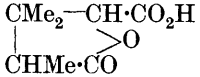
CCCXLIV.—*Experiments on the Synthesis of Certain γ-Ketonic Acids Closely Allied to Balbiano's Acid. Part II. Syntheses of αββ- and ααβ-Trimethyllævulic Acids, of the Lactone of α′-Hydroxy-ααβ-trimethylglutaric Acid, and of γ-Keto-αββ-trimethylpropane-αγ-dicarboxylic Acid (Balbiano's Acid).*

By JOGENDRA CHANDRA BARDHAN.

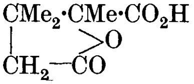
DURING his classical experiments on the oxidation of camphoric acid (*e.g.*, *Rend. Accad. Lincei*, 1892, i, 278; *Ber.*, 1894, **27**, 2133), Balbiano isolated a considerable quantity of a dibasic acid, $C_8H_{12}O_5$, and an equivalent of oxalic acid, along with small amounts of camphanic, camphoronic, and trimethylsuccinic acids. The new acid, on reduction with hydriodic acid and red phosphorus, yielded a mixture of a monobasic lactonic acid, $C_8H_{12}O_4$, and a dibasic acid, $C_8H_{14}O_4$, which Balbiano considered to be αββ-trimethylglutaric acid because on oxidation it gave *as*-dimethylsuccinic acid. This structure was subsequently confirmed when Perkin and Thorpe synthesised the acid (J., 1899, **75**, 61).

Since the trimethylglutaric acid is also formed from the lactonic acid $C_8H_{12}O_4$ on reduction, the latter might have been either (I) or (II), but Blanc (*Bull. Soc. chim.*, 1901, **25**, 68) synthesised the acid (II) and found it to be different from Balbiano's lactonic acid, which is therefore (I) (compare Pandya and Thorpe, J., 1923, **123**, 2852).

(I.)



$$\begin{array}{l}CMe_2\text{—}CH\cdot CO_2H \\ \vert \qquad\quad >O \\ CHMe\cdot CO\end{array}$$

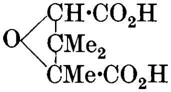


$$\begin{array}{l}CMe_2\cdot CMe\cdot CO_2H \\ \vert \qquad\quad >O \\ CH_2\text{—}CO\end{array}$$

(II.)

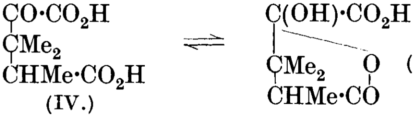
For many years two views were held as to the constitution of the acid $C_8H_{12}O_5$: Balbiano (*Ber.*, 1897, **30**, 289, 1901), as a result of his examination of the reduction products, represented the acid by the oxide formula (III), and suggested that the corresponding dihydroxy-acid was a stage in its formation from camphoric acid; whereas Mahla and Tiemann (*Ber.*, 1895, **28**, 2151) preferred the keto-formula (IV) on account of the fact that the acid, when heated at 160—180°, is completely decomposed with the formation of trimethylsuccinic anhydride and carbon monoxide. These authors could not, however, satisfactorily establish the ketonic character of the acid, and the somewhat ill-defined *p*-bromophenylhydrazone which they prepared proved to be an addition product (compare Balbiano, *loc. cit.*).

More recently, Kon, Stevenson, and Thorpe (J., 1922, **121**, 656) were led to represent the acid in the liquid state or in solution as an equilibrium mixture of the forms (IV) and (V), and this tautomeric structure was further supported by Rothstein, Stevenson, and Thorpe (J., 1925, **127**, 1078). Although it had thus been shown that Balbiano's oxide structure is incorrect, it was still necessary to prove definitely the correctness of the keto-formula, and this has now been achieved by the synthesis of an acid of this structure which is identical with the acid obtained from camphoric acid.



$$O\left\langle\begin{array}{l}CH\cdot CO_2H \\ CMe_2 \\ CMe\cdot CO_2H\end{array}\right.$$

(III.)

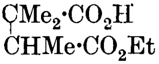


$$\begin{array}{l}CO\cdot CO_2H \\ CMe_2 \\ CHMe\cdot CO_2H\end{array} \rightleftharpoons \begin{array}{l}C(OH)\cdot CO_2H \\ \vert \qquad\quad \diagdown \\ CMe_2 \qquad O \\ CHMe\cdot CO\end{array}$$

(IV.) (V.)

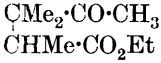
αββ-Trisubstituted ketoglutaric acids are peculiarly difficult to prepare, for the usual methods of synthesis fail, but since it had been found (preceding paper) that ethyl 1-acetyl*cyclo*pentane-1-acetate on treatment with alkaline permanganate was smoothly oxidised to α-keto*cyclo*pentane-1 : 1-diacetic acid, it appeared possible that the desired ketonic acid might be obtainable by similarly oxidising the acetyl group of αββ-trimethyl-lævulic acid to the $\mathrm{CO{\cdot}CO_2H}$ group.

Synthesis of αββ-*Trimethyl-lœvulic Acid.*—This acid was prepared by the following series of reactions : Trimethylsuccinic anhydride was converted by sodium ethoxide into the half ester (VI), the acid chloride of which reacted with zinc methyl iodide to give the keto-ester (VII) in good yield. This ester, however, contained an appreciable quantity of the isomeric ester (VIII), evidently derived from the alternative acid ester formed during esterification of the anhydride. A somewhat similar mixture of ketonic esters was also obtained when the acid ester was prepared by the partial saponification of the neutral ester. Bone, Sudborough, and Sprankling's statement (J., 1904, **85**, 536), that they obtained two different acid esters of trimethylsuccinic acid according as they started from the anhydride or the neutral ester, must therefore be regarded as incorrect.



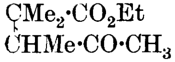
$$\begin{array}{l}\mathrm{CMe_2{\cdot}CO_2H}\\ \mathrm{CHMe{\cdot}CO_2Et}\end{array}$$

(VI.)



$$\begin{array}{l}\mathrm{CMe_2{\cdot}CO{\cdot}CH_3}\\ \mathrm{CHMe{\cdot}CO_2Et}\end{array}$$

(VII.)

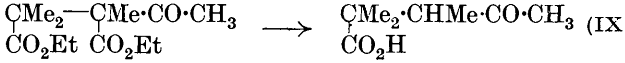


$$\begin{array}{l}\mathrm{CMe_2{\cdot}CO_2Et}\\ \mathrm{CHMe{\cdot}CO{\cdot}CH_3}\end{array}$$

(VIII.)

