

XV.—*aa-Dimethylbutane- $\alpha\beta\delta$ -tricarboxylic Acid,  $\gamma$ -Keto- $\beta\beta$ -dimethylpentamethylene- $\alpha$ -carboxylic Acid, and the Synthesis of Inactive  $\alpha$ -Campholactone of Inactive  $\alpha$ -Campholytic Acid and of  $\beta$ -Campholytic Acid (isoLauronic Acid).*

By WILLIAM HENRY PERKIN, jun., and JOCELYN FIELD THORPE.

DURING the course of a long series of researches on the constitution of camphor and its derivatives, attention has been repeatedly directed to the advisability of synthesising the more important substances obtained by the degradation of camphor, in order, thus, to definitely establish their constitution. It has frequently been found that analytical methods have, alone, not been sufficient to prove the constitutions of such degradation products, and in the more difficult cases, as, for example, in the determination of the constitutions of camphoronic and isocamphoronic acids, a definite proof was first obtained by synthetical means (Perkin and Thorpe, *Trans.*, 1897, 71, 1169; 1899, 75, 897; Perkin, *Trans.*, 1902, 81, 246).

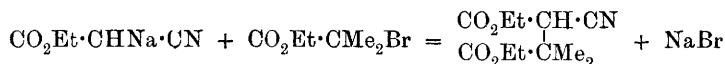
In continuing our experiments in this direction, we have endeavoured to find some means of synthesising, not only open chain acids, such as those mentioned above, but also closed chain compounds more closely allied to camphor and camphoric acid. We hope that it may eventually be found possible to prepare these substances themselves, in quantities sufficient for definite identification, by synthetical means, but the problem is an exceedingly difficult one.\*

In the present paper, we describe a series of reactions which has led

\* This investigation, an abstract of which appeared in the *Proceedings*, 1903, 19, 61, was completed and this paper written before the publication of G. Komppa's complete synthesis of camphoric and dehydrocamphoric acids (*Ber.*, 1903, 36, 4332).

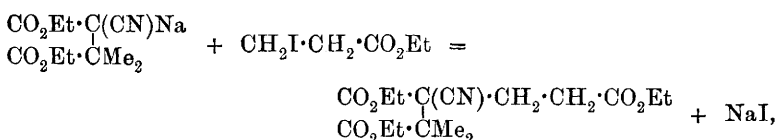
to the synthesis of inactive  $\alpha$ -campholytic acid, and indirectly to that of  $\beta$ -campholytic acid (*isolauronic acid*).

When ethyl cyanoacetate is digested in alcoholic solution with sodium ethoxide and ethyl bromoisobutyrate, sodium bromide separates and ethyl cyanodimethylsuccinate is formed, thus:



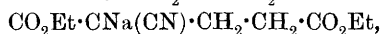
(compare Bone and Sprankling, *Trans.*, 1899, '75, 854).

The sodium compound of this cyano-ester interacts readily with ethyl  $\beta$ -iodopropionate, forming *ethyl  $\beta$ -cyano- $\alpha\alpha$ -dimethylbutane- $\alpha\beta\delta$ -tricarboxylate*,

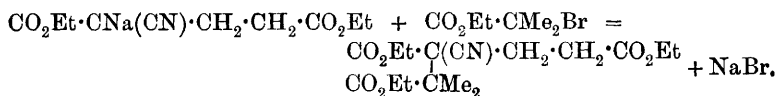


but, unfortunately, during this reaction, a large amount of the  $\beta$ -iodopropionic ester is decomposed with the elimination of hydrogen iodide and formation of ethyl acrylate,  $\text{CH}_2\cdot\text{CH}\cdot\text{CO}_2\text{Et}$ , and by no variation in conditions could this be avoided. This loss of valuable material would have made further progress impossible had it not been discovered that the acrylate thus produced may be converted into ethyl cyanodimethylbutanetricarboxylate by the following series of reactions.

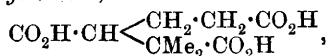
Ethyl acrylate condenses with the sodium compound of ethyl cyanoacetate, yielding the sodium compound of ethyl  $\alpha$ -cyanoglutarate, thus:  $\text{CO}_2\text{Et}\cdot\text{CHNa}\cdot\text{CN} + \text{CH}_2\cdot\text{CH}\cdot\text{CO}_2\text{Et} =$



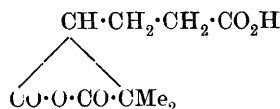
an ester which had already been prepared by L. Barthe (*Compt. rend.*, 1894, 118, 1268) from the sodium compound of ethyl cyanoacetate and ethyl  $\beta$ -bromopropionate. The sodium compound of ethyl  $\alpha$ -cyanoglutarate, when digested in alcoholic solution with ethyl  $\alpha$ -bromoisobutyrate, gives a good yield of ethyl cyanodimethylbutanetricarboxylate,



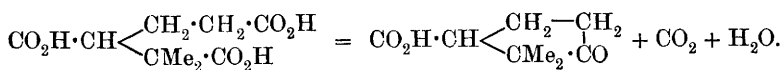
When boiled with hydrochloric acid, this cyano-ester is hydrolysed with the elimination of carbon dioxide and formation of  *$\alpha\alpha$ -dimethylbutane- $\alpha\beta\delta$ -tricarboxylic acid*,



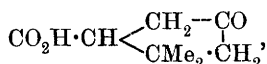
a crystalline, readily soluble acid which melts at 155—157°. When this acid is distilled under reduced pressure, it loses water and is converted into the *internal*  $\alpha\beta$ -anhydride of dimethylbutanetricarboxylic acid,



which melts at 98° and dissolves in water, regenerating the tribasic acid. If the dry sodium salt of the acid is heated with acetic anhydride at 140°, carbon dioxide is evolved and a new acid is produced,\* decomposition taking place according to the equation :



The  $\gamma$ -keto- $\beta\beta$ -dimethylpentamethylene- $\alpha$ -carboxylic acid thus obtained melts at 109—110° and yields an oxime and a sparingly soluble semicarbazone ; it is isomeric with, and very closely allied to, the  $\delta$ -keto- $\beta\beta$ -dimethylpentamethylene- $\alpha$ -carboxylic acid,



which Perkin and Thorpe (Trans., 1901, 79, 782) obtained by the reduction of dimethylketodicyclopentanedicarboxylic acid, and which melts at 103°. The latter acid is not easily acted on by sodium amalgam, but if a large excess is employed, it is ultimately reduced to the corresponding hydroxydimethylpentamethylenecarboxylic acid (m. p. 115°) :



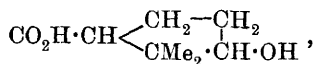
This acid must exist in *trans*- and *cis*-modifications, the latter of which should, like all *cis*- $\gamma$ -hydroxy-acids, readily yield a lactone, and since the acid (m. p. 115°) which was actually obtained showed no tendency to lose water with formation of a lactone, it is evidently the *trans*-modification.

