

36. 1 : 3 : 3-Trimethyl- $\Delta^1$ -cyclohexene-4-carboxylic Acid : its Formation from  
1- $\Delta^3$ -Carene-5 : 6-epoxide.

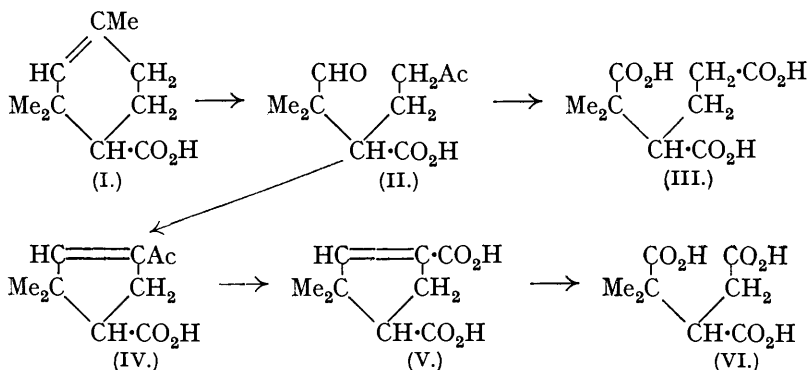
By A. R. PENFOLD and J. L. SIMONSEN.

The acid,  $C_{10}H_{16}O_2$ , formed by the action of cold ethyl-alcoholic potassium hydroxide on *l*- $\Delta^3$ -carene-5 : 6-epoxide (VII) has been shown to be 1 : 3 : 3-trimethyl- $\Delta^1$ -cyclohexene-4-carboxylic acid (I) by its oxidation to  $\beta$ -methylpentane- $\beta\gamma\epsilon$ -tricarboxylic acid (III). A further product of the oxidation was 1 : 1-dimethyl- $\Delta^2$ -cyclopentene-3 : 5-dicarboxylic acid (V), which gave on ozonolysis  $\beta$ -methylbutane- $\beta\gamma\delta$ -tricarboxylic acid (VI).

THE suggestion (Penfold, Ramage, and Simonsen, J., 1939, 1501) that the acid,  $C_{10}H_{16}O_2$ , m. p. 83°, formed by the action of cold ethyl-alcoholic potassium hydroxide on *l*- $\Delta^3$ -carene-5 : 6-epoxide (VII) was one of the optically active modifications of *dl*- $\Delta^2$ -cyclogeranic acid was disproved by Bennett, Ramage,

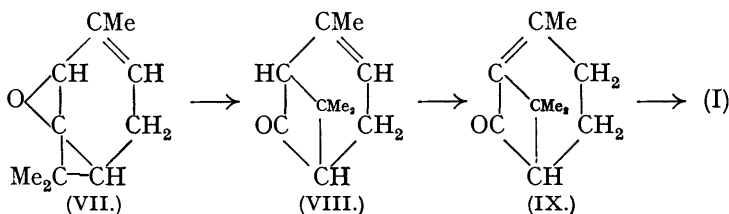
and Simonsen (J., 1940, 418). We have now determined the structure of the acid by an investigation of its degradation products.

On ozonolysis it yielded a liquid acid, which reacted readily with carbonyl reagents. A semicarbazone,  $C_{11}H_{17}O_3N_3$ , decomp.  $252^\circ$ , was prepared, but purification could not be thus effected. An alkaline solution of the acid was therefore oxidised with sodium hypobromite: two crystalline acids were obtained, (A),  $C_9H_{12}O_4$ , m. p.  $198-199^\circ$ , and (B), m. p. ca.  $141^\circ$ . The acid (B) gave on analysis figures agreeing approximately with the formula  $C_9H_{14}O_6$  and it was thought at first that it might be identical with  $\beta$ -methylpentane- $\beta\delta\epsilon$ -tricarboxylic acid, which according to Roberts (*J. Amer. Chem. Soc.*, 1926, **28**, 1975) melts at this temperature (see below). On further purification, however, the melting point of the acid was raised to  $153^\circ$  and it was found by direct comparison to be identical with  $\beta$ -methylpentane- $\beta\gamma\epsilon$ -tricarboxylic acid (III). The formation of this acid from the unsaturated cyclic acid left no doubt that the latter must be represented by (I).



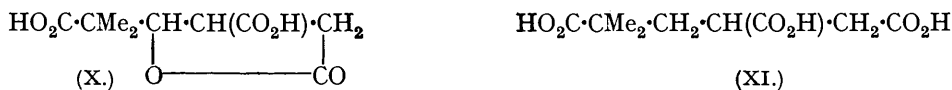
The acid (A), which was sparingly soluble in water and was optically active, was unstable to potassium permanganate in alkaline solution. On ozonolysis it gave  $\beta$ -methylbutane- $\beta\gamma\delta$ -tricarboxylic acid (VI) and therefore it is 1 : 1-dimethyl- $\Delta^2$ -cyclopentene-3 : 5-dicarboxylic acid (V). This acid is formed by the cyclisation of the primary ozonolysis product, the keto-aldehyde (II), to the unsaturated keto-acid (IV), which is oxidised by sodium hypobromite to (V). The semicarbazone, decomp.  $252^\circ$ , referred to above is derived from (IV).

