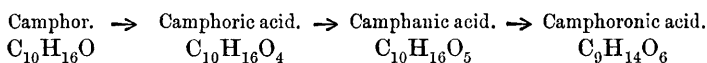


CXII.—*Synthesis of i-Camphoronic Acid.*

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

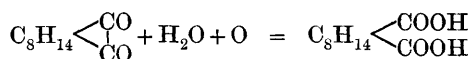
AMONG the reactions which, up to the present, have thrown light on the constitution of camphor, its oxidation by means of nitric acid has probably yielded by far the most valuable results. Laurent (*Annalen*, 1837, 22, 135) first showed that camphoric acid was formed during this process, and Kachler (*Annalen*, 1871, 159, 302) first isolated camphoronic acid from the products of the oxidation; subsequently, Roser (*Ber.*, 1885, 18, 3112) obtained camphanic acid (hydroxy-camphoric acid) from the mother liquors which remain when the camphoric and camphoronic acids have been separated. Since camphoric acid may be converted into camphanic acid by careful oxidation (Balbiano, *Rend. Acc. Lincei*, 1893, ii, 240), whilst camphanic acid itself, by treatment with nitric acid or chromic acid, yields considerable quantities of camphoronic acid (Bredt, *Ber.*, 1835, 18, 2989; Koenigs, *Ber.*, 1893, 26, 2337), it is evident that these three acids represent, as Bredt has pointed out, distinct stages in the decomposition of the camphor molecule; the oxidation of camphor may consequently be represented thus:



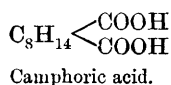
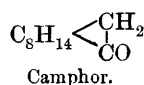
Camphoric acid has been obtained from camphor by Claisen and Manasse (*Annalen*, 274, 86) by a second very interesting method. These chemists converted camphor into isonitrosocamphor, $\text{C}_8\text{H}_{14} \begin{smallmatrix} \diagup \text{C:NOH} \\ \diagdown \text{CO} \end{smallmatrix}$, by the action of amylic nitrite and sodium methoxide;

by subsequently treating this substance with nitrous acid, they discovered camphorquinone, $\text{C}_8\text{H}_{14} \begin{smallmatrix} \diagup \text{CO} \\ \diagdown \text{CO} \end{smallmatrix}$, an interesting substance

which, when digested with a solution of potash in methylic alcohol, is slowly oxidised (probably by the oxygen of the air) to camphoric acid,



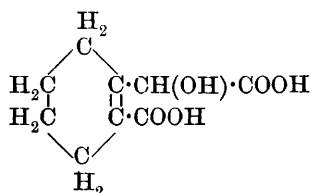
This series of reactions indicates that camphoric acid is very closely related to camphor, and, indeed, it is usually supposed that the former is derived from the latter by the oxidation of the group $-\text{CH}_2\cdot\text{CO}-$ to two carboxyl groups, the relationship being well understood from the formulæ



Many experiments have been made with the object of determining the constitution of camphoric acid, and many formulæ have been suggested for this substance ; but it is hardly likely that its constitution will be definitely established until the acid has been prepared synthetically.

In the meantime, chemists have also been busily engaged in endeavouring to discover the constitution of camphoronic acid, as, if the constitution of this acid, which contains only one carbon atom less than camphoric acid, could be definitely settled, very important deductions could obviously be made with regard to the constitution of camphoric acid, and of camphor itself.

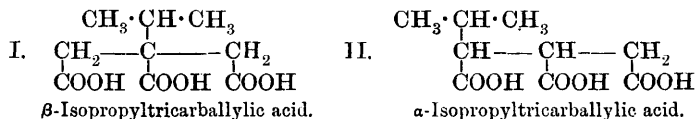
Kichler (*Annalen*, 1873, 169, 185), who first obtained camphoronic acid in a pure state, considered the acid to be a hydroxydibasic acid, $C_9H_{12}O_5$, crystallising with $1H_2O$, and he suggested the following formula as best expressing its constitution :



Kissling (*Inaug. Diss. Würzburg*, 1878) first showed that camphoronic acid had the formula $C_9H_{14}O_6$, and both he and Reyher (*Inaug. Diss. Leipzig*, 1891) considered the acid to be a hydroxyketodicarboxylic acid of the formula $CH(CH_3)_2 \cdot CH(COOH) \cdot CO \cdot CH_2 \cdot CH(OH) \cdot COOH$.

Bredt (*Annalen*, 1884, 226, 249—261) it was who, as the result of a careful investigation of the salts of camphoronic acid, first clearly showed that the acid was tribasic ; and further, as the acid distilled under diminished pressure without decomposing, he concluded that the three carboxyl groups must be attached to three different carbon atoms, otherwise, if any two carboxyl groups were attached to the same carbon atom, the acid would be a substituted malonic acid, and like this acid lose carbon dioxide at high temperatures.

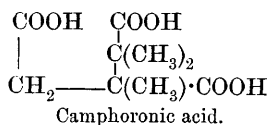
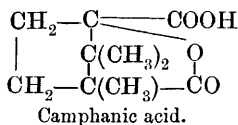
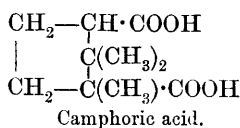
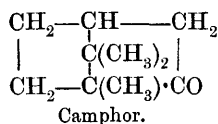
Bredt, at that time, thought it possible that the constitution of camphoronic acid was represented by one of the following formulæ, of which he considered I the more probable :



Subsequently, Collie (*Ber.*, 1892, 25, 1116) arrived at the second formula for camphoronic acid, from the consideration of a new constitution for

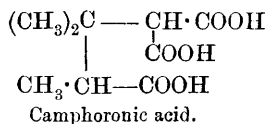
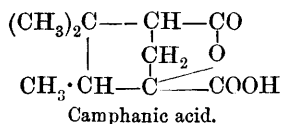
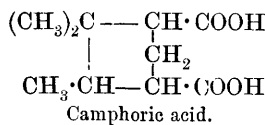
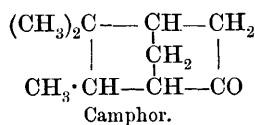
camphor which he had suggested, but this formula was clearly proved to be incorrect by Kölner and von Meyenburg (*Ber.*, 1891, **24**, 2899), who prepared α -isopropyltricarballic acid synthetically, and showed that its properties were quite different from those of camphoronic acid.

The next important step, which had a direct bearing on the question of the constitution of camphoronic acid, was the discovery by Bredt and Helle (*Ber.*, 1885, **18**, 2990; 1893, **26**, 3049) that this acid, when distilled under the ordinary pressure, is slowly but almost completely decomposed with formation of trimethylsuccinic acid, isobutyric acid, and other products. Since the formation of trimethylsuccinic acid in this way is an indication that camphoronic acid probably contains the group $\text{COOH} \cdot \text{C}(\text{CH}_3)_2 \cdot \text{C}(\text{CH}_3) \cdot \text{COOH}$, Bredt proposed the formula $\text{COOH} \cdot \text{C}(\text{CH}_3)_2 \cdot \text{C}(\text{CH}_3)(\text{COOH}) \cdot \text{CH}_2 \cdot \text{COOH}$ for camphoronic acid, and represented the series—camphor, camphoric acid, camphanic acid, and camphoronic acid—in the following way:



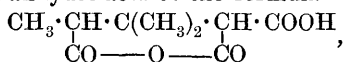
bringing out very clearly the relationship which exists between them.

Recently Tiemann (*Ber.*, 1895, **28**, 1089) suggested a modification of Bredt's formula as the probable constitution of camphor, and was thus led to represent the above series in quite a different way.



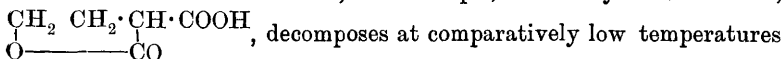
It is remarkable that Tiemann should have suggested a formula for camphoronic acid which contains the group $-\text{CH}(\text{COOH})_2$, especially when it is borne in mind that this acid may be distilled without loss of carbon dioxide at 200° under reduced pressure, a behaviour which is shown by no other derivative of malonic acid. In order to get over

this difficulty, Tiemann assumes that camphoronic acid, when heated, is converted into an anhydro-acid of the formula



and that this acid is stable at high temperatures.

