LXXX.—*Experiments on the Synthesis of Camphoric Acid. Part IV.* The Action of Sodium and Methyl Iodide on Ethyl Dimethylbutanetricarboxylate, $\text{CO}_2\text{Et}\cdot\text{CH}_2\cdot\text{CH}(\text{CO}_2\text{Et})\text{CMe}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$.*

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DURING the course of a series of experiments on the constitution of isocamphoronic acid (Trans., 1899, 75, 901; compare Trans., 1902, 81, 246), we gave a description of the synthesis and properties of $\beta\beta$ -dimethylbutane- $\alpha\gamma\delta$ -tricarboxylic acid,

This acid was, at that time, of special interest because Baeyer (*Ber.*, 1896, 29, 2780) had put forward the suggestion that the constitution of isocamphoronic acid was probably represented by this formula. But this acid interested us to an even greater extent for another reason, namely, on account of the possibility that it might prove to be a convenient starting point for the synthesis of camphoric acid.

Dieckmann (*Ber.*, 1894, 27, 103) had shown that sodium reacts with ethyl adipate with formation of the sodium derivative of ethyl β -ketopentamethylenecarboxylate,

* Part I was published in Trans., 1898, 73, 45; Part II, Trans., 1899, 75, 909; Part III, Trans., 1904, 85, 128.

Since, then, ethyl $\beta\beta$ -dimethylbutane- $\alpha\gamma\delta$ -tricarboxylate is a substitution derivative of ethyl adipate, it seemed likely that an analogous condensation might take place if it were treated with sodium under similar conditions. The problem would, however, in this case necessarily be a difficult and complicated one owing to the fact that this ester, unlike adipic ester, is unsymmetrical, that is, it contains two CH_2 -groups (*a* and *b*) which can react with the two carboxyethyl groups (*c* and *d*) in such a manner as to give rise to two different condensation products :

Such sodium derivatives might be expected to react readily with methyl iodide with formation of the two isomeric trimethylketopentamethylenedicarboxylic esters,

and the first of these is, obviously, nothing more nor less than the ester of ketocamphoric acid, and ought therefore to yield camphoric acid

if subjected to the action of suitable reducing agents.

When the experiment was instituted, it was found that the product of the action of sodium and then of methyl iodide on ethyl $\beta\beta$ -dimethylbutane- $\alpha\gamma\delta$ -tricarboxylate was in fact a *trimethylketopentamethylenedicarboxylic ester*, but the greatest difficulty was experienced in determining whether its constitution was that represented by formula I or formula II, and for this reason the research had to be set aside on more than one occasion.

Ultimately, however, the investigation of the behaviour of this ester on hydrolysis under certain definite conditions and the subsequent synthesis of the products formed during this hydrolysis furnished the

solution of the problem. When the keto-ester is hydrolysed, first with cold alcoholic potash and then by boiling dilute sulphuric acid, it yields three substances, namely, *A*, a tribasic acid, $C_{10}H_{16}O_6$, melting at 174° , which is readily soluble in water, *B*, a tribasic acid, $C_{10}H_{16}O_6$, which is formed in much smaller quantity, melts at 204° , and is more sparingly soluble in water, and *C*, a keto-acid, $C_{10}H_{16}O_6$, of melting point 110° , which is present only in minute quantities, and can be separated from the acids *A* and *B* owing to the fact that it is volatile in steam. If we confine our attention in the meantime to the tribasic acid *A*, of melting point 174° , which constitutes the principal product of the reaction, it is evident that this acid is produced from ethyl trimethylketopentamethylenedicarboxylate according to the equation

and, further, that the third molecule of water has brought about the disruption of the trimethylketopentamethylene ring.

This disruption will take place (as, for example, in the case of methylacetoacetic ester) at the keto-group, and, since the acid of melting point 174° is tribasic, does not eliminate carbon dioxide on heating, and is derived from either formula I or II (see above), it follows that its constitution must be represented by one of the formulæ $CO_2H \cdot CH_2 \cdot CH(CO_2H)CMe_2 \cdot CHMe \cdot CO_2H$ (from I), or $CO_2H \cdot CH_2 \cdot CMe_2 \cdot CH(CO_2H)CHMe \cdot CO_2H$ (from II).

The only really satisfactory way of deciding between these formulæ was to prepare one of these acids synthetically and, after many failures, this was ultimately accomplished by the following process.

Ethyl $\beta\beta$ -dimethylacrylate, $CO_2Et \cdot CH : CMe_2$, was digested in alcoholic solution with the sodium derivative of ethyl cyanoacetate, $CN \cdot CHNa \cdot CO_2Et$, when direct addition took place, with the result that the sodium derivative of ethyl α -cyano- $\beta\beta$ -dimethylglutarate,

was formed (compare *Trans.*, 1899, **75**, 63). When this sodium derivative was treated with ethyl bromopropionate, it yielded *ethyl $\alpha\gamma$ -trimethyl- β -cyanobutane- $\alpha\beta\delta$ -tricarboxylate*,

Hydrolysis with caustic potash converted this ester into *$\alpha\gamma$ -trimethylbutane- $\alpha\beta\delta$ -tetracarboxylic acid*, which melts at 186° and, when heated at 200° , is decomposed with elimination of carbon dioxide and formation of *$\alpha\gamma$ -trimethylbutane- $\alpha\beta\delta$ -tricarboxylic acid*,

This acid melted at 174° and was shown, by careful comparison, to

be identical with the acid *A* obtained by the hydrolysis of ethyl trimethylketopentamethylenedicarboxylate. Since, then, this synthesis proves that the acid *A* has the above constitution, it follows that the keto-ester must be represented by the formula

Ethyl 1:1:3-trimethyl-4-ketopentamethylene-2:3-dicarboxylate.

and it was therefore clearly impossible that camphoric acid could result from the reduction of this ester.

