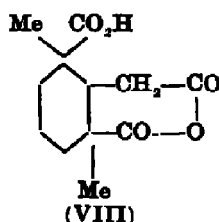
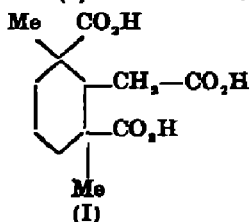


# ON RESIN ACIDS. SYNTHESIS OF AN ANHYDRIDE OF 1:3-DIMETHYL-1:3-DICARBOXYCYCLOHEXYL-2-ACETIC ACID

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Diethyl 1:3-dimethylcyclohexane-2-one-1:3-dicarboxylate reacts with zinc and ethyl bromoacetate to give the corresponding hydroxy-ester, which on dehydration, catalytic reduction and subsequent hydrolysis affords the anhydride of 1:3-dimethyl-1:3-dicarboxycyclohexyl-2-acetic acid.

On energetic oxidation of abietic acid with potassium permanganate (Ruzicka *et al.*, *Helv. Chim. Acta*, 1925, 9, 637; 1931, 14, 545) or with nitric acid (Levy, *Ber.*, 1929, 62, 2494) a  $C_{12}$ -acid (I) has been isolated.



An attempt has been made to synthesise the above acid along the following line, but unfortunately the anhydride (VIII) obtained synthetically happens to have a melting point different from that obtained from the natural sources.

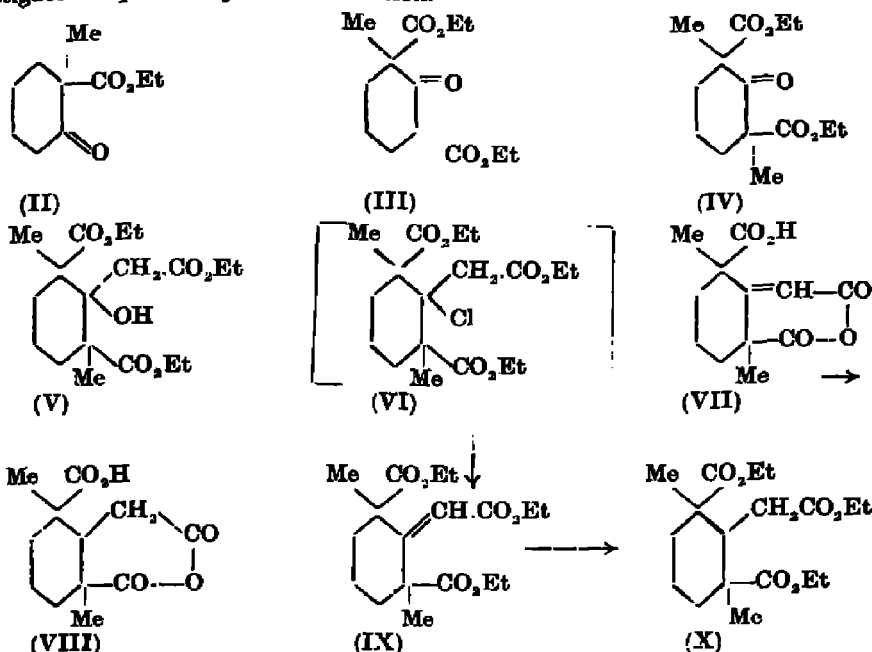
Ethyl 2-methylcyclohexanone-2-carboxylate (II) is condensed with ethyl oxalate in presence of molecular quantity of sodium ethoxide in ether (cf. Kotz and Michels, *Annalen*, 1908, 350, 212). In the present case the only precaution taken is that the temperature at which the reaction to be carried out is kept throughout the experiment below  $-10^{\circ}$ , when a satisfactory yield of the oxalo derivative is obtained which, on being heated with powdered soft glass (Bachmann *et al.*, *J. Amer. Chem. Soc.*, 1940, 62, 824; at  $160^{\circ}$ - $170^{\circ}$  for 3 hours, undergoes smooth decarboxylation to afford the keto-diester (III) imparting a deep red coloration to an alcoholic solution of ferric chloride. The keto-diester (III) is methylated by means of sodium dust in benzene and methyl iodide.

To study the spatial relationship of the two tertiary carboxyl groups attempts have been made to reduce the keto group in (IV) according to Wolff-Kishner method, but unfortunately, in spite of several attempts, the semicarbazone of the keto-diester could not be prepared, owing presumably to considerable steric hindrance.

The keto-diester (IV) is subjected to Reformatsky's reaction with zinc and ethyl bromoacetate according to the conditions laid down by Bachmann *et al.* (*loc. cit.*). The hydroxy-ester (V) is converted into the chloro derivative (VI) with thionyl chloride and pyridine, which on treatment with caustic potash undergoes unsaturation and hydrolysis giving an unsaturated anhydride (VII) on acidification. Reduction of the anhydride could not be effected by means of sodium amalgam. This has been reduced catalytically by means of platinum oxide in acetic acid when the reduced anhydride (VIII) is obtained in good yield.

