

The triethyl ester was obtained by esterifying the acid by the alcohol-vapour method, b.p., 145°/4 mm. (Found: C, 57.9; H, 8.5.  $C_{14}H_{24}O_6$  requires C, 58.3; H, 8.3 per cent).

The author takes this opportunity of expressing his indebtedness to Dr. J. C. Bardhan for his valuable help during the progress of this work.

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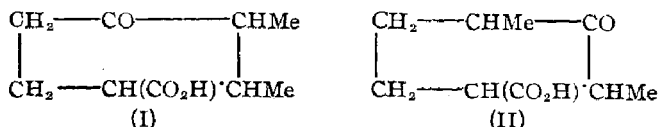
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### STUDIES IN THE CAMPHORQUINONE REARRANGEMENT. PART III. SYNTHESES OF 2:3-DIMETHYLCYCLOHEXAN-1-ONE-4-CARBOXYLIC ACID AND 3:6-DIMETHYLCYCLOHEXAN-1-ONE-4-CARBOXYLIC ACID

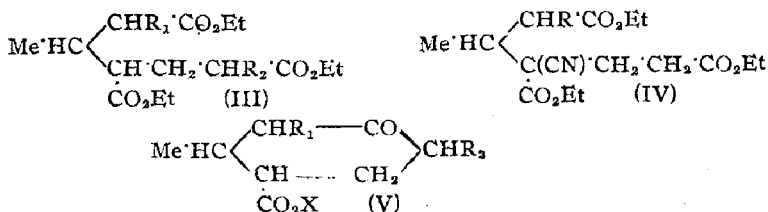
BY RAM NARAYAN CHAKRAVARTI

The ketonic acid,  $C_9H_{14}O_5$ , obtained by the rearrangement of santenonequinone in presence of sulphuric acid has now been definitely identified as 2:3-dimethylcyclohexan-1-one-4-carboxylic acid by direct synthesis of this acid, as well as the isomeric 3:6-dimethylcyclohexan-1-one-4-carboxylic acid by unambiguous methods. Incidentally it has been shown that the Dieckmann condensation of ethyl  $\beta$ -methylpentane- $\alpha\gamma\epsilon$ -tricarboxylate leads to the formation of ethyl 3-methylcyclohexan-1-one-4:6-dicarboxylate and not the isomeric ester ethyl 3-methyl-cyclohexan-1-one-2:4-dicarboxylate.

In a previous communication (*J. Indian Chem. Soc.*, 1944, 21, 319) evidence was brought forward which appeared to show that the keto-acid,  $C_9H_{14}O_5$ , obtained by the action of sulphuric acid on santenonequinone, could be best represented by the alternative structures (I) and (II). The most satisfactory way of deciding between these two formulæ seemed to be to prepare these acids synthetically and to compare the synthetical acids with the acid obtained from santenonequinone.



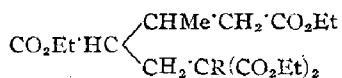
Ethyl crotonate has been condensed with ethyl sodio-cyanoacetate (*cf.* Hope and Perkin, *J. Chem. Soc.*, 1911, 99, 762) and the resulting product on treatment with ethyl  $\beta$ -chloropropionate gives ethyl  $\beta$ -methyl- $\gamma$ -cyanopentane- $\alpha\gamma\epsilon$ -tricarboxylate (IV, R=H). This on hydrolysis and esterification furnishes the desired ester (III,  $R_1=R_2=H$ ). Ethyl  $\beta$ -methylpentane- $\alpha\gamma\epsilon$ -tricarboxylate on treatment with sodium gives a ketonic ester which can be represented by the alternative structures (V,  $R_1=H$ ;  $R_2=CO_2Et$ ; X=Et) and (V,  $R_1=CO_2Et$ ;  $R_2=H$ ; X=Et).



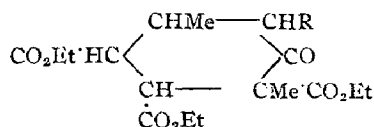
The product on hydrolysis furnishes 3-methylcyclohexan-1-one-4-carboxylic acid (V,  $R_1=R_2=X=H$ ), m.p. 95-96° (semicarbazone, m.p. 208-209°).

The Dieckmann condensation product (V,  $R_1=H$ ;  $R_2=CO_2Et$ ;  $X=Et$ ) or (V,  $R_1=CO_2Et$ ;  $R_2=H$ ;  $X=Et$ ) on methylation, hydrolysis and esterification gives a tricarboxylic ester (III,  $R_1=Me$ ;  $R_2=H$ ) or (III,  $R_1=H$ ;  $R_2=Me$ ). This has been cyclised with sodium to give the keto-ester (V,  $R_1=Me$ ;  $R_2=CO_2Et$ ;  $X=Et$ ) or (V,  $R_1=CO_2Et$ ;  $R_2=Me$ ;  $X=Et$ ) and the latter on hydrolysis yields a keto-acid, m.p. 98-99° (semicarbazone, m.p. 216°) having the alternative structures (V,  $R_1=Me$ ;  $R_2=X=H$ ) or (V,  $R_1=X=H$ ;  $R_2=Me$ ). The keto-acids (V,  $R_1=Me$ ;  $R_2=X=H$ ) and (V,  $R_1=X=H$ ;  $R_2=Me$ ) have accordingly been synthesised by unambiguous methods in order to establish definitely the constitution of the keto-acid, m.p. 98-99°.

