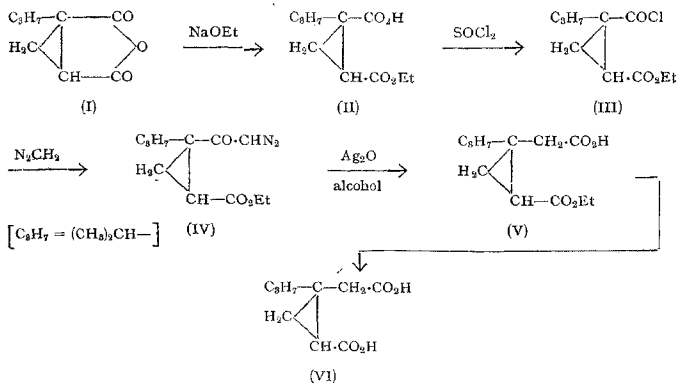


## SYNTHETICAL INVESTIGATIONS IN THE THUJANE SERIES. PART X.

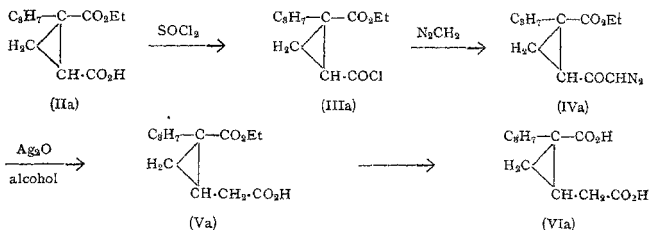
### Experiments on a total synthesis of Thujone: Synthesis of an isomer of $\alpha$ -Thujadicarboxylic acid (1-isopropyl- 1-carboxy-cyclopropane-3-acetic acid).

By P. C. Guha and M. S. Muthanna.

Ruzicka and Koolhaas (*Helv. Chim. Acta.*, 1932, **15**, 944) have effected a partial synthesis of thujone starting from thujaketonic ester, similar to the synthesis of pinocampnone from pinonic acid (Ruzicka and Trebler, *Helv. Chim. Acta.*, 1921, **4**, 666). Thujaketonic acid having been recently synthesised from the anhydride of  $\alpha$ -thujadicarboxylic acid (Guha and Muthanna, *Ber.*, 1938, **71**, 2671) and the synthesis of umbellularic acid having been achieved already (Guha and Muthanna, *Ber.*, 1938, **71**, 2668; Simonsen, *J. C. S.*, 1936, 828; Rydon, *ibid.*, 829; Ranganathan, *J. Indian Chem. Soc.*, 1936, **13**, 419), for the total synthesis of thujone, it only remains now that umbellularic acid should be converted to thujadicarboxylic acid. The following scheme was designed to achieve the end.



If the anhydride ring opens up in an alternative way, as shown below, an isomer of thujadicarboxylic acid (VIa) would be ultimately formed as follows:—



The mono-ester (II or IIa of umbellularic acid) was prepared by treating its anhydride with one molecular proportion of sodium ethoxide in alcohol. The acid chloride (III or IIIa) was prepared by treating the mono-acid mono-ester with thionyl chloride.

The mono-ester mono-acid chloride with excess of diazomethane yielded the diazoketone (IV or IVa) which, with silver oxide in alcoholic solution, yielded an acidic product from which umbellularic acid, m.p. 95°, and another acid melting at 80-81° were isolated. The latter cannot possibly be thujadicarboxylic acid which should melt at 142°. The fact that the substance melts at 80-81° suggested that it might be  $\beta$ -isopropyl adipic acid (m.p. 81°) which could be formed from (IV) or (IVa) by the rupture of the *cyclo*-propane ring. So, at this stage, to confirm its identity or difference from  $\beta$ -isopropyl adipic acid, the latter was prepared according to the method of Blanc (*Bl.*, [4], 3, 294) starting from  $\beta$ -isopropyl glutaric acid. But on taking mixed m.p. of the supposed  $\beta$ -isopropyl adipic acid with the genuine sample, it was found that the mixed m.p. got definitely depressed by about 8°. This proves that the compound formed at the last stage (m.p. 80-81°) is not  $\beta$ -isopropyl adipic acid.

As the only other plausible alternative, it is proposed that the acid obtained by the action of silver oxide on the diazoketone (IV or IVa) is an isomer of thujadicarboxylic acid represented by the formula (VIa).

## EXPERIMENTAL.

*Monoester of umbellularic acid (IIa).*—Umbellularic anhydride (10 g.) was slowly added to a well cooled solution of sodium ethoxide prepared by dissolving sodium (1.52 g.) in absolute alcohol (25 c.c.). After an hour, ice cold water was added to the mixture and the solution extracted with ether to remove the neutral products. The alkaline layer was acidified with dilute hydrochloric acid and extracted with ether, dried and ether removed, the residue distilled at 136-138°/5 mm.; yield 7 g. (Found: C, 60.53; H, 8.27; Eq. Wt. 196.  $C_{10}H_{16}O_4$  requires C, 60.0; H, 8.0 per cent.; Eq. Wt. 200).