On the other hand, it is interesting to note that the  $\gamma$ -keto-acid (m. p. 110°), unlike the  $\delta$ -keto-acid (m. p. 103°), is not reduced at all even when the aqueous solution of its sodium salt is boiled with a large excess of sodium amalgam, and this difference in behaviour is doubtless due to the proximity of the  $>\text{CMe}_2$  complex to the keto-

\* If this curious reaction should prove to be a general one, it will afford a convenient means of synthesising many important closed chain keto-acids and, for this reason, experiments are being carried out by one of us with the object of ascertaining the exact conditions under which the change takes place.

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group in the latter case. Reduction of the  $\gamma$ -keto-acid may, however, be effected by adding sodium to the boiling alcoholic solution of the acid, when an almost quantitative yield of *trans-γ-hydroxy-ββ-dimethylpentamethylene-α-carboxylic acid* (m. p. 101°),

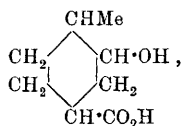


is obtained. The most remarkable property of this acid is its great stability\* since, although it is a  $\gamma$ -hydroxy-acid, it does not yield a lactone on boiling with dilute sulphuric acid and, even when distilled, it passes over for the most part unchanged.

This unusual stability, even of a *trans*-modification of a  $\gamma$ -hydroxy-acid, led us to suspect that some intramolecular change might have taken place during the energetic reduction with sodium and alcohol, but that this is not the case is proved by the behaviour of the hydroxy-acid on treatment with chromic acid, when it is very readily oxidised and converted into the  $\gamma$ -keto-acid from which it had been obtained by reduction.

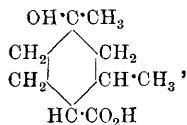
When *trans-γ-hydroxydimethylpentamethylenecarboxylic acid* is heated with hydrobromic acid, it yields *γ-bromodimethylpentamethylenecarboxylic acid*, and this viscid, syrupy substance, when boiled with sodium carbonate, loses hydrogen bromide with the formation of *dimethylcyclopentenecarboxylic acid* (b. p. 236°):

\* The reason for the remarkable stability of this hydroxy-acid is difficult to understand, but it may be mentioned that other closed chain  $\gamma$ -hydroxy-acids are known—for example, the  $\gamma$ -hydroxyhexahydro-*p*-toluic acid:



prepared by Tiemann and Semmler (*Ber.*, 1895, **28**, 2143)—which also exhibit very little tendency to yield lactones (compare Perkin and Yates, *Trans.*, 1901, **79**, 1375).

On the other hand, *trans*-hydroxyhexahydroxylic acid,



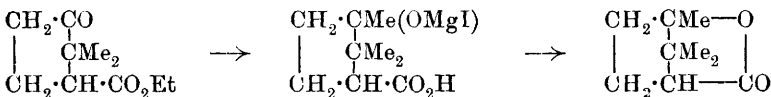
in which the hydroxy-group is in the  $\delta$ -position with respect to the carboxyl radicle, readily yields a lactone on distillation (Perkin and Lees, *Trans.*, 1901, **79**, 344), and this and other similar observations seem to point to the possibility of lactone formation taking place more readily in the  $\delta$ - than in the  $\gamma$ -position in ring compounds.



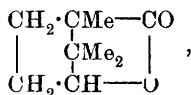
*Action of Magnesium Methyl Iodide on Ethyl Ketodimethylpentamethylenecarboxylate. Formation of  $\alpha$ -Campholactone and Synthesis of  $\alpha$ -Campholytic Acid and  $\beta$ -Campholytic Acid (isoLauronic Acid).*

As stated on p. 128, the primary object of this research was the synthesis of closed chain compounds closely allied to camphor and this was accomplished in the following way.

Ethyl ketodimethylpentamethylenecarboxylate is readily acted on by magnesium methyl iodide with the formation of several substances, among which is a new lactone produced according to the following scheme :



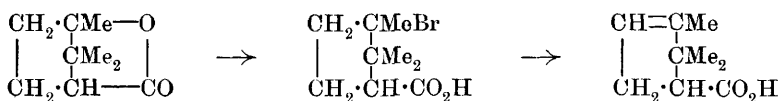
On account of its close relationship to campholactone,



from which, indeed, it only differs in the reversal of the position of the lactone group, this new lactone has been named *inactive  $\alpha$ -campholactone*.\*

Inactive  $\alpha$ -campholactone is an oil which smells strongly of peppermint and distils at 155—157° under 50 mm. pressure; when treated with hydrobromic acid, it yields *inactive  $\gamma$ -bromotrimethylpentamethylenecarboxylic acid*, which melts at 108° and, when digested with sodium carbonate, loses hydrogen bromide with the formation of the corresponding unsaturated acid :

\* In the preliminary notice of this research in the *Proceedings (loc. cit.)*, we named the new lactone "*isocampholactone*" in order to emphasise its great similarity to campholactone. We subsequently found, however, that this name had already been given to a lactone of unknown constitution which Noyes (*Ber.*, 1895, 28, 553) had prepared by the action of nitrous acid on aminolauronic acid. This latter lactone, which melts at 23° and has quite different properties to our synthetical lactone, was not obtained in sufficient quantity for analysis, but its method of formation makes it probable that it is isomeric (possibly stereoisomeric) with campholactone. Owing to the name "*isocampholactone*" having been previously used by Noyes, we have altered that of our lactone to " *$\alpha$ -campholactone*."



The formula of this unsaturated acid is that of *inactive α-campholytic acid*, an acid which was first obtained by one of us (Perkin, *Trans.*, 1903, 83, 853) by the reduction of *α*-camphylic acid,  $\text{C}_8\text{H}_{11} \cdot \text{CO}_2\text{H}$ , with sodium amalgam. In order to prove that the synthetical acid is *inactive α-campholytic acid*, it was digested with dilute sulphuric acid when crystals were formed which melted at  $132^\circ$  and were easily identified as *β-campholytic acid (isolauronolic acid)*, the well-known remarkable isomeric change indicated by the formulæ,



having taken place. That the *isolauronolic acid* thus synthesised is identical with the acid obtained from camphoric acid was shown by mixing equal quantities of the two preparations when the mixture melted at  $132^\circ$ , the melting point of the constituents. Furthermore, the synthetical acid, on oxidation with permanganate, yielded *isolauronic acid*.