*The Synthesis of 3:6-Dimethylcyclohexan-1-one-4-carboxylic Acid* (V,  $R_1=X=H$ ;  $R_2=Me$ ).—Ethyl  $\beta$ -methylpentane- $\alpha\gamma$ -tricarboxylate (III,  $R_1=R_2=H$ ) has been condensed with ethyl oxalate. The resulting product on distillation under reduced pressure gives ethyl- $\beta$ -methylpentane- $\alpha\gamma$ -tetracarboxylate (VI,  $R=H$ ). This is methylated to give (VI,  $R=Me$ ) and the latter on cyclisation with sodium furnishes the keto-ester (VII,  $R=CO_2Et$ ) which on hydrolysis gives 3:6-dimethylcyclohexan-1-one-4-carboxylic acid (V,  $R_1=X=H$ ;  $R_2=Me$ ) (semicarbazone, m.p. 217°) identical with the product<sup>†</sup> described above.



(VI)



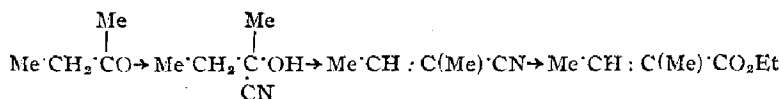
(VII)

It is quite conceivable, however, that the tetracarboxylic ester (VI,  $R=H$ ) may have an alternative structure (III,  $R_1=CO_2Et$ ;  $R_2=H$ ) and cannot, therefore, provide an adequate basis for the constitution of the keto-acid, m.p. 98-99°. 3:6-Dimethylcyclohexan-1-one-4-carboxylic acid has, therefore, been synthesised by an alternative route :

Ethyl 3-methylcyclohexan-1-one-4-carboxylate (V,  $R_1=R_2=H$ ;  $X=Et$ ) is condensed with ethyl oxalate and the resulting product on distillation furnishes ethyl 3-methylcyclohexan-1-one-4:6-dicarboxylate (V,  $R_1=H$ ;  $R_2=CO_2Et$ ;  $X=Et$ ). This is methylated to give ethyl 3:6-dimethylcyclohexan-1-one-4:6-dicarboxylate (VII,  $R=H$ ) and the latter on treatment with sodium ethylate yields ethyl  $\beta$ -dimethylpentane- $\alpha\gamma$ -tricarboxylate (III,  $R_1=H$ ;  $R_2=Me$ ). This on cyclisation with sodium gives ethyl 3:6-dimethylcyclohexan-1-one-2:4-dicarboxylate (V,  $R_1=CO_2Et$ ;  $R_2=Me$ ;  $X=Et$ ) which could be smoothly hydrolysed to give 3:6-dimethylcyclohexan-1-one-4-carboxylic acid (V,  $R_1=X=H$ ;  $R_2=Me$ ), m.p. 98-99° (semicarbazone, m.p. 217°). It follows, therefore, that the sodium condensation of ethyl  $\beta$ -methylpentane- $\alpha\gamma$ -tricarboxylate (III,  $R_1=R_2=H$ ) leads to the formation of ethyl 3-methylcyclohexan-1-one-4:6-dicarboxylate (V,  $R_1=H$ ;  $R_2=CO_2Et$ ;  $X=Et$ ).

*The Synthesis of 2:3-Dimethylcyclohexan-1-one-4-carboxylic Acid* (V,  $R_1=Me$ ;  $R_2=X=H$ ).—Ethyl  $\alpha\beta$ -dimethylacrylate (cf. Frankland and Duppa, *Annalen*, 1900, 236, 9; Wislicenus, *ibid.*, 1910, 272, 9), prepared from the cyanohydrin of methyl ethyl ketone according to the method described in the experimental portion, has been condensed with ethyl sodio-

cyanoacetate and the resulting product allowed to react with ethyl  $\beta$ -chloropropionate to give ethyl  $\alpha\beta$ -dimethyl- $\gamma$ -cyanopentane- $\alpha\gamma\epsilon$ -tricarboxylate (IV, R=Me). The latter on hydrolysis yields



a liquid acid which is esterified according to the alcohol-vapour method to give ethyl  $\alpha\beta$ -dimethylpentane- $\alpha\gamma\epsilon$ -tricarboxylate (III,  $R_1=\text{Me}$ ;  $R_2=\text{H}$ ). Sodium condensation then furnishes ethyl 2 : 3-dimethylcyclohexan-1-one-4 : 6-dicarboxylate (V,  $R_1=\text{Me}$ ;  $R_2=\text{CO}_2\text{Et}$ ; X=Et) which on hydrolysis gives 2 : 3-dimethylcyclohexan-1-one-4-carboxylic acid (V,  $R_1=\text{Me}$ ;  $R_2=\text{X}=\text{H}$ ), m.p.  $132^\circ$  (semicarbazone, m.p.  $191^\circ$ ) which proves to be identical in every way with the keto-acid obtained from santenonequinone.