But, as was pointed out by one of us (*Proc.*, 1896, p. 189), compounds of this nature when heated lose carbon dioxide in the same way as derivatives of malonic acid; for example, carbobutyrolactonic acid,



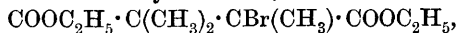
decomposes at comparatively low temperatures quite readily into butyrolactone and carbon dioxide, but a still better example is given by Bredt (*Annalen*, 1896, **292**, 130) in ethylmethylcarboxyglutaric acid, $\text{COOH} \cdot \text{CH}(\text{CH}_3)_2 \cdot \text{CH}_2 \cdot \text{C}(\text{C}_2\text{H}_5)(\text{COOH})_2$ (Bischoff, *Ber.*, 1891, **24**, 1050), the formula of which is closely related to Tiemann's formula for camphoronic acid, and which, when heated at 166.5° , melts with evolution of carbon dioxide.

In order, however, to bring still further evidence against Tiemann's formula camphoronic acid was heated under conditions which precluded the possibility of the formation of the anhydro-acid, namely, in solution in water at 230° , and still no decomposition could be detected, the acid being recovered quite unchanged on evaporating the solution (Perkin, *loc. cit.*).

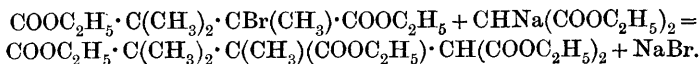
Subsequently, Bredt (*Annalen*, 1896, **292**, 131) showed that the tri-ethylic salt of camphoronic acid does not react with sodium, as it would be expected to do if it contained the group $-\text{CH}(\text{COOC}_2\text{H}_5)_2$.

Whilst, then, it had been shown that Tiemann's formula was incorrect, it still remained to prove definitely the correctness of Bredt's formula, and the most satisfactory way of doing this seemed to be to prepare an acid of this formula synthetically, and to compare the synthetical acid with that obtained from camphor.

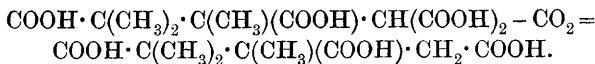
The first experiments on this subject were instituted by Dr. Bone and one of us, and the method which was then tried was the following. Ethylic bromotrimethylsuccinate,



was first prepared by brominating trimethylsuccinic anhydride and treating the bromo-anhydride thus obtained with alcohol. This ethereal salt was then digested in alcoholic solution with ethylic sodiomalonate, when it was expected that the following reaction would take place.

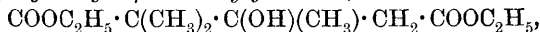


The ethereal salt thus formed should, on hydrolysis and elimination of carbon dioxide, yield camphoronic acid,

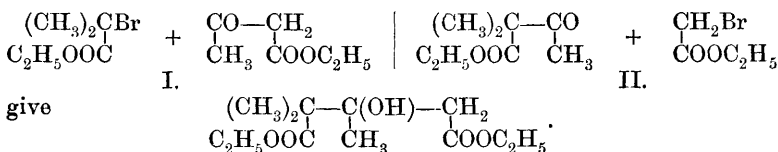


The product of this reaction, after hydrolysis and subsequent heating at 180°, was carefully investigated, but it did not appear to contain camphoronic acid. As, however, we were at that time not sufficiently well acquainted with the method of isolation of small quantities of camphoronic acid, we are again investigating this reaction, and hope soon to be able to communicate the results of our experiments to the Society. Several other reactions which seemed likely to yield camphoronic acid were subsequently investigated, but also without success, until ultimately the method which is described in this paper was devised and found on trial to give the desired result.

Ethylic β-hydroxy-ααβ-trimethylglutarate,



was prepared by two different reactions which left no doubt as to its constitution, namely, the action of zinc on mixtures of (I) ethylic acetoacetate with ethylic bromisobutyrate, and (II) ethylic dimethyl-acetoacetate with ethylic bromacetate.*



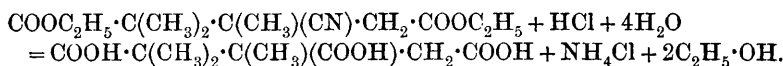
In both cases, an ethereal salt boiling at 165° (30 mm.) was obtained; this consisted for the most part of ethylic hydroxytrimethylglutarate, but mixed with varying quantities of ethylic trimethylglutaconate, $\text{COOC}_2\text{H}_5 \cdot \text{C}(\text{CH}_3)_2 \cdot \text{C}(\text{CH}_3) : \text{CH} \cdot \text{COOC}_2\text{H}_5$, the latter being produced by the elimination of water from the hydroxy-compound, either during the condensation, or more probably during the subsequent fractionation of the ethereal salt under reduced pressure. Since, then, the products from the two reactions represented above are identical, there can be no doubt as to the constitution of the compound used as the starting point in this synthesis. When ethylic hydroxytrimethylglutarate, obtained by either of these methods, is hydrolysed with dilute hydrochloric acid, β-hydroxy-ααβ-trimethylglutaric acid, $\text{COOH} \cdot \text{C}(\text{CH}_3)_2 \cdot \text{C}(\text{OH})(\text{CH}_3) \cdot \text{CH}_2 \cdot \text{COOH}$, melting at 128° is produced, together with small quantities of trimethylglutaconic acid, $\text{COOH} \cdot \text{C}(\text{CH}_3)_2 \cdot \text{C}(\text{CH}_3) : \text{CH} \cdot \text{COOH}$; if, however, concentrated hydrochloric acid is employed, the product of the reaction consists almost entirely of the latter acid. Boiling with alcoholic potash decomposes ethylic hydroxytrimethylglutarate with formation of acetic and isobutyric acids.

* Compare Trans., 1896, 69, 1463.

Ethyl hydroxytrimethylglutarate is readily acted on by phosphorus pentachloride with formation of ethyl chlorotrimethylglutarate, $\text{COOC}_2\text{H}_5 \cdot \text{C}(\text{CH}_3)_2 \cdot \text{CCl}(\text{CH}_3) \cdot \text{CH}_2 \cdot \text{COOC}_2\text{H}_5$, boiling at 139° under 20 mm. pressure; this has been obtained in a pure condition only on one or two occasions, as usually it contains varying quantities of ethyl trimethylglutaconate, which, as stated above, is present in the hydroxy-ethereal salt prepared by the methods adopted. Ethyl bromotrimethylglutarate, prepared in an analogous way, boils at 160° (35 mm.). If either the chloro- or bromo-derivative is heated with potassium cyanide and alcohol at 160° for 12 hours, ethyl cyano-trimethylglutarate, $\text{COOC}_2\text{H}_5 \cdot \text{C}(\text{CH}_3)_2 \cdot \text{C}(\text{CN})(\text{CH}_3) \cdot \text{CH}_2 \cdot \text{COOC}_2\text{H}_5$, is obtained as a colourless oil which distils approximately at $170\text{--}175^\circ$ (25 mm.); this, like the bromo- and chloro-derivatives, always contains varying quantities of ethyl trimethylglutaconate, so much of the latter sometimes being present that it must evidently be produced by the action of the potassium cyanide on the halogen ethereal salt.

When the cyano-ethereal salt is hydrolysed by boiling with hydrochloric acid, and the product allowed to cool, large quantities of trimethylglutaconic acid separate; and the amount is usually so considerable that we are forced to the conclusion that some of it must be formed by the elimination of hydrogen cyanide during the hydrolysis.

If now the crystals of trimethylglutaconic acid are removed by filtration, and the filtrate, after being rendered strongly alkaline with ammonia, is mixed with barium chloride, no precipitate is produced in the cold, but, on boiling, a small quantity of a sparingly soluble barium salt separates; this has been proved to be the barium salt of *i*-camphoronic acid, the synthesis of the acid having taken place thus:



Aschan (*Ber.*, 1895, 28, 16 and 224), who has so carefully examined camphoronic acid, has shown that this acid is capable of existing in three well-defined modifications, namely, as *d*-, *l*-, and *i*-camphoronic acid. *d*-Camphoronic acid,* produced by the oxidation of *d*-camphor and of *d*-camphoric acid, melts at 156° , dissolves in 6 parts of water at 20° , and is laevorotatory, $[\alpha]_D = -26.9$.

l-Camphoronic acid, which was isolated by Aschan from the residues

* As ordinary camphoronic acid is derived from the oxidation of *d*-camphor and *d*-camphoric acid, it appears to us that, although it happens to be laevorotatory, it must nevertheless be called *d*-camphoronic acid; the relationship between these substances being somewhat similar to that of *d*-glucose and *d*-fructose, the latter receiving the prefix *d* in spite of its powerful laevorotatory action, owing to its belonging to the same class as *d*-glucose. For this reason we have taken the liberty of reversing the prefixes *d* and *l* used by Aschan.

obtained in the preparation of *l*-camphoric acid from *l*-borneol, melts at 158—159°, dissolves in 6 parts of water at 20°, and is dextrorotatory, the value $[\alpha]_D^{20} = +27.05$ corresponding exactly with the reverse value of the *d*-acid.

i-Camphoronic acid was prepared by Aschan by mixing solutions of equal proportions of the *d*- and *l*-acids; it differs from the active acids in being much less soluble in water (1 part requires 27 parts of water at 20°), in crystallising in much better defined crystals, and in melting at a somewhat higher temperature, namely, about 172°.