The constitution of the second tribasic acid (*B*) of melting point 204° could not be determined because of the very small quantity of material at our disposal. It is not improbable that it is the *trans*-modification of the acid *A*. On the other hand, it is possible that the product of the action of sodium and methyl iodide on ethyl dimethylbutanetricarboxylate may contain small quantities of the isomeric keto-ester represented by formula I (p. 779), in which case the acid *B* might have the constitution

The third substance, *C* (p. 780), is a keto-monobasic acid of the formula $\text{C}_{10}\text{H}_{16}\text{O}_3$, and yields a characteristic oxime and semicarbazone. The constitution of this interesting substance (which is isomeric with and closely allied in properties to pinonic acid) was at first very difficult to explain, but the method of its formation is probably a comparatively simple one. If the formula of ethyl trimethylketopentamethylenedicarboxylate (see above) is examined, it will be seen that it contains a methylene group which is adjacent to the keto-group, and therefore capable of undergoing condensation with one of the two carbethoxy-groups.

It is therefore not improbable that, during the action of the sodium and methyl iodide, internal condensation may take place to a small extent with the formation of a diketo-ester, the constitution of which would be represented by one of the formulæ

Such bridged-ring compounds would be decomposed on hydrolysis

with disruption of the bridge, and the resulting keto-monobasic acid, $C_{10}H_{16}O_3$, would then possess one of the following formulæ:

But a substance of the constitution represented by the second of these formulæ would decompose at once, with elimination of carbon dioxide, if it were distilled in a current of steam, and that formula cannot therefore represent the keto-acid of melting point 110° .

For this reason we have adopted the first formula for this acid, and have named it 1:1:3:5-tetramethyl-4-ketopentamethylene-2-carboxylic acid (p. 787).

Lastly, we have submitted ethyl trimethylketopentamethylenedicarboxylate to reduction and find that, when treated with sodium amalgam under the conditions described on p. 789, it is reduced with formation of 1:1:3-trimethyl-4-hydroxypentamethylene-2:3-dicarboxylic acid.

This hydroxy-acid is a syrup which is readily converted into its anhydride (or lactone?) on distillation. It is reduced only with great difficulty, but when treated first with hydriodic acid and then with sodium amalgam in the manner described on p. 790, the hydroxyl group is ultimately replaced by hydrogen and 1:1:3-trimethylpentamethylene-2:3-dicarboxylic acid,

is formed. Although purified as far as possible by conversion into the anhydride and methyl ester, both of which distil without decomposition, the acid has, so far, not been obtained in a crystalline condition. This may be due in part to the syrupy acid consisting of *cis*- and *trans*-modifications, but there is also reason to suspect that slight impurities were present which may have been sufficient to retard or prevent crystallisation.

A careful investigation of the acid and its derivatives would be of considerable interest on account of its close relationship to camphoric acid.

EXPERIMENTAL.

Ethyl 1 : 1 : 3-Trimethyl-4-ketopentamethylene-2 : 3-dicarboxylate.

The ethyl dimethylbutanetricarboxylate required for these experiments was prepared by the process described in detail in a previous communication (Trans., 1899, 75, 902), and the treatment with sodium and methyl iodide was carried out under the following conditions.

Sodium (7 grams) was melted under boiling toluene (50 c.c.) and vigorously shaken in a closed flask so as to bring the sodium into as fine a state of division as possible, the whole being then allowed to cool. The ester (45 grams) was dissolved in toluene (150 c.c.) in a large flask connected with a reflux apparatus, the finely-divided sodium was added all at once, and the flask heated on the sand-bath until action just commenced. The sand-bath was then removed and the violent reaction allowed to proceed; when this slackened, the heating was repeated for about one hour and until the whole of the sodium had disappeared. The product was cooled in ice-water and methyl iodide (50 grams) added through the condenser tube in small quantities at a time, when a vigorous decomposition set in with separation of sodium iodide. After all the iodide had been added, the mass was mixed with methyl alcohol (50 c.c.) and heated on the water-bath for one hour to complete the decomposition.

Water and ether were then added, the oily ethereal layer separated, washed well with water and sodium carbonate,* dried over calcium chloride and evaporated, and the residual oil fractionated under a pressure of 60 mm. As soon as the toluene had passed over, the thermometer rose rapidly to 190°, between which temperature and 220° the product of the reaction passed over.† On refractionation, a

* The sodium carbonate extract always yielded a thick oil when it was acidified and extracted with ether. This was esterified with alcohol and sulphuric acid and found to consist of a mixture of ethyl trimethylketopentamethylenedicarboxylate and unchanged ethyl dimethylbutanetricarboxylate, as well as a very thick oil of high boiling point which was not investigated.