There can thus be no doubt that the above series of reactions constitutes a synthesis of both *inactive α-campholytic acid* and of *isolauronolic acid (β-campholytic acid)* and therefore the constitution of these important acids may now be taken as definitely established.

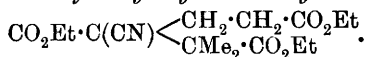
If the formulæ of *α-campholactone* and the derivatives obtained from it are carefully examined, it will be at once seen how very closely these synthetical substances are related to camphoric acid. Thus if *γ-bromotrimethylpentamethylenecarboxylic acid* be taken as an example, it is only necessary to replace the bromine atom in that substance by the carboxyl group in order to accomplish a synthesis of camphoric acid :



Many experiments were made, under the most varied conditions, in the hope of being able to bring about this change, but with little success. Thus the bromo-acid and its ester were treated with silver cyanide, with solid potassium cyanide, alone and in the presence of anhydrous hydrogen cyanide, and with aqueous and alcoholic solutions of potassium cyanide, but although small quantities of a crystalline sub-

stance having properties identical with those of *i*-camphoric acid were obtained in two cases (see p. 146), the amount was too small for analysis and definite identification. The cause of the failure in these experiments is the great readiness with which the bromo-acid loses hydrogen bromide with the formation of  $\alpha$ -campholytic acid. Again  $\alpha$ -campholactone was heated with potassium cyanide and with anhydrous formic acid, but in both cases,  $\alpha$ -campholytic acid was the product of the reaction. Lastly, a synthesis, similar to that of benzoic acid from bromobenzene by the action of magnesium powder and carbon dioxide, was attempted with the ester of bromotrimethylpentamethylene-carboxylic acid, but again without success. It has not been thought worth while to describe all these various experiments in detail in this paper, the above short account being sufficient to indicate the reactions which were attempted with the object of synthesising camphoric acid from  $\alpha$ -campholactone.

*Condensation of Ethyl Cyanodimethylsuccinate with Ethyl  $\beta$ -Iodopropionate. Formation of Ethyl Cyanodimethylbutanetricarboxylate,*



In carrying out this condensation, it was found that even slight differences in temperature and other conditions had a very marked influence on the yield of the condensation product, and the best results were usually obtained by working in the following way. Sodium (23 grams) is dissolved in absolute alcohol (350 c.c.) and, after cooling thoroughly, mixed with ethyl cyanodimethylsuccinate (227 grams) and then ethyl  $\beta$ -iodopropionate (228 grams) added in small quantities, care being taken, by cooling with water, that the temperature never rises above 25°. After 12 hours, the product is heated on the water-bath for 2 hours, water is then added, and the oily ester, which smells strongly of ethyl acrylate, is twice extracted with ether. The ethereal solution is thoroughly washed with water, dried over calcium chloride, and the ether very slowly distilled off; the residual oil is then distilled at first under the ordinary pressure until the temperature rises to 130° in order that the ethyl acrylate which comes over below this may be collected for subsequent use (see p. 136).

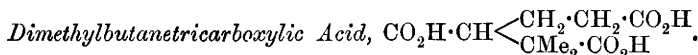
The distillation flask is then attached to the vacuum apparatus and the distillation continued under 20 mm. pressure when, after several fractionations, *ethyl cyanodimethylbutanetricarboxylate* is readily obtained pure as a colourless oil boiling at about 210° (20 mm.).

0.2976 gave 11.3 c.c. of nitrogen at 23° and 760 mm. N = 4.3.

$\text{C}_{16}\text{H}_{25}\text{O}_6\text{N}$  requires N = 4.3 per cent.

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The yield of this ester varies in a remarkable way in different experiments carried out, apparently, under precisely the same conditions. In one instance, an almost theoretical yield was obtained, but in other cases hardly a trace was produced, the average yield being about 25 per cent. of the theoretical. The remainder consists of ethyl acrylate and unchanged ethyl cyanodimethylsuccinate and sometimes a considerable quantity of an oil having a high boiling point is produced.



The cyanogen group in ethyl cyanodimethylbutanetricarboxylate is hydrolysed only with great difficulty, even on long boiling with hydrochloric or dilute sulphuric acid the process is far from complete, and it was only by employing concentrated sulphuric acid in the first instance that a satisfactory result was ultimately obtained. The cyano-ester (in quantities of 50 grams) is dissolved in an equal volume of concentrated sulphuric acid, and, when the solution is cold, water is added until oily drops just commence to separate. The whole is then boiled on the sand-bath, the alcohol produced being allowed to escape through the air-condenser, and small quantities of water are added from time to time in order to prevent charring. After 8 hours, the solution is diluted with an equal volume of water, saturated with ammonium sulphate, and extracted several times with ether; the solvent is then evaporated and the residue dissolved in a small quantity of water and mixed with an equal volume of concentrated hydrochloric acid. After two days, the crystalline crust which has separated is collected and purified by recrystallisation from hydrochloric acid, from which it separates as a sandy powder.

0.1444 gave 0.2615  $\text{CO}_2$  and 0.0860  $\text{H}_2\text{O}$ . C = 49.4 ; H = 6.6.

0.1298 ,, 0.2359  $\text{CO}_2$  ,, 0.0750  $\text{H}_2\text{O}$ . C = 49.5 ; H = 6.4.

$\text{C}_9\text{H}_{14}\text{O}_6$  requires C = 49.5 ; H = 6.4 per cent.

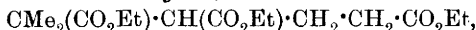
*Dimethylbutanetricarboxylic acid* melts at 155—157° and is readily soluble in water, but sparingly so in concentrated hydrochloric acid. It is rather sparingly soluble in dry ether, and crystallises from this solvent in small, glistening prisms or leaflets.

On titration with decinormal caustic soda, 0.2018 gram neutralised 0.1108 gram of NaOH, whereas this quantity of a tribasic acid,  $\text{C}_9\text{H}_{14}\text{O}_6$ , should neutralise 0.1110 gram of NaOH.

The hydrochloric acid mother liquors from the purification of the acid contain a large quantity of very impure material ; this is extracted with ether, and, after evaporating off the solvent, the residue is esterified by boiling with alcohol and sulphuric acid. The ester is extracted



in the usual way and fractionated under reduced pressure, when pure *ethyl dimethylbutanetricarboxylate*,



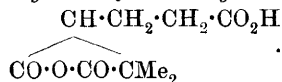
is obtained as a colourless oil boiling at about 195° (40 mm.).

0.1722 gave 0.3761 CO<sub>2</sub> and 0.1319 H<sub>2</sub>O. C = 59.5 ; H = 8.5.

C<sub>15</sub>H<sub>26</sub>O<sub>6</sub> requires C = 59.6 ; H = 8.6 per cent.