The separation of the pure constituents from the mixture of the corresponding acids thus obtained proved to be very difficult, but was ultimately accomplished by the fractional crystallisation of the mixed semicarbazones from methyl alcohol. The regenerated acids melted at 65—66° and 77—78°, and since they showed mutual depression of m. p. when mixed, there can be no doubt that they are different. Their respective structures were therefore ascertained by effecting a rational synthesis of ααβ-trimethyl-lævulic acid, which proved to be identical with the less fusible acid, so the acid of m. p. 65—66° must be the αββ-isomeride.

Synthesis of ααβ-*Trimethyl-lœvulic Acid.*—The first experiment to be tried for this purpose was the reaction of ethyl α-bromo*iso*butyrate with ethyl sodiomethylacetoacetate, since it was expected that the condensation product would give the required acid (IX) on hydrolysis :



$$\begin{array}{ll}\mathrm{CMe_2{-}CMe{\cdot}CO{\cdot}CH_3} & \\ \mathrm{CO_2Et\ \ CO_2Et} & \end{array} \longrightarrow \begin{array}{l}\mathrm{CMe_2{\cdot}CHMe{\cdot}CO{\cdot}CH_3}\\ \mathrm{CO_2H}\end{array} \quad \text{(IX.)}$$

but the condensation did not proceed in the expected manner, and all efforts to obtain this acid from the products of the reaction were fruitless.

It was then thought possible that methylmesityl oxide might react with hydrocyanic acid according to the method of Lapworth

(J., 1904, **85**, 1216) to give a product which on hydrolysis should furnish the desired keto-acid :

$$\mathrm{CMe_2{:}CMe\cdot CO\cdot CH_3} \longrightarrow \mathrm{CMe_2(CN)\cdot CHMe\cdot CO\cdot CH_3} \longrightarrow \text{(IX.)}$$

Although methylmesityl oxide was readily synthesised from trimethylacrylic acid (Blaise reaction), it reacted with hydrocyanic acid with such reluctance under the usual conditions that after prolonged heating there was obtained a considerable quantity of a stable cyanohydrin (X), evidently produced by the further action of hydrocyanic acid on the mononitrile first formed; traces of the expected acid (IX) were isolated in the form of its semicarbazone, but in insufficient quantity for characterisation.

The cyanohydrin (X) on hydrolysis yielded a nitrogenous *substance* (XI), closely analogous to mesitylic acid prepared by Pinner (*Ber.*, 1881, **14**, 1075) and by Lapworth (*loc. cit.*) from mesityl oxide by a somewhat similar process.

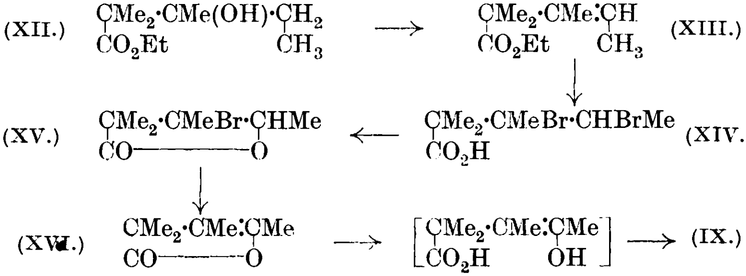
$$\mathrm{CMe_2(CN)\cdot CHMe\cdot CMe(OH)\cdot CN}$$

(X.)

$$\begin{array}{l}\mathrm{CMe_2\cdot CHMe\cdot CMe\cdot CO_2H}\\ \mathrm{CO\text{————}NH}\end{array}$$

(XI.)

Ultimately the following method was devised and found to give the desired synthesis. Methyl ethyl ketone was condensed with ethyl α-bromo*iso*butyrate and zinc, a good yield of *ethyl* β-*hydroxy*-ααβ-*trimethyl*-n-*valerate* (XII) being obtained. This hydroxy-ester on dehydration with phosphorus pentoxide yielded *ethyl* ααβ-*trimethyl*-Δ^{β}-*pentenoate* (XIII), the structure of which was established by oxidation with ozone, one of the products being acetaldehyde. When the corresponding *acid* was treated with bromine, it gave a somewhat unstable dibromide (XIV), which at the moment of its formation partly eliminated hydrobromic acid with the production of the bromo-lactone (XV) (compare Perkin and Smith, J., 1904, **85**, 157); but on distillation of the crude bromination product under the ordinary pressure, a considerable evolution of hydrobromic acid took place, and the chief product was the unsaturated *lactone* (XVI). This was finally hydrolysed by means of alcoholic potash to ααβ-*trimethyl-lævulic acid* (IX), presumably through the intermediate stage shown.



(XII.) $\begin{array}{l}\mathrm{CMe_2\cdot CMe(OH)\cdot CH_2}\\ \mathrm{CO_2Et\qquad\qquad CH_3}\end{array}$ $\longrightarrow$ $\begin{array}{l}\mathrm{CMe_2\cdot CMe{:}CH}\\ \mathrm{CO_2Et\quad CH_3}\end{array}$ (XIII.)

$\downarrow$

(XV.) $\begin{array}{l}\mathrm{CMe_2\cdot CMeBr\cdot CHMe}\\ \mathrm{CO\text{————}O}\end{array}$ $\longleftarrow$ $\begin{array}{l}\mathrm{CMe_2\cdot CMeBr\cdot CHBrMe}\\ \mathrm{CO_2H}\end{array}$ (XIV.)

$\downarrow$

(XVI.) $\begin{array}{l}\mathrm{CMe_2\cdot CMe{:}CMe}\\ \mathrm{CO\text{———}O}\end{array}$ $\longrightarrow$ $\left[\begin{array}{l}\mathrm{CMe_2\cdot CMe{:}CMe}\\ \mathrm{CO_2H\qquad OH}\end{array}\right]$ $\longrightarrow$ (IX.)

In spite of the many stages involved in the above synthesis, the yield of the keto-acid was quite good. The synthetic acid agreed in all its properties with the acid, m. p. 77—78°, prepared from trimethylsuccinic anhydride (above).