It follows, therefore, that the keto-acid, obtained by the rearrangement of santenonequinone must be best represented as 2 : 3-dimethylcyclohexan-1-one-4-carboxylic acid.

#### EXPERIMENTAL

*Condensation of Ethyl Crotonate with Ethyl Sodio-cyanoacetate and Ethyl  $\beta$ -Chloropropionate : Formation of Ethyl  $\beta$ -Methyl- $\gamma$ -cyanopentane- $\alpha\gamma\epsilon$ -tricarboxylate (IV, R=H).—*Ethyl cyanoacetate (67.8 g.) was added to an ice-cold solution of sodium (13.8 g.) in absolute alcohol (225 c.c.). Ethyl crotonate (68.4 g.) was then added to the curdy mass and the whole heated on a water-bath for 16 hours. The dark coloured solution was cooled in ice and ethyl  $\beta$ -chloropropionate (84 g.) added and kept overnight. It was then heated on the water-bath for 7 hours. The product was isolated by diluting the reaction mixture with water and extracting with ether. The extract was washed with water, and the ether evaporated. The cyano-ester (IV, R=H) was obtained as a colourless mobile liquid boiling at  $195^\circ/4$  mm., yield 156 g. (Found : C, 58.7; H, 7.6.  $\text{C}_{16}\text{H}_{26}\text{O}_6\text{N}$  requires C, 58.7; H, 7.6 per cent).

*Ethyl  $\beta$ -Methylpentane- $\alpha\gamma\epsilon$ -tricarboxylate (III,  $R_1=R_2=\text{H}$ ).—*The above condensation product (156 g.) was hydrolysed by heating on a sand-bath for 40 hours with concentrated sulphuric acid (175 c.c.) diluted with water (210 c.c.). It was then diluted with water, saturated with salt and extracted with ether. The crude tricarboxylic acid (85 g.) was obtained as a viscous liquid on evaporation of the ether. It was heated to  $110^\circ$  with absolute alcohol (170 c.c.) and concentrated sulphuric acid (17 c.c.) and esterified in a current of alcohol vapour for 6 hours. The product was worked up in the usual manner and distilled. The pure tricarboxylic ester (III,  $R_1=R_2=\text{H}$ ) boils at  $168^\circ/6$  mm., yield 93 g. (Found : C, 59.3; H, 8.6;  $\text{C}_{15}\text{H}_{26}\text{O}_6$  requires C, 59.6; H, 8.6 per cent).

*Sodium Condensation of Ethyl  $\beta$ -Methylpentane- $\alpha\gamma\epsilon$ -tricarboxylate : Formation of (V,  $R_1=\text{CO}_2\text{Et}$ ;  $R_2=\text{H}$ ; X=Et) or (V,  $R_1=\text{H}$ ;  $R_2=\text{CO}_2\text{Et}$ ; X=Et).—*The triethyl ester (30.2 g.), obtained above, was heated on the water-bath with finely divided sodium (3.4 g.) and dry benzene (70 c.c.). The reaction started after about 45 minutes and was complete in 2 hours more. It was then cooled, treated with ice-water and acidified with ice-cold dilute hydrochloric acid. The benzene layer was separated and washed well with water. The oil obtained after removal of the benzene, was distilled in *vacuo*, when practically the whole of it distilled over at  $158^\circ/6$  mm., yield 22.5 g. It gave a violet colouration with alcoholic ferric chloride. (Found : C, 60.4; H, 7.7;  $\text{C}_{15}\text{H}_{20}\text{O}_6$  requires C, 60.9; H, 7.8 per cent).

*Hydrolysis of the Above Sodium Condensation Product: Formation of 3-Methylcyclohexan-1-one-4-carboxylic Acid* (V,  $R_1=R_2=X=H$ ).—The  $\beta$ -ketonic ester (22 g.), obtained above, was refluxed on the sand-bath for 6 hours with 10 volumes of 6% hydrochloric acid. The clear solution thus obtained was cooled, neutralised with soda and extracted with ether to remove any neutral matter. The aqueous solution was acidified, saturated with salt and extracted repeatedly with ether. On evaporation of the solvent the keto-acid (V,  $R_1=R_2=X=H$ ) (11 g.) was obtained as a liquid, which solidified in a vacuum desiccator.