From this ester, the pure tribasic acid is readily obtained by hydrolysis with concentrated hydrochloric acid.

*The Internal Anhydride of Dimethylbutanetricarboxylic Acid,*



When dimethylbutanetricarboxylic acid is heated under reduced pressure (45 mm.), it melts and then, at once, gives off water, and the anhydro-acid distils at about 255° as a viscid, colourless syrup which soon begins to crystallise in stellate groups and gradually becomes solid. By dissolving in hot benzene and allowing to cool slowly, the substance is obtained in well-defined, four-sided plates, but if the solution is rapidly stirred, it separates as a sandy, crystalline precipitate.

0.1776 gave 0.3503 CO<sub>2</sub> and 0.0959 H<sub>2</sub>O. C = 53.8 ; H = 6.0.

C<sub>9</sub>H<sub>12</sub>O<sub>5</sub> requires C = 54.0 ; H = 6.0 per cent.

The anhydride melts at 98° and is sparingly soluble in cold water ; it dissolves, however, readily on boiling with water, and if an equal volume of hydrochloric acid is added to the concentrated solution, crystals separate which melt at 155—157° and consist of the pure tribasic acid.

*Formation of Ethyl Cyanodimethylbutanetricarboxylate from Ethyl Acrylate, Ethyl Cyanoacetate, and Ethyl Bromoisobutyrate.*

The reasons which led to this method being carefully worked out are given in the introduction. Sodium (23 grams) was dissolved in 300 grams of alcohol, mixed with ethyl cyanoacetate (113 grams), and, after well cooling, ethyl acrylate (100 grams) added in several portions. The condensation takes place very rapidly and with evolution of a considerable amount of heat, and in a short time the whole of the sodium compound of the ethyl cyanoacetate will have passed into solution. The mixture is heated on the water-bath for about two hours, and until a drop of the liquid, on dilution with water, no

longer deposits an oil; it is then mixed with ethyl bromoisobutyrate (195 grams) and heated in soda-water bottles in a boiling salt-bath for eight hours. On diluting with water, extracting the oily product with ether, and fractionating under reduced pressure, pure ethyl cyanodimethylbutanetricarboxylate is obtained, the yield being 75—80 per cent. of the theoretical.

0·2646 gave 10·2 c.c. of nitrogen at 20° and 755 mm. N = 4·4.

$C_{16}H_{25}O_6N$  requires N = 4·3 per cent.

That this cyano-ester has the same constitution as that obtained by the process described on p. 134 was proved by hydrolysis with sulphuric acid, when a good yield of dimethylbutanetricarboxylic acid was obtained which melted at 155—157°.

0·1516 gave 0·2759  $CO_2$  and 0·0886  $H_2O$ . C = 49·6; H = 6·5.

$C_9H_{14}O_6$  requires C = 49·5; H = 6·4 per cent.

Much of the acid required for this investigation was prepared by the foregoing process.

*Partial Hydrolysis of Ethyl Cyanodimethylbutanetricarboxylate.*

During the course of this investigation, a number of experiments were instituted with the object of eliminating the carboxyl radicle adjacent to the cyanogen group in ethyl cyanodimethylbutanetricarboxylate, and the results obtained may be briefly described as follows.

When an alcoholic solution of 12 grams of pure caustic potash is mixed with 35 grams of the cyano-ester and the whole allowed to remain overnight, a crystalline potassium salt separates in quantity. This was collected at the pump, washed with alcohol, in which it is sparingly soluble, and dried at 100°; it then weighed 10 grams.

0·3484 gave 0·1781  $K_2SO_4$ . K = 22·9.

$C_{12}H_{15}O_6NK_2$  requires K = 22·4 per cent.

The constitution of this salt is probably represented by the formula

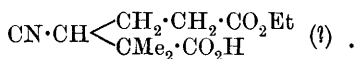


It was very soluble in water and gave no precipitate on acidifying with hydrochloric acid; the whole was therefore repeatedly extracted with ether, the ethereal solution dried over calcium chloride and evaporated, when a colourless oil was obtained, which, over sulphuric acid in a vacuum desiccator, became very viscid but did not crystallise. The analysis shows that this substance is *ethyl dihydrogen cyanodimethylbutanetricarboxylate*, corresponding with the above potassium salt.

0.1974 gave 8.3 c.c. of nitrogen at 17° and 759 mm. N = 4.9.

$C_{12}H_{17}O_6N$  requires N = 5.2 per cent.

When this dibasic acid is heated at 150°, it decomposes with evolution of carbon dioxide, and, when the evolution of gas has ceased, the residue distils almost completely at 245—250° (50 mm.) as a viscid oil which consists of *ethyl hydrogen cyanodimethylbutanedicarboxylate*,



0.2138 gave 11.5 c.c. of nitrogen at 20° and 759 mm. N = 6.2.

$C_{11}H_{17}O_4N$  requires N = 6.2 per cent.

*Ketodimethylpentamethylenecarboxylic Acid*,  $CO_2H \cdot CH \left\langle \begin{array}{l} CH_2 - CH_2 \\ CMe_2 \cdot CO \end{array} \right.$

This acid is formed when the sodium salt of dimethylbutanetricarboxylic acid is heated with acetic anhydride. The sodium salt is prepared by dissolving the pure acid (109 grams) in water, adding 80 grams of anhydrous sodium carbonate, and evaporating the alkaline liquid to dryness. In order to obtain the salt as finely divided as possible, it is powdered and passed through a fine wire sieve, being then again dried at 100° and transferred to a flask, into the neck of which is fitted a tube bent twice at right angles. After adding 150 grams of freshly distilled acetic anhydride, the whole is slowly heated in an oil-bath when it will be noticed that carbon dioxide begins to come off below 100°, as can be readily seen by causing the tube attached to the flask to dip under baryta water. The temperature is kept at 135—140° for about 6 hours, then 50 grams of acetic anhydride are added and the heating continued until the evolution of carbon dioxide has practically ceased, which is the case after about three hours. As soon as the product is cold, it is esterified by adding an excess of a solution of one volume of sulphuric acid in three volumes of alcohol and heating for 6 hours on the water-bath in an open flask in order that as much ethyl acetate as possible may be removed by evaporation. The product, which smells strongly of ethyl acetate, is diluted with water and extracted several times with ether; the ethereal solution is then thoroughly washed with water and dilute sodium carbonate solution\* and evaporated.

On fractionating this oil under 100 mm. pressure, about 50 grams distil at 160—180° leaving a viscid, nearly black residue† in the retort

\* The dark sodium carbonate extract, on acidifying and extracting with ether, yields a brown oil from which considerable quantities of ketodimethylpentamethylenecarboxylic acid may be obtained by treatment with semicarbazide or by esterification and distillation under reduced pressure and subsequent hydrolysis.