† During this operation, a small quantity of oil of lower boiling point is always obtained. This was gradually collected and carefully fractionated under the ordinary pressure, when it distilled constantly at 197—200° and yielded the following results on analysis :

0.1566 gave 0.3248 CO₂ and 0.1260 H₂O. C = 59.7 ; H = 8.9.

C₁₀H₁₈O₄ requires C = 59.5 ; H = 8.9 per cent.

Since this ester yielded ββ-dimethylglutaric acid on hydrolysis, it is probably the

nearly colourless oil (20 grams) was obtained which distilled at 200—205° (60 mm.).

0.1945 gave 0.4386 CO₂ and 0.144 H₂O. C = 61.5; H = 8.3.

0.2072 „ 0.4701 CO₂ „ 0.1531 H₂O. C = 61.9; H = 8.2.

C₁₄H₂₂O₅ requires C = 62.2; H = 8.2 per cent.

Ethyl 1:1:3-trimethyl-4-ketopentamethylene-2:3-dicarboxylate is a pale yellow oil which, when pure, may be distilled in small quantities at the ordinary pressure almost without decomposition. Its alcoholic solution gives no coloration with ferric chloride, an important fact, since it shows that the action of the methyl iodide in the above synthesis had been complete and the product did not contain any of the corresponding dimethyl derivative.

Action of Phosphorus Pentachloride on the Keto-ester.—The pure ester (20 grams) was mixed with phosphorus pentachloride (25 grams), when little action took place at the ordinary temperature but, on heating on the water-bath, decomposition set in and a good deal of hydrogen chloride was evolved. As soon as the pentachloride had completely dissolved, the whole was heated to boiling for ten minutes and poured into alcohol. After remaining overnight, water was added, the product was extracted in the usual way and fractionated under reduced pressure, when a considerable quantity of oil was obtained which distilled at 192—194° (35 mm.) and gave the following results on analysis:

0.2107 gave 0.4565 CO₂ and 0.1510 H₂O. C = 58.7; H = 7.9.

0.3085 „ 0.1438 AgCl. Cl = 11.7.

C₁₄H₂₁ClO₄ requires C = 58.2; H = 7.3; Cl = 12.3 per cent.

This ester is therefore *ethyl 1:1:3-trimethyl-4-chlorocyclopentene-dicarboxylate*,

Many attempts were made with the object of reducing this ester to the corresponding trimethylcyclopentenedicarboxylic acid, but were all unsuccessful, principally because the chlorine atom is very firmly bound and not easily replaced by treatment with reducing agents.

Hydrolysis of Ethyl Trimethylketopentamethylenedicarboxylate.

When this ester was mixed with dilute methyl-alcoholic potash, a deep yellow solution was produced, and, on boiling, potassium carbonate methyl ethyl ester of this acid, namely, CO₂Me·CH₂·CMe₂·CH₂·CO₂Et, a substance which must have been produced during the vigorous action described above by a curious decomposition of some of the ethyl dimethylbutanetricarboxylate employed.

separated in quantity. After adding water and filtering from a little neutral oil, the alkaline solution was evaporated until free from alcohol and acidified with hydrochloric acid.

The thick, pale yellow oil which separated was extracted with ether, the ethereal solution washed with water, dried over calcium chloride, and evaporated, when a syrup remained, the aqueous solution of which gave no precipitate with semicarbazide hydrochloride and sodium acetate. Since the oil showed no signs of crystallising, it was dissolved in boiling water, mixed with a slight excess of barium hydroxide, and the excess removed by passing carbon dioxide.

The barium carbonate carried down with it a little coloured impurity and, after filtering and acidifying and extracting with ether, a nearly colourless syrup was obtained which was left for some days over sulphuric acid in an evacuated desiccator and analysed:

0.153 gave 0.3186 CO_2 and 0.1139 H_2O . $\text{C} = 56.8$; $\text{H} = 8.3$.

$\text{C}_9\text{H}_{16}\text{O}_4$ requires $\text{C} = 57.4$; $\text{H} = 8.5$ per cent.

The *silver* salt was also prepared and analysed:

0.2172 gave 0.1149 Ag. $\text{Ag} = 52.9$.

$\text{C}_9\text{H}_{14}\text{Ag}_2\text{O}_4$ requires $\text{Ag} = 53.7$ per cent.

The acid which might be expected to result from the hydrolysis of ethyl trimethylketopentamethylenedicarboxylate under the above conditions is α -ethyl $\beta\beta$ -dimethylglutaric acid,

one of the acids of the formula $\text{C}_9\text{H}_{16}\text{O}_4$ which does not appear to have been prepared. This acid might, like the isomeric α -ethylpimelic acid (Crossley and Perkin, *Trans*, 1894, **65**, 990), be syrupy, but more probably a slight impurity, indicated by the results of analysis, prevented the syrup from crystallising. A second series of experiments on the hydrolysis of the keto-ester, carried out under quite different conditions, gave much more satisfactory results.

