

LXXXIII.— *β -Isopropylglutaric Acid and cis- and trans-Methylisopropylglutaric Acids.*

By F. H. HOWLES, JOCELYN F. THORPE, and WILLIAM UDALL.

ETHYL α -BROMISOBUTYLACETATE is best prepared in the following manner. Isobutylacetic acid, obtained by treating ethyl sodiomalonate with isobutyl bromide, hydrolysing the product after fractionation with ethyl alcoholic potash, and distilling the tribasic acid obtained, is brominated by the Volhard method with phosphorus pentabromide and bromine, and the product poured into absolute alcohol.

The bromo-ester separates as a heavy, yellow oil on pouring the alcoholic solution into water and extracting with ether.

Ethyl β -Isopropylacrylate.

Fifty grams of the bromo-ester without further purification are mixed with 75 grams diethylaniline and boiled on the sand-bath for 9 hours; the solid mass is then treated with hydrochloric acid (1:1) and shaken out with ether, the ethereal solution being washed repeatedly with hydrochloric acid until the last traces of diethylaniline have been washed out; the unsaturated ethyl salt obtained on distilling off the ether boils at 174° under 757 mm. pressure.

I. Condensation of Ethyl β -Isopropylacrylate with Ethyl Sodicyanacetate.

Ethyl cyanacetate (19.9 grams) was added to an alcoholic solution of sodium (4 grams) and, after the addition of ethyl β -isopropylacrylate (25 grams), the mixture was heated on the water-bath for 10 hours. On adding the unsaturated ethyl ester, considerable heat was evolved. The product, which consisted of a dark coloured gelatinous solid, was mixed with water and extracted with ether, the ethereal solution giving an oil on evaporation which, on distillation under 30 mm. pressure, gave 13 grams of an oil boiling at 195° ; this proved to be ethyl α -cyano- β -isopropylglutarate, $\text{CO}_2\text{Et}\cdot\text{CH}(\text{CN})\cdot\text{CHPr}^{\beta}\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$. On analysis :

0.2215 gave 0.4989 CO_2 and 0.1618 H_2O . C = 61.43; H = 8.12.

$\text{C}_{13}\text{H}_{21}\text{O}_4\text{N}$ requires C = 61.17; H = 8.23 per cent.

On acidifying the mother liquor, a quantity of oil separated, which after extraction was found to weigh 10 grams. On distillation under ordinary pressure, a vigorous evolution of gas ensued, the liquid after three distillations passing over as a mobile oil boiling at 234° under 755 mm. pressure and consisting of ethyl γ -cyano- β -isopropylbutyrate, $\text{CN}\cdot\text{CH}_2\cdot\text{CHPr}^{\beta}\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$.

0.2113 gave 0.5060 CO_2 and 0.1731 H_2O . C = 65.31; H = 9.10.

$\text{C}_{10}\text{H}_{17}\text{O}_2\text{N}$ requires C = 65.57; H = 9.29.

Another experiment, in which the time of heating was only 3 hours instead of twelve, the same quantities being used, yielded only a trace of diethyl ester, but 30 grams of ethyl hydrogen salt.

Hydrolysis of the Diethyl Ester.

On adding an equal weight of potash dissolved in methyl alcohol to the ester, a large quantity of a crystalline potassium salt separated; this was filtered off, washed with methyl alcohol, dissolved in water, and the solution boiled until the last traces of methyl alcohol had been removed. The solution on acidifying, saturating with ammonium sulphate, and extracting with ether, yielded a liquid substance which when boiled for 10 minutes with concentrated hydrochloric acid evolved large quantities of carbon dioxide, and on cooling deposited crystals of β -isopropylglutarimide, $\text{CHPr}^{\beta}\cdot\begin{matrix} \text{CH}_2\cdot\text{CO} \\ \text{CH}_2\cdot\text{CO} \end{matrix}\text{NH}$, this separating from hot water in glistening plates melting at 120° .