† The residues from several preparations were mixed and fractionated under

and, on repeatedly fractionating the distillate, an oil (35 grams) is obtained which boils at 170—172° (100 mm.) and consists of pure *ethyl ketodimethylpentamethylenecarboxylate*.

0·1765 gave 0·4196 CO<sub>2</sub> and 0·1397 H<sub>2</sub>O. C = 64·8; H = 8·8.

0·1584 „ 0·3771 CO<sub>2</sub> „ 0·1242 H<sub>2</sub>O. C = 64·9; H = 8·7.

C<sub>10</sub>H<sub>16</sub>O<sub>3</sub> requires C = 65·2; H = 8·7 per cent.

This ester is hydrolysed by boiling with an excess of methyl-alcoholic potash; the solution is diluted with water, neutralised, and evaporated until free from alcohol. After acidifying with hydrochloric acid and extracting six times with pure ether, the ethereal solution is dried over calcium chloride and evaporated, when a pale yellow oil is obtained which, on cooling, rapidly solidifies. The mass is left in contact with porous porcelain to remove a trace of oily impurity, and then dissolved in a small amount of water, from which the pure acid separates slowly in groups of colourless needles.

0·1485 gave 0·3360 CO<sub>2</sub> and 0·1043 H<sub>2</sub>O. C = 61·6; H = 7·8.

0·1634 „ 0·3686 CO<sub>2</sub> „ 0·1144 H<sub>2</sub>O. C = 61·5; H = 7·8.

C<sub>8</sub>H<sub>12</sub>O<sub>3</sub> requires C = 61·5; H = 7·7 per cent.

*Ketodimethylpentamethylenecarboxylic acid* melts at 109—110°; it dissolves readily in benzene, acetone, ether, alcohol, and chloroform, but is sparingly soluble in light petroleum. It is exceedingly soluble in hot water but much less so in the cold, and it may be obtained in long, colourless needles if the hot solution is allowed to cool very slowly. The pure acid also crystallises readily from ether in the form of hard, glistening prisms.

A slightly alkaline solution of the ammonium salt of the acid gives no precipitate with barium or calcium chloride, even on boiling; with copper sulphate, no precipitate is formed in the cold, but, on boiling, a pale blue, apparently crystalline, copper salt separates.

The *oxime*, C<sub>8</sub>H<sub>11</sub>(C:N·OH)·CO<sub>2</sub>H, was prepared by dissolving the acid in a considerable excess of caustic potash solution, adding twice the calculated quantity of hydroxylamine hydrochloride, and allowing the whole to remain for two days. On acidifying with hydrochloric acid, a crystalline precipitate separated, which was extracted with ether, the ethereal solution was carefully dried with calcium chloride and evaporated to a small bulk, when the oxime soon began to separate in crystalline crusts.

30 mm. pressure, when about one-third distilled at 180—190°. This portion, on hydrolysis with hydrochloric acid, yielded a considerable quantity of crude dimethylbutanetricarboxylic acid, which was purified by recrystallisation, first from hydrochloric acid and then from ether.

0.203 gave 15.3 c.c. nitrogen at 19° and 737 mm.  $N = 8.3$ .

$C_8H_{12}O_3N$  requires  $N = 8.2$  per cent.

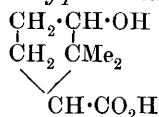
*Ketoximodimethylpentamethylenecarboxylic acid* melts at about 195°, but it turns brown and commences to decompose below this temperature. It is somewhat sparingly soluble even in boiling water, and separates, on cooling, as a sandy powder. It dissolves readily in sodium carbonate, and, when heated in a test-tube, it decomposes with a slight explosion, and yields an oily distillate which crystallises on cooling.

The *semicarbazone*,  $C_6H_{11}(C:N \cdot NH \cdot CO \cdot NH_2) \cdot CO_2H$ , separates at once as a sandy powder when a concentrated aqueous solution of the acid is mixed with semicarbazide hydrochloride and sodium acetate. It melts at about 217° and is very sparingly soluble in water.

0.1544 gave 26.6 c.c. nitrogen at 19° and 751 mm.  $N = 19.5$ .

$C_9H_{15}O_3N_3$  requires  $N = 19.7$  per cent.

*Reduction of Ketodimethylpentamethylenecarboxylic Acid. Formation of trans-γ-Hydroxydimethylpentamethylenecarboxylic Acid,*



It is stated in the introduction that ketodimethylpentamethylenecarboxylic acid is not reduced by sodium amalgam, and this was shown by the fact that when 30 grams of the acid, dissolved in dilute aqueous caustic soda, was boiled with 2500 grams of 4 per cent. sodium amalgam, and the solution subsequently acidified and extracted with ether, almost the whole of the keto-acid was recovered unchanged. When, however, the boiling alcoholic solution of the acid is treated with sodium, reduction is readily effected. The pure acid (30 grams) was dissolved in about 500 c.c. of absolute alcohol, heated to boiling in a reflux apparatus, and treated, as rapidly as possible, with 70 grams of sodium, boiling alcohol being added from time to time as the reaction slackened. The product was dissolved in much water, evaporated on the water-bath until free from alcohol, acidified with an excess of hydrochloric acid, and heated on the water-bath for half an hour in the expectation that the hydroxy-acid, if present, would thus be converted into its lactone. As, however, no neutral oil separated, the whole was saturated with ammonium sulphate, and extracted 10 times with ether. The ethereal solution was dried over calcium chloride and evaporated, when 28 grams of a viscid oil remained and solidified on cooling. That no unchanged keto-acid was present in this product was shown by treating a small portion with semicarbazide and sodium

acetate, when no trace of the very sparingly soluble semicarbazone (p. 140) was formed. Considerable difficulty was experienced in re-crystallising the crude reduced acid, but this was ultimately accomplished by dissolving it in dry ether, adding an equal volume of benzene, and allowing the solution to evaporate slowly at the ordinary temperature. The crystalline crusts thus obtained were drained on porous porcelain, and dissolved in a small quantity of hot water, when, on slowly cooling, the pure acid separated in well-defined, glistening prisms.

0.1690 gave 0.3762 CO<sub>2</sub> and 0.1326 H<sub>2</sub>O. C = 60.7; H = 8.7.

0.1353 ,, 0.3012 CO<sub>2</sub> ,, 0.1075 H<sub>2</sub>O. C = 60.7; H = 8.8.

C<sub>8</sub>H<sub>14</sub>O<sub>3</sub> requires C = 60.8; H = 8.8 per cent.