The *semicarbazone* crystallises from spirit and melts with decomposition at 208-209° (Found: C, 50.5; H, 6.9.  $C_9H_{15}O_3N_3$  requires C, 50.7; H, 7.0 per cent).

The *pure* keto-acid was prepared by hydrolysing the semicarbazone with dilute hydrochloric acid. It crystallises from a mixture of benzene and petroleum ether, m.p. 95-96°. (Found: C, 61.6; H, 7.6.  $C_9H_{12}O_3$  requires C, 61.5; H, 7.7 per cent).

The *ethyl ester* was prepared by heating the crude keto-acid (8 g.) for 10 hours on the water-bath with absolute alcohol (30 c.c.) and 5 c.c. of alcoholic hydrogen chloride (saturated at 0°). The alcohol was then distilled off and the liquid remaining in the flask was diluted with water and extracted with ether. The ethereal solution was washed with dilute sodium carbonate solution and water. *Ethyl 3-methylcyclohexan-1-one-4-carboxylate* was obtained as a light colourless liquid boiling at 112°/5mm., yield 7 g. (Found: C, 65.0; H, 8.6.  $C_{10}H_{16}O_3$  requires C, 65.2; H, 8.7 per cent).

The *semicarbazone* of the ethyl ester crystallises from dilute alcohol, m.p. 136°. (Found: C, 54.6; H, 7.9.  $C_{11}H_{19}O_3N_3$  requires C, 54.7; H, 7.9 per cent).

*Methylation of the Sodium Condensation Product of Ethyl  $\beta$ -methylpentane- $\alpha$ -tricarboxylate*.—For this purpose the sodiosalt, obtained by heating the triethyl ester (III,  $R_1=R_2=H$ ) (30.2 g.), with finely divided sodium (4.6 g.) in benzene (75 c.c.) was cooled in ice and treated with methyl iodide (13 c.c.) and kept overnight. It was then heated on the water-bath for 8-10 hours with the addition of a little methyl iodide from time to time. When cold it was treated with water, the benzene layer separated, washed with water, and the benzene evaporated. The methylated product boiled at 160°/7mm., yield 24 g. It gave no colouration with alcoholic ferric chloride. (Found: C, 61.8; H, 8.3.  $C_{14}H_{22}O_5$  requires C, 62.2; H, 8.15 per cent).

*Acid Hydrolysis of the above Methylated Product and its subsequent Esterification: Formation of* (III,  $R_1=Me$ ;  $R_2=H$ ) or (III,  $R_1=H$ ;  $R_2=Me$ ).—The methylated product (18 g.) obtained above was heated on the water-bath for 3 hours with excess of 20% alcoholic potash. The alcohol was then evaporated off with the addition of water. The aqueous alkaline solution was acidified, saturated with salt and extracted with ether. The gummy residue (14.3 g.), obtained on evaporation of the solvent, was esterified by the alcohol-vapour method. The triethyl ester (III,  $R_1=Me$ ;  $R_2=H$ ) or (III,  $R_1=H$ ;  $R_2=Me$ ) was obtained as a colourless oil boiling at 160°/5mm., yield 13.9 g. (Found: C, 60.3; H, 8.6.  $C_{16}H_{26}O_5$  requires C, 60.7; H, 8.8 per cent).

*Sodium Condensation of the above Triethyl Ester: Formation of* (V,  $R_1=Me$ ;  $R_2=CO_2Et$ ;  $X=Et$ ) or (V,  $R_1=CO_2Et$ ;  $R_2=Me$ ;  $X=Et$ ).—The triethyl ester, obtained in the preceding experiment, was heated on the water-bath with finely divided sodium (1.8 g) suspended in dry benzene (34 c.c.). A vigorous evolution of hydrogen started after half an hour and in another two hours the whole of the sodium went into solution. The brown liquid was cooled in ice, treated with ice-water and acidified with ice-cold dilute hydrochloric acid.

The upper benzene layer was separated, and washed with water. The product obtained on distillation of the solvent boiled constantly at  $154^{\circ}/5\text{mm.}$ , yield 6 g. It gave a strong colouration with alcoholic ferric chloride. (Found: C, 61.9; H, 8.0.  $\text{C}_{14}\text{H}_{22}\text{O}_6$  requires C, 62.2; H, 8.1 per cent).

*Ketonic Hydrolysis of the above Product: Formation of the Keto-acid*, m.p.  $98-99^{\circ}$ .—The  $\beta$ -ketonic ester (5.7 g.), obtained above, was heated on a sand-bath for 6-7 hours with 60 c.c. of 6% hydrochloric acid. It was then neutralised with soda and extracted with ether to remove any neutral matter. The alkaline solution was acidified, saturated with salt and extracted with ether. The crude keto-acid, thus obtained, was converted into the *semicarbazone*. After crystallisation from spirit it melted at  $216^{\circ}$  with decomposition. (Found: C, 52.6; H, 7.3.  $\text{C}_{10}\text{H}_{17}\text{O}_3\text{N}_3$  requires C, 52.8; H, 7.4 per cent).