Thanks to the kindness of Dr. Aschan in sending us a small sample of his inactive acid, we were enabled to compare its properties with those of the synthetical acid obtained by us, the result proving that the two acids are identical, the following points being perhaps especially worthy of notice.

(1) Both acids crystallise from water in hard, transparent prisms, which, when examined under the microscope, are seen to be identical in form.

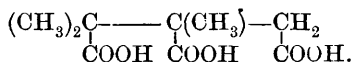
(2) Both acids when heated side by side on the same thermometer soften at about 167° and melt at 169—172°, moreover, no alteration in the melting point could be observed when they were mixed in equal proportions.

(3) A solution of either acid in water, after the addition of excess of ammonia, gives no precipitate with barium chloride in the cold, but on warming a very sparingly soluble barium salt separates, closely resembling barium sulphate in appearance.

(4) When heated with acetic anhydride under the conditions described in the experimental part of this paper, both acids give the same *anhydrocamphoronic acid*, melting at about 136—137°.

(5) An aqueous solution of the synthetical acid was examined by Dr. W. H. Perkin, sen., and found to be inactive.

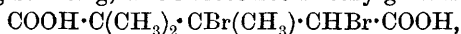
There can be no doubt that the synthetical acid is *i*-camphoronic acid, and this synthesis proves conclusively that camphoronic acid must, as was first suggested by Brecht (*Ber.*, 1893, 26, 3049), have the constitution of a trimethyltricarballic acid of the formula



It is very unfortunate that, for reasons stated above, the yield of camphoronic acid obtained in this synthesis should be small, so small, indeed, as to necessitate the employment of large quantities of material in order to prepare a few grams of the acid. In order to determine whether an independent worker would get the same result as we had done, we requested Mr. Hodgson, a student of Owens College, to repeat from the commencement the whole of our experiments on the synthesis

and isolation of camphoronic acid, and he prepared in the course of his repetition of our work about 2 grams of the pure synthetical acid. We are much indebted to Mr. Hodgson for so kindly placing his time (nearly 4 months) at our disposal, and for the skill with which he carried out this very difficult piece of experimental work.

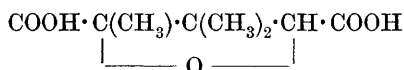
During the course of the above synthetical experiments, a considerable quantity of trimethylglutaconic acid had accumulated, and this we have very carefully investigated, and with very interesting results. Trimethylglutaconic acid, $\text{COOH} \cdot \text{C}(\text{CH}_3)_2 \cdot \text{C}(\text{CH}_3) : \text{CH} \cdot \text{COOH}$, although unsaturated, is scarcely attacked in the cold by alkaline permanganate, and its solution in chloroform does not decolorise bromine except on long standing, when dibromotrimethylglutaric acid,



melting at 169° , is produced. Sodium amalgam appears to have no action on the solution of the acid in caustic soda even on boiling, and, indeed, great difficulty was experienced in reducing the acid at all; ultimately, however, this was accomplished by repeatedly treating the acid in boiling alcoholic solution with sodium.*

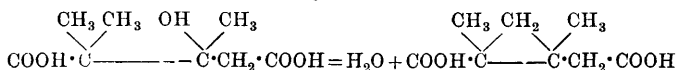
ααβ-Trimethylglutaric acid, obtained in this way, is a beautifully crystalline substance which melts at 112° and shows all the properties of a substituted glutaric acid: it is an acid of more than ordinary interest for the following reasons.

In 1894, Balbiano (*Berichte*, 1894, 27, 2133), by the oxidation of camphoric acid with permanganate at the ordinary temperature, obtained a crystalline acid of the formula $\text{C}_8\text{H}_{12}\text{O}_5$, the constitution of which, after very careful examination, he now (*Berichte*, 1897, 30, 1908) expresses by the formula

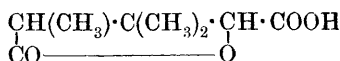


This acid on reduction with hydriodic acid is converted into a monobasic lactone acid of the probable formula

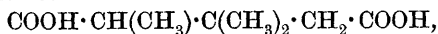
* This extraordinary stability of trimethylglutaconic acid seems to suggest that there is a possibility of the constitution of the acid being represented by a formula different from that given above. In the elimination of water from hydroxytrimethylglutaric acid or its ethereal salt (or of hydrogen chloride or bromide from the corresponding chloro- or bromo-derivative), it is possible that the change may take place thus with formation of a trimethylene derivative



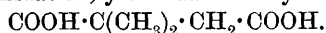
If the acid, called by us trimethylglutaconic acid, should prove to have the constitution represented by the latter formula, it would be easy to understand its stability towards permanganate, bromine, and reducing agents.



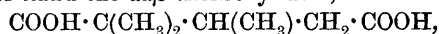
and this, on further reduction, yields a trimethylglutaric acid, which Balbiano assumed to have the formula



since this acid, on oxidation, yields $\alpha\alpha$ -dimethylsuccinic acid,



This decomposition is no doubt best explained on the assumption that this trimethylglutaric acid has the formula given to it by Balbiano, but on the other hand the $\alpha\alpha\beta$ -trimethyl acid,

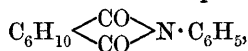


might also yield $\alpha\alpha$ -dimethylsuccinic acid on oxidation, and therefore, in order to determine the constitution of Balbiano's acid, it was necessary to synthesise either the $\alpha\alpha\beta$ - or the $\alpha\beta\beta$ -trimethylglutaric acid, and directly compare the synthetical acid with the acid from camphor.

In view of the great interest attaching to Balbiano's work, we have carefully studied our $\alpha\alpha\beta$ -trimethylglutaric acid, and we find that, when pure, this acid melts at 112° , that it gives an *anhydride* melting at 39° , and an *anilic acid* melting at 155° . Balbiano's trimethylglutaric acid, on the other hand, melts at $88-89^\circ$, gives an anhydride melting at 81° , and an anilic acid * melting, not quite sharply, at $149-150^\circ$.

From this, it is evident that Balbiano's acid is isomeric with our $\alpha\alpha\beta$ -trimethylglutaric acid, and it must therefore be, as its discoverer suggested, the $\alpha\beta\beta$ -acid, $\text{COOH} \cdot \text{C}(\text{CH}_3) \cdot \text{C}(\text{CH}_3)_2 \cdot \text{CH}_2 \cdot \text{COOH}$.

During the course of our experiments on the reduction of trimethylglutaconic acid, we found that this acid, when treated in boiling amyllic alcohol solution with sodium is, curiously enough, *not reduced*, but is converted into a most beautifully crystalline substance of the formula $\text{C}_8\text{H}_{10}\text{O}_3$. This compound crystallises from water unchanged, but it is, nevertheless, the anhydride of a dibasic acid, since it gives, with aniline, an *anilic acid*, $\text{C}_6\text{H}_{10}(\text{COOH}) \cdot \text{CO} \cdot \text{NH} \cdot \text{C}_6\text{H}_5$ (m. p. 138°) and this, when heated, is readily converted into the corresponding *anil*,



melting at 148° .

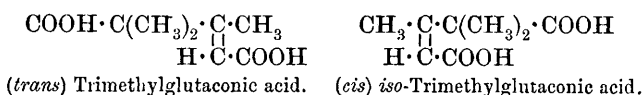
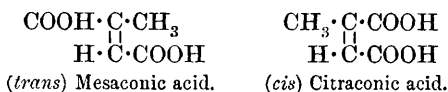
* This $\alpha\beta\beta$ -trimethylglutaranilic acid had not been described, and we prepared it for comparison with our isomeric anilic acid by dissolving 0.7 gram of the anhydride of Balbiano's acid in benzene, adding 0.7 gram of aniline and allowing the mixture, which became very warm, to stand. The crystals which separated were collected, recrystallised from dilute methylic alcohol, and the glistening, crystalline mass, which melted approximately at 149° , was analysed with the following result:

0.1117 gram gave 5.4 c.c. nitrogen at 17° and 760 mm. $\text{N} = 5.60$.

