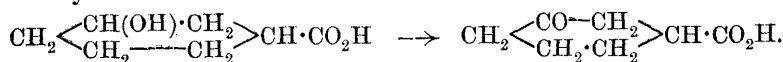


CCXX.—*Synthesis of cycloHexanone-3-carboxylic Acid.*

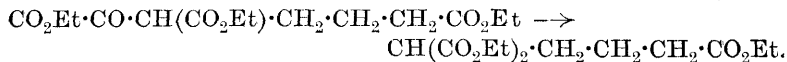
By MARY ELIZABETH DOBSON, JOHN FERNS, and  
WILLIAM HENRY PERKIN, jun.

THE synthesis of carvestrene (Perkin and Tattersall, *Trans.*, 1907, **91**, 480) had for its starting point *m*-hydroxybenzoic acid, which was reduced by sodium and alcohol to *cyclohexanol*-3-carboxylic acid, and the latter then converted into *cyclohexanone*-3-carboxylic acid by oxidation with chromic acid mixture:

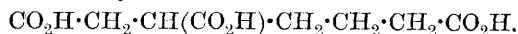


The yield of this ketonic acid was very unsatisfactory, and the preparation of the amount required for the synthesis of carvestrene proved to be so laborious that it was found impossible to investigate that important terpene and its derivatives in so thorough a manner as we had hoped to have done. In order, if possible, to overcome this difficulty, new experiments are being actively carried on, and the present communication deals with a series of reactions which have been undertaken with the object of synthesising *cyclohexanone*-3-carboxylic acid, and, although we have been successful in this, the process is, unfortunately, still not suitable for the preparation of large quantities of this acid. The various steps in the synthesis are the following.

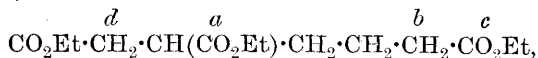
In the first place, ethyl oxaladipate is prepared by condensing ethyl oxalate with ethyl adipate in the presence of sodium ethoxide (compare Wislicenus and Schwanhäuser, *Annalen*, 1897, **297**, 110), and, on distilling this, it decomposes with elimination of carbon monoxide and formation of ethyl butane-*αδδ*-tricarboxylate:



The sodium derivative of the latter ester reacts readily with ethyl bromoacetate, with the formation of *ethyl pentane-αδδε-tetracarboxylate*,  $\text{CO}_2\text{Et·CH}_2\text{·C(CO}_2\text{Et)}_2\text{·CH}_2\text{·CH}_2\text{·CH}_2\text{·CO}_2\text{Et}$ , and, when the product of the hydrolysis of this ester is heated, it yields *pentane-αδε-tricarboxylic acid*,

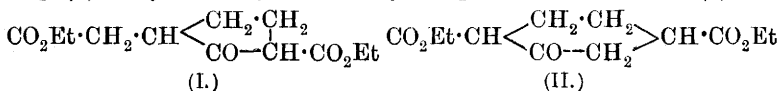


The next step was to investigate the action of sodium on the ester of this acid. When the formula of *ethyl pentane-αδε-tricarboxylate*,

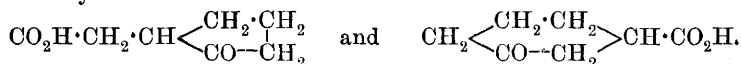


is examined, it is readily seen that condensation with elimination

of alcohol can take place either between the  $\text{CO}_2\text{Et}$  (a) and the  $\text{CH}_2$  (b) to yield ethyl 5-carboxycyclopentanone-2-acetate (I), or

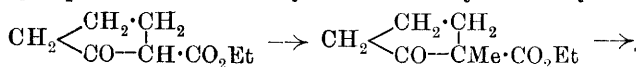


between the  $\text{CO}_2\text{Et}$  (c) and the  $\text{CH}_2$  (d), in which case ethyl cyclohexanone-3: 6-dicarboxylate (II) would be produced. On hydrolysis and elimination of carbon dioxide, the former would yield cyclopentanone-2-acetic acid, and the latter cyclohexanone-3-carboxylic acid:



Now, in condensations of this nature, where the two possibilities exist, the usual experience is that the five-carbon ring is almost invariably formed in preference to the six-carbon ring, and we were therefore greatly surprised when we found that the product of the action of sodium on ethyl pentane- $\alpha\delta\epsilon$ -tricarboxylate is evidently *ethyl cyclohexanone-3: 6-dicarboxylate*. This is proved by the fact that the ester actually obtained yielded, on hydrolysis and elimination of carbon dioxide, an acid melting at  $73-75^\circ$ , which was proved, by direct comparison with a specimen of the acid prepared from *m*-hydroxybenzoic acid by Perkin and Tattersall (*loc. cit.*), to be *cyclohexanone-3-carboxylic acid*. These experiments therefore constitute a synthesis of this important acid, but the process is very costly and the yield too small to make the synthesis, in the meantime, of practical importance.