The formation of the cyclohexene acid from the epoxide (VII) is undoubtedly connected with the marked tendency which the latter exhibits to isomerise to ketones (compare Penfold, Ramage, and Simonsen,



*loc. cit.*, p. 1497). This isomerisation may result in the formation of the bicyclic ketone (VIII), in which, under the influence of the alkali, the ethylenic linkage will tend to pass into the  $\alpha\beta$ -position, yielding the unstable ketone (IX); this on hydration gives (I). The fact that the cyclic acid (I) has the ethylenic linkage in the  $\Delta^1$ -position lends support to this interpretation of the mechanism of the reaction.

As mentioned above, it was at first regarded as possible that the acid (B) might be identical with  $\beta$ -methylpentane- $\beta\delta\epsilon$ -tricarboxylic acid (XI). Roberts (*loc. cit.*) records the preparation of an acid having this structure by the reduction of the lactone of  $\gamma$ -hydroxy- $\beta$ -methylpentane- $\beta\delta\epsilon$ -tricarboxylic acid (X), m. p.  $145^\circ$ . We had no difficulty in preparing the lactone by Roberts's procedure, but all attempts to



reduce it to (XI) failed. An acid having this structure has, however, been prepared by the condensation of ethyl sodiomalonate with ethyl  $\gamma$ -bromo- $\alpha\alpha$ -dimethylglutarate, followed by the hydrolysis of the tetracarboxylic ester so obtained. The acid prepared in this manner had m. p.  $180^\circ$  and there can therefore

be little doubt that Roberts's acid, m. p.  $141^\circ$ , was actually a somewhat impure specimen of the original lactone.

#### EXPERIMENTAL.

*Ozonolysis of 1 : 3 : 3-Trimethyl- $\Delta^1$ -cyclohexene-4-carboxylic Acid.*—The acid (2.9 g.) in methyl acetate (25 c.c.) was ozonised at  $0^\circ$ , the issuing gases being passed through water. Formaldehyde was absent from the wash water. After removal of the solvent under diminished pressure the ozonide was decomposed by heating with water (5 c.c.) on the water-bath for 1 hour. On evaporation the solution gave a gum, from which a small amount of a crystalline acid, m. p. ca.  $50$ – $70^\circ$ , separated; it could not be purified. A *semi-carbazone* was prepared which was very sparingly soluble in alcohol and crystallised from dilute acetic acid in small plates, decomp.  $252^\circ$  (Found: C, 55.8; H, 7.0; N, 17.7.  $C_{11}H_{17}O_3N_3$  requires C, 55.2; H, 7.1; N, 17.6%).

The liquid acid (1.7 g.) obtained by evaporation of the aqueous solution was dissolved in dilute aqueous sodium hydroxide and oxidised with aqueous sodium hypobromite (NaOH, 4 g.;  $Br_2$ , 1.6 c.c.) at  $0^\circ$ , bromoform separating immediately. After 1 hour the bromoform was removed, the excess of hypobromite destroyed with sulphur dioxide, the solution concentrated, and the acid products isolated by ether. The oil obtained partly crystallised and after trituration with hydrochloric acid the solid was collected. This, on fractional crystallisation from water, gave a sparingly soluble acid (*A*), separating in bayonet-shaped needles, m. p.  $197^\circ$ , raised to  $198$ – $199^\circ$  by two further crystallisations from water (Found: C, 58.8; H, 6.5.  $C_9H_{12}O_4$  requires C, 58.7; H, 6.5%). 1 : 1-Dimethyl- $\Delta^2$ -cyclopentene-3 : 5-dicarboxylic acid had  $[\alpha]_{5461} -15^\circ$  in acetone (*c*, 2.0).

The aqueous solution from which the acid (*A*) had been deposited gave on saturation with hydrogen chloride a more soluble acid (*B*), m. p.  $137^\circ$ , raised to  $140$ – $141^\circ$  by two further crystallisations from hydrochloric acid (Found: C, 50.0; H, 6.6. Calc. for  $C_9H_{14}O_6$ : C, 49.5; H, 6.4%). After further purification through its sparingly soluble copper salt, prepared by the addition of copper acetate to its aqueous solution, the acid after crystallisation from hydrochloric acid had m. p.  $153^\circ$  both alone and in admixture with authentic  $\beta$ -methylpentane- $\beta\gamma\epsilon$ -tricarboxylic acid (Found: C, 49.4; H, 6.4%).

The mixture of liquid acids remaining after the separation of the acids (*A*) and (*B*) was oxidised with nitric acid (*d* 1.4) on the water-bath. The acid remaining after the removal of the excess of mineral acid solidified on trituration with formic acid and after crystallisation from water had m. p.  $147^\circ$ , raised to  $150^\circ$  on admixture with  $\beta$ -methylbutane- $\beta\gamma\delta$ -tricarboxylic acid.