*trans-γ-Hydroxydimethylpentamethylenecarboxylic acid* melts at 100—101° and is readily soluble in water, alcohol, and ether. That it is a monobasic acid was shown by its behaviour with decinormal caustic soda, when 0.1977 gram of the acid required for neutralisation 0.0507 gram of NaOH, whereas this amount of a monobasic acid, C<sub>8</sub>H<sub>14</sub>O<sub>3</sub>, should neutralise 0.0506 gram of NaOH.

This *γ*-hydroxy-acid is remarkably stable, and shows no tendency to become converted into a lactone when boiled with dilute hydrochloric or sulphuric acid, and, even on distillation, it does not yield a lactone, as is proved by the following experiment.

Three grams of the pure acid were distilled under 40 mm. pressure, when the whole passed over at 205—210° as a viscid, colourless oil resembling glycerol, and this, on cooling, solidified to a brittle, transparent, glassy mass. This product was completely soluble in cold dilute sodium carbonate solution, showing that it was not a lactone, and, without further purification, it yielded numbers which differ little from those required by the hydroxy-acid.

0.1649 gave 0.3718 CO<sub>2</sub> and 0.1348 H<sub>2</sub>O. C = 61.4; H = 9.0.

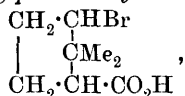
C<sub>8</sub>H<sub>14</sub>O<sub>3</sub> requires C = 60.8; H = 8.8 per cent.

*Oxidation by Means of Chromic Acid.*—Owing to the curious properties of this hydroxy-acid, it was thought necessary to investigate its behaviour on oxidation in order to prove that its constitution is that represented by the formula indicated on p. 140. The pure acid (2 grams) was dissolved in water, mixed with potassium dichromate (1.4 grams) and a small amount of sulphuric acid, and gradually heated to boiling when oxidation readily took place. The product was extracted with ether, the ethereal solution dried over calcium chloride and evaporated to a small bulk, when crystalline crusts (1.5 grams) slowly separated, which melted at 109°, and consisted of pure ketodimethylpentamethylenecarboxylic acid.

0·1558 gave 0·3513  $\text{CO}_2$  and 0·1096  $\text{H}_2\text{O}$ .  $\text{C} = 61\cdot5$ ;  $\text{H} = 7\cdot8$ .

$\text{C}_8\text{H}_{12}\text{O}_3$  requires  $\text{C} = 61\cdot5$ ;  $\text{H} = 7\cdot7$  per cent.

*$\gamma$ -Bromodimethylpentamethylenecarboxylic Acid,*



and *Dimethylcyclopentenecarboxylic Acid,*

$$\begin{array}{c} \text{CH} = \text{CH} \\ | \quad | \\ \text{CH}_2 \cdot \text{CMe}_2 \\ | \quad | \\ \text{CH}_2 \cdot \text{CH} \cdot \text{CO}_2\text{H} \end{array}.$$

Finely powdered  $\gamma$ -hydroxydimethylpentamethylenecarboxylic acid dissolves readily in fuming hydrobromic acid (saturated at  $0^\circ$ ), but the bromo-acid does not separate after a time as is the case with the corresponding trimethyl acid (see p. 145). The solution was therefore heated in a sealed tube at  $100^\circ$  for about fifteen minutes, when, on cooling, an oily layer had separated on the surface of the hydrobromic acid. The whole was diluted with water, extracted with ether, the ethereal solution thoroughly washed with water, dried over calcium chloride, and evaporated, when an almost colourless oil remained which, after leaving for some hours over sulphuric acid in a vacuum desiccator, was analysed with the following result :

0·3373 gave 0·2346  $\text{AgBr}$ .  $\text{Br} = 35\cdot9$ .

$\text{C}_8\text{H}_{13}\text{O}_2\text{Br}$  requires  $\text{Br} = 36\cdot2$  per cent.

*$\gamma$ -Bromodimethylpentamethylenecarboxylic acid*, when prepared in this way, shows no signs of crystallising, even when left for a long time in a freezing mixture, and, on exposure to the air, it becomes darker and finally almost black. A quantity of the freshly prepared bromo-acid was dissolved in excess of sodium carbonate and boiled for several minutes; the solution was then acidified and extracted with ether. After drying over calcium chloride and evaporating, an oil was obtained which distilled for the most part at  $160$ — $170^\circ$  (50 mm.), but there was a considerable quantity of a viscid oil left in the flask, which probably consisted of regenerated  $\gamma$ -hydroxy-acid. The distillate was fractionated under the ordinary pressure, when almost the whole passed over at  $236^\circ$  (760 mm.) as an oil which was colourless when hot but became deep sage-green on cooling, a behaviour often observed in connection with substances belonging to the camphor and terpene series.

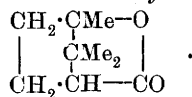
Owing to its method of formation, there can be no doubt that the oily acid thus obtained is *dimethylcyclopentenecarboxylic acid*. That it is an unsaturated acid is shown by the fact that its solution in sodium carbonate instantly decolorises permanganate.

0.2128 gave 0.5315 CO<sub>2</sub> and 0.1638 H<sub>2</sub>O. C = 68.2 ; H = 8.5.

0.1730 ,, 0.4336 CO<sub>2</sub> ,, 0.1335 H<sub>2</sub>O. C = 68.3 ; H = 8.6.

C<sub>8</sub>H<sub>12</sub>O<sub>2</sub> requires C = 68.6 ; H = 8.6 per cent.

*The Action of Magnesium Methyl Iodide on Ethyl Ketodimethylpentamethylenecarboxylate. Formation of Inactive  $\alpha$ -Campholactone.*



After a long series of comparative experiments, the following process was ultimately adopted for the preparation of  $\alpha$ -campholactone. Finely-divided magnesium filings (7.2 grams) are placed in a 2 litre flask connected with a long water condenser and covered with ether (300 c.c.) which had been very carefully freed from water, and finally distilled over phosphoric oxide. Methyl iodide (45 grams) is then added in two portions, the vigorous reaction being kept under control by immersing the flask in ice water occasionally.