The pure keto-acid was obtained by hydrolysing the semicarbazone with dilute hydrochloric acid. It was obtained as a colourless viscous liquid, b.p.  $155^{\circ}/4\text{mm.}$  It solidified completely on keeping for several days. The solid acid crystallises from a mixture of benzene and petroleum ether, m.p.  $98-99^{\circ}$ . (Found: C, 63.3; H, 8.1.  $\text{C}_9\text{H}_{14}\text{O}_3$  requires C, 63.5; H, 8.2 per cent).

*Synthesis of 3:6-Dimethylcyclohexan-1-one-4-carboxylic Acid* (V,  $\text{R}_1=\text{H}$ ;  $\text{R}_2=\text{Me}$ ;  $\text{X}=\text{H}$ ).

*Ethyl  $\beta$ -Methylpentane- $\alpha$ - $\gamma$ -tetracarboxylate* (VI,  $\text{R}=\text{H}$ ).—Absolute alcohol (2.96 g.), distilled over calcium, dissolved in dry ether (6 c.c.) was added dropwise to a suspension of finely divided potassium (2.5 g.) in dry ether (65 c.c.) cooled in ice-water. It was then kept at the room temperature till the whole of the potassium disappeared. It was again cooled in ice and diethyl oxalate (9.4 g.) was added slowly. Ethyl  $\beta$ -methylpentane- $\alpha$ - $\gamma$ -tricarboxylate (19.4 g.) was then added dropwise to the cold solution. It was kept for 24 hours and then diluted with ice-water. The ethereal layer was separated and the aqueous layer extracted once with ether. The aqueous alkaline solution was then acidified with ice-cold dilute sulphuric acid and extracted with ether. The extract was washed well with water and the ether evaporated. The residual oil was heated to  $110-120^{\circ}$  in *vacuo* for about an hour and then heated under atmospheric pressure for about 24 hours, till it gave no colouration with alcoholic ferric chloride, the temperature being gradually raised from  $160^{\circ}$  to  $190^{\circ}$  during this period. It was finally distilled in *vacuo*, b.p.  $175^{\circ}/5\text{mm.}$ , yield 13.8 g. (Found: C, 57.3; H, 7.8.  $\text{C}_{18}\text{H}_{30}\text{O}_8$  requires C, 57.7; H, 8.0 per cent).

*Ethyl- $\beta$ -Dimethylpentane- $\alpha$ - $\gamma$ -tetracarboxylate* (VI,  $\text{R}=\text{Me}$ ).—The above tetraethyl ester (13.5 g.) was added to molecular sodium (0.84 g.) suspended in dry benzene (35 c.c.), cooled in ice, and kept overnight. It was again cooled in ice and methyl iodide (5 c.c.) was added and again kept overnight. The methylation was completed by heating on the water-bath for 8 hours with the addition of a little methyl iodide from time to time. When cold it was treated with water, the benzene layer was separated, washed, dried and the benzene evaporated. The liquid remaining was then distilled in *vacuo*, b.p.  $180^{\circ}/6\text{mm.}$ , yield 11.4 g. (Found: C, 58.5; H, 8.2.  $\text{C}_{19}\text{H}_{32}\text{O}_8$  requires C, 58.7; H, 8.2 per cent).

*Ethyl 3:6-Dimethylcyclohexan-1-one-2:4:6-tricarboxylate* (VII,  $\text{R}=\text{CO}_2\text{Et}$ ).—The methylated tetracarboxylic ester (11.2 g.) was heated on the water-bath with a fine suspension of sodium (1.08 g.) in benzene (25 c.c.). After about 3 hours the sodium completely went into solution. The liquid was treated with ice-water and acidified with ice-cold dilute hydrochloric acid. The benzene layer was separated, washed well with water and the benzene evaporated.

The residual liquid was then distilled in *vacuo*, b.p.  $170^{\circ}/6\text{mm.}$ , yield 8.7 g. (Found: C, 59.8; H, 7.4.  $\text{C}_{17}\text{H}_{26}\text{O}_7$  requires C, 59.6; H, 7.6 per cent).

