 g.), shaken with a saturated aqueous solution of sodium bisulphite, rapidly deposited a crystalline bisulphite compound. An aqueous solution of potassium cyanide was added, the resulting cyanohydrin extracted with ether, and the solvent removed. The residue was refluxed with ethyl-alcoholic hydrogen chloride (6 c.c.), ammonium chloride being quickly deposited; water was added, and the ester extracted with ether. After removal of the solvent, the hydroxy-ester (0·6 g.) was hydrolysed with methyl-alcoholic potassium hydroxide solution. The alcohol was evaporated; the hydroxy-acid, isolated from the acidified solution in the usual manner, crystallised from ligroin (b. p. 80—100°) in flat needles, m. p. 83°, both alone and in admixture with the hydroxy-acid described on p. 1213 (Found: C, 57·9; H, 8·1%).

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