The ester (27 grams) was mixed with methyl-alcoholic potash (17 grams KOH) at 0° , and, after remaining overnight, the product was acidified with a large excess of dilute sulphuric acid (20 per cent.) and distilled in steam until four litres of distillate (A) had collected. The sulphuric acid in the residue was exactly removed by means of baryta water, the filtrate from the barium sulphate evaporated to a small bulk and mixed with an equal volume of strong hydrochloric acid, when a considerable quantity of a crystalline substance gradually separated. This was collected at the pump and several times fractionally crystallised from hydrochloric acid, by which means it was separated into a large proportion of an acid of melting point 172 — 174° and a small proportion of a much less soluble acid of melting point

204°. As explained in the introduction (p. 780), the acid of melting point 172—174°* is $\alpha\gamma\gamma$ -trimethylbutane- $\alpha\beta\delta$ -tricarboxylic acid,

and is identical with the acid of this constitution which was subsequently synthesised by the process described on p. 794.

0.1689 gave 0.3216 CO_2 and 0.1078 H_2O . C = 51.9; H = 7.1.

0.1185 „ 0.2250 CO_2 „ 0.0752 H_2O . C = 51.8; H = 7.0.

$\text{C}_{10}\text{H}_{16}\text{O}_6$ requires C = 51.7; H = 6.9 per cent.

When titrated with decinormal caustic soda solution, it was found that 0.2311 required for neutralisation 0.118 NaOH, whereas this amount of a tribasic acid, $\text{C}_{10}\text{H}_{16}\text{O}_6$, should neutralise 0.119 NaOH.

The silver salt, $\text{C}_{10}\text{H}_{13}\text{Ag}_3\text{O}_6$, was obtained from the ammonium salt by precipitation with silver nitrate as a white, amorphous powder.

0.2441 gave 0.1425 Ag. Ag = 58.4.

$\text{C}_{10}\text{H}_{13}\text{Ag}_3\text{O}_6$ requires Ag = 58.6 per cent.

Anhydrotrimethylbutanetricarboxylic acid,

is formed when the acid is boiled with acetyl chloride until solution is complete and the evolution of hydrogen chloride has ceased.

The product is evaporated on the water-bath and the residue left over solid potash until the syrup has crystallised. The solid mass is digested with a little boiling benzene, which dissolves the anhydro-acid, but in which any unchanged acid is very sparingly soluble, and the anhydro-acid then separates from the concentrated filtrate in small prisms which melt at about 105—107°.

0.1504 gave 0.3116 CO_2 and 0.0911 H_2O . C = 56.5; H = 6.7.

0.1359 „ 0.2800 CO_2 „ 0.0819 H_2O . C = 56.2; H = 6.7.

$\text{C}_{10}\text{H}_{14}\text{O}_5$ requires C = 56.1; H = 6.5 per cent.

Anhydrotrimethylbutanetricarboxylic acid dissolves readily in boiling water and, if the solution is evaporated to a small bulk, mixed with an equal volume of hydrochloric acid, and allowed to cool slowly, small, glistening crystals separate which melt with decomposition at 180°. Although the melting point of this acid is higher than that of the specimen from which the anhydro-acid had been prepared, there can be no doubt that they have the same constitution, since the melting point of the mixed acids was found to be 174—175°.

* This melting point was unchanged by further recrystallisation from hydrochloric acid, and it was not until the anhydro-acid (see below) had been prepared and reconverted into the acid that the melting point rose to 180°.

Examination of the Acid B, of Melting Point 204°.

This acid is formed only in very small quantities when ethyl trimethylketopentamethylenedicarboxylate is hydrolysed under the conditions described on p. 785. Fortunately it is much less soluble in water than the acid of melting point 174°, otherwise it might have escaped detection. It separates from water as a sandy powder which, under the microscope, is seen to consist of warty nodules.

0.1192 gave 0.2256 CO₂ and 0.0756 H₂O. C = 51.6 ; H = 7.1.

0.1492 „ 0.2817 CO₂ „ 0.0943 H₂O. C = 51.5 ; H = 7.0.

C₁₀H₁₆O₆ requires C = 51.7 ; H = 7.0 per cent.

When rapidly heated, this acid softens at 200° and melts at 204° ; it is almost insoluble in acetyl chloride even on boiling, but it dissolves in hot acetic anhydride, and, if the solution is boiled for a few minutes and evaporated, a thick gum remains which has the properties of a double anhydride of the acid and acetic acid.

It is suggested in the introduction (p. 781) that this acid may be the trans-modification of $\alpha\gamma$ -trimethylbutane- $\alpha\beta\delta$ -tricarboxylic acid, but no experimental evidence bearing on this point could be obtained. That the acid is tribasic is indicated by the following titration, which, however, had to be carried out with a specimen of the acid which was not quite pure and melted at 194–197° : 0.1116 required for neutralisation, 0.056 NaOH, whereas this amount of a tribasic acid, C₁₀H₁₆O₆, should neutralise 0.058 NaOH.