*Weak Hydrolysis of the above Product: Formation of 3:6-Dimethylcyclohexan-1-one-4-carboxylic Acid* (V,  $\text{R}_1 = \text{X} = \text{H}$ ;  $\text{R}_2 = \text{Me}$ ).—The ketonic ester, obtained above (8.5 g.), was heated on a sand-bath for about 10 hours with 100 c.c. of 10% sulphuric acid. The solution was made alkaline with sodium carbonate and extracted with ether to remove any neutral matter present. The aqueous solution was then acidified, saturated with salt and extracted with ether. The light brown liquid residue, obtained after evaporation of the solvent, was converted into the *semicarbazone*, which after crystallisation from spirit melted at  $217^{\circ}$  with decomposition and was found to be identical with the *semicarbazone* of the keto-acid, m.p.  $98-99^{\circ}$ , previously described. (Found: C, 52.6; H, 7.4.  $\text{C}_{10}\text{H}_{17}\text{O}_3\text{N}_3$  requires C, 52.8; H, 7.4 per cent).

*Condensation of Ethyl 3-Methylcyclohexan-1-one-4-carboxylate* (V,  $\text{R}_1 = \text{R}_2 = \text{H}$ ;  $\text{X} = \text{Et}$ ) with *Ethyl oxalate*; *Formation of pure Ethyl 3-methylcyclohexan-1-one-4:6-dicarboxylate* (V,  $\text{R}_1 = \text{H}$ ;  $\text{R}_2 = \text{CO}_2\text{Et}$ ;  $\text{X} = \text{Et}$ ).—A mixture of ethyl 3-methylcyclohexan-1-one-4-carboxylate (23 g.) and ethyl oxalate (18.3 g.) was added slowly with shaking to a solution of sodium (2.88 g.) in absolute alcohol (37.5 c.c.) kept cooled in a freezing mixture and the solution kept overnight. The product was treated with ice-water and extracted with ether to remove any unreacted ester present. The aqueous solution was then acidified with ice-cold dilute sulphuric acid, extracted with ether and the extract washed well with water. The oily liquid, obtained after removal of the solvent, was heated at  $110-120^{\circ}$  under reduced pressure for an hour and then heated under atmospheric pressure for about 3 hours till the evolution of carbon monoxide ceased completely. The temperature of the bath during this period was raised gradually from  $170-90^{\circ}$ . It was finally distilled under diminished pressure when ethyl 3-methylcyclohexan-1-one-4:6-dicarboxylate (V,  $\text{R}_1 = \text{H}$ ;  $\text{R}_2 = \text{CO}_2\text{Et}$ ;  $\text{X} = \text{Et}$ ) (12.8 g.), unmixed with the isomeric ester (V,  $\text{R}_1 = \text{CO}_2\text{Et}$ ;  $\text{R}_2 = \text{H}$ ;  $\text{X} = \text{Et}$ ), was obtained boiling at  $155^{\circ}/6\text{mm.}$  It gave a violet colouration with alcoholic ferric chloride.

*Ethyl 3:6-Dimethylcyclohexan-1-one-4:6-dicarboxylate* (VII,  $\text{R} = \text{H}$ ).—The above ester (12.8 g.) was added to molecular sodium (1.15 g.) suspended in dry benzene (25 c.c.), cooled in ice and kept overnight. Methyl iodide (6 c.c.) was added to the ice-cold sodio-salt and it was again kept overnight. The methylation was completed by heating on the water-bath for 8 hours with the addition of a little methyl iodide from time to time. The product was treated with water. The benzene layer was separated, washed with cold 15 per cent caustic potash solution to remove any trace of unmethylated ester, and finally with water. The product was then distilled. Ethyl 3:6-dimethylcyclohexan-1-one-4:6-dicarboxylate was obtained as a colourless mobile liquid, b.p.  $158^{\circ}/6\text{mm.}$ , yield 11.8 g. It gave no colouration with ferric chloride. (Found: C, 61.7; H, 8.2.  $\text{C}_{14}\text{H}_{22}\text{O}_5$  requires C, 62.2; H, 8.1 per cent).

*Ethyl  $\beta$ : $\delta$ -Dimethylpentane- $\alpha$ : $\gamma$ -tricarboxylate* (III,  $\text{R}_1 = \text{H}$ ;  $\text{R}_2 = \text{Me}$ ).—The methylated product (11.6 g.), obtained above, was heated on the water-bath for 4 hours with a solution of sodium (0.25 g.) in absolute alcohol (11 c.c.). It was then cooled, diluted with water, acidified with hydrochloric acid and extracted with ether. The product obtained on removal of the ether was distilled in *vacuo*. Ethyl  $\beta$ : $\delta$ -dimethylpentane- $\alpha$ : $\gamma$ -tricarboxylate boils at  $163^{\circ}/6\text{mm.}$ , yield 11.5 g.