*Ozonolysis of 1 : 1-Dimethyl- $\Delta^2$ -cyclopentene-3 : 5-dicarboxylic Acid.*—The acid (0.4 g.) in methyl acetate (20 c.c.) was ozonised at  $0^\circ$ . The oxidation proceeded rapidly and after removal of the solvent in a vacuum the ozonide was, after dilution with water (5 c.c.), decomposed by heating on the water-bath for 1 hour. The solution was made alkaline with sodium carbonate, hydrogen peroxide (2 c.c.; 20-vol.) added, and the mixture kept overnight. The alkaline solution was concentrated, acidified with hydrochloric acid, and evaporated to dryness, and the residue extracted with acetone. Evaporation of the solvent left a solid (0.5 g.), which crystallised readily from hydrochloric acid or benzene-acetone in thin plates, m. p.  $143^\circ$ , raised to  $150$ – $151^\circ$  by repeated crystallisation. This m. p. was not depressed by  $\beta$ -methylbutane- $\beta\gamma\delta$ -tricarboxylic acid (Found: C, 47.0; H, 6.0. Calc. for  $C_8H_{12}O_6$ : C, 47.1; H, 5.9%). The acid was optically inactive.

*$\beta$ -Methylpentane- $\beta\delta\epsilon$ -tricarboxylic Acid.*—The keto-ester, ethyl  $\beta$ -methylpentan- $\gamma$ -one- $\beta\delta\epsilon$ -tricarboxylate, prepared as described by Roberts (*loc. cit.*), was a mobile, pale yellow oil, b. p.  $184^\circ/16$  mm.,  $n_D^{17} 1.458$  (Found: C, 57.4; H, 7.8. Calc. for  $C_{15}H_{24}O_7$ : C, 56.9; H, 7.6%). Reduction of the keto-ester (14 g.) to the hydroxy-ester was readily effected in ethereal solution with aluminium amalgam (Al, 20 g.). The ester was a colourless oil which gave no ferric chloride reaction. After digestion with hydriodic acid (40 g., *d* 1.94) and red phosphorus (2 g.) for 8 hours, evaporation of the filtered solution gave an oil which rapidly crystallised. The lactone of  $\gamma$ -hydroxy- $\beta$ -methylpentane- $\beta\delta\epsilon$ -tricarboxylic acid separated from ether or acetone-benzene in acetone of needles, m. p.  $145$ – $146^\circ$  (Found: C, 50.0; H, 5.8; *M*, 217.7. Calc. for  $C_9H_{12}O_6$ : C, 50.0; H, 5.6%; *M*, 216). Other attempts to reduce the lactone by heating with hydriodic acid (*d* 1.7) and red phosphorus at  $160^\circ$  or by the method of Miescher and Billeter (*Helv. Chim. Acta*, 1939, 22, 601) failed.

*Condensation of Ethyl  $\gamma$ -Bromo- $\alpha\alpha$ -dimethylglutarate and Ethyl Sodiomalonnate.* Ethyl  $\beta$ -Methylpentane- $\beta\delta\epsilon$ -tetracarboxylate.— $\alpha\alpha$ -Dimethylglutaric acid was prepared by the ozonolysis of isolauronic acid, followed by oxidation with sodium hypobromite as described by Haworth and Perkin (J., 1908, 83, 588). Ethyl  $\gamma$ -bromo- $\alpha\alpha$ -dimethylglutarate had b. p.  $155$ – $160^\circ/26$  mm.; Perkin (J., 1902, 81, 252) gives  $165$ – $170^\circ/35$  mm. To a suspension of ethyl sodiomalonate (from ethyl malonate, 16 g.) in alcohol (50 c.c.), the bromo-ester (29.5 g.) was cautiously added, rise of temperature being prevented by cooling in ice-water. After being kept overnight, the mixture, from which much sodium bromide had separated, was heated on the water-bath for 1 hour to complete the reaction. The *tetracarboxylic ester* (20 g.), a somewhat viscid oil, isolated in the usual manner, had b. p.  $210$ – $216^\circ/25$  mm. (Found: C, 57.9; H, 7.9.  $C_{18}H_{30}O_8$  requires C, 57.8; H, 8.0%). Digestion of the ester (3 g.) with hydrochloric acid (15 c.c.) gave  $\beta$ -methylpentane- $\beta\delta\epsilon$ -tricarboxylic acid, m. p.  $180^\circ$ , unchanged by crystallisation from hot water, from which the acid separated in hexagonal prisms (Found: C, 49.8; H, 6.7; *M*, 219.7.  $C_9H_{14}O_6$  requires C, 49.5; H, 6.4%; *M*, 218). The acid was somewhat sparingly soluble in

water and in the ordinary organic solvents with the exception of alcohol and acetic acid; addition of copper acetate to its aqueous solution precipitated a sparingly soluble copper salt. The *quinine* salt crystallised from dilute alcohol in balls of needles, m. p. 199—201°,  $[\alpha]_{5461}^{20} -160^\circ$  in alcohol (*c*, 1.0) (Found : C, 66.9; H, 7.2.  $C_9H_{14}O_6, 2C_{20}H_{24}O_2N_2, H_2O$  requires C, 66.5; H, 7.2%). The rotatory power of the salt was unaltered by further crystallisation.

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