$\text{C}_{14}\text{H}_{19}\text{NO}_3$ requires $\text{N} = 5.63$ per cent.

The anhydride, which we have named *iso-trimethylglutaconic anhydride*, dissolves in boiling potash solution, and if the solution be cooled to 0° and acidified with hydrochloric acid, the corresponding *iso-trimethylglutaconic acid* is obtained.

At its melting point (133°), this acid is converted into its anhydride with elimination of water, and the ease with which the anhydride is formed is shown by the fact that if the aqueous solution of the acid is boiled, the anhydride, and not the acid, separates on cooling. It seems probable that trimethylglutaconic acid and *iso*-trimethylglutaconic acid like fumaric and maleic acids, or mesaconic and citraconic acids, are stereoisomeric. The similarity in constitution between the two latter acids and the glutaconic acids becomes very clear from an examination of the following formulæ.



The *cis*-modification of trimethylglutaconic acid would, like maleic and citraconic acids, readily yield an anhydride, but it is certainly remarkable that the formation of this anhydride should take place so very easily, the only analogous case being that of xeronic acid (diethylmaleic acid), an acid which is in many respects very similar to *iso*-trimethylglutaconic acid in its properties.

We are at present engaged in a further investigation of the trimethylglutaconic acids with a view of determining whether, and under what conditions, they may be converted into one another.

EXPERIMENTAL.

Condensation of Ethylic Dimethylacetoacetate with Ethylic Bromacetate in the presence of Zinc. Formation of Ethylic αβ-Trimethyl-β-hydroxyglutarate, $\text{COOC}_2\text{H}_5 \cdot \text{C}(\text{CH}_3)_2 \cdot \text{C}(\text{OH})(\text{CH}_3) \cdot \text{CH}_2 \cdot \text{COOC}_2\text{H}_5$.

After numerous experiments, it was found that this condensation could best be carried out in the following way.

Ethylic dimethylacetoacetate (50 grams) mixed with ethylic bromacetate (50 grams) is heated in a reflux apparatus on a water bath until the mixture has reached the temperature of 90—95°; a small quantity of zinc* (about 1 gram) is then added, and the flask shaken

* In order that this reaction may proceed satisfactorily, the zinc used must be thoroughly cleaned, that is, it must be quite free from grease and oxide; with this object, commercial zinc turnings are first passed through a sieve to remove the

vigorously until the metal has almost dissolved; another gram of zinc is then added and the process continued until the metal is only very slowly attacked; excess of zinc is now added and the whole heated on the water bath for 10—12 hours.

The addition of the zinc* to the hot mixture of ethylic salts in this experiment should be carefully carried out, as otherwise a very violent action may set in, in which case there is a great decrease in the yield owing to overheating and loss of the bromethylic salt by evaporation and decomposition.

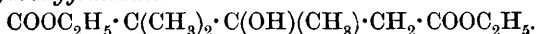
The product consists of a brown, viscous zinc compound containing large quantities of unchanged zinc. On adding dilute sulphuric acid (1:10), the zinc compound is decomposed and a brown oil separates which is extracted by three successive treatments with ether, the ethereal solution is washed at least six times with dilute sulphuric acid, then with water, dried over potassium carbonate, and the ether distilled off. It is most important that the ethereal solution should be thoroughly and repeatedly washed with dilute sulphuric acid, as insufficient washing always yields a product containing zinc salts and which decomposes on subsequent distillation. On distilling the oil under reduced pressure (30 mm.), a large quantity of a fraction of low boiling point is first obtained consisting largely of unchanged ethylic dimethylacetoacetate, the thermometer then rises rapidly to 160°, the crude condensation product passing over between this temperature and 180°, leaving a small quantity of substance of high boiling point. On refractionation, the bulk distils at 160—170° (30 mm.). The fraction distilling at 165° (30 mm.) gave the following results on analysis.

0.1420 gave 0.3056 CO₂ and 0.1140 H₂O. C = 58.69; H = 8.92.

0.1278 „ 0.2751 CO₂ and 0.1041 H₂O. C = 58.60; H = 9.05.

C₁₂H₂₂O₅ requires C = 58.54; H = 8.94 per cent.

The substance prepared in this way is a colourless, moderately limpid liquid with a peculiar smell, and consists for the most part of *ethylic trimethylhydroxyglutarate*.

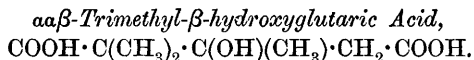


It appears, however (see p. 1173), always to contain some ethylic $\alpha\alpha\beta$ -trimethylglutaconate, $\text{COOC}_2\text{H}_5 \cdot \text{C}(\text{CH}_3)_2 \cdot \text{C}(\text{CH}_3) : \text{CH} \cdot \text{COOC}_2\text{H}_5$,

coarser particles, and well washed, first with water, then with hot dilute soda, again with water, and lastly with very dilute hydrochloric acid and water. Finally, the zinc is dried by treatment with alcohol and ether, and subsequent heating in a steam oven.

* In some cases, no action takes place for a long time, the zinc being only very slowly attacked, whilst in others, apparently under exactly the same conditions, the zinc dissolves at once, with considerable rise of temperature. The yield of condensation product is undoubtedly more satisfactory when the reaction proceeds quietly.

produced probably by elimination of water during distillation; sometimes it contains traces only of the unsaturated ethereal salt, whilst at other times large quantities are present.



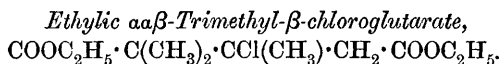
When ethylic trimethylhydroxyglutarate is digested with alcoholic potash, it is entirely split up into acetic and isobutyric acids, but if carefully boiled with dilute hydrochloric acid (3 acid : 1 water) for about 10 to 12 hours, hydrolysis ensues without appreciable decomposition; on cooling, a small quantity of trimethylglutaconic acid, $\text{COOH}\cdot\text{C}(\text{CH}_3)_2\cdot\text{C}(\text{CH}_3)\cdot\text{CH}\cdot\text{COOH}$ (p. 1182), separates in the crystalline state.

On allowing the mother liquor from these crystals to evaporate to dryness over potash in a vacuum desiccator, an acid was obtained which, after recrystallisation from a mixture of ethylic acetate and light petroleum, gave the following results on analysis.

0.2134 gave 0.3936 CO_2 and 0.1421 H_2O . C = 50.30; H = 7.4.

$\text{C}_8\text{H}_{14}\text{O}_5$ requires C = 50.52; H = 7.36 per cent.

This acid is evidently *trimethylhydroxyglutaric acid*, produced by the direct hydrolysis of the ethereal salt; it crystallises in well-defined, colourless prisms, melts at 128° , and is readily soluble in water and in most solvents except light petroleum.



This ethereal salt was prepared by gradually adding phosphorus pentachloride (25 grams) to ethylic trimethylhydroxyglutarate (25 grams) contained in a flask connected with a long tube to lead off the hydrogen chloride produced during the action.

The pentachloride rapidly attacks the oil, and a vigorous reaction takes place with considerable rise of temperature and evolution of much hydrogen chloride; after about an hour, and as soon as the pentachloride has entirely disappeared, the reaction is completed by heating for 15 minutes on the water bath.

The product is now carefully poured into ice cold alcohol, the alcoholic solution, after some time, is mixed with water, the oily deposit extracted with ether, and the ethereal solution well washed with water and dilute sodium carbonate. After drying over calcium chloride and distilling off the ether, crude ethylic trimethylchloroglutarate is obtained as a slightly yellowish oil, which is somewhat unstable, as on distilling it under the ordinary pressure, hydrogen chloride is eliminated

with production of ethylic trimethylglutaconate; under diminished pressure (20 mm.), however, it passes over unchanged at 139° as a colourless oil. On analysis, it yielded the following numbers.

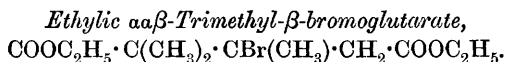
0.2010 gave 0.1935 AgCl. Cl = 13.39.

$C_{12}H_{21}ClO_4$ requires Cl = 13.42 per cent.

The action of phosphorus pentachloride on ethylic trimethylhydroxyglutarate has been carried out in a variety of ways and under various conditions, but only on rare occasions has the product been found to contain the theoretical amount of chlorine as in the case given above.