Synthesis of Balbiano's Acid.—αββ-Trimethyl-lævulic acid was readily oxidised by alkaline permanganate to γ-keto-αββ-trimethylpropane-αγ-dicarboxylic acid. The acid thus obtained melted at the same temperature as Balbiano's acid, and showed no depression of m. p. when mixed with an equal quantity of the acid obtained from camphoric acid (kindly lent by Professor Thorpe). The identity of the synthetic acid was also established by the preparation of its quinoxaline derivative, and by its conversion into αββ-trimethylglutaric acid by means of hydriodic acid and red phosphorus. Finally, the synthetic acid when heated is converted into trimethylsuccinic acid with evolution of carbon monoxide.

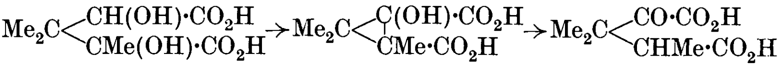
The synthesis of Balbiano's acid just described is consistent only with the keto-formula, and the solid acid most probably exists in this form; this follows, not only because Balbiano's acid does not give ψ-esters corresponding to the lactol form (compare for instance, opianic acid, phthalonic acid, and the semi-aldehyde of trimethylsuccinic acid), but also because on treatment with acetic anhydride it forms a normal anhydride (Balbiano, *Ber.*, 1897, **30**, 1902) and not an acetyl derivative.

In the light of the keto-formula, the anhydride of the acid should be represented by (XVII) (compare 3 : 4-dimethoxyphthalonic anhydride; Kuroda and Perkin, J., 1923, **123**, 2094). The anhydride reacts normally with β-naphthylamine, giving a crystalline naphthylamic acid (XVIII), which does not react with *o*-phenylenediamine.

(XVII.)  (XVIII.)

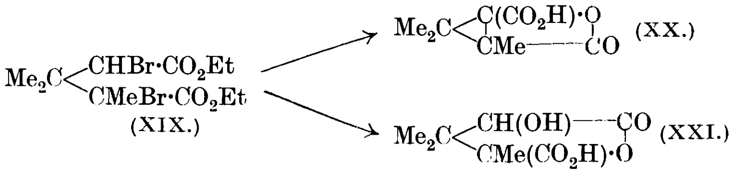
$$\begin{array}{l}\mathrm{CMe_2{-}CO{-}CO}\\ \mathrm{CHMe{\cdot}CO{\cdot}O}\end{array}\longrightarrow\begin{array}{l}\mathrm{CMe_2{\cdot}CO{\cdot}CO{\cdot}NH{\cdot}C_{10}H_7}\\ \mathrm{CHMe{\cdot}CO_2H}\end{array}$$

The formation of an acid of the keto-formula from camphoric acid is somewhat remarkable. Kon, Stevenson, and Thorpe (*loc. cit.*) suggested the following mechanism of its formation, starting from αα′-dihydroxy-αββ-trimethylglutaric acid, which, according to Balbiano, constitutes the first step in the oxidation of camphoric acid :



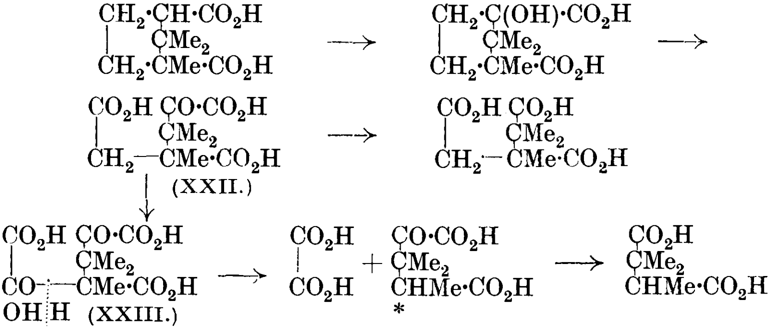
$$\mathrm{Me_2C}\!\begin{array}{l}\mathrm{\diagup CH(OH){\cdot}CO_2H}\\ \mathrm{\diagdown CMe(OH){\cdot}CO_2H}\end{array}\!\rightarrow\mathrm{Me_2C}\!\begin{array}{l}\mathrm{\diagup C(OH){\cdot}CO_2H}\\ \mathrm{\diagdown CMe{\cdot}CO_2H}\end{array}\!\rightarrow\mathrm{Me_2C}\!\begin{array}{l}\mathrm{\diagup CO{\cdot}CO_2H}\\ \mathrm{\diagdown CHMe{\cdot}CO_2H}\end{array}$$

In spite of the apparent simplicity of this explanation, the issue is not in reality quite so clear, for it has been shown by Pandya and Thorpe (*loc. cit.*) that the dibromo-ester (XIX) on treatment with alkali passes into a mixture of the lactonic acids (XX) and (XXI), from which no trace of any keto-acid can be obtained. Since the dihydroxytrimethylglutaric acids, which are presumably formed in these reactions, show no tendency whatever to pass into a hydroxy*cyclo*propane acid, it follows that Balbiano's acid cannot be formed from camphoric acid by way of dihydroxytrimethylglutaric acid.



Quite apart from this, it is difficult to understand why camphoric acid, which is such an exceedingly stable substance, should undergo oxidative fission at those bonds which would have to be ruptured in order to give this dihydroxyglutaric acid—a mode of oxidation which suggested to Balbiano his oxide structure.

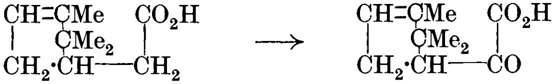
There is, however, no need to assume the formation of a dihydroxyglutaric acid. An adequate explanation is provided for the formation, not only of the keto-acid, but also of the accompanying camphanic, camphoronic, and trimethylsuccinic acids, if it be assumed that the oxidation of camphoric acid proceeds through the following stages :



A similar mechanism has been postulated by Bredt (*Ber.*, 1893, **26**, 3050) in order to explain the formation of camphoronic acid from camphoric acid by oxidation with nitric acid, but there is a difference between the two cases in that the intermediate keto-acid (XXII) is somewhat stable towards alkaline permanganate and is not therefore broken down into camphoronic acid to any large extent; on the contrary it is oxidised at the methylene group and the resulting diketo-acid (XXIII) is hydrolysed as shown above.

The formation of an α-ketonic acid by the direct oxidation of an acetic acid residue is not without precedent, for Chandrasena and

Ingold (J., 1922, **121**, 1553) have shown that α-campholenic acid on treatment with mild oxidising agents gives a keto-acid as the principal product :



Owing to the obvious difficulty of devising suitable experiments, it has not been found possible definitely to establish the correctness of the mechanism suggested above. It is hoped, however, that the experiments on the oxidation of camphanic, dehydrocamphoric, and camphoronic acids, which are now in hand, will throw further light on the matter.