1 : 1 : 3 : 5-Tetramethyl-4-ketopentamethylene-2 carboxylic Acid,

During the experiments on the hydrolysis of ethyl trimethylketopentamethylenedicarboxylate, about 20 litres of the steam distillate (A, p. 785) had accumulated. The clear liquid was saturated with salt and extracted three times with ether, the ethereal solution dried over calcium chloride and evaporated, when about 6 grams of a colourless syrup were obtained which, after remaining for several months over sulphuric acid, became semi-solid. In contact with porous porcelain, the oily impurity was gradually absorbed and the dry residue, after digesting in aqueous solution with animal charcoal, crystallised from water in beautiful, colourless prisms of melting point 110°.

0.1584 gave 0.3736 CO_2 and 0.1292 H_2O . $\text{C} = 64.7$; $\text{H} = 9.1$.

0.1630 „ 0.3884 CO_2 „ 0.1278 H_2O . $\text{C} = 65.2$; $\text{H} = 8.7$.

$\text{C}_{10}\text{H}_{16}\text{O}_8$ requires $\text{C} = 65.2$; $\text{H} = 8.7$ per cent.

The method of preparation and properties of this interesting substance point to the probability of its being a tetramethylketopentamethylenecarboxylic acid of the constitution represented at the head of this section (see also p. 782).

The basicity of the acid was determined by titration with decinormal caustic soda, when 0.1890 neutralised 0.0408 NaOH , whereas this amount of a monobasic acid, $\text{C}_{10}\text{H}_{16}\text{O}_8$, should neutralise 0.0411 NaOH .

The *oxime*, $\text{C}_8\text{H}_{15}(\text{CO}_2\text{H})\text{C}:\text{N}:\text{OH}$. In order to prepare this derivative, the keto-acid is dissolved in a considerable excess of caustic potash and mixed with excess of hydroxylamine hydrochloride.

After twenty-four hours, the product is acidified with hydrochloric acid, the viscid mass collected, and washed with water, in which it is sparingly soluble. The most satisfactory way of recrystallising it is to dissolve the substance in methyl alcohol and, after diluting with water, to boil off the methyl alcohol and then stir the solution vigorously as it cools. The oxime then separates as a heavy, granular, crystalline powder which softens at 170° and melts at about 180° with decomposition.

0.1920 gave 11.3 c.c. of nitrogen at 17° and 769 mm. $\text{N} = 6.9$.

$\text{C}_{10}\text{H}_{17}\text{O}_3\text{N}$ requires $\text{N} = 7.0$ per cent.

The *semicarbazone*, $\text{C}_8\text{H}_{15}(\text{CO}_2\text{H})\text{C}:\text{N}_2\text{H}:\text{CO}:\text{NH}_2$, separates in colourless plates when the aqueous solution of the keto-acid is warmed with semicarbazide hydrochloride and sodium acetate, and may be purified by recrystallisation from much alcohol.

0.1044 gave 15.9 c.c. of nitrogen at 14° and 764 mm. $\text{N} = 17.9$.

$\text{C}_{11}\text{H}_{19}\text{O}_3\text{N}_3$ requires $\text{N} = 17.4$ per cent.

This *semicarbazone* melts at about 215 — 217° with decomposition, and is very sparingly soluble even in boiling water. It separates from boiling alcohol or dilute acetic acid in well-defined, four-sided plates with bevelled edges.

1 : 1 : 3-Trimethyl-4-hydroxypentamethylene-2 : 3-dicarboxylic Acid,

In preparing this acid, pure ethyl trimethylketopentamethylenedicarboxylate (10 grams) was dissolved in alcohol and mixed with water until a faint turbidity was produced; the solution was then treated, in a porcelain beaker fitted with a mechanical stirrer, with five times the theoretical quantity of 3 per cent. sodium amalgam, the temperature being kept below 10° and a rapid stream of carbon dioxide passed during the operation. The product which, owing to the separation of sodium bicarbonate, was semi-solid, was extracted with ether, when 8 grams of oil were obtained, showing that little hydrolysis had taken place. This oil, together with that obtained by acidifying the sodium bicarbonate and extracting with ether, was again reduced exactly as before and subsequently hydrolysed by boiling with excess of methylalcoholic potash (10 grams KOH); the solution was then diluted with water, evaporated until free from methyl alcohol, acidified, and extracted with ether. After drying over calcium chloride and evaporating, a syrup was obtained which consisted, as analysis showed, of the almost pure hydroxy-acid. This was esterified by dissolving it in alcohol (4 vols.) and sulphuric acid (1 vol.), and after standing for three days water was added, the oil extracted with ether, washed well with sodium carbonate (which extracts a considerable quantity of acid-ester), and dried over calcium chloride.

The ethereal solution was then evaporated and the ester purified by fractionation under reduced pressure, when almost the whole quantity passed over at $194-196^\circ$ (30 mm.). Two different preparations gave the following results on analysis:

0.1548 gave 0.3451 CO_2 and 0.1244 H_2O . C = 60.8; H = 8.9.

0.1772 „ 0.3974 CO_2 „ 0.1428 H_2O . C = 61.2; H = 8.9.

$\text{C}_{14}\text{H}_{24}\text{O}_5$ requires C = 61.7; H = 8.8 per cent.