Frequently the oil has contained only 7—8 per cent. of chlorine, whilst on one occasion it was almost free from halogen, and was found on examination to consist of almost pure ethylic trimethylglutaconate. This unpleasant behaviour, which very much retarded the progress of this research, may be explained by the unsuspected presence of large quantities of ethylic trimethylglutaconate in some of the samples of crude ethylic trimethylhydroxyglutarate used, and also by the elimination of hydrogen chloride from the product of the reaction during distillation, this being due possibly to the presence of moisture and other impurities.

The elimination of hydrogen chloride from ethylic trimethylchloroglutarate undoubtedly takes place very readily; it was found, for example, impossible to reduce it even when ice-cold alcoholic hydrogen chloride and zinc dust were employed as the reducing agent; the temperature was never allowed to rise above 0°, but notwithstanding these precautions the product consisted entirely of ethylic trimethylglutaconate.



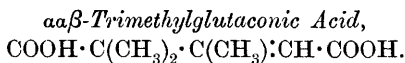
This is prepared in a precisely similar manner to the chloro-derivative just described, namely, by the gradual addition of phosphorus pentabromide (52 grams) to ethylic trimethylhydroxyglutarate (25 grams), and subsequently heating the product for a short time on the water bath. It was isolated, exactly as in the case of the chlorinated compound, as a yellowish oil (28 grams) which distilled with slight decomposition at about 145° (18 mm.).

0.2542 gave 0.138 AgBr. Br = 23.12.

$C_{12}H_{21}BrO_4$ requires Br = 25.23 per cent.

The percentage of bromine in the various samples of this bromo-ethereal salt which were prepared during the course of this research varied considerably, although not nearly to the same extent as in the

case of the corresponding chlorinated ethereal salt ; it appears, therefore, that the former is more stable than the latter, and this was borne out by subsequent experiments with these compounds.



During the course of this investigation, this acid has been prepared by a variety of methods, of which the following may be described.

I. *By the Hydrolysis of Ethylic Trimethylhydroxyglutarate.*—It has already been mentioned (p. 1180) that this ethereal salt, when treated with alkalis, does not yield the corresponding acid, but is split up into acetic and isobutyric acids ; if, however, the hydrolysis is carried out by boiling with concentrated hydrochloric acid until the oily ethereal salt has disappeared, the solution on cooling deposits crystals of trimethylglutaconic acid.

After recrystallisation from water, this acid was readily obtained pure, melting at 148° .

0.1663 gave 0.3378 CO_2 and 0.1061 H_2O . $\text{C} = 55.31$; $\text{H} = 7.08$.

$\text{C}_8\text{H}_{12}\text{O}_4$ requires $\text{C} = 55.80$; $\text{H} = 6.97$ per cent.

II. *By the Action of Diethylaniline on Ethylic Trimethylbromoglutarate.*—In this experiment, the brominated ethereal salt (23 grams) mixed with diethylaniline (50 grams) was heated to gentle ebullition in a reflux apparatus for about an hour. The dark coloured product, when cold, was mixed with excess of dilute hydrochloric acid, extracted three times with ether, and the ethereal solution, after being well washed with dilute acid, was dried over potassium carbonate and evaporated ; the oily residue, on being submitted to two fractionations under reduced pressure, passed over almost entirely at $160\text{--}165^\circ$ (30 mm.), and consisted of nearly pure ethylic trimethylglutaconate as the following analysis shows.

0.1390 gave 0.3210 CO_2 and 0.1140 H_2O . $\text{C} = 62.98$; $\text{H} = 9.11$.

$\text{C}_{12}\text{H}_{20}\text{O}_4$ requires $\text{C} = 63.16$; $\text{H} = 8.77$ per cent.

The results of the hydrolysis of this ethereal salt with alcoholic potash were not very satisfactory, the acid obtained being contaminated with some sticky substance which rendered it difficult to purify. It is far better to boil it with hydrochloric acid until the oily drops have disappeared ; on cooling, crystals of trimethylglutaconic acid separate and can be readily purified by a single crystallisation from water.

0.1110 gave 0.2279 CO_2 and 0.0710 H_2O . $\text{C} = 55.95$; $\text{H} = 7.10$.

$\text{C}_8\text{H}_{12}\text{O}_7$ requires $\text{C} = 55.80$ $\text{H} = 6.97$ per cent.

Alcoholic potash appears to act on ethylic trimethylchloro- or bromoglutarate in somewhat the same way as diethylaniline, since in both cases considerable quantities of trimethylglutaconic acid are formed.

III. *By the Action of Zinc Dust on Ethylic Trimethylchloroglutarate.*—This method, which is a rather curious one to employ in obtaining an unsaturated acid, gives such a good yield of trimethylglutaconic acid that it was usually employed in preparing this substance.

Ethylic trimethylchloroglutarate (25 grams) dissolved in absolute alcohol (100 grams) was saturated with hydrogen chloride, and about 20 grams of zinc dust was then gradually added to the well cooled solution; when all had dissolved, the product was poured into water and extracted three times with ether. The ethereal solution, after being thoroughly washed with water and with dilute sodium carbonate, was dried over anhydrous potassium carbonate, evaporated, and the residual almost colourless oil purified by distillation under reduced pressure (30 mm.); almost the whole passed over between 160° and 165°, the distillate consisting of nearly pure ethylic trimethylglutaconate containing evidently, at the most, only a trace of ethylic trimethylglutarate.

0.2204 gave 0.5113 CO₂ and 0.1733 H₂O. C = 63.27; H = 8.74.

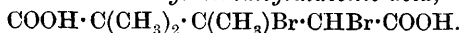
C₁₂H₂₀O₄ requires C = 63.15; H = 8.77 per cent.

On hydrolysing this ethereal salt with hydrochloric acid as before, the oily drops disappeared after 12 hours' boiling, and on cooling a large quantity of a crystalline acid slowly separated. This, after being collected and recrystallised from water, was analysed and found to be trimethylglutaconic acid.

0.1510 gave 0.3074 CO₂ and 0.0948 H₂O. C = 55.59; H = 6.97.

C₈H₁₂O₄ requires C = 55.80; H = 6.97 per cent.

Trimethylglutaconic acid is sparingly soluble in cold water, but dissolves readily in boiling water, and separates on cooling in well-defined, lustrous plates which melt at 148°. It is remarkable that its solution in sodium carbonate does not decolorise permanganate except on long standing; bromine also acts only very slowly on the acid, with ultimate formation of *trimethyldibromoglutaconic acid*,



(see next section).

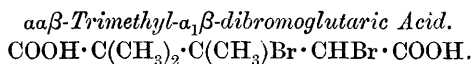
Salts of Trimethylglutaconic Acid. The silver salt, C₈H₁₀Ag₂O₄.—This is obtained as a white precipitate on adding silver nitrate to a slightly alkaline solution of the ammonium salt

0.2170, on ignition, gave 0.1211 Ag. Ag = 55.85.

C₈H₁₀Ag₂O₄ requires Ag = 55.87 per cent.

The most characteristic salt of this acid is the *copper salt* which separates from the neutral solution of the ammonium salt on the addition of copper acetate, as a bright blue, crystalline precipitate which is sparingly soluble in water. This salt, which is useful in separating trimethylglutaconic acid from other acids, yields the acid in a beautifully pure condition when decomposed with sulphuretted hydrogen.

Trimethylglutaconic acid dissolves in acetyl chloride, but without formation of an anhydride, the solution, even after boiling for some time, depositing the unchanged acid on evaporation. On the other hand, prolonged boiling with acetic anhydride gives rise to the formation of an oil boiling at about 160—170° (30 mm.); this is at present under examination.



Bromine acts only very slowly on trimethylglutaconic acid dissolved in chloroform, but on long standing it is gradually absorbed with formation of the dibromo-acid above mentioned. In preparing it, excess of bromine was added to a solution of the unsaturated acid in chloroform and the mixture left for some weeks, during which time a quantity of crystals of the dibromo-compound had separated. The colourless crystals were washed with chloroform and analysed.

0.2901 gave 0.2433 AgBr. Br = 48.10.

$\text{C}_8\text{H}_{12}\text{O}_4\text{Br}_2$ requires Br = 48.19 per cent.

Trimethyldibromoglutaric acid melts and decomposes at about 169°; it is readily soluble in ether, alcohol, acetone, and ethylic acetate, less so in carbon bisulphide and chloroform, and almost insoluble in benzene and light petroleum. It is readily decomposed by boiling with aqueous silver nitrate solution, with separation of silver bromide.

iso-Trimethylglutaconic Anhydride.