*Umbellularic mono-ester mono-acid chloride (IIIa).*—Mono-ester of umbellularic acid (5 g.) was treated with thionyl chloride (4 g.) and after the evolution of hydrochloric acid was over, the product was freed from hydrochloric acid and thionyl chloride on waterbath under suction.

The acid chloride (IIIa) was treated with excess of diazomethane in dry ethereal solution and kept over-night. Next day on removal of ether on water-bath a thick viscous liquid containing nitrogen was left behind. This could not be purified further by distillation without decomposition and hence was used as such for the next operation.

*Treatment of the diazomethane reaction product (IVa) with silver oxide: Formation of 1-isopropyl-1-carboxy-cyclopropane-3-acetic acid (VIa).*—The above diazomethane reaction product (9 g.) was warmed on water-bath with alcohol (150 g.) and silver oxide obtained from 10 c.c. of 10 per cent. silver nitrate solution. There was a vigorous evolution of nitrogen followed by deposition of a fine mirror of silver in the flask. After the evolution of nitrogen had subsided, the mixture was heated under reflux for an hour on water-bath. The cooled mixture was filtered, alcohol removed, the residue treated with dilute sodium carbonate solution and a small quantity of neutral product removed by ether extraction. The alkaline solution was acidified with dilute hydrochloric acid and extracted repeatedly with ether. Ether was removed and the semi-solid residue was digested with water. On concentration

of the aqueous solution, a crop of crystals was obtained melting at  $95^{\circ}$ , and was identified to be umbellularic acid. On further concentration of the mother liquor, another crop of crystals was obtained which after crystallisation from water melted at  $80-81^{\circ}$ . (Found: C, 57.66; H, 7.91; Eq. Wt., 93.15.  $C_9H_{14}O_4$  requires C, 58.06; H, 7.53 per cent., Eq. Wt. 93).

*Preparation of  $\beta$ -isopropyl- $\alpha\alpha'$ -dicyano-glutaramide.*—Isobutyraldehyde (44.5 g.) was added to a solution of cyanacetamide (104 g.) dissolved in the minimum quantity of water and 50 per cent. potassium hydroxide solution (1.5 c.c.) was added. The mixture was shaken thoroughly for 20 minutes in a shaking machine. Crystals separated on standing which after crystallisation from water melted at  $147-48^{\circ}$ . (Found: N, 31.52.  $C_{10}H_{14}O_2N_4$  requires N, 31.40 per cent.).

*$\beta$ -Isopropyl glutaric acid.*—A mixture of  $\beta$ -isopropyl- $\alpha\alpha'$ -dicyano-glutaramide (95 g.) and 500 c.c. of 18% hydrochloric acid was heated under reflux for 5 hours when a clear solution was obtained. The cooled reaction product was extracted with ether, ether removed, when the residue solidified. It was crystallised from water after animal charcoal treatment, m.p.  $100-101^{\circ}$ ; yield 50 g. The mixed m.p. with a sample of  $\beta$ -isopropyl glutaric acid prepared according to the method of Guha and Muthanna (loc. cit.) remained undepressed.

*Reduction of  $\beta$ -isopropyl glutaric anhydride to the lactone.*—The anhydride was prepared by refluxing the acid with excess of acetic anhydride for half-an-hour and fractionating the product. The pure compound boiled at  $145^{\circ}/5$  mm. Sodium (52 g.) in thin slices was added gradually to the anhydride (50 g.) in absolute alcohol (300 c.c.) and the mixture heated on water-bath for half-an-hour under shaking till all the sodium had dissolved. The cooled product was treated with 25 % ice-cold sulphuric acid and extracted with ether. The ethereal solution was freed from acidic substances by washing with dilute sodium bicarbonate solution, ether removed and the residue distilled under reduced pressure and the fraction coming at  $140^{\circ}/15$  mm. was collected; yield 28 g. (cf. Blanc. *Bull. Chim. Soc.*, [4], 3, 294).

*Conversion of the above lactone into  $\beta$ -isopropyl adipic acid.-*

Phosphorus pentabromide (150 g.) was added to the above lactone (50 g.) when during half-an-hour the evolution of HBr was over, the product was added to absolute alcohol (200 c.c.). After 12 hours, the alcohol was removed and the residue taken in ether and the ethereal solution washed with dilute sodium carbonate solution, dried and ether removed. The residue distilled at 150-165°/15 mm. yield, 80 g.

Glacial acetic acid (2 c.c.) and sodium iodide (2 g.) dissolved in the minimum quantity of water, were added under ice cooling to potassium cyanide (15 g.) dissolved in the minimum quantity of water. With the addition of the above bromo compound (25 g.) dissolved in enough alcohol to give a uniform solution, the mixture was heated under reflux for 7 hours. Potassium hydroxide solution (50 c.c. of 30% strength) was then added and the mixture refluxed for 3 more hours. After removal of alcohol, the residue was digested with water at 100° till the smell of ammonia disappeared. After treatment with animal charcoal, it was filtered, acidified and extracted with ether. Evaporation of ether left a solid which after crystallisation from water melted at 80-81°.

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