The hydroxy-ester (V) is again treated with thionyl chloride and excess of pyridine when the unsaturated ester (IX) is obtained in good yield, which on catalytic reduction with  $PtO_2$  in acetic acid solution gives the reduced ester (X). The tri-ester on hydrolysis under drastic condition gives the reduced anhydride (VIII). In no case, however, could the tricarboxylic acid be isolated.

It is intended to prepare sufficient quantities of the acid anhydride (VIII) in order to investigate the possibility of its resolution.



#### EXPERIMENTAL

**Diethyl 1-Methylcyclohexan-2-one-1:3-dicarboxylate (III).**—Sodium dust (3 g.) was taken under dry ether (60 c. c.) and cooled. To this was added calcium-dried alcohol (6 g.) in drops and the mixture was left overnight. Ethyl oxalate (20 g.) was then added in the cold when the sodium derivative of the oxalic ester separated as light yellow crystals. The reaction mixture, after standing for 2 hours, was cooled in a freezing mixture (ice-salt,  $-15^\circ$ ) and ethyl 2-methylcyclohexanone-2-carboxylate (23 g.) was added dropwise with continuous shaking. Gradually the solid mass went into solution assuming a deep red colour. Then the mixture was kept in the ice-chest for 48 hours and diluted with cold water and extracted with ether to remove the unreacted products. The aqueous layer on acidification with ice-cold dilute sulphuric acid gave a thick, heavy layer at the bottom which was extracted with ether, the ethereal layer washed with sodium bicarbonate solution, water and then dried ( $\text{CaCl}_2$ ). After removal of the solvent the thick red liquid was heated at  $160^\circ\text{--}170^\circ$  together with some powdered soft glass, until evolution of carbon monoxide ceased. It was then distilled in vacuum: when the desired product passed over at  $142\text{--}145^\circ/6\text{ mm.}$ , yield 26 g. A drop of it imparted a deep red coloration to an alcoholic solution of ferric chloride. (Found: C, 61.15; H, 7.66.  $\text{C}_{13}\text{H}_{20}\text{O}_4$  requires C, 60.93; H, 7.81 per cent).

**Diethyl 1:3-Dimethylcyclohexan-2-one-1:3-dicarboxylate (IV).**—The above  $\beta$ -keto-ester (III, 25.6 g.) was added dropwise with shaking to sodium dust (2.7 g.) in 75 c. c. of dry benzene, cooled in ice-water. Gradually sodium went into solution which assumed a deep red colour. The mixture was allowed to stand overnight and then 20 c. c. of

methyl iodide added and refluxed for 2 hours on the water-bath. After diluting the cooled reaction mixture with water the benzene layer was separated, washed and dried. On removal of the solvent and distillation of the residue in *vacuo* 24 g. of the product (b. p.  $142^{\circ}/6$  mm.) were obtained which did not respond to ferric reaction. (Found: C, 61.66; H, 8.12.  $C_{14}H_{22}O_3$  requires C, 62.22; H, 8.15 per cent). Semicarbazone of (IV) could not be prepared in spite of several attempts.

*Ethyl 1:3-Dimethyl-1:3-dicarbethoxycyclohexane-2-ol-2-acetate* (V).—The above keto-diester (IV, 27 g.) was dissolved in thiophen-free benzene (50 c.c.) and to this was added 16 g. of zinc wool (washed with dilute hydrochloric acid, water and acetone, and dried before use), 12 c. c. of ethyl bromoacetate and 0.5 g. of iodine. As the mixture was refluxed on the water-bath, the colour of iodine faded and the solution became cloudy. After 10-15 minutes a vigorous reaction took place and a brown-coloured addition product was deposited. Four additions of 16 g. of zinc and a trace of iodine were made at 45 minutes' intervals and an additional 12 c. c. of ethyl bromoacetate was introduced after  $1\frac{1}{2}$  hours. The mixture was refluxed for a total of 4 hours. Frequently the mixture was vigorously shaken in order to free the zinc from the adhering mass of the deposit. The addition product was decomposed by adding acetic acid and methanol, and the solution decanted from the zinc into water and the mixture acidified with acetic acid and extracted with ether. The ether-benzene layer was separated, washed with water, then with dilute ammonia until no more colour was removed. The residue, obtained by evaporation of the dried ether benzene solution, was distilled when 17 g. of the desired product passed over at  $180-184^{\circ}/7$  mm. giving a blue fluorescence. (Found: C, 61.1; H, 8.52.  $C_{14}H_{22}O_3$  requires C, 60.3; H, 8.38 per cent). The analysis showed that the product consisted mainly of the hydroxy compound (V) contaminated with the corresponding unsaturated ester (IX).