It has already been stated that trimethylglutaconic acid is only reduced with great difficulty, and in investigating this subject, we on one or two occasions experimented on the action of sodium and boiling amyl alcohol on the acid, and with very remarkable results. The pure unsaturated acid (5 grams) was dissolved in amyl alcohol (600 c.c.), the solution heated to boiling, and then sodium (10 grams) added as rapidly as possible. When all the sodium had dissolved, the product was mixed with water, the amyl alcohol separated, and the aqueous solution boiled until the odour of amyl alcohol was no longer perceptible. The concentrated solution of the sodium salt was then acidified and extracted with ether, when a substance melting at

145—149° was obtained, which consisted chiefly of the unchanged acid. However, in subsequent experiments where the above process of reduction was repeated five times with the same substance, a product was isolated from the sodium salt which melted at 94—97°, and on recrystallisation from water at 107°. The analysis gave the following results.

0.1081 gave 0.2470 CO₂ and 0.0660 H₂O. C = 62.31 ; H = 6.79.

0.1201 „ 0.2734 CO₂ „ 0.0738 H₂O. C = 62.13 ; H = 6.83.

C₈H₁₀O₃ requires C = 62.33 ; H = 6.50 per cent.

This substance, which is an anhydride, and which we propose to name *iso*-trimethylglutaconic anhydride, crystallises from water unchanged ; it is insoluble in dilute solution of sodium carbonate, but dissolves slowly on boiling, and on carefully acidifying the cold solution, it deposits needles of the corresponding acid (see next section). The anhydride crystallises from acetic anhydride unchanged, and separates from a mixture of benzene and light petroleum in magnificent, glistening plates. *iso*-Trimethylglutaconic anhydride was subsequently obtained in considerable quantity in an experiment instituted with the object of preparing ethylic trimethylbromoglutarate (p. 1181), but in which by accident the wrong proportions of the materials were used. Ethylic trimethylhydroxyglutarate (50 grams) was mixed with phosphorus pentabromide (40 grams), and the mixture heated for 6 hours on the water bath ; the product, when cold, was poured into alcohol, without allowing the temperature to rise above 30°, water was then added, and the oily precipitate extracted with ether. After washing the ethereal solution well with water and dilute sodium carbonate solution, and evaporating the ether, a brownish, oily residue was left, the greater part of which distilled between 175° and 185° (35 mm.). The distillate, after being left in an ice chest for a few days, deposited a large quantity of crystals ; these were collected with the aid of the pump and crystallised from benzene and light petroleum. The product consisted of pure *iso*-trimethylglutaconic anhydride melting at 107°.

0.1356 gave 0.3088 CO₂ and 0.0822 H₂O. C = 62.11 ; H = 6.73.

0.1394 „ 0.3197 CO₂ „ 0.0846 H₂O. C = 62.60 ; H = 6.73.

C₈H₁₀O₃ requires C = 62.33 ; H = 6.50 per cent.

The oily filtrate from these crystals, on distillation, boiled at 158—165° under a pressure of 25 mm. ; it contained large quantities of bromine, and apparently consisted of ethylic trimethylbromoglutarate.

iso-Trimethylglutaconanilic Acid, $C_{14}H_{17}NO_3 = C_6H_{10} \begin{smallmatrix} \text{CO} \cdot \text{NH} \cdot C_6H_5 \\ \text{COOH} \end{smallmatrix}$.

In order to prepare this substance, the pure anhydride was dissolved in benzene and the solution mixed with aniline; very little rise of temperature took place, but on standing for a few days crystals gradually separated. These, when collected and recrystallised from warm dilute methylic alcohol, formed colourless needles.

0.1627 gave 8.2 c.c. nitrogen at 14° and 758 mm. $N = 5.91$.

$C_{14}H_{17}NO_3$ requires $N = 5.67$ per cent.

Trimethylglutaconanilic acid melts at about 138° with rapid decomposition and formation of the corresponding anil.

iso-Trimethylglutaconanil, $C_{14}H_{15}NO_2 = C_6H_{10} \begin{smallmatrix} \text{CO} \\ \text{CO} \end{smallmatrix} \text{N} \cdot C_6H_5$.

This is readily obtained by heating the anilic acid to boiling for a few minutes and recrystallising the residue from dilute methylic alcohol, when it separates in long, colourless needles melting at 148° .

0.1418 gave 7.2 c.c. nitrogen at 15° and 760 mm. $N = 5.96$.

$C_{14}H_{15}NO_2$ requires $N = 6.11$ per cent.

iso-Trimethylglutaconic Acid.

This acid could not be prepared by the action of water on the anhydride, as the latter is not acted on by water in the cold, and on boiling, although the anhydride dissolves, it separates again on cooling unchanged. If, however, the anhydride be boiled with excess of aqueous potash, and the solution after cooling to 0° be acidified with dilute hydrochloric acid, the acid will gradually separate as a woolly mass of very fine needles, which, after collecting by means of the pump, washing with ice-cold water, and drying on porous porcelain at the ordinary temperature, gave the following results on analysis.

0.1372 gave 0.2830 CO_2 and 0.0916 H_2O . $C = 56.25$; $H = 7.42$.

0.1522 „ 0.3117 CO_2 „ 0.0996 H_2O . $C = 55.90$; $H = 7.28$.

$C_8H_{12}O_4$ requires $C = 55.81$; $H = 7.00$ per cent.

iso-Trimethylglutaconic acid if rapidly heated melts at about 133° , with evolution of aqueous vapour and formation of the anhydride. It is readily soluble in alcohol, ether, or warm water, moderately so in cold water, and although it is possible to recrystallise the acid from water, the aqueous solution must not be boiled, otherwise the anhydride crystallises out on cooling.

Salts of iso-Trimethylglutaconic Acid.—The silver salt, $C_8H_{10}Ag_2O_4$, separates, on the addition of silver nitrate to the neutral solution of the ammonium salt, as a white, amorphous precipitate which, after washing well, and drying first on a porous plate and then at 100° , gave the following results on analysis.

0.2539 gave, on ignition, 0.1424 Ag. Ag = 56.08.

$C_8H_{10}Ag_2O_4$ requires Ag = 55.87 per cent.

The neutral solution of the ammonium salt shows the following behaviour with reagents.

Barium chloride gives at first no precipitate, but after a few minutes a beautifully crystalline barium salt separates in four-sided plates which are very sparingly soluble even in boiling water.

Calcium chloride gives at once a microcrystalline precipitate which is very sparingly soluble in boiling water.

Copper acetate gives no immediate precipitate even on boiling, but the solution, if left, gradually deposits a beautifully crystalline, copper salt; the crystals under the microscope are deep blue, but not well defined.

$\alpha\alpha\beta$ -Trimethylglutaric Acid, $COOH \cdot C(CH_3)_2 \cdot CH(CH_3) \cdot CH_2 \cdot COOH$.

On account of the interest attaching to the isolation and identification of this acid, which has already been noticed in the introduction to this paper, we made numerous experiments with the object of preparing it from ethylic trimethylhydroxyglutarate, but in performing this apparently simple experiment we met with quite unexpected difficulties. We, in the first place, endeavoured to reduce the hydroxy-etheral salt directly by heating it with fuming hydriodic acid, and as this failed, we next tried the action of various reducing agents on ethylic trimethylchloroglutarate and on the corresponding bromo-derivative, but in all cases we obtained either trimethylglutaconic acid or uninviting oily products. The results of these experiments seemed to point to the reduction of trimethylglutaconic acid as the only way of preparing trimethylglutaric acid, but it was a long time before a suitable reagent could be found for this purpose.

Sodium amalgam has no action on the unsaturated trimethylglutaconic acid, even when the acid is boiled with a large excess of the amalgam, and heating with hydriodic acid converted the acid into dark coloured, oily substances which could not be purified. Sodium and boiling amyl alcohol gave rise to a very remarkable result, *iso*-trimethylglutaconic anhydride being produced, as explained on p. 1184.

The right reducing agent was, however, at length found in sodium and boiling ethylic alcohol, and the method which we adopted for preparing trimethylglutaric acid was the following.

Five grams of trimethylglutaconic acid was dissolved in 200 c.c. of absolute alcohol and the solution boiled in a reflux apparatus on a sand bath; 20 grams of sodium was then added through the condenser tube as rapidly as possible. When all the sodium had disappeared, the product was dissolved in water, evaporated until free from alcohol, acidified, and the acid extracted several times with ether. The ethereal solution was then evaporated, and the residue reduced again exactly as before. After the whole process had been repeated five times, the acid was extracted with ether, when, on evaporating the solvent, the residue solidified almost completely. The crystalline mass thus obtained melted at 80—95°, and it was found necessary to recrystallise it a great many times from water before the melting point rose to 112°, which appears to be the correct melting point of $\alpha\alpha\beta$ -trimethylglutaric acid.