This communication also contains an account of an attempt to convert ethyl cyclopentanone-2-carboxylate into ethyl 1-methylcyclopentan-2-one-1-carboxylate, and then into ethyl 1-methylcyclopentan-2-ol-1-carboxylate and ethyl 1-methyl- $\Delta^2$ -cyclopentene-



1-carboxylate, in order that the latter ester might be used in the further synthesis of terpenes containing a five-carbon ring (compare Haworth and Perkin, *Trans.*, 1908, **93**, 573):

#### EXPERIMENTAL.

##### *Ethyl Pentane- $\alpha\delta\epsilon$ -tetracarboxylate,* $\text{CO}_2\text{Et} \cdot \text{CH}_2 \cdot \text{C}(\text{CO}_2\text{Et})_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{Et}.$

As explained on p. 2010, this ester is obtained when ethyl bromoacetate reacts with the sodium derivative of ethyl butane-

$\alpha\delta\delta$ -tricarboxylate,  $\text{CH}(\text{CO}_2\text{Et})_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{Et}$ , an ester which we prepared in quantity by the method described by Wislicenus and Schwanhäuser (*loc. cit.*). Sodium (2.3 grams) was dissolved in absolute alcohol (40 grams), mixed with ethyl butane- $\alpha\delta\delta$ -tricarboxylate (27.4 grams) and ethyl bromoacetate (16.7 grams), and the whole heated in a reflux apparatus on the water-bath for two hours. The product was mixed with water, extracted with ether, the ethereal solution washed, dried, and evaporated, and the residual oil several times fractionated under diminished pressure, when a considerable quantity of a colourless oil distilled at  $210\text{--}212^\circ/10\text{ mm.}$ , and consisted of pure *ethyl pentane- $\alpha\delta\delta$ -tetracarboxylate*:

0.2112 gave 0.4371  $\text{CO}_2$  and 0.1519  $\text{H}_2\text{O}$ .  $\text{C}=56.4$ ;  $\text{H}=8.0$ .

$\text{C}_{17}\text{H}_{28}\text{O}_8$  requires  $\text{C}=56.7$ ;  $\text{H}=7.8$  per cent.

*Ethyl Pentane- $\alpha\delta\epsilon$ -tricarboxylate,*  
 $\text{CO}_2\text{Et} \cdot \text{CH}_2 \cdot \text{CH}(\text{CO}_2\text{Et}) \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{Et}.$

In order, in the first place, to obtain pentane- $\alpha\delta\epsilon$ -tricarboxylic acid, ethyl pentane- $\alpha\delta\delta\epsilon$ -tetracarboxylate was boiled with a mixture of three times its volume of concentrated hydrochloric acid, diluted with an equal volume of water, for seventeen hours in a reflux apparatus, the condenser of which was removed from time to time to allow alcohol to escape. The hydrochloric acid was then distilled off under diminished pressure, and the syrupy residue heated in an oil-bath until the evolution of carbon dioxide ceased. The crude pentane- $\alpha\delta\epsilon$ -tricarboxylic acid thus obtained was esterified by digesting with alcohol and sulphuric acid for several hours, the ester was then precipitated with water, extracted with ether, the ethereal solution washed with sodium carbonate, dried, and fractionated, when almost the whole quantity distilled at  $195\text{--}197^\circ/15\text{ mm.}$ , and consisted of pure *ethyl pentane- $\alpha\delta\epsilon$ -tricarboxylate*:

0.1502 gave 0.3212  $\text{CO}_2$  and 0.1134  $\text{H}_2\text{O}$ .  $\text{C}=58.3$ ;  $\text{H}=8.4$ .

$\text{C}_{14}\text{H}_{24}\text{O}_6$  requires  $\text{C}=58.3$ ;  $\text{H}=8.3$  per cent.