The ester was now hydrolysed by boiling with excess of methylalcoholic potash, the product repeatedly evaporated with water so as to completely remove the methyl alcohol, acidified, and extracted twice with pure ether. The ethereal solution was then dried over calcium chloride, evaporated, and the syrupy hydroxy-acid left over sulphuric acid in an evacuated desiccator for several days.

0.1568 gave 0.3198 CO_2 and 0.1128 H_2O . $\text{C} = 55.6$; $\text{H} = 7.9$.

0.1725 „ 0.3522 CO_2 „ 0.1220 H_2O . $\text{C} = 55.7$; $\text{H} = 7.8$.

$\text{C}_{10}\text{H}_{16}\text{O}_5$ requires $\text{C} = 55.5$; $\text{H} = 7.4$ per cent.

Trimethylhydroxypentamethylenedicarboxylic acid is readily soluble in water, and the solution, after neutralising with sodium carbonate, is stable to permanganate. The basicity of the acid was determined by titration with decinormal caustic soda, when 0.4117 required for neutralisation 0.151 NaOH , whereas this amount of a dibasic acid, $\text{C}_{10}\text{H}_{16}\text{O}_5$, should neutralise 0.152 NaOH .

When the acid is distilled under the ordinary pressure, almost the whole quantity passes over at $297\text{--}303^\circ$ as a pale yellow syrup which consists for the most part of the anhydride (or lactone?) of the acid, since the following results were obtained on analysis:

0.1720 gave 0.3818 CO_2 and 0.1178 H_2O . $\text{C} = 60.5$; $\text{H} = 7.6$.

$\text{C}_{10}\text{H}_{14}\text{O}_4$ requires $\text{C} = 60.6$; $\text{H} = 7.1$ per cent.

When, however, the syrup was dissolved in sodium carbonate, it readily reduced permanganate, a behaviour which indicates that, during distillation, some unsaturated acid had been produced.

The hydroxy-acid is not readily attacked by reagents, and, although a large number of experiments were made with the object of converting it into the corresponding chloro- and bromo-acids by the action of phosphorus pentachloride or pentabromide under very varied conditions, no definite products could be isolated.

1 : 1 : 3-*Trimethylpentamethylene-2 : 3-dicarboxylic Acid*,

This interesting acid, isomeric with camphoric acid, was obtained when trimethylhydroxypentamethylenedicarboxylic acid was reduced under the following conditions. The pure hydroxy-acid was heated in a sealed tube with fuming hydriodic acid and amorphous phosphorus for four hours at 130° and four hours at $140\text{--}145^\circ$. The product was diluted with water, extracted with ether, and the syrup, which remained after evaporating the ether and which contained iodine, was dissolved in dilute sodium carbonate and treated with a large excess of sodium amalgam, at first in the cold and then on the water-bath.

Since even after this the reduction was not complete, the whole process was repeated, and the resulting acid dissolved in sodium carbonate and oxidised with permanganate at 0° until the colour remained for ten minutes. The acid was again extracted and distilled,

when a considerable quantity of a pale yellow oil was collected at 285—295°, which gave on analysis numbers agreeing approximately with those required for the *anhydride* of *trimethylpentamethylenedicarboxylic acid*.

0.1471 gave 0.3505 CO_2 and 0.1058 H_2O . $\text{C} = 65.0$; $\text{H} = 8.0$.

$\text{C}_{10}\text{H}_{14}\text{O}_3$ requires $\text{C} = 65.9$; $\text{H} = 7.7$ per cent.

The anhydride was, however, not pure, since when boiled with water a small quantity of a neutral oil smelling of peppermint remained undissolved. This was removed by filtration through wet paper and the filtrate extracted with pure ether. The ethereal solution was carefully dried over calcium chloride and evaporated, but the almost colourless syrup, even after remaining for fourteen days over sulphuric acid in an evacuated desiccator, showed no signs of crystallisation.

0.2187 gave 0.4793 CO_2 and 0.1591 H_2O . $\text{C} = 59.8$; $\text{H} = 8.1$.

0.1693 „ 0.3708 CO_2 „ 0.1236 H_2O . $\text{C} = 59.7$; $\text{H} = 8.1$.

$\text{C}_{10}\text{H}_{16}\text{O}_4$ requires $\text{C} = 60.0$; $\text{H} = 8.0$ per cent.

Although these numbers agree so closely with those required for *trimethylpentamethylenedicarboxylic acid*, the acid is nevertheless not quite pure, as was shown by the results obtained on titration with decinormal sodium hydrate and by the analysis of the silver salt. On titration, 0.2750 of the syrupy acid required for neutralisation 0.105 NaOH, whereas this amount of a dibasic acid, $\text{C}_{10}\text{H}_{16}\text{O}_4$, should have neutralised 0.110 NaOH.

The *silver* salt, prepared by adding silver nitrate to a slightly alkaline solution of the ammonium salt, gave the following results on analysis :

0.3345 gave 0.1721 Ag. $\text{Ag} = 51.4$.

$\text{C}_{10}\text{H}_{14}\text{O}_4\text{Ag}_2$ requires $\text{Ag} = 52.2$.