0.1280 gave 0.2584 CO_2 and 0.0938 H_2O . $\text{C} = 55.08$; $\text{H} = 8.14$.

$\text{C}_8\text{H}_{14}\text{O}_4$ requires $\text{C} = 55.17$; $\text{H} = 8.05$ per cent.

$\alpha\alpha\beta$ -Trimethylglutaric acid, is very readily soluble in water and most organic solvents, but separates readily from its aqueous solution on saturating it with hydrogen chloride.

Salts of Trimethylglutaric Acid.—The silver salt, $\text{C}_8\text{H}_{12}\text{Ag}_2\text{O}_4$, was obtained in the usual manner as a white, sparingly soluble precipitate, and on analysis, the details of which have unfortunately been lost, gave the correct results.

A neutral solution of the ammonium salt shows the following behaviour with reagents.

Lead acetate produces no precipitate in the cold, but, on boiling, a characteristic, heavy, white precipitate separates.

Mercuric chloride gives no precipitate with cold moderate dilute solutions, but, on warming, a heavy, yellowish-white, insoluble salt separates.

Mercurous nitrate gives, at once, a heavy white precipitate, which dissolves on warming, and separates again as the solution cools.

Anhydride of $\alpha\alpha\beta$ -Trimethylglutaric Acid, $\text{CH}_3 \cdot \text{CH} \begin{array}{c} \text{CH}_2 \text{---} \text{CO} \\ \text{CH}(\text{CH}_3)_2 \text{---} \text{CO} \end{array} \text{O}$.

This anhydride was prepared by heating the acid to boiling for some time and then distilling the product. The distillate was dissolved in ether, the ethereal solution rapidly shaken with sodium carbonate solution, dried over calcium chloride and evaporated, when the residue, kept overnight in an ice-chest, solidified completely; this anhydride, purified by recrystallisation from light petroleum, was obtained in fine, colourless prisms; it melts at 39°, and dissolves in boiling water with re-formation of trimethylglutaric acid.

0.2107 gave 0.4774 CO₂ and 0.1443 H₂O. C = 61.78 ; H = 7.61.

C₈H₁₂O₃ requires C = 61.53 ; H = 7.62 per cent.

ααβ-Trimethylglutaranilic Acid.

C₁₄H₁₉NO₃ = C₆H₅·NH·CO·C(CH₃)₂·CH(CH₃)·CH₂·COOH (?).

On adding aniline to a solution of trimethylglutaric anhydride in pure benzene, a crystalline precipitate of the anilic acid is at once produced. This, after being washed with a little benzene and purified by recrystallisation from dilute alcohol, was obtained in lustrous plates melting at 155°.

0.2060 gave 10 c.c. N₂ at 18° and 773 mm. N = 5.70.

C₁₄H₁₉NO₃ requires N = 5.63 per cent.

Trimethylglutaranilic acid is readily soluble in most organic solvents, and its general behaviour corresponds closely with that of other known anilic acids of the glutaric series. It dissolves in sodium carbonate solution, but when heated, it does not readily yield the corresponding anil, in fact, small quantities of the anilic acid, if rapidly heated, distil almost without decomposition. On hydrolysis, the anilic acid is decomposed with some difficulty into aniline and trimethylglutaric acid.

Ethylic ααβ-Trimethyl-β-cyanoglutarate,
COOC₂H₅·C(CH₃)₂·C(CN)(CH₃)·CH₂·COOC₂H₅.

The preparation of this substance and its subsequent conversion into *i*-camphoronic acid were found to be problems of such experimental difficulty as to necessitate more than a year's work before the desired result could be accomplished.

In the first series of experiments, ethylic trimethyl-β-chloroglutarate (p. 1180) was treated with pure potassium cyanide, with or without alcohol and other solvents, at temperatures up to 100°, but even when the constituents had been heated together for 12 hours at that temperature the product was found to contain only traces of nitrogen.

A similar result was obtained when the corresponding bromo-derivative was substituted for the chlorinated compound in the same series of experiments, and a variety of experiments in which very carefully purified, neutral, double cyanides, such as KCN, AgCN ; 2KCN, Zn(CN)₂ ; 2KCN, Hg(CN)₂, were used instead of the slightly alkaline potassium cyanide, also gave negative results.

Ultimately, however, the desired cyanide was obtained in the following comparatively simple manner.

Ethylic-ααβ-trimethyl-β-chloroglutarate (22 grams) was heated in a sealed tube with pure potassium cyanide (10 grams) and a little alcohol for 6 hours at 150—160°. The dark-coloured product was mixed with

water, extracted with ether, and the ethereal solution, after separation from a considerable quantity of dark brown insoluble matter, was dried over calcium chloride, filtered, and the ether distilled off. In this way, a brown oil was obtained which distilled for the most part at 170—180° (30 mm.), and gave the following result on analysis.

0.1850 gave 6.3 c.c. nitrogen at 15° and 760 mm. $N = 4.02$.

$C_{13}H_{21}NO_4$ requires $N = 5.48$ per cent.

This oil contained, therefore, about 73 per cent. of ethylic cyanotrimethylglutarate, but the percentage of nitrogen was found to vary very considerably in different preparations. This is, of course, due, in the first place, to the fact, already noticed on p. 1181, that the ethylic trimethylchloroglutarate employed always contains some, and often a considerable quantity of, ethylic trimethylglutaconate; it is also due, in a less degree, to the fact that, during the heating with potassium cyanide, a certain amount of the chlorinated ethereal salt appears to be converted into ethylic trimethylglutaconate by elimination of hydrogen chloride. Unfortunately, the boiling points of the cyano-compound, and of the ethylic trimethylglutaconate lie so close together, that separation cannot be effected by fractional distillation; but the presence of the unsaturated ethereal salt is of no great importance in the synthesis for which the cyano-compound was employed.

Synthesis of i-Camphoronic Acid ($\alpha\alpha\beta$ -Trimethyltricarballic Acid),
 $COOH \cdot C(CH_3)_2 \cdot C(CH_3)(COOH) \cdot CH_2 \cdot COOH$.

When the mixture of ethylic trimethylcyanoglutarate and ethylic trimethylglutaconate, obtained as described in the previous section, is digested in a reflux apparatus with concentrated hydrochloric acid, it is gradually hydrolysed, and after about 16 hours the oily layer disappears almost entirely. If now the liquid be allowed to stand in an ice chest for 24 hours, practically the whole of the trimethylglutaconic acid present crystallises out, which is fortunate, since the presence of this acid greatly interferes with the isolation of the camphoronic acid. The filtrate from these crystals, which contains the camphoronic acid, is made distinctly alkaline with ammonia, cooled, mixed with an excess of a strong solution of barium chloride, and filtered from any slight precipitate which may have formed. If, now, the filtrate be heated on a water bath and subsequently to boiling, the whole of the camphoronic acid is precipitated in the form of an exceedingly sparingly soluble barium salt. This salt is collected by means of the pump, well washed, and decomposed with the calculated quantity of dilute sulphuric acid; the filtrate from the barium sulphate, if concentrated and allowed to stand in an ice-chest, deposits beautiful, colourless, transparent prisms

melting at about 158—160°; after recrystallisation, however, the melting point rose to about 168°,* decomposition occurring at the same time. The results of the analysis agree with those required by camphoronic acid.

0.1258 gave 0.2276 CO₂ and 0.0746 H₂O. C = 49.34; H = 6.58.

0.1294 „ 0.2348 CO₂ „ 0.0766 H₂O. C = 49.38; H = 6.57.

C₉H₁₄O₆ requires C = 49.50; H = 6.40 per cent.

This acid is much less soluble in water than ordinary *d*-camphoronic acid, and crystallises in much more definite crystals; it was further characterised by converting it into the following derivatives, which were carefully compared with the corresponding derivatives obtained from a small quantity of *i*-camphoronic acid which Dr. O. Aschan kindly sent us, and which had been prepared by crystallising together equal quantities of the *d*- and *l*-acids.

i-Anhydrocamphoronic Acid, C₉H₁₂O₅.—As the result of experiments with *d*-camphoronic acid, it was found that, in cases like the present, where only very small quantities of substance are available, the conversion of camphoronic acid into the corresponding anhydro-acid is best accomplished as follows.