*Dehydration of the Reformatsky Product*.—Thionyl chloride (12 g.) was slowly added with shaking to an ice-cold mixture of the above hydroxy-ester (V, 17 g.) and dry pyridine, which was then heated on the water-bath for 2 hours. The supernatant liquid was poured into ice and the solid mass decomposed with iced hydrochloric acid. The two solutions were combined and extracted with ether, the ethereal extract washed with dilute hydrochloric acid, water, sodium bicarbonate solution and again with water and then dried. After removal of the solvents distillation of the residue gave the desired compound containing much dissolved sulphur which was removed by refluxing with precipitated copper in benzene (50 c. c.) for 1 hour on the water-bath. After the removal of benzene from the filtered solution, the residue gave 12 g. of the unsaturated ester (IX), b.p.  $170-172^{\circ}/8$  mm. (Found: C, 63.36; H, 8.21;  $C_{14}H_{20}O_2$  requires C, 63.53; H, 8.23 p.c.).

*Ethyl 1:3-Dimethyl-1:3-dicarbethoxycyclohexane-2-acetate* (X).—The above unsaturated ester (IX, 12 g.) was hydrogenated in presence of platinum oxide catalyst (0.2 g.) in glacial acetic acid solution when a rather slow absorption of hydrogen took place. After the theoretical volume of hydrogen had been absorbed, the product was worked up in the usual manner when 11.5 g of the saturated ester were obtained, b. p.  $165-67^{\circ}/6$  mm. (Found: C, 62.86; H, 8.62.  $C_{16}H_{26}O_4$  requires C, 63.15; H, 8.77 per cent).

*Anhydride of 1:3-Dimethyl-1:3-dicarboxycyclohexane-2-acetic Acid* (VIII).—The above tricarboxylic ester (X, 10 g.) was hydrolysed by boiling with a solution of caustic potash

(6.5 g.) in methyl alcohol (13 c. c.) for 10 hours, when the potassium salt of the tri-carboxylic acid was deposited. Water (5 c. c.) was added just to dissolve the precipitate and refluxing continued for 2 hours more. The cooled solution was then diluted with water and extracted with ether to remove unhydrolysed material. The alkaline extract was then acidified with dilute sulphuric acid when a clear solution was obtained. It was saturated with ammonium sulphate and extracted with ethyl acetate for several times. The combined ethyl acetate extract was washed with a little amount of water and dried over freshly calcined sodium sulphate. The solvent being removed by distillation the residue was evacuated at 5 mm. pressure when well defined crystals were deposited. On crystallisation from a little ethyl acetate it melted at  $163.64^{\circ}$ . (Found: C, 59.56; H, 6.52.  $C_{12}H_{10}O_5$  requires C, 60.00; H, 6.66 per cent). The mother-liquor on evaporation left a resinous mass which could not be solidified.

*The Unsaturated Anhydride (VII).*—The reformatsky product (V, 5 g.) was dissolved in dry benzene (5 c.c.) and dry pyridine (1 c.c.). To this was added with shaking in the cold 2 g. of thionyl chloride. After standing for 1 hour the mixture was evaporated under reduced pressure at room temperature and finally at  $40^{\circ}$ . The chloride was dissolved in 5 c. c. of benzene and decanted from the insoluble pyridine hydrochloride; the latter was digested several times with small portions of benzene and the extracts were added to the main portion. The solvent was then driven off and to the chilled residue was added 7 g. of caustic potash in 65 c.c. of methyl alcohol and the mixture refluxed for 15 minutes. Aqueous caustic potash solution (45%, 18 c.c.) was added to the cooled solution and refluxing continued. After an hour a large amount of precipitate was observed. Sufficient water was added to dissolve the precipitate and refluxing continued for 4 hours. After dilution the solution was extracted with ether to remove any unchanged material. The alkaline liquor was then acidified with ice-cold sulphuric acid, saturated with ammonium sulphate and extracted with ether for several times. The combined extract was washed with a little water, dried and the solvent removed. The residue after being kept under low pressure for some time solidified on addition of a drop or two of methyl alcohol. The solid was crystallised in clusters from glacial acetic acid, m.p.  $146^{\circ}$ . (Found: C, 60.36; H, 5.83.  $C_{12}H_{11}O_5$  requires C, 60.5; H, 5.88 per cent). The mother-liquor was evaporated, but the residue could not be solidified.

*Reduction of the Unsaturated Acid-anhydride (VII).*—The reduction of the above unsaturated anhydride (VII) was attempted with sodium amalgam (2%) according to the procedure of Bachmann. *et al* (*loc. cit.*) but curiously enough satisfactory results could not be obtained.

The unsaturated anhydride was then successfully reduced catalytically by means of platinum oxide catalyst in glacial acetic acid. The hydrogenated product was worked up in the usual way and crystallised from glacial acetic acid, m.p.  $162^{\circ}$  (mixed m. p. with the acid anhydride obtained by catalytic hydrogenation of the un-saturated tricarboxylic ester, IX followed by hydrolysis was  $160.61^{\circ}$ ).

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