The remainder of the acid (8 grams) was digested with methyl alcohol and sulphuric acid and the ester isolated in the usual manner. The *methyl trimethylpentamethylenedicarboxylate* thus obtained distilled at 145° (13 mm.).

0.1504 gave 0.3465 CO_2 and 0.1215 H_2O . $\text{C} = 62.9$; $\text{H} = 9.0$.

$\text{C}_{12}\text{H}_{20}\text{O}_4$ requires $\text{C} = 63.2$; $\text{H} = 8.8$ per cent.

This ester was hydrolysed with methyl-alcoholic potash, but although the acid again gave good results on analysis, the syrup did not show any signs of crystallising.*

* Since this was written the acid has commenced to crystallise.

The Action of Ethyl α -Bromopropionate on the Sodium Derivative of Ethyl α -Cyano- $\beta\beta$ -dimethylglutarate.

The sodium derivative of ethyl α -cyano- $\beta\beta$ -dimethylglutarate required for this synthesis was prepared by condensing the sodium derivative of ethyl cyanoacetate with ethyl $\beta\beta$ -dimethylacrylate. Sodium (25 grams) was dissolved in alcohol (300 grams), mixed with ethyl cyanoacetate (113 grams), and, after cooling well, ethyl dimethylacrylate (128 grams) was added and the whole heated on the water-bath for six hours. The condensation between the sodium derivative formed and ethyl α -bromopropionate was effected by cautiously adding 200 grams of the bromo-ester, care being taken that the mixture was kept well cooled during the addition. The mixture was then left for twenty-four hours in running water, and finally heated on the water-bath for two hours. The product was isolated by adding water, extracting with ether, washing the ethereal solution with water and dilute sodium carbonate, drying over calcium chloride, and distilling off the ether. The oily residue was fractionated under diminished pressure and yielded 60 grams of a thick, colourless liquid which boiled constantly at 220—223° (20 mm.).

0.1446 gave 0.3098 CO₂ and 0.1018 H₂O. C = 58.4; H = 7.8.

0.1585 „ 0.3415 CO₂ „ 0.1099 H₂O. C = 58.7; H = 7.8.

0.2941 „ 11.4 c.c. of nitrogen at 16° and 758 mm. N = 4.6.

C₁₇H₂₇O₆N requires C = 59.8; H = 7.8; N = 4.1 per cent.

C₁₅H₂₃O₆N „ C = 57.5; H = 7.3; N = 4.5 „

These figures and the subsequent examination of the oil showed that it consisted of a mixture of about equal proportions of two ethyl salts of the formulæ C₁₇H₂₇O₆N and C₁₅H₂₃O₆N.

By a process of hydrolysis, described below, it was found to yield both $\alpha\gamma$ -trimethylbutane- $\alpha\beta\delta$ -tricarboxylic acid,

and the *trans*-modification of $\alpha\gamma$ -dimethyltricarballic acid,

and there can therefore be little doubt that it consisted of about equal proportions of *ethyl $\alpha\gamma$ -trimethyl- β -cyanobutane- $\alpha\beta\delta$ -tricarboxylate*, CO₂Et·CH₂·CMe₂·C(CN)(CO₂Et)CHMe·CO₂Et, formed by the direct action of ethyl α -bromopropionate on the sodium compound of derivative of ethyl α -cyano- $\beta\beta$ -dimethylglutarate, and *ethyl $\alpha\gamma$ -dimethyl- β -cyano-propene- $\alpha\beta\gamma$ -tricarboxylate*, formed by the action of two molecules of ethyl α -bromopropionate on the sodium derivative of ethyl cyanoacetate. This latter condensation can be readily understood when it

is remembered that the interaction of ethyl dimethylacrylate with the sodium derivative of ethyl cyanoacetate is never complete and that a considerable quantity of ethyl sodiocyanoacetate always remains unchanged.

This then subsequently reacts with ethyl α -bromopropionate and a series of decompositions represented by the following equations takes place (compare Zelinsky and Tschernoswitoff, *Ber.*, 1896, 29, 333):

*$\alpha\gamma\gamma$ -Trimethylbutane- $\alpha\beta\beta\delta$ -tetracarboxylic Acid,
 $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CMe}_2\cdot\text{C}(\text{CO}_2\text{H})_2\cdot\text{CHMe}\cdot\text{CO}_2\text{H}.$*

When the mixed ethyl salts just described (34 grams) were treated with caustic potash (20 grams) dissolved in methyl alcohol, a copious precipitate of a potassium salt (A) soon separated. Since, after standing for fifteen minutes, this separation appeared to be complete, the salt was collected, washed with a little methyl alcohol, and then, without further purification, transferred to a flask and boiled with a solution of caustic potash (15 grams) dissolved in methyl alcohol until the odour of ammonia ceased to be apparent. The acid was then isolated by evaporating until free from methyl alcohol, acidifying, saturating with ammonium sulphate, and extracting at least fifteen times with ether.

After drying over calcium chloride and evaporating, a gum remained which, when stirred with a little concentrated hydrochloric acid, deposited a crystalline acid in small quantity. It was subsequently found that the same acid could be more conveniently isolated, and in much larger quantity, by dissolving the gum in water, neutralising with ammonia, and adding an excess of copper sulphate solution.