When this ester was digested with dilute hydrochloric acid, it was readily hydrolysed, and, after distilling off the hydrochloric acid under diminished pressure, a syrup remained which gradually crystallised.

The mass was left in contact with porous porcelain until quite dry, and then crystallised from a very little hydrochloric acid, in which the acid is very readily soluble. The following analyses were made with different preparations; the first was carried out with a specimen of the acid which had remained for some days simply exposed to the air, and the second with a specimen of the

acid which had been dried for twenty-four hours over sulphuric acid:

0.1135 gave 0.1890 CO<sub>2</sub> and 0.0640 H<sub>2</sub>O. C=45.4; H=6.3.

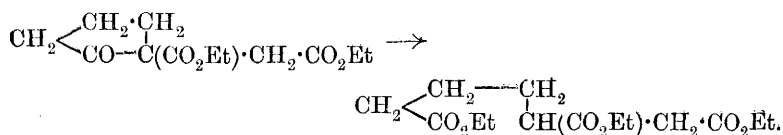
0.1260 „ 0.2100 CO<sub>2</sub> „ 0.0710 H<sub>2</sub>O. C=45.4; H=6.3.

C<sub>8</sub>H<sub>12</sub>O<sub>6</sub>·½H<sub>2</sub>O requires C=45.1; H=6.1 per cent.

It appears, therefore, from these analyses, that *pentane-αδε-tricarboxylic acid* crystallises from hydrochloric acid with ½H<sub>2</sub>O.

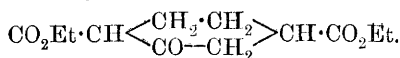
It crystallises in crusts, melts at about 96°, and, on cooling, sets to a resin which remains in that condition for months.

Ethyl pentane-αδε-tricarboxylate has been obtained by Kötze and Schüler (*Annalen*, 1906, **350**, 241) by treating the sodium derivative of ethyl cyclopentanone-2-carboxylate with ethyl bromoacetate and then hydrolysing the ethyl cyclopentanone-2-carboxylate-2-acetate thus produced with sodium ethoxide, when fission of the ring takes place according to the scheme:



These investigators give the boiling point of ethyl pentane-αδε-tricarboxylate as 188—189°/18 mm., which is rather lower than the boiling point (195—197°/15 mm.) recorded by us. They also hydrolysed the ester with hydrochloric acid, but were unable to obtain the acid in a crystalline condition; they, however, describe a crystalline anhydride, C<sub>8</sub>H<sub>10</sub>O<sub>5</sub>, which melted at 95°.

*Ethyl cycloHexanone-3: 6-dicarboxylate,*



This ester is produced when sodium reacts with ethyl pentane-αδε-tricarboxylate under the following conditions.

In a flask fitted with a ground-in condenser tube, sodium (4.7 grams) is melted under boiling toluene, vigorously shaken, and, when cold, the toluene is decanted from the “molecular sodium,” the latter washed with benzene, mixed with 150 c.c. of dry benzene, and then ethyl pentane αδε-tricarboxylate (30 grams) added, and the whole heated on the water-bath for three hours. The brown product is mixed with ether (400 c.c.) and excess of dilute hydrochloric acid, the ether-benzene solution well washed, dried, and the ether and benzene distilled off. The brown oil which remained was twice fractionated, when a good yield of a colourless oil was

obtained which distilled at 175—180°/20 mm., but apparently with slight decomposition, since the analytical results agreed only approximately with the theoretical:

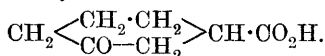
0·1655 gave 0·3524 CO<sub>2</sub> and 0·1201 H<sub>2</sub>O. C=58·1; H=8·1.

0·1096 „ 0·2335 CO<sub>2</sub> „ 0·0782 H<sub>2</sub>O. C=58·1; H=7·9.

C<sub>12</sub>H<sub>18</sub>O<sub>5</sub> requires C=59·5; H=7·5 per cent.

*Ethyl cyclohexanone-3: 6-dicarboxylate* has an odour somewhat resembling that of ethyl acetoacetate, and gives in alcoholic solution a purple coloration on the addition of ferric chloride.

*Synthesis of cycloHexanone-3-carboxylic Acid,*



As explained on p. 2011, this acid is produced when ethyl *cyclohexanone-3: 6-dicarboxylate* is hydrolysed with hydrochloric acid.