*Ethyl 3:6-Dimethylcyclohexan-1-one-2:4-dicarboxylate* (V,  $\text{R}_1 = \text{CO}_2\text{Et}$ ;  $\text{R}_2 = \text{Me}$ ;  $\text{X} = \text{Et}$ ) was prepared by heating the above trimethyl ester (11.5 g.) on the water-bath with a suspension of finely divided sodium (1.15 g.) in dry benzene (27 c.c.). A vigorous reaction started on heating and it was complete in an hour and a half. The product was

cooled, treated with ice-water and acidified with ice-cold dilute hydrochloric acid. The upper benzene layer was separated, washed with water and the benzene was then evaporated. The residue on distillation under diminished pressure gave a colourless mobile liquid, b.p.  $150^{\circ}/6$  mm., yield 8.2 g. It gave a colouration with ferric chloride. (Found: C, 62.0; H, 8.0.  $C_{11}H_{22}O_2$  requires C, 62.2; H, 8.1 per cent).

3:6-Dimethylcyclohexan-1-one-4-carboxylic Acid (V,  $R_1=X=H$ ;  $R_2=Me$ ) was obtained from the above ester (8 g.) by heating on a sand-bath with 6 % hydrochloric acid (80 c.c.). After about 8 hours an almost clear solution was obtained. It was then cooled, neutralised with sodium carbonate and extracted with ether to remove any neutral matter. The aqueous solution was acidified, saturated with salt and extracted repeatedly with ether. The keto-acid (4.5 g.) was obtained as a light brown liquid on evaporation of the solvent.

The semicarbazone crystallises from spirit as a sandy white powder which melts with decomposition at  $217^{\circ}$ , and is identical with the semicarbazone of the keto-acid, m.p.  $98-99^{\circ}$  as described previously (mixed m.p.). (Found: C, 52.5; H, 7.3.  $C_{10}H_{17}O_2N_3$  requires C, 52.8; H, 7.4 per cent).

The pure keto-acid was obtained by hydrolysing the semicarbazone with hydrochloric acid (1:1). It crystallises from a mixture of benzene and petroleum ether, m.p.  $98-99^{\circ}$ , and is identical with the keto-acid, m.p.  $98-99^{\circ}$ , as obtained previously (mixed m.p.). (Found: C, 63.3; H, 8.1.  $C_9H_{14}O_2$  requires C, 63.5; H, 8.2 per cent).

*Synthesis of 2:3-Dimethylcyclohexan-1-one-4-carboxylic Acid (V,  $R_1=Me$ ,  $R_2=X=H$ ).*

*Methyl ethyl ketone cyanohydrin.*—Pure methyl ethyl ketone (84 c.c.) was added dropwise, during the course of one hour and a quarter, to a solution of sodium cyanide in water (90 c.c.), cooled in ice and stirred mechanically. Sulphuric acid (40%, 68 c.c.) was then added to it in 3 hours and the stirring (7.5 g.) was continued for another half hour. The liquid was then filtered at the pump and the salts washed with ether. The filtrate was extracted with ether. The total ethereal extract was dried over anhydrous calcium chloride and the solvent evaporated after adding a drop of sulphuric acid. The residual oil on distillation gave the cyanohydrin boiling at  $130^{\circ}/60$  mm., yield 56 g.

*Ethyl  $\alpha\beta$ -Dimethylacrylate.*—Methyl ethyl ketone cyanohydrin (72 g.), dry ether (215 c.c.) and dry pyridine (200 c.c.) were taken in a litre three-necked flask provided with a mercury-sealed stirrer, a dropping funnel and a reflux condenser. The contents were cooled in ice and stirred vigorously while thionyl chloride (80 c.c.) was added through the dropping funnel during 3 hours. The stirring was continued for 15 minutes after the addition was complete. The flask was then heated to  $50^{\circ}$  for 3 hours. During this time the reaction mixture was stirred occasionally. The product was finally decomposed with powdered ice and the ethereal layer separated. The aqueous portion was extracted several times with ether. The ether solution was washed with dilute hydrochloric acid, then with dilute caustic soda solution and finally with water. It was then dried over anhydrous calcium chloride and the solvent evaporated. The residual liquid on distillation gave the unsaturated nitrile (45.5 g.) boiling at  $90^{\circ}/60$  mm.

The unsaturated nitrile, thus obtained, was heated in an oil-bath at  $140-150^{\circ}$  for 20 hours with absolute alcohol (75 c.c.), rectified spirit (75 c.c.) and concentrated sulphuric acid (64 c.c.). It was then diluted with water and extracted several times with ether. The ethereal extract was washed with dilute sodium carbonate solution and water. It was then dried over anhydrous calcium chloride and fractionated when ethyl  $\alpha\beta$ -dimethylacrylate was obtained as a

colourless liquid with a characteristic odour boiling at  $140^{\circ}$ - $145^{\circ}$ , yield, 32.5 g. Some unesterified acid can be recovered from the sodium carbonate extract.