The copper salt which was precipitated was collected, washed, suspended in water, and treated with sulphuretted hydrogen until completely decomposed. The filtrate from the copper sulphide yielded, on evaporation on the water-bath, a gum which, when stirred with an

equal quantity of concentrated hydrochloric acid, deposited a considerable amount of a solid acid. This was recrystallised from concentrated hydrochloric acid, from which it separated in microscopic prisms.

0.1442 gave 0.2495 CO_2 and 0.0806 H_2O . $\text{C} = 47.2$; $\text{H} = 6.2$.

0.1516 „ 0.2639 CO_2 „ 0.0822 H_2O . $\text{C} = 47.5$; $\text{H} = 6.0$.

$\text{C}_{11}\text{H}_{16}\text{O}_8$ requires $\text{C} = 47.8$; $\text{H} = 5.8$ per cent.

$\alpha\gamma\gamma$ -Trimethylbutane- $\alpha\beta\delta$ -tetracarboxylic acid melts at about 186° with evolution of gas and is readily soluble in water, but rather sparingly so in cold concentrated hydrochloric acid.

$\alpha\gamma\gamma$ -Trimethylbutane- $\alpha\beta\delta$ -tricarboxylic Acid,
 $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CMe}_2\cdot\text{CH}(\text{CO}_2\text{H})\text{CHMe}\cdot\text{CO}_2\text{H}.$

This acid was prepared by heating the tetracarboxylic acid, described above, in an oil-bath at about 200° until the evolution of gas had ceased. The gummy residue was dissolved in water, evaporated to a small bulk, mixed with concentrated hydrochloric acid and allowed to remain for twenty-four hours, when a considerable amount of a crystalline acid was found to have been deposited.

This was collected and recrystallised from concentrated hydrochloric acid, from which it separated in small needles which melted at 172 — 174° with decomposition, due to conversion into the anhydro-acid (p. 786).

0.1238 gave 0.2358 CO_2 and 0.0784 H_2O . $\text{C} = 51.9$; $\text{H} = 7.0$.

0.1547 „ 0.2941 CO_2 „ 0.0970 H_2O . $\text{C} = 51.8$; $\text{H} = 6.9$.

$\text{C}_{10}\text{H}_{16}\text{O}_6$ requires $\text{C} = 51.7$; $\text{H} = 7.0$ per cent.

The *silver* salt, $\text{C}_{10}\text{H}_{13}\text{Ag}_3\text{O}_6$, is precipitated as a white, amorphous powder when silver nitrate is added to a slightly alkaline solution of the ammonium salt.

0.2218 gave 0.1294 Ag. $\text{Ag} = 58.4$.

$\text{C}_{10}\text{H}_{13}\text{Ag}_3\text{O}_6$ requires $\text{Ag} = 58.6$ per cent.

It has already been shown that this trimethylbutanetricarboxylic acid is identical with one of the acids produced by the hydrolysis of trimethylketopentamethylenedicarboxylic acid with dilute sulphuric acid (p. 786).

trans- $\alpha\gamma$ -Dimethyltricarballic Acid,
 $\text{CHMe}(\text{CO}_2\text{H})\text{CH}(\text{CO}_2\text{H})\text{CHMe}\cdot\text{CO}_2\text{H}.$

The methyl-alcoholic filtrate from the potassium salt (p. 793) was evaporated on the water-bath until free from methyl alcohol, and the residue heated with three times its volume of concentrated hydrochloric acid on the sand-bath for twelve hours.

The clear solution was evaporated nearly to dryness on the water-bath and the partially solid residue, which contained large quantities of ammonium chloride, extracted with ether. The ether extract, dried over calcium chloride, yielded, on evaporation, an oil which rapidly crystallised. After remaining in contact with porous porcelain until quite free from oil, the residue was purified by two crystallisations from water, from which it separated in the form of small prisms which melted at 203° with decomposition into water and the anhydro-acid.

0.2365 gave 0.4084 CO_2 and 0.1286 H_2O . $\text{C} = 47.1$; $\text{H} = 6.0$.

$\text{C}_8\text{H}_{12}\text{O}_6$ requires $\text{C} = 47.1$; $\text{H} = 5.9$ per cent.

The *silver* salt, $\text{C}_8\text{H}_9\text{Ag}_3\text{O}_6$, obtained by adding silver nitrate to the ammonium salt, is a white, amorphous powder.

0.2192 gave 0.1348 Ag. $\text{Ag} = 61.5$.

$\text{C}_8\text{H}_9\text{O}_6\text{Ag}_3$ requires $\text{Ag} = 61.6$ per cent.

The *anhydro-acid* was prepared by boiling the acid with excess of acetyl chloride for fifteen minutes and then evaporating on the water-bath. It was purified by recrystallisation from a mixture of chloroform and light petroleum, and thus obtained in the form of microscopic needles melting at 112° .

These properties characterise the acid of melting point 203° as *trans- $\alpha\gamma$ -dimethyltricarballic acid*, which was first obtained by Zelinsky and Tschernoswitoff (*Ber.*, 1896, 29, 334) from dimethylcyanotricarballic ester by hydrolysis with dilute sulphuric acid.

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