0.3036 gave 24.2 c.c. nitrogen at 20° and 756 mm. N = 9.03.

$\text{C}_8\text{H}_{13}\text{O}_2\text{N}$ requires N = 9.07 per cent.

The *silver* salt is obtained as a white, crystalline precipitate on adding a solution of silver nitrate to a slightly alkaline solution of the imide. On analysis :

0.2913 gave 0.2085 AgBr. Ag = 40.97.

$C_8H_{12}O_2N$ Ag requires Ag = 41.13 per cent.

β -Isopropylglutaric acid, $CO_2H \cdot CH_2 \cdot CHPr^\beta \cdot CH_2 \cdot CO_2H$,

can be prepared either by hydrolysing the pure imide with a 50 per cent. solution of sulphuric acid, the operation usually being finished after heating for 2 hours on the sand-bath, or by heating the imide in a sealed tube with concentrated hydrochloric acid for 6 hours at 150° . In both cases, the acid can be obtained on extracting with ether. It separates from water in needles, and melts at 100° . On analysis :

0.2081 gave 0.4198 CO_2 and 0.1524 H_2O . C = 55.02 ; H = 8.12.

$C_8H_{14}O_4$ requires C = 55.17 ; H = 8.04 per cent.

The *anhydride*, $CHPr^\beta \langle \begin{smallmatrix} CH_2 \cdot CO \\ CH_2 \cdot CO \end{smallmatrix} \rangle O$, is obtained as a liquid on treating the acid with excess of acetyl chloride for 2 hours on the water-bath. It boils at 171° under 30 mm. pressure.

0.2134 gave 0.4839 CO_2 and 0.1442 H_2O . C = 61.85 ; H = 7.51.

$C_8H_{10}O_3$ requires C = 61.54 ; H = 7.69 per cent.

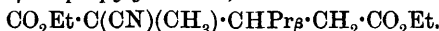
β -Isopropylglutaranilic acid, $C_6H_5 \cdot NH \cdot CO \cdot CH_2 \cdot CHPr^\beta \cdot CH_2 \cdot CO_2H$, is precipitated when benzene solutions of aniline and the anhydride are mixed together. It crystallises from alcohol in colourless, lustrous plates, melts at 121° , and dissolves in sodium carbonate solution. On analysis :

0.1508 gave 7.5 c.c. nitrogen at 22° and 765 mm. N = 5.68.

$C_{14}H_{19}O_3N$ requires N = 5.62 per cent.

Action of Methyl Iodide on the Sodium Compound of the Condensation Product.

Since the object in this case was to produce the methyl derivative, the reaction product was heated for only 3 hours on the water-bath before excess of methyl iodide was gradually added, and the heating continued for 6 hours. On adding water, extracting with ether, and removing the ether by evaporation, a thick, yellow oil remained, which boiled at 180 — 183° under 19 mm. pressure, and consisted of *ethyl α -cyano- α -methyl- β -isopropylglutarate*,



On analysis :

0.2950 gave 0.6741 CO₂ and 0.2240 H₂O. C = 62.33 ; H = 8.44.

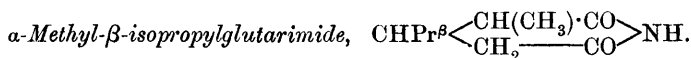
C₁₄H₂₃O₄N requires C = 62.45 ; H = 8.55 per cent.

On adding an equal weight of potash dissolved in methyl alcohol to this ester, hydrolysis at once ensues with evolution of heat, and at the same time a copious precipitation of a crystalline potassium salt takes place. This salt can be separated by filtration and purified by washing with methyl alcohol, when it is obtained as a slightly yellow, crystalline solid, evidently consisting of potassium α -cyano- α -methyl- β -isopropylglutarate.

0.9814 gave 0.6012 K₂SO₄. K = 27.46.

C₁₀H₁₂O₄NK₂ requires K = 26.99 per cent.