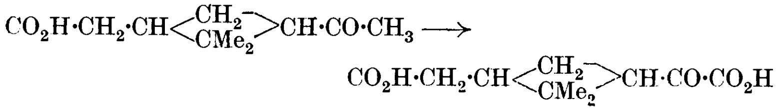
The keto-acid contains an asymmetric carbon atom (marked *) and would therefore be expected to exist in one inactive and two active modifications. The acid actually isolated by Balbiano from *d*-camphoric acid was, however, inactive. This is to be expected, for examination of the scheme above shows that during the hydrolysis of the diketo-acid (XXIII) a new asymmetric carbon atom is being produced, and consequently the resulting product should be inactive owing to the formation in equal quantities of the two optically enantiomorphous forms. The case of camphoronic acid is somewhat different because it still retains one of the asymmetric carbon atoms originally present in the camphoric acid.

Balbiano (*Ber.*, 1899, **32**, 1022) apparently succeeded in resolving his acid, $C_8H_{12}O_5$, by a fractional crystallisation of its quinine salts, but the rotations, $[\alpha]_D + 5{\cdot}48°$ and $- 3{\cdot}35°$, which he found for the two active forms are far from satisfactory. Experiments are now being undertaken to prepare the two active modifications of the acid from the *d*- and *l*-modifications of trimethylsuccinic acid by applying the same scheme as has been used for the synthesis of the inactive acid.

During the course of the foregoing experiments a considerable quantity of ααβ-trimethyl-lævulic acid had accumulated, and it seemed of interest to investigate whether on oxidation with alkaline permanganate it would give the keto-acid

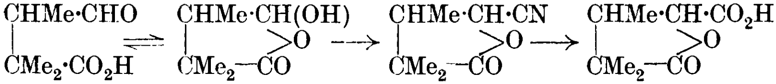
$$CO_2H{\cdot}CMe_2{\cdot}CHMe{\cdot}CO{\cdot}CO_2H \quad \text{(XXIV.)},$$

but it was found to yield only trimethylsuccinic acid. This is somewhat remarkable, especially as Baeyer, in the course of the oxidation of pinene, isolated an appreciable quantity of a keto-acid which he considered to be formed by the oxidation of pinonic acid :



$$CO_2H{\cdot}CH_2{\cdot}CH{<}{}^{CH_2}_{CMe_2}{>}CH{\cdot}CO{\cdot}CH_3 \longrightarrow CO_2H{\cdot}CH_2{\cdot}CH{<}{}^{CH_2}_{CMe_2}{>}CH{\cdot}CO{\cdot}CO_2H$$

Attempts were also made to prepare the keto-acid (XXIV) by the oxidation of the lactonic acid (XXVIII), which was obtained in good yield by the action of hydrocyanic acid on the lactone (XXVI) (Blaise and Courtout, *Bull. Soc. chim.*, 1902, **35**, 998), followed by the hydrolysis of the lactonic nitrile (XXVII) with the aid of concentrated hydrochloric acid, the reaction probably taking place through the tautomeric aldehyde-form (XXV). Theoretically, the


(XXV.) (XXVI.) (XXVII.) (XXVIII.)

lactonic acid should exist in two inactive forms, but only one has yet been isolated. On treatment with alkaline permanganate, the lactonic acid passes into trimethylsuccinic acid, no trace of the desired keto-acid being formed, although Balbiano's lactonic acid (I) under similar conditions furnishes the keto-acid (IV). Further experiments for the synthesis of the keto-acid are in progress.

EXPERIMENTAL.

Preparation of Trimethylsuccinic Acid.—At the commencement of this research most of the trimethylsuccinic acid was prepared according to the method of Bone and Sprankling (J., 1899, **75**, 862). It was subsequently found, however, that Higson and Thorpe's method (J., 1906, **89**, 1466) was by far the best for obtaining the acid in quantity.

The condensation of acetonecyanohydrin with ethyl sodiocyanoacetate is best carried out as follows: A suspension of the sodio-derivative of ethyl cyanoacetate, prepared from sodium (30 g.), alcohol (480 c.c.), and cyanoacetic ester (155 c.c.), was gradually added with vigorous shaking to a solution of freshly distilled acetonecyanohydrin (118 g.) in 80 c.c. of alcohol, cooled in ice. The product was kept in ice for 12 hours and then at the ordinary temperature for 2 days. The viscous mass was mixed with methyl iodide (90 c.c.) and gently heated under reflux until neutral; the ethyl $\alpha\beta$-dicyano-$\alpha\beta\beta$-trimethylpropionate, b. p. 159—162°/25 mm., isolated in the usual way, was hydrolysed by 12 hours' boiling with seven times its volume of concentrated hydrochloric acid, thus giving an almost quantitative yield of trimethylsuccinic acid, which had m. p. 149° after one crystallisation from dilute hydrochloric acid.

The anhydride, prepared by boiling the acid with an excess of acetyl chloride, is best purified by distillation under reduced pressure from a Claisen flask provided with a fractionating side arm. It is obtained as a colourless oil, b. p. 110°/10 mm., which on cooling solidifies to a crystalline mass (Found : C, 58·8; H, 7·3. Calc. : C, 59·2; H, 7·0%).

Synthesis of αββ-*Trimethyl-lævulic Acid* (formula as VII).—*Action of sodium ethoxide on trimethylsuccinic anhydride.* To the anhydride (35·5 g.), dissolved in absolute alcohol (120 c.c.) and cooled in a freezing mixture, was gradually added a solution of sodium ethoxide (sodium, 5·75 g.; alcohol, 144 c.c.) so that the temperature did not rise above 0°; after 2—3 hours the excess of alcohol was distilled off under reduced pressure at 40°. The solid residue was dissolved in water, and the solution extracted with ether to remove any neutral ester. The aqueous solution was slightly acidified with dilute sulphuric acid, and the liberated oil collected in ether. On drying and distilling off the ether, a viscous oil remained which did not solidify in a vacuum, and when cooled in a freezing mixture passed into a thick jelly-like mass (Found, in silver salt : Ag, 38·8. Calc. : Ag, 38·4%). It decomposed on distillation under reduced pressure (compare Bone, Sudborough, and Sprankling, *loc. cit.*, p. 551).