Ethyl ketodimethylpentamethylenecarboxylate (37 grams) is dissolved in pure ether (300 c.c.) in a large flask, connected with a reflux condenser, and immersed in powdered ice and water; the ethereal solution of magnesium methyl iodide is then cautiously poured down the condenser tube in several small quantities, the flask being well agitated and allowed to cool thoroughly after each addition. As each quantity of the magnesium methyl iodide comes into contact with the ethereal solution of the keto-ester, a yellowish-white turbidity is produced, and ultimately the magnesium compound separates on the sides of the flask as a sticky mass. After half an hour, the product is decomposed by the careful addition of dilute hydrochloric acid, the yellow ethereal solution is separated, washed with dilute hydrochloric acid and evaporated, and the residue, which is a mixture of the lactone, unchanged keto-ester, and a neutral substance (which has not yet been investigated), is treated as follows. The deep yellow oil is dissolved in methyl alcohol, and digested for 10 minutes with a solution of caustic potash (20 grams) in methyl alcohol, by which means the lactone and keto-ester are hydrolysed; water is then added, and the neutral substance removed by extraction with ether. The aqueous solution is evaporated on the water-bath until free from ether and methyl alcohol; it is then diluted with water and acidified, when a viscid oil separates, which, on heating on the water-bath for 15 minutes, becomes limpid, owing to the conversion of the hydroxy-acid into the corresponding lactone. The whole is extracted with ether, the ethereal solution repeatedly washed with dilute aqueous sodium carbonate, dried over calcium chloride, and evaporated, when an oil



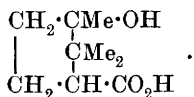
(6—8 grams) is obtained which, after repeated fractionation, distils constantly at 155—157° (50 mm.), and consists of pure *inactive*  $\alpha$ -campholactone.

0.1649 gave 0.4227 CO<sub>2</sub> and 0.1392 H<sub>2</sub>O. C = 69.9 ; H = 9.3.

0.1485 „ 0.3819 CO<sub>2</sub> „ 0.1238 H<sub>2</sub>O. C = 70.0 ; H = 9.2.

C<sub>9</sub>H<sub>14</sub>O<sub>2</sub> requires C = 70.1 ; H = 9.1 per cent.

*Inactive*  $\alpha$ -campholactone is a pale yellow oil which has a most pungent odour of peppermint ; it is readily volatile in steam, and distils under the ordinary pressure almost without decomposition. It is insoluble in sodium carbonate solution, but dissolves readily and completely in warm dilute aqueous caustic soda, and the well-cooled solution, on acidifying, remains clear for a considerable time, indicating that the hydroxy-acid corresponding with the lactone is present ; this acid is slowly decomposed at the ordinary temperature, and more rapidly on warming, with a separation of the lactone. A special experiment was made in the hope of being able to obtain the hydroxy-acid in a crystalline condition, in order that a direct comparison might be made with the hydroxydihydrocampholytic acid described by Noyes\* (*Amer. Chem. J.*, 1894, 16, 307, 502 ; 1896, 18, 685), and which he considers has the same constitution, namely,



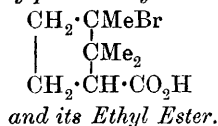
The pure lactone (2 grams) was dissolved in hot baryta water, the solution cooled with ice, acidified, and extracted with ether. On removing the ether by a current of dry air, a viscid oil remained, which was obviously the hydroxy-acid, since it dissolved readily and completely in dilute sodium carbonate solution.

0.1496 gave 0.3454 CO<sub>2</sub> and 0.1252 H<sub>2</sub>O. C = 64.0 ; H = 9.3.

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

*Inactive*  $\gamma$ -*cis*-hydroxytrimethylpentamethylenecarboxylic acid, when left over sulphuric acid in a vacuum desiccator, rapidly loses water with the formation of  $\alpha$ -campholactone and, when boiled with hydrochloric acid, the change is complete in a few minutes. Hydroxydihydrocampholytic acid, on the contrary, is perfectly stable and, indeed, does not show any tendency to yield a lactone even when boiled with acids ; if then it has the constitution represented above, it must obviously be the *trans*-modification.

\* Compare Meyer and Jacobson (*Lehrbuch der Org. Chem.*, Vol. II, 1021).

*Inactive γ-Bromotrimethylpentamethylenecarboxylic Acid,*

When *α*-campholactone is mixed with three times its volume of fuming hydrobromic acid (saturated at 0°) it dissolves, but almost immediately the liquid clouds and a viscid oil separates on the surface of the acid. This oily layer soon darkens in colour and crystallises, and in preparing the pure bromo-acid it is best to stir vigorously with a glass rod, so that solidification may be complete before decomposition sets in. The solid is thoroughly washed with water to remove hydrobromic acid and spread on porous porcelain to separate the oily impurity. The residue, which should be almost colourless, is made into a paste with a small quantity of formic acid (sp. gr. 1.22) and again transferred to porous porcelain, and after the operation has been repeated, a colourless, crystalline mass is obtained which softens at 105° and melts at about 108° with decomposition.

0.2202 gave 0.1735 AgBr. Br = 33.5.

$\text{C}_9\text{H}_{15}\text{O}_2\text{Br}$  requires Br = 34.0 per cent.

Inactive *γ*-bromotrimethylpentamethylenecarboxylic acid readily decomposes with loss of hydrogen bromide and formation of *inactive α*-campholytic acid (see p. 147) and therefore no attempts were made to purify it by recrystallisation. As explained in the introduction, it is exactly similar in its chemical properties to the hydrobromide of *α*-campholytic acid (*cistrans*-campholytic acid), which, according to Noyes (*Ber.*, 1898, 28, 551), melts at 98—100° and decomposes in moist air, evolving hydrogen bromide.

The *ethyl* ester,  $\text{C}_8\text{H}_{14}\text{Br} \cdot \text{CO}_2\text{Et}$ .—In preparing this ester, the pure lactone (4 grams) was mixed with phosphorous pentabromide (15 grams), when a vigorous action took place and much hydrogen bromide was evolved. After 10 minutes, the whole was heated on the water-bath for 5 minutes and then poured, in a thin stream, into a large excess of absolute alcohol. As soon as the reaction had subsided, the solution was allowed to cool, diluted with water, and the heavy oil extracted with ether, the ethereal solution was washed with water and dilute sodium carbonate solution, dried over calcium chloride, evaporated, and the residual oil rapidly fractionated under 70 mm. pressure.

A small quantity of oil passed over below 165° and then almost

the whole of the remainder distilled at 165—170° leaving only a small, black residue in the flask.

0·1854 gave 0·1377 AgBr. Br = 31·6.

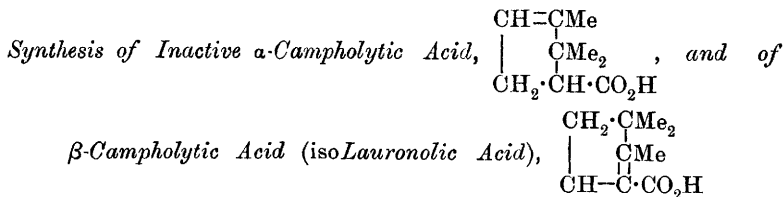
$C_{11}H_{19}O_2Br$  requires Br = 30·5 per cent.