The salt is extremely soluble in cold water.



On acidifying the concentrated aqueous solution of the potassium salt with hydrochloric acid and extracting with ether, a solid consisting of the dibasic cyano-acid is obtained on evaporation. On boiling this with concentrated hydrochloric acid for 1 hour and again extracting, an ethereal solution of the imide and the *trans*-acid is obtained, which can be freed from the *trans*-acid by shaking with a dilute solution, of sodium carbonate, the imide remaining in the ethereal solution, from which it can be obtained on evaporation. The end point of this reaction, that is to say, the point at which it can be safely assumed that all the *cis*-amic acid formed during the hydrolysis has been converted into imide and all the *trans*-amic acid hydrolysed to *trans*-acid, is usually that point at which the evolution of carbon dioxide ceases.

α -Methyl- β -isopropylglutarimide crystallises from water in colourless needles and melts at 114—115°. On analysis :

0.1438 gave 10.5 c.c. nitrogen at 14° and 765 mm. N = 8.51.

C₉H₁₅O₂N requires N = 8.28 per cent.

The *silver* salt is precipitated as a white, crystalline powder on adding a solution of silver nitrate to a slightly alkaline solution of the imide. On analysis :

0.3001 gave 0.2042 AgBr. Ag = 39.10.

C₉H₁₄O₂NAg requires Ag = 39.04 per cent.

cis- α -Methyl- β -isopropylglutaric Acid,
 $\text{CO}_2\text{H} \cdot \text{CH}(\text{CH}_3) \cdot \text{CHPr}^\beta \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$.

The *cis*-acid is best prepared by hydrolysing the imide with 50 per cent. sulphuric acid, the reaction being complete after boiling for 3 hours on the sand-bath. On cooling and extracting with ether, a solid acid remains on evaporation, which separates from hot water in glistening plates melting at 137° . On analysis:

0.1421 gave 0.3001 CO_2 and 0.1080 H_2O . $\text{C} = 57.57$; $\text{H} = 8.44$.

$\text{C}_9\text{H}_{16}\text{O}_4$ requires $\text{C} = 57.45$; $\text{H} = 8.51$ per cent.

The *silver* salt is a white amorphous powder.

0.1471 gave 0.0783 Ag. $\text{Ag} = 53.23$.

$\text{C}_9\text{H}_{14}\text{O}_4\text{Ag}_2$ requires $\text{Ag} = 53.64$ per cent.

The *anhydride*, $\text{CHPr}^\beta \left\langle \begin{array}{c} \text{CH}(\text{CH}_3) \cdot \text{CO} \\ \text{CH}_2 \quad \quad \quad \text{CO} \end{array} \right\rangle \text{O}$.—On boiling the *cis*-acid with acetyl chloride, it slowly dissolves with evolution of hydrogen chloride, and if the solution is evaporated to dryness after boiling for 1 hour on the water-bath, a solid residue remains. This is insoluble in sodium carbonate solution and crystallises from light petroleum (b. p. 40 — 60°) in glistening plates melting at 44° . On analysis:

0.1445 gave 0.3308 CO_2 and 0.1068 H_2O . $\text{C} = 62.41$; $\text{H} = 8.21$.

$\text{C}_9\text{H}_{14}\text{O}_3$ requires $\text{C} = 62.35$; $\text{H} = 8.24$ per cent.

trans- α -Methyl- β -isopropylglutaric acid,
 $\text{CO}_2\text{H} \cdot \text{CH}(\text{CH}_3) \cdot \text{CHPr}^\beta \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$.