The acid ester (42 g.) was warmed with freshly distilled thionyl chloride (25 c.c.) in a glycerol-bath at 55°, and excess of thionyl chloride was removed under diminished pressure. The residual oil was dissolved in an equal volume of dry benzene, and the solution gradually added to a solution of zinc methyl iodide, prepared by heating over-night a mixture of zinc copper couple (60 g.), benzene (30 c.c.), methyl iodide (30 c.c.), and ethyl acetate (15 c.c.); the mixture was vigorously shaken and kept at 0° during the reaction, and then allowed to attain the ordinary temperature (1 hour). Dilute sulphuric acid was added, the benzene layer separated, washed successively with dilute caustic potash solution, water, and saturated ammonium sulphate solution, dried, and the solvent removed. The residue on distillation under diminished pressure boiled constantly at 113°/18 mm., giving a colourless oil with a terpene-like smell. Preliminary examination showed this to consist of a mixture of several substances, which were separated as follows: The oil (30 g.) was heated under reflux for 1 hour with a solution of potassium hydroxide (30 g.) in water (30 c.c.) and methyl alcohol (60 c.c.); the excess of alcohol was evaporated, the residue extracted with ether to remove unchanged ester, the aqueous solution acidified, again extracted with ether, and the solvent removed. The residual oil (24 g., moist) was dissolved in water (30 c.c.) and the solution gently warmed on the steam-bath for ½ hour with the addition of semicarbazide hydrochloride (15 g.), sodium acetate (30 g.), and water (60 c.c.). On standing at the ordinary temperature for 20 hours, a considerable amount of a crystalline semicarbazone separated; this was collected and the filtrate extracted several times with ether, dried, and evaporated, giving an oil which, when purified in the usual way, proved to be trimethylsuccinic acid.

The crude semicarbazone was repeatedly crystallised (at least 20 times) from methyl alcohol, whereby two fractions were obtained, m. p.'s 174° and 155°, together with a large middle fraction melting indefinitely between 160—168°, from which no definite product could be isolated. The *semicarbazone*, m. p. 155°, is readily soluble in methyl alcohol and crystallises in minute, colourless prisms (Found : C, 50·1 ; H, 7·9. $C_9H_{17}O_3N_3$ requires C, 50·2 ; H, 7·9%).

The pure semicarbazone (17 g.) was heated on the steam-bath with concentrated hydrochloric acid (25 c.c.) and water (25 c.c.) until the crystals had entirely disappeared. The product was then extracted with ether and dried. The residue obtained on evaporation of the ether readily solidified in an evacuated desiccator to a crystalline mass (10 g.). (It is essential that the semicarbazone used be very pure; otherwise the acid is obtained as a gum which is difficult to purify.)

αββ-*Trimethyl-lævulic acid* crystallises from light petroleum (b. p. 40—60°) in clusters of flattened prisms, m. p. 65—66° (Found : C, 60·9 ; H, 8·9. $C_8H_{14}O_3$ requires C, 60·8 ; H, 8·9%), moderately soluble in most solvents. The *ethyl* ester, prepared from the pure acid by Phelp and Tillotson's alcohol-vapour method, had b. p. 110°/14 mm., $d_4^{19^\circ}$ 0·981537, $n_D^{19^\circ}$ 1·43638, $[R_L]_D$ 49·6 (calc., 50·0) (Found : C, 64·3 ; H, 9·8. $C_{10}H_{18}O_3$ requires C, 64·5 ; H, 9·7%).

The less soluble *semicarbazone* crystallises from methyl alcohol in beautiful iridescent prisms, m. p. 174° (Found : C, 50·2 ; H, 7·7. $C_9H_{17}O_3N_3$ requires C, 50·2 ; H, 7·9%). When this was treated with dilute hydrochloric acid, as described for the other semicarbazone, *ααβ-trimethyl-lævulic acid* was obtained as an oil which gradually solidified to a hard crystalline mass; it was purified by careful evaporation of its ice-cold solution in ethyl bromide–light petroleum (b. p. 40—60°), and thus obtained in minute, transparent prisms, m. p. 77—78° (mixed m. p. with αββ-trimethyl-lævulic acid, 52°) (Found : C, 60·8 ; H, 8·9. $C_8H_{14}O_3$ requires C, 60·8 ; H, 8·9%). Its constitution follows from its rational synthesis (see below).

Oxidation of αββ-*Trimethyl-lævulic Acid with Sodium Hypobromite.*—The pure acid (1 g.) was dissolved in aqueous caustic potash, cooled to 0°, and mixed with a solution of potassium hypobromite, prepared from bromine (1 c.c.), potassium hydroxide (2·5 g.), and water (45 c.c.). After remaining for 3 hours, the liquid was treated with sulphur dioxide, strongly acidified with dilute sulphuric acid, and extracted with ether. The dried extract on evaporation left a solid residue which was identified as trimethylsuccinic acid by its m. p. and by direct comparison.

Attempted Synthesis of ααβ-*Trimethyl-lævulic Acid* (IX).

Trimethylacrylic Acid.—Ethyl β-hydroxy-αββ-trimethylpropionate was prepared by the condensation of acetone with ethyl α-bromopropionate and zinc in accordance with the directions of Perkin and Thorpe (J., 1896, **69**, 1482), and obtained as a colourless oil, b. p. 99°/28 mm. The low-boiling fractions on distillation at the ordinary pressure yielded an appreciable amount of mesityl oxide. The hydroxy-ester (32 g.) was gradually mixed with phosphorus pentachloride (50 g.), and the clear liquid gently heated on the steam-bath for 1 hour. After being cooled, the product was poured into ice-water, the oil extracted with ether, and the solvent evaporated. The residue was hydrolysed by boiling with an excess of alcoholic potash, and after removal of the excess of alcohol, the solution was acidified, extracted with ether, the extract dried, and the ether evaporated. On distillation, αββ-trimethylacrylic acid was obtained as a colourless oil, b. p. 114—115°/27 mm., which partly solidified on cooling, and was recrystallised from methyl alcohol; colourless plates, m. p. 70—71° (Found: C, 63·1; H, 8·8. Calc.: C, 63·2; H, 8·8%).