The crude ester is boiled in a reflux apparatus with a considerable quantity of 2 per cent. hydrochloric acid for about three days, and until a small quantity, after extraction with ether, gives no coloration with ferric chloride. The clear solution is saturated with ammonium sulphate, extracted many times with ether, the ethereal solution dried, evaporated, and the crude dark brown ketonic acid (20 grams) converted into the ester by leaving it in contact with alcoholic hydrogen chloride (75 c.c. of a 2 per cent. solution) at the ordinary temperature. After three or four days, the bulk of the alcohol is removed by distillation under diminished pressure, the residue mixed with water, extracted with ether, the ethereal solution well washed, dried, and evaporated, and the ester purified by distillation, when almost the whole quantity passes over at 135—137°/20 mm. (compare Perkin and Tattersall, *Trans.*, 1907, **91**, 491):

0·1086 gave 0·2565 CO<sub>2</sub> and 0·0842 H<sub>2</sub>O. C=64·1; H=8·6.

0·1019 „ 0·2372 CO<sub>2</sub> „ 0·0795 H<sub>2</sub>O. C=63·0; H=8·5.

C<sub>9</sub>H<sub>14</sub>O<sub>3</sub> requires C=63·5; H=8·2 per cent.

This ethyl *cyclohexanone-3-carboxylate* was digested with 50 c.c. of a 2·5 per cent. solution of hydrochloric acid until a clear solution resulted, ammonium sulphate was then added, and the whole very thoroughly extracted with ether. The ethereal extract, after drying and evaporating, yielded a viscid syrup, which distilled at 195—197°/20 mm., and the distillate gradually crystallised.

In contact with porous porcelain, traces of oily impurity were rapidly removed, and the residue separated from benzene in small, glistening prisms, which melted at 73—75°, whereas the melting

point of *cyclohexanone-3-carboxylic acid* is stated by Perkin and Tattersall (*loc. cit.*, p. 492) to be 75—76°:

0.1392 gave 0.3001 CO<sub>2</sub> and 0.0864 H<sub>2</sub>O. C=58.8; H=6.9.

C<sub>7</sub>H<sub>10</sub>O<sub>3</sub> requires C=59.1; H=7.0 per cent.

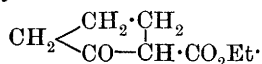
*The semicarbazone*.—When an aqueous solution of the acid was mixed with semicarbazide hydrochloride and sodium acetate there was no immediate precipitation of the semicarbazone, but, on long standing, this derivative separated as a sandy powder, which, after crystallisation from methyl alcohol, melted and decomposed at 183—184°:

0.0699 gave 12.7 c.c. N<sub>2</sub> at 14° and 767 mm. N=21.6.

C<sub>8</sub>H<sub>13</sub>O<sub>3</sub>N<sub>3</sub> requires N=21.2 per cent.

The properties of the ketonic acid are therefore exactly those of *cyclohexanone-3-carboxylic acid* described by Perkin and Tattersall (*loc. cit.*), and the identity of the specimens, prepared in such different ways, was confirmed by the fact that, when intimately mixed, there was no alteration in melting point.

*Ethyl cyclopentanone-2-carboxylate*,



This ester was first prepared by Dieckmann (*Ber.*, 1894, **27**, 103) by the action of sodium on ethyl adipate and a little alcohol at 120°, but, as the result of several experiments, we have found that the reaction is best carried out under the following conditions.

Sodium (11.5 grams) is melted under boiling toluene and vigorously shaken, the whole is then allowed to cool, the toluene decanted from the “molecular” sodium, and then a solution of ethyl adipate (50 grams) in dry benzene (100 c.c.) is added, and the whole heated on the water-bath in a reflux apparatus for two hours. The product is mixed with ether, decomposed with ice and dilute hydrochloric acid, the ether-benzene solution washed, dried, and evaporated, and the residual oil fractionated under diminished pressure, when almost the whole quantity distils constantly at 132°/30 mm. The distillate, which was obtained in a yield of 27 grams, gave a blue coloration when ferric chloride was added to its alcoholic solution:

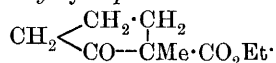
0.1302 gave 0.2924 CO<sub>2</sub> and 0.0913 H<sub>2</sub>O. C=61.3; H=7.8.

C<sub>8</sub>H<sub>12</sub>O<sub>3</sub> requires C=61.5; H=7.7 per cent.