The finely powdered substance is boiled, in a reflux apparatus, with a large excess of acetyl chloride until it has entirely dissolved, which is usually the case in about half an hour, the acetyl chloride is then evaporated off on the water bath, and the residue allowed to remain over solid potash in a vacuum desiccator until it has completely solidified. The product is then dissolved in a small quantity of boiling benzene, which had previously been carefully dried by repeated distillation over sodium, and the solution allowed to stand overnight. The crystals of the anhydro-acid which separate are collected, washed with a little benzene, and dried at 100°.

The anhydro-acid obtained from synthetical *i*-camphoronic acid in this way began to soften slightly at 128—130°, and melted suddenly at 136—137°.†

0.1284 gave 0.2544 CO₂ and 0.0706 H₂O. C = 54.03; H = 6.11.

C₉H₁₂O₅ requires C = 54.00; H = 6.00 per cent.

The anhydro-acid, prepared from Aschan's *i*-camphoronic acid under the same conditions, could not be distinguished from the synthetical substance, and as the former has not previously been described, it was also analysed.

* The melting point of camphoronic acid depends very much on the conditions observed during the determination; this has also been noticed by Aschan.

† It is not improbable that this melting point may be somewhat too low, but the amount of substance at our disposal was so small that we could not subject it to further crystallisation.

0.1322 gave 0.2610 CO_2 and 0.0718 H_2O . $\text{C} = 53.84$; $\text{H} = 6.03$.

$\text{C}_9\text{H}_{12}\text{O}_5$ requires $\text{C} = 54.00$; $\text{H} = 6.00$ per cent.

i-Camphoronanilic acid, $\text{C}_{15}\text{H}_{19}\text{NO}_5$.^{*}—This was obtained by treating anhydrocamphoronic acid with aniline, parallel experiments being made both with our synthetical acid and with Aschan's acid, the conditions observed being exactly the same in both cases. The anhydro-acid was dissolved in hot benzene in a test-tube, the bulk of the benzene was then boiled away, and the cold, supersaturated solution mixed with rather more than the requisite quantity of aniline. The clear solution becomes warm, then suddenly turbid, and deposits either a mass of colourless crystals or an oil which rapidly solidifies on rubbing with a glass rod. The crystals were washed with benzene, drained on a porous plate, and dried at 100° , they then melted at about 140° . This substance is not very easy to purify by recrystallisation, but if it is dissolved in a little hot alcohol, and the solution is then mixed with about three times its bulk of benzene, the anilic acid gradually separates in colourless crystals which melt at about 149° with decomposition.

The anilic acid prepared from synthetical *i*-camphoronic acid gave the following results on analysis.

0.0580 gave 2.44 c.c. nitrogen at 16° and 762 mm. $\text{N} = 4.85$.

$\text{C}_{15}\text{H}_{19}\text{NO}_5$ requires $\text{N} = 4.77$.

i-Camphoronanilic acid, prepared from Aschan's *i*-camphoronic acid, had the same melting point and properties as the synthetical substance.

0.1022 gave 4.4 c.c. nitrogen at 20°C . and 754 mm. $\text{N} = 4.88$.

$\text{C}_{15}\text{H}_{19}\text{NO}_5$ requires $\text{N} = 4.77$ per cent.

Condensation of Ethylic Acetoacetate with Ethylic α -Bromisobutyrate in presence of Zinc. Second Synthesis of Ethylic $\alpha\alpha\beta$ -Trimethylhydroxy-glutarate, $\text{COOC}_2\text{H}_5 \cdot \text{C}(\text{CH}_3)_2 \cdot \text{C}(\text{OH})(\text{CH}_3) \cdot \text{CH}_2 \cdot \text{COOC}_2\text{H}_5$.

As already stated in the introduction, this condensation was investigated in order to prove the constitution of the ethylic trimethylhydroxyglutarate used in this research. The experiment was carried out in a manner precisely similar to that with ethylic dimethylaceto-

^{*} *d*-Camphoronanilic acid.—In order to determine the conditions for preparing the anilic acid from *i*-camphoronic acid, experiments were, in the first place, made with the *d*-acid, and by using the above method considerable quantities of *d*-camphoronanilic acid were prepared. This compound, which has not been previously described melts, after recrystallisation, at 147 — 148° , and closely resembles the *i*-modification in its properties.

0.112 gave 5 c.c. nitrogen at 24° and 754 mm. $\text{N} = 5.00$.

$\text{C}_{15}\text{H}_{19}\text{NO}_5$ requires $\text{N} = 4.77$ per cent.

acetate and ethylic bromacetate already described. The bromo-ether (84 grams) was mixed with ethylic dimethylacetoacetate (58 grams), and the zinc gradually added to the hot mixture, the same precautions being observed as in the previous case, great care being taken to prevent the temperature rising too high, as, unless this is done, a most violent action sets in and the yield of product is then very small. The product, treated exactly as described on p. 1179, gave an oil boiling at 160—170° (30 mm.).

0.1775 gave 0.3828 CO₂ and 0.1722 H₂O. C = 58.82 ; H = 8.90.

C₁₂H₂₂O₅ requires C = 58.53 ; H = 8.94 per cent.

As will be shown below, this ethereal salt is identical with the condensation product obtained by the action of zinc on a mixture of ethylic dimethylacetoacetate and ethylic bromacetate, and both products, therefore, must consist of ethylic *ααβ*-trimethyl-*β*-hydroxyglutarate. The yield obtained with the bromacetate is as much as 20—25 per cent. of the theoretical, whilst if ethylic bromisobutyrate is employed the yield hardly ever rises above 8—10 per cent. of the theoretical.

This appears to be due to the fact that zinc acts more readily on ethylic bromisobutyrate than on ethylic bromacetate, and when the former is employed large quantities of product of low boiling point are obtained. These oils, on refractionation under the ordinary pressure, were readily separated into two fractions, namely, a very large one, 110—125°, consisting of a mixture of ethylic isobutyrate and ethylic methylacrylate, CH₂:C(CH₃)·COOC₂H₅, and a fraction, 170—185° consisting of unchanged ethylic acetoacetate.

Experiments were now made with the object of proving that the compound produced by the condensation of ethylic acetoacetate and ethylic bromisobutyrate is identical with that obtained by the condensation of ethylic dimethylacetoacetate with ethylic bromacetate, and in order to do this the same derivatives were prepared from the former product as have already been described as resulting from the latter. When treated with phosphorus pentachloride or pentabromide, the condensation product from ethylic bromisobutyrate yielded halogen derivatives identical in boiling point and other properties with those described on pp. 1180 and 1181.

Both the chloro- and the bromo-derivative, on treatment with zinc and subsequent hydrolysis (see p. 1183), yielded trimethylglutaconic acid melting at 148°. On analysis, this gave the following result.

0.2091 gave 0.4265 CO₂ and 0.1302 H₂O. C = 55.63 ; H = 6.92

C₈H₁₂O₄ requires C = 55.81 ; H = 6.97 per cent.

From this acid, on reduction with sodium and alcohol, *ααβ*-trimethyl-

1194 PERKIN: YELLOW COLOURING MATTERS OBTAINED FROM

glutaric acid (m. p. 112°) was prepared, and its identity proved by analysis and by converting it into its anhydride (m. p. 39°) and into its anilic acid (m. p. 155°).

These experiments prove conclusively the identity of the two condensation products.

In preparing large quantities of the condensation product from ethylic bromisobutyrate and ethylic acetoacetate, we found it convenient to distil off the oil of low boiling point formed during the condensation, and to reserve the residue until a considerable quantity had accumulated, before purifying it by fractionation. On standing, this crude product deposited a small quantity of a solid substance; this was collected, washed with ether to free it from oil, and the sparingly soluble crystals were recrystallised from boiling alcohol. The substance was thus obtained in the form of magnificent, long needles, closely resembling asbestos in appearance, but the quantity at our disposal was so small that only one analysis could be carried out, and this gave us no clue as to its constitution.

0.1214 gave 0.2768 CO_2 and 0.0588 H_2O . $\text{C} = 62.28$; $\text{H} = 5.38$.

$\text{C}_{10}\text{H}_{10}\text{O}_4$ requires $\text{C} = 61.85$; $\text{H} = 5.15$ per cent.

This substance melts at 169° and dissolves in soda, forming a bright yellow solution, the colour of which disappears on boiling; on acidifying the colourless solution with hydrochloric acid, it deposits an oil. It is nearly insoluble in ether, but dissolves readily in alcohol, especially on warming, and the solution gives an intense violet coloration with ferric chloride.

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