Methylmesityl Oxide.—αββ-Trimethylacrylyl chloride, b. p. 144—145°/766 mm. (compare Perkin and Thorpe, *loc. cit.*, p. 1480), was treated with zinc methyl iodide in the usual way and the ketone isolated and distilled (b. p. 145°); its *semicarbazone* separated from dilute alcohol in colourless plates, m. p. 186° (Found: C, 57·3; H, 8·9. $C_8H_{15}ON_3$ requires C, 56·8; H, 8·9%). Methylmesityl oxide condensed with malonic ester under the following conditions: A solution of ethyl sodiomalonate (sodium, 1·15 g.; absolute alcohol, 14 c.c.; ethyl malonate, 8·5 g.) was heated under reflux with methylmesityl oxide (5·6 g.) for 18 hours; the excess of alcohol was distilled off, the mixture diluted with water (100 c.c.), and the neutral products were extracted with ether. The aqueous solution was then mixed with potassium hydroxide (4·5 g.), the whole boiled for 15 minutes, acidified with dilute sulphuric acid, and boiled until no more carbon dioxide was evolved; the yellow oil which separated solidified on cooling and was crystallised from water (charcoal) with the addition of a few drops of alcohol. The colourless needles, m. p. 100—101°, were evidently trimethyldihydroresorcinol (compare Crossley, J., 1901, **79**, 141) (Found: C, 70·1; H, 9·3. Calc.: C, 70·1; H, 9·1%).

Action of Potassium Cyanide on Methylmesityl Oxide.—Attempts to condense the ketone with 1 mol. of hydrocyanic acid were fruitless, for its reaction with 2 mols. could not be prevented. The ketone (11·2 g.) was dissolved in alcohol (75 c.c.), and the solution boiled under reflux with potassium cyanide (26 g. in 78 c.c. of water) for 4 hours. The mixture was evaporated on the steam-bath, and the viscous product boiled with a large excess of concentrated hydrochloric acid. The excess of acid was then removed, and the solid residue mixed with water and filtered. The solid (XI) was crystallised (charcoal) from acetic acid, separating in colourless, silky needles, m. p. 238° (decomp.) (Found : C, 58·4; H, 8·1. $C_9H_{15}O_3N$ requires C, 58·4; H, 8·1%), easily soluble in glacial acetic acid, moderately soluble in boiling acetone, and sparingly soluble in other organic solvents. The compound was acidic, and resembled mesitylic acid in its general properties.

The aqueous filtrate (above) was repeatedly extracted with ether, and the extract dried and evaporated; the oily residue readily gave a crystalline semicarbazone, which separated from alcohol in colourless, shining prisms, m. p. 175° (decomp.) (Found : C, 50·5; H, 8·1. $C_9H_{17}O_3N_3$ requires C, 50·2; H, 7·9%). There can be no doubt that this is the semicarbazone of ααβ-trimethyl-lævulic acid, but owing to the small yield the solid acid could not be obtained from it.

Synthesis of ααβ-Trimethyl-lævulic Acid.

*Ethyl β-Hydroxy-ααβ-trimethyl-*n*-valerate* (XII).—A mixture of dry methyl ethyl ketone (55 g.), ethyl α-bromo*iso*butyrate (150 g.), benzene (300 c.c.), and zinc turnings (60 g.) was boiled under reflux on the steam-bath for ½ hour. Minute quantities of iodine were then added until the reaction started. The flask was removed from the steam-bath and the vigorous reaction allowed to proceed by its own heat, the mixture being finally heated on the steam-bath for 15 minutes. *Ethyl β-hydroxy-ααβ-trimethyl-*n*-valerate* was isolated from the mixture and purified in the usual way, being obtained as a colourless, mobile oil, having a faint ethereal smell (yield, 55%), b. p. 92°/11 mm. (Found : C, 63·5; H, 10·2. $C_{10}H_{20}O_3$ requires C, 63·8; H, 10·6%).

ααβ-Trimethyl-Δ^{β}-pentenoic Acid (formula as XIII).—The hydroxy-ester (68 g.) was mixed with phosphorus pentoxide (40 g.) under dry benzene (75 c.c.), and the mixture was slowly distilled under ordinary pressure until most of the benzene had passed over. The distillation was then continued under reduced pressure and a considerable amount of a low-boiling fraction collected; on redistillation, almost the whole fraction boiled at 100—102°/45 mm., giving the *ester* (XIII) as a colourless, transparent oil, having a sweet smell; $d_{4^\circ}^{16\cdot8^\circ}$ 0·906942, $n_D^{16\cdot8^\circ}$ 1·43878, $[R_L]_D$ 49·3 (calc., 49·5) (Found : C, 70·1; H, 10·8. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6%). A chloroform solution of the ester was ozonised and then gave a good yield of acetaldehyde, identified as ethylidene-β-dinaphthyl oxide, m. p. 170° (mixed m. p. with an authentic specimen 171°)

The ester was hydrolysed with 10% methyl-alcoholic potash, and the resulting *ααβ-trimethyl-Δ^{β}-pentenoic acid* had b. p. 113°/10 mm., $d_{4^\circ}^{19\cdot2^\circ}$ 0·963434, $n_{D}^{19\cdot2^\circ}$ 1·45283, $[R_L]_D$ 39·8 (calc., 40·2) (Found, for *silver* salt: Ag, 43·8. $C_8H_{13}O_2Ag$ requires Ag, 43·4%); the p-*toluidide*, prepared from the acid chloride and *p*-toluidine, crystallised from light petroleum (b. p. 40—60°) in long, silky needles, m. p. 71° (Found: C, 77·9; H, 9·0. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·1%).

Lactone of γ-Hydroxy-ααβ-trimethyl-Δ^{β}-pentenoic Acid (XVI).—The foregoing acid was dissolved in dry carbon disulphide, and to the solution, cooled to 0°, a slight excess of bromine was added. After remaining in the cold for a few hours, the solvent was removed. The solid residue thus obtained could not be purified owing to the ease with which it lost hydrobromic acid. The crude product was therefore distilled from a glycerol-bath; a considerable evolution of hydrobromic acid took place, and between 210° and 260° (bath temperature) a large amount of brown oil distilled over. This was collected in ether, washed with a dilute solution of sodium carbonate, dried with sodium sulphate, evaporated, and the residue distilled under reduced pressure. After several distillations, a considerable amount of a low-boiling fraction (b. p. 75—80°/13 mm.) was isolated, together with a small amount of a higher-boiling fraction (b. p. 110°/13 mm.) which still contained some bromine and was not further investigated. The first fraction was again washed with sodium carbonate, dried, and distilled, the *lactone* being obtained as a colourless, halogen-free liquid, b. p. 80°/13 mm., having a characteristic burning smell (Found: C, 68·7; H, 8·8. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%).