*Ethyl  $\alpha\beta$ -Dimethyl- $\gamma$ -cyanopentane- $\alpha\gamma$ -tricarboxylate* (IV, R=Me).—Ethyl cyanoacetate (22.6 g.) was added to an ice-cold solution of sodium (4.6 g.) in absolute alcohol (75 c.c.). Ethyl  $\alpha\beta$ -dimethylacrylate (25.6 g.) was then added and it was refluxed on the water-bath for 14 hours. The dark coloured solution was cooled in ice and ethyl  $\beta$ -chloropropionate (27.4 g.) was added drop by drop, and kept overnight. The reaction was completed by heating on the water-bath for 6 hours. When cold it was diluted with ether. The ethereal solution was washed, dried and the ether evaporated. The *cianoester* (IV, R=Me) was obtained as a colourless oil boiling at  $200^{\circ}$ - $204^{\circ}$ /6mm., yield 46 g. (Found: C, 60.3; H, 7.8.  $C_{17}H_{27}O_6N$  requires C, 59.8; H, 7.9 per cent).

*Ethyl  $\alpha\beta$ -Dimethylpentane- $\alpha\gamma$ -tricarboxylate* (III,  $R_1$ =Me;  $R_2$ =H).—The above cyanoester (45 g.) was dissolved in concentrated sulphuric acid (52 c.c.) and then diluted with water (63 c.c.). It was heated on a sand-bath for 40 hours and then diluted with water, saturated with salt and extracted with ether. The residue (30 g.), obtained on evaporation of the ether, was esterified by the alcohol-vapour method. *Ethyl  $\alpha\beta$ -dimethylpentane- $\alpha\gamma$ -tricarboxylate* was obtained as a colourless mobile liquid boiling at  $178^{\circ}$ /7 mm., yield 29 g. (Found: C, 60.5; H, 8.7.  $C_{16}H_{26}O_6$  requires C, 60.7; H, 8.8 per cent).

*Ethyl 2:3-Dimethylcyclohexan-1-one-4:6-dicarboxylate* (V,  $R_1$ =Me;  $R_2$ =CO<sub>2</sub>Et; X=Et).—The triethyl ester (27.6 g.), obtained above, was heated on the water-bath with a fine suspension of sodium (3.7 g.) in dry benzene (66 c.c.). After an hour's heating a vigorous evolution of hydrogen started when the flask was removed from the water-bath. The reaction was finally completed by heating for 2 hours more. When cold the product was treated with ice-water and acidified with ice-cold dilute hydrochloric acid. The benzene layer was separated, washed and the benzene evaporated. The oil was then distilled under reduced pressure when it was obtained as a colourless oil, b. p.  $170^{\circ}$ /8 mm., yield 20 g. It gave a strong ferric reaction. (Found: C, 61.9; H, 8.1.  $C_{14}H_{22}O_5$  requires C, 62.2; H, 8.1 per cent).

*2:3-Dimethylcyclohexan-1-one-4-carboxylic acid* (V,  $R_1$ =Me;  $R_2$ =X=H) was prepared by hydrolysing the above  $\beta$ -ketonic ester (19 g.) with concentrated hydrochloric acid (37 c.c.) diluted with water (106 c.c.). The mixture was heated on the sand-bath for 6 hours, cooled, saturated with salt and extracted with ether. The residue, obtained on evaporation of the ether, was heated on the water-bath for an hour with caustic potash (8 g.) in 10 per cent aqueous alcoholic solution. It was worked up in the usual way and the crude keto-acid (11.5 g.) obtained was converted into the *semicarbazone*. It crystallises from water as a sandy white powder melting with decomposition at  $191^{\circ}$  and identical with the semicarbazone of the keto-acid by the rearrangement of santenonequinone (mixed m. p.). (Found: C, 52.6; H, 7.4.  $C_{10}H_{17}O_3N_3$  requires C, 52.8; H, 7.4 per cent).

The *pure* keto-acid was obtained by the hydrolysis of the semicarbazone with 10% hydrochloric acid. It crystallises from a mixture of benzene and petroleum ether, m. p.  $132^{\circ}$  and is identical with the keto-acid, obtained by the rearrangement of santenonequinone (mixed m. p.). (Found: C, 63.4; H, 8.2.  $C_9H_{14}O_3$  requires C, 63.5; H, 8.2 per cent).

The *ethyl ester* of the above keto-acid (2.5 g.) was prepared by heating it with 2 c.c. of alcoholic hydrogen chloride (saturated at  $0^{\circ}$ ) and absolute alcohol (20 c.c.) and working up in the usual manner. It was obtained as a colourless liquid, b. p.  $110^{\circ}$ /5mm., yield 2.5 g. (Found: C, 66.5; H, 9.1.  $C_{11}H_{18}O_3$  requires C, 66.6; H, 9.09 per cent).



The *semicarbazone* of the ethyl ester crystallises from dilute alcohol in colourless shining laminae, melting at  $187^{\circ}$  with decomposition. (Found: C, 56.1; H, 8.1.  $C_{12}H_{21}O_3N_3$  requires C, 56.4; H, 8.2 per cent).

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