The solution obtained from the hydrochloric acid hydrolysis by extracting the ethereal extract with sodium carbonate gave a solid acid on acidifying, saturating with ammonium sulphate, extracting with ether, and removing the ether by evaporation. When recrystallised from water, this acid melted at 101° , and at first was thought to be β -isopropylglutaric acid, due to the presence of non-methylated ethyl ester in the product. Its properties, however, were found to be very different from those of β -isopropylglutaric acid, for not only were the crystalline forms of the acids different, but the acid melting at 101° yielded no anhydride on treatment with acetyl chloride, and further, could be completely converted into *cis*- α -methyl- β -isopropylglutaric anhydride on heating with acetic anhydride in a closed tube. On analysis:

0.1332 gave 0.2794 CO_2 and 0.1030 H_2O . $\text{C} = 57.25$; $\text{H} = 8.59$.

0.1878 „ 0.3942 CO_2 „ 0.1437 H_2O . $\text{C} = 57.25$; $\text{H} = 8.50$.

$\text{C}_9\text{H}_{16}\text{O}_4$ requires $\text{C} = 57.45$; $\text{H} = 8.51$ per cent.

The conversion of the *cis*- into the *trans*-form is partially effected by heating the *cis*-acid in a sealed tube with concentrated hydrochloric acid for 6 hours at 180°. The acids can be separated by repeated recrystallisation from water.

The conversion of the *cis*- into the *trans*-form is completely brought about by heating the *trans*-acid with acetic anhydride in a sealed tube at 150° for 4 hours. On evaporating the product and boiling with water, the *cis*-acid melting at 137° separates on cooling.

II. *Condensation of Ethyl α-Methylacrylate with Ethyl Sodiocyanacetate.*

Ethyl α-methylacrylate is best prepared by the action of diethylaniline on ethyl α-bromisobutyrate. The bromo-ester (50 grams) is boiled with diethylaniline (75 grams) for 3 hours on the sand-bath. After cooling, ether is added, and the solution filtered with the aid of a pump, care being taken to thoroughly wash the diethylaniline hydrobromide with ether. The ethereal solution is then quickly shaken with dilute hydrochloric acid solution to remove excess of diethylaniline, and, after drying and distilling, fractionated. The clear, mobile liquid which passes over between 117° and 120° consists of pure ethyl α-methylacrylate; it must be at once used, however, since on standing it slowly polymerises to a white, transparent substance resembling gelatine.

The largest yield of this ester was obtained by this method, but it in no case exceeded 28 per cent. of the theoretical.

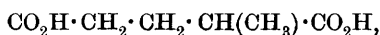
Condensation of Ethyl α-Methylacrylate with Ethyl Sodiocyanacetate.

This condensation, in which the usual equivalent proportions of the constituents were used, was found to take place with great ease, considerable heat being evolved on adding the unsaturated ester to the alcoholic sodium compound. After heating for 1 hour on the water-bath, the product was worked up in the usual manner, and found to consist almost entirely of ethyl hydrogen salt, which, on distillation under ordinary atmospheric pressure, lost carbon dioxide and passed into *ethyl γ-cyano-α-methylbutyrate*, $\text{CN} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{CH}_3) \cdot \text{CO}_2\text{Et}$ a mobile liquid boiling at 210°. On analysis:

0.2810 gave 0.6358 CO_2 and 0.2076 H_2O . $\text{C} = 61.71$; $\text{H} = 8.21$.

$\text{C}_8\text{H}_{13}\text{O}_2\text{N}$ requires $\text{C} = 61.93$; $\text{H} = 8.39$ per cent.

On boiling this nitrile with 50 per cent. sulphuric, it is converted, after heating for 3 hours, into *α-methylglutaric acid*,



948 HOWLES, THORPE, AND UDALL: β -ISOPROPYLGUTARIC ACID

melting at 76° (Wislicenus and Limpach, *Annalen*, 1878, 192, 134).
On analysis :

0.2701 gave 0.4872 CO_2 and 0.1631 H_2O . $\text{C} = 49.20$; $\text{H} = 6.71$.

$\text{C}_6\text{H}_{10}\text{O}_4$ requires $\text{C} = 49.31$; $\text{H} = 6.84$ per cent.