ααβ-Trimethyl-lævulic Acid (IX).—The unsaturated lactone was boiled under reflux with 20% methyl-alcoholic potash for 2 hours. The alcohol was evaporated, the residue acidified, and extracted six times with ether; when freed from solvent, ultimately in a vacuum desiccator over sulphuric acid, the acid was obtained as a colourless solid, m. p. 77—78° after recrystallisation from ethyl bromide–light petroleum (b. p. 60—80°) (Found: C, 60·7; H, 9·0. Calc. for $C_8H_{14}O_3$: C, 60·8; H, 8·9%), and was identical in all essential respects with the acid obtained previously (p. 2613), giving a semicarbazone, m. p. 173° (Found: C, 50·6; H, 7·9. Calc.: C, 50·2; H, 7·9%).

The p-*nitrophenylhydrazone* forms yellow, flattened needles, m. p. 207° (with previous softening), showing slight dichroism (Found: C, 57·2; H, 6·5. $C_{14}H_{19}O_4N_3$ requires C, 57·3; H, 6·5%). The *piperonylidene* derivative crystallises from dilute alcohol (charcoal) in lemon-yellow needles, m. p. 115° (Found: C, 66·2; H, 6·1. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·2%).

Synthesis and Properties of γ-Keto-αββ-trimethylpropane-αγ-dicarboxylic Acid (*Balbiano's Acid*) (IV).

Oxidation of αββ-Trimethyl-lævulic Acid.—To a mixture of αββ-trimethyl-lævulic acid (5 g.), potassium hydroxide (2 g.), and water (200 c.c.), was added a solution of permanganate (12 g.) and caustic potash (4 g.) in 300 c.c. of water, the mixture being cooled in running water. In the course of 2—3 hours the colour of the permanganate disappeared, and after a further 12 hours the greenish liquid became practically colourless. The manganese precipitate was collected and washed several times with hot water, and the combined aqueous filtrates were concentrated, cooled, acidified with hydrochloric acid, and extracted with ether. The solid residue (3·5 g.), which remained after removal of the last traces of ether in a vacuum desiccator, was exactly neutralised with caustic soda, mixed with a 30% solution of calcium chloride, filtered, and the clear solution boiled on a sand-bath for 1 hour. The crystalline precipitate which separated on cooling was collected, washed, suspended in water, and decomposed with concentrated hydrochloric acid in presence of an excess of ether. The ethereal layer was separated, washed, dried with anhydrous sodium sulphate, and evaporated. On being kept in a desiccator, the residue solidified to a snow-white, crystalline mass, which melted at 119° after having been rubbed with a little chloroform, and consisted of pure Balbiano's acid (Found: C, 51·1; H, 6·5. Calc.: C, 51·0; H, 6·4%). The identity was further established by direct comparison with an authentic specimen of the acid prepared from camphoric acid and by the following characteristic reactions.

(1) *Formation of quinoxaline derivative.* A considerable quantity of this substance accumulated in the course of the preliminary experiments on the oxidation of trimethyl-lævulic acid and its ethyl ester.* The crude acid resulting from the oxidation was mixed with an excess of *o*-phenylenediamine and glacial acetic acid and gently warmed on the steam-bath for $\frac{1}{2}$ hour; excess of acetic acid was removed, and addition of a large excess of water then precipitated a solid which crystallised from methyl alcohol (charcoal) in magnificent shining plates, m. p. 223—224° with previous softening (mixed m. p. with an authentic specimen 223—224°; compare Kon, Stevenson, and Thorpe, *loc. cit.*) (Found: C, 64·5; H, 6·5. Calc.: C, 64·6; H, 6·2%).

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* Owing to the extraordinary ease with which ethyl *αββ*-trimethyl-lævulate is hydrolysed by alkali, twice the theoretical quantity of permanganate must be used when this ester is employed in the synthesis of Balbiano's acid, as otherwise the alcohol produced reduces the whole of the permanganate, leaving the lævulic acid practically unchanged.

(2) *Formation of* αββ-*trimethylglutaric acid.* The synthetic acid (2 g.) was heated with hydriodic acid (12 c.c., *d* 1·9) and red phosphorus (1 g.) for 15 hours in a closed tube at 150—160°. The colourless solution was extracted with ether and the solid residue from the extract was dissolved in ammonia and boiled with a solution of calcium chloride. The precipitated calcium salt was collected and decomposed with dilute hydrochloric acid; the free acid, isolated in the usual way, crystallised from dilute hydrochloric acid in glistening prisms, m. p. 86—87° (Found : C, 55·4; H, 8·2. Calc. : C, 55·2; H, 8·1%).

(3) *Formation of trimethylsuccinic acid.* The crude oxidation acid was heated in a sulphuric acid bath, the melt extracted with boiling water, and the succinic acid isolated and purified in the form of its calcium salt; after one crystallisation from dilute hydrochloric acid it melted at 148° (compare Mahla and Tiemann, *loc. cit.*) (Found : C, 52·4; H, 7·5. Calc. : C, 52·5; H, 7·5%).

The following experiments were made with a specimen of Balbiano's acid prepared from camphoric acid by oxidation with alkaline permanganate (Balbiano, *loc. cit.*; Rothstein, Stevenson, and Thorpe, *loc. cit.*). The yield of the keto-acid is considerably reduced if the temperature is allowed to rise above 30°. The acid was isolated as the characteristic calcium salt and purified in the usual way.

The anhydride (XVII) was prepared by the following modification of Balbiano's method : The acid (5 g.) was boiled under reflux with acetic anhydride (20 c.c.) for 2 hours, the excess of acetic anhydride was removed under reduced pressure, and the residue kept in a desiccator. Since the product did not show any tendency to solidify, its constitution was confirmed by conversion into a crystalline naphthylamic acid by dissolving it in benzene and boiling the solution under reflux with a slight excess of β-naphthylamine for $\frac{1}{2}$ hour. It was then diluted with ether and washed with dilute hydrochloric acid and water. The naphthylamic acid (XVIII) was dissolved in sodium carbonate and precipitated with dilute acid; it crystallised from dilute methyl alcohol (charcoal) in colourless, shining scales, m. p. 177° (decomp.), and behaved on titration as a monobasic acid (Found: C, 68·8; H, 6·3; *M*, 315. Calc.: C, 69·0; H, 6·1%; *M*, 313). It does not condense with *o*-phenylenediamine, and decomposes on heating with the formation of resinous products.