Wislicenus and Schwanhäuser (*Annalen*, 1897, **297**, 112) state that ethyl *cyclopentanone-2-carboxylate* distils at 120°/22 mm. When this ester (25 grams) was added to a solution of magnesium methyl iodide (containing 7.7 grams of magnesium) a vigorous

action took place, and the yellow magnesium derivative, which first separated, soon became colourless. The product, isolated in the usual manner, and hydrolysed with alcoholic potassium hydroxide, yielded adipic acid, and there was no evidence that any hydroxymethyl acid had been produced. It is obvious, therefore, that ethyl *cyclopentanone-2-carboxylate* reacts with magnesium methyl iodide as an enolic modification.

*Ethyl 1-Methylcyclopentan-2-one-1-carboxylate,*



This ester has already been described by Bouveault (*Bull. Soc. chim.*, 1899, [iii], **21**, 1019), who obtained it from the sodium derivative of ethyl *cyclopentanone-2-carboxylate* by the action of methyl iodide, and he states that it distils at 108°/22 mm. We have prepared it in considerable quantities by the same process, and observed the somewhat higher boiling point, 120—122°/30 mm.:

0.126 gave 0.2932 CO<sub>2</sub> and 0.0918 H<sub>2</sub>O. C=63.5; H=8.1.

C<sub>9</sub>H<sub>14</sub>O<sub>3</sub> requires C=63.5; H=8.2 per cent.

Ethyl 1-methyl*cyclopentan-2-one-1-carboxylate* is a colourless oil with a pleasant odour; it gives no coloration with ferric chloride.

*Reduction with Sodium Amalgam.*—The results obtained in our experiments on the reduction of the above ketonic ester with sodium amalgam varied very much; in some cases the reduction appeared to proceed normally, with the formation of 1-methyl*cyclopentan-2-ol-1-carboxylic acid*, whilst, in other cases, the ketonic ester suffered hydrolysis with formation of methyladipic acid. On one occasion, an experiment, carried out under the following conditions, appeared to proceed normally. The pure ketonic ester (20 grams), dissolved in dilute alcohol, was treated in the cold with 1 kilo. of freshly prepared sodium amalgam (3 per cent.), hydrochloric acid being added from time to time in such a way that the solution was always nearly neutral. The product was acidified, saturated with ammonium sulphate, extracted twelve times on the machine, the extracts were combined, dried, evaporated, and the residue esterified by warming on the water-bath with alcoholic sulphuric acid (10 per cent.) for six hours. The ester, isolated in the usual manner, distilled at 158—160°/100 mm., and gave the following results, which agree fairly well with those required for ethyl 1-methyl*cyclopentan-2-ol-1-carboxylate*:

0.1721 gave 0.3926 CO<sub>2</sub> and 0.1411 H<sub>2</sub>O. C=62.3; H=9.1.

C<sub>9</sub>H<sub>16</sub>O<sub>3</sub> requires C=62.8; H=9.3 per cent.

When this ester was boiled for three hours with three times

its volume of acetic anhydride, an oil was obtained which distilled at  $147\text{--}151^\circ/40$  mm., and yielded numbers agreeing closely with those required for ethyl 2-acetoxy-1-methylcyclopentane-1-carboxylate:

0.1731 gave 0.3907  $\text{CO}_2$  and 0.1318  $\text{H}_2\text{O}$ .  $\text{C}=61.5$ ;  $\text{H}=8.5$ .

$\text{C}_{11}\text{H}_{18}\text{O}_4$  requires  $\text{C}=61.7$ ;  $\text{H}=8.4$  per cent.

Some of the ethyl 1-methylcyclopentan-2-ol-1-carboxylate was heated with two molecular proportions of phosphorus pentachloride for one and a-half hours on the sand-bath, and the product poured into alcohol. The ester thus obtained distilled at  $160\text{--}170^\circ/40$  mm., and, on analysis:

0.1696 gave 0.1504  $\text{AgCl}$ .  $\text{Cl}=21.9$ ,

whereas ethyl 2-chloro-1-methylcyclopentane-1-carboxylate contains 18.3 per cent. of chlorine. This chloro-ester proved to be remarkably stable, since it was scarcely attacked by boiling with diethylaniline, and, as all our other attempts to eliminate hydrogen chloride and to obtain the corresponding unsaturated ester were unavailing, the subject was not further investigated.

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