This oil was made the starting-point in a long series of experiments instituted in the hope of synthesising camphoric acid (see p. 133) but without success. The above analysis and general properties of the oil leave, however, scarcely any doubt that it is *inactive ethyl  $\gamma$ -bromotrimethylpentamethylenecarboxylate*.

*Action of Potassium Cyanide on Bromotrimethylpentamethylenecarboxylic Acid.*—It was stated in the introduction that, in experimenting on the action of cyanides on this bromo-acid, an acid identical in properties with *i*-camphoric acid was obtained in very small quantities in two cases. In one instance, the experiment was carried out as follows: freshly prepared bromotrimethylpentamethylenecarboxylic acid (10 grams) was dissolved in alcohol, mixed with a concentrated aqueous solution of pure potassium cyanide (5 grams) and 5 c.c. of anhydrous hydrogen cyanide, the mixture being allowed to remain for 14 days. The dark brown product was heated on the water-bath for one hour, evaporated, and the residue mixed with concentrated hydrochloric acid and, after remaining overnight, heated for three hours on the water-bath. Water was then added and the whole distilled in steam until the distillate was free from  $\beta$ -campholytic acid (see p. 147). The residue was digested with animal charcoal, filtered, evaporated to a small bulk, and repeatedly extracted with ether, when a yellow oil was obtained which became semi-solid when left for some weeks over sulphuric acid.

This substance was drained on porous porcelain until all the oil had been absorbed and the residue recrystallised from a little water. As the crystalline product, which could not have weighed more than a few milligrams, melted indefinitely between 180° and 190°, it was heated in a test-tube with a small quantity of acetic anhydride when, on cooling, crystals separated which were drained on porous porcelain and washed with a little acetic anhydride. These crystals closely resembled the anhydride of *i*-camphoric acid, since they melted at 215—217° and gave on hydrolysis an acid, melting at 204°, whereas *i*-camphoric acid melts at 200—203° and yields an anhydride melting at 221°. Unfortunately, the amount at our disposal was quite insufficient to enable us to establish the identity of the substance by analysis.\*

\* The method of formation of this small quantity of acid and its properties leave scarcely room for doubt that it was *i*-camphoric acid, and experiments were in progress which it was hoped would have yielded enough material for definite



When  $\gamma$ -bromotrimethylpentamethylenecarboxylic acid is mixed with excess of sodium carbonate solution, it rapidly dissolves, and if the liquid is heated just to boiling, cooled, and acidified with hydrochloric acid, a viscid, oily layer of *inactive  $\alpha$ -campholytic acid* separates. This was extracted with ether, the ethereal solution washed until quite free from hydrochloric acid, dried over calcium chloride, evaporated, and the residual oil distilled under reduced pressure, when the whole passed over at 162—164° (45 mm.) as a colourless, viscid oil.

0.1441 gave 0.3696 CO<sub>2</sub> and 0.1185 H<sub>2</sub>O. C = 69.9; H = 9.1.

C<sub>9</sub>H<sub>14</sub>O<sub>2</sub> requires C = 70.1; H = 9.1 per cent.

*Methyl  $\alpha$ -Campholytate*.—This ester was prepared by leaving the acid in contact with methyl alcohol and sulphuric acid for a short time and then precipitating with water. After extracting with ether, washing with sodium carbonate, drying over calcium chloride, and evaporating, an oil was obtained which distilled constantly at 200°.

0.1475 gave 0.3882 CO<sub>2</sub> and 0.1287 H<sub>2</sub>O. C = 71.7; H = 9.7.

C<sub>8</sub>H<sub>13</sub>·CO<sub>2</sub>Me requires C = 71.4; H = 9.5 per cent.

On hydrolysis with caustic potash and acidifying, this ester yielded liquid  $\alpha$ -campholytic acid, showing that no isomeric change had taken place during esterification (see below).

That the acid obtained in the way described above was inactive  $\alpha$ -campholytic acid and identical with the acid first obtained by the reduction of  $\alpha$ -camphylic acid with sodium amalgam (Trans., 1903, 83, 853) was proved by digesting a small quantity with 25 per cent. sulphuric acid for a few minutes, when, on cooling, a mass of crystals of  $\beta$ -campholytic acid (*isolauronic acid*) separated.

These were collected, washed with water, and recrystallised from dilute acetic acid, when leaflets were obtained which melted at 130°.

0.1681 gave 0.4318 CO<sub>2</sub> and 0.1394 H<sub>2</sub>O. C = 70.0; H = 9.1.

C<sub>9</sub>H<sub>14</sub>O<sub>2</sub> requires C = 70.1; H = 9.1 per cent.

identification. In the meantime, Komppa (*loc. cit.*) has published his brilliant synthesis of camphoric acid, which, once for all, establishes the correctness of Bredt's formula, and it is therefore quite unnecessary to investigate our much less satisfactory process any further.

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The identity of this acid with the  $\beta$ -campholytic acid, obtained by the action of aluminium chloride on camphoric anhydride, was proved, firstly, by mixing equal quantities of the two acids, when no alteration in the melting point could be detected, and, secondly, by converting the synthetical acid into *isolauronic acid* by oxidation.

Two grams of the synthetical acid were dissolved in aqueous sodium carbonate, cooled with powdered ice, and then 2 per cent. potassium permanganate solution run in, drop by drop, until the pink colour just remained. The slight excess was destroyed by the addition of sodium sulphite, the whole was then heated to boiling and filtered, and the filtrate evaporated to a small bulk. The yellow liquid gave, on acidifying, a mass of pale yellow crystals which, after crystallising from water, melted at  $133^{\circ}$  and consisted of pure *isolauronic acid*.

0.1149 gave 0.2720  $\text{CO}_2$  and 0.0753  $\text{H}_2\text{O}$ . C = 64.5; H = 7.3.

$\text{C}_9\text{H}_{12}\text{O}_3$  requires C = 64.3; H = 7.1 per cent.

Inactive  $\alpha$ -campholytic acid has been repeatedly obtained during the course of the experiments which have been carried out with  $\gamma$ -bromo-trimethylpentamethylenecarboxylic acid and with  $\alpha$ -campholactone. Thus, for example, it is formed almost quantitatively when the bromo-acid is digested with potassium cyanide in alcoholic solution and when  $\alpha$ -campholactone is heated with dry potassium cyanide at  $110^{\circ}$ .

The authors wish to express their thanks to Mr. D. T. Jones for his valuable assistance in carrying out these experiments, and to state that much of the expense incurred during this investigation has been met by repeated grants from the Government Grant Fund of the Royal Society.

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MANCHESTER.

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