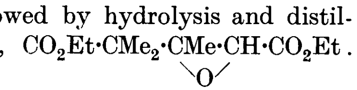
Action of Alkali on Balbiano's Acid.—The acid (5 g.) was boiled with a solution of potassium hydroxide (60 g.) in water (40 c.c.) for 3 hours, the product cooled in ice, acidified with hydrochloric acid, and extracted several times with ether. On evaporation of the solvent, a solid (3·9 g.) remained, which was proved to be unchanged

Balbiano's acid by its m. p. (119°) and by the formation of the quinoxaline derivative (m. p. 223—224°). Under the above conditions, therefore, Balbiano's acid remains practically unchanged and does not show any tendency to pass into a hydroxy*cyclo*propane acid.

Reduction with Sodium Amalgam.—The acid (5 g.) was dissolved in sodium carbonate and mechanically stirred with 300 g. of 3% sodium amalgam; the solution was concentrated, cooled, acidified with dilute hydrochloric acid, and extracted with ether. The residue from the ethereal extract was neutralised with alkali and boiled with a solution of calcium chloride to remove any unchanged keto-acid. The clear filtrate was acidified with hydrochloric acid and extracted with ether. The residue from evaporation of the extract was repeatedly crystallised from ethyl acetate–light petroleum (b. p. 60—80°) and yielded the expected lactonic acid in flattened needles, m. p. 163° (Found: C, 56·0; H, 7·3. Calc.: C, 55·8; H, 7·0%).

Attempt to Prepare the Keto-acid (XXIV).—The oxidation of ααβ-trimethyl-lævulic acid (IX) was carried out in an exactly similar manner to that of αββ-trimethyl-lævulic acid and appeared to proceed as before, but the product did not condense with *o*-phenylenediamine, and after recrystallisation from dilute hydrochloric acid it was identified as trimethylsuccinic acid, m. p. 149°.

Condensation of Chloroacetic Ester with Dimethylacetoacetic Ester.—Since a considerable amount of dimethylacetoacetic ester had accumulated in course of the preparation of ααβ-trimethylglutaconic acid, which had been used in unsuccessful efforts to prepare the lactone (XXVIII) by reduction, an attempt was made to convert it into the semi-aldehyde of trimethylsuccinic acid (XXV) by condensation with chloroacetic ester and sodium ethoxide (Darzens, *Compt. rend.*, 1904, **139**, 1215), followed by hydrolysis and distillation of the resulting oxidic ester,



$CO_2Et\cdot CMe_2\cdot \underset{\diagdown O \diagup}{CMe\cdot CH}\cdot CO_2Et$.

A mixture of dimethylacetoacetic ester (80 g.) and chloroacetic ester (90 g.) was cooled in a freezing mixture, and finely powdered sodium ethoxide (50 g.) added in small quantities with vigorous shaking. After remaining at the ordinary temperature over-night, the mixture was heated on the steam-bath for 5 hours. The dark-coloured mass was then mixed with water and extracted with ether. The ethereal extract was washed with sodium carbonate, dried, and evaporated. On distillation the residue gave a considerable amount of unchanged dimethylacetoacetic ester in the low-boiling fractions, and subsequently the oxidic *ester* was obtained as a colourless liquid, b. p. 162°/26 mm. (yield, 30%) (Found: C, 58·6; H, 7·8. $C_{12}H_{20}O_5$ requires C, 59·0; H, 8·2%). This ester on hydrolysis and distillation yielded an extremely viscous oil, which did not give any semicarbazone and is still under investigation.

Synthesis of the Lactonic Acid (XXVIII).—Preliminary attempts were made to prepare this acid from ααβ-trimethylglutaric acid, but the latter could not be obtained in suitable condition either by Perkin and Thorpe's method (J., 1896, **69**, 1187), by catalytic reduction of the corresponding glutaconic acid, or by the condensation of *iso*butaldehyde with ethyl ethylidenemalonate. Ultimately, however, the semi-aldehyde of trimethylsuccinic acid was prepared by Blaise and Courtout's method (*loc. cit.*), and, although it exists in the lactol form (XXVI), it was found to condense with hydrocyanic acid, thereby enabling the synthesis to be effected as follows: A mixture of the semi-aldehyde (5 g.), potassium cyanide (98%, 9·2 g.), and water (15 c.c.) was cooled in a freezing mixture, and to it was gradually added (2 hours) the calculated amount of concentrated hydrochloric acid (11·5 c.c.); after remaining in the cold over-night, the mixture was warmed on the steam-bath with the addition of hydrochloric acid (5 c.c.). The resulting oil was collected in ether, washed with dilute sodium carbonate, dried, and the ether distilled off. The residue of almost pure *cyano-lactone* (XXVII) was hydrolysed with concentrated hydrochloric acid, and the clear solution extracted several times with ether. Removal of the solvent left an oil which slowly solidified to a crystalline mass, and repeated crystallisation from toluene gave the *lactone* of *α'-hydroxy-ααβ-trimethylglutaric acid* in stellate clusters of fan-shaped needles, m. p. 110° (Found: C, 55·5; H, 7·0. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%). The mother-liquor from the crystallisation yielded on evaporation a gum which was not further investigated. On oxidation with alkaline permanganate the lactonic acid gave trimethylsuccinic acid as the sole product.

αα-Dihydroxy-ββ-dimethylglutaric Acid.—This substance was prepared by the oxidation of ββ-dimethyl-lævulic acid with alkaline permanganate. The crude product, which was obtained as a gum, was dissolved in ammonia, and the sparingly soluble calcium salt precipitated by warming with a solution of calcium chloride. The acid was regenerated with dilute hydrochloric acid and extracted with ether. The solid residue, purified by repeated crystallisation from chloroform, was obtained in silky needles, m. p. 82–83° (Found: C, 43·9; H, 6·4. Calc.: C, 43·7; H, 6·3%); the identity of this substance with αα-dihydroxy-ββ-dimethylglutaric acid (Perkin and Thorpe, J., 1901, **79**, 757) was established by direct comparison and by a mixed m. p. This shows, therefore, that the method by which Balbiano's acid has been synthesised is a very general one.

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