III. *Condensation of Ethyl β -Methylacrylate with Ethyl Sodiocyanacetate.*

Ethyl β -methylacrylate can be prepared in the usual way by boiling a mixture of 50 grams of ethyl α -bromobutyrate and 75 grams of diethylaniline on a sand-bath for 12 hours, and since this ethyl salt shows no tendency to polymerise on standing, no special precautions are necessary in working up the product.

Ethyl β -methylacrylate does not condense so readily with ethyl sodiocyanacetate as the corresponding α -compound, 6 hours heating on the water-bath being necessary to produce the maximum quantity of ethyl hydrogen salt, the yield of this substance, as in the former cases, being dependent on the duration of heating.

On distilling this ethyl hydrogen salt under the ordinary pressure, carbon dioxide is evolved, and it is converted into *ethyl γ -cyano- β -methylbutyrate*, $\text{CN}\cdot\text{CH}_2\cdot\text{CH}(\text{CH}_3)\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$, a mobile liquid boiling at 205° . On analysis :

0.2135 gave 0.4839 CO_2 and 0.1572 H_2O . $\text{C} = 61.81$; $\text{H} = 8.18$.

$\text{C}_8\text{H}_{13}\text{O}_2\text{N}$ requires $\text{C} = 61.93$; $\text{H} = 8.39$ per cent.

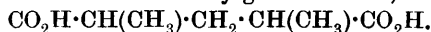
When hydrolysed with 50 per cent. sulphuric acid, the nitrile is converted after 6 hours boiling into *β -methylglutaric acid*, $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}(\text{CH}_3)\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$, melting at 86° (Auwers, Köbner, and von Meyenburg, *Ber.*, 1891, 24, 2888). On analysis :

0.1956 gave 0.3526 CO_2 and 0.1185 H_2O . $\text{C} = 49.17$; $\text{H} = 6.73$.

$\text{C}_6\text{H}_{10}\text{O}_4$ requires $\text{C} = 49.31$; $\text{H} = 6.84$ per cent.

IV. *Condensation of Ethyl β -Methylacrylate with Ethyl Sodiocyanacetate and subsequent Treatment with Methyl Iodide.* [With H. A. NEALE.]

As explained in the general introduction (p. 932), the object of this experiment was to prepare synthetically *as-aa*-dimethylglutaric acid, $\text{CO}_2\text{H}\cdot\text{C}(\text{CH}_3)_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$, which is of importance, since it bears upon the constitution of camphor. It was found, however, that the reaction between unsaturated esters and ethyl cyanacetate did not proceed as usually supposed, and the product obtained consisted entirely of the symmetrical *aa*-dimethylglutaric acids,



The details of the condensation between ethyl sodiocyanacetate and ethyl β -methylacrylate have already been given (p. 948). It was found that the length of time during which the condensation mixture must be heated to produce the maximum quantity of ethyl hydrogen salt was 6 hours; hence on treating the product after this time with excess of methyl iodide, a corresponding quantity of *ethyl α -cyano- $\alpha\alpha'$ -dimethylglutarate*, $\text{CO}_2\text{Et} \cdot \text{C}(\text{CN})(\text{CH}_3) \cdot \text{CH}_2 \cdot \text{CH}(\text{CH}_3) \cdot \text{CO}_2\text{C}_2\text{H}_5$, was obtained on working up the product. This ester boils at $181-185^\circ$ under 30 mm. pressure. On analysis:

0.2214 gave 0.4839 CO_2 and 0.1531 H_2O . $\text{C} = 59.61$; $\text{H} = 7.69$.

$\text{C}_{12}\text{H}_{19}\text{O}_4\text{N}$ requires $\text{C} = 59.75$; $\text{H} = 7.88$ per cent.

On hydrolysis with an equal weight of potash dissolved in methyl alcohol, the ester is converted into a *potassium* salt, evidently that of the dibasic cyano-acid, which can be separated by filtration and purified by washing with methyl alcohol. On analysis:

0.5134 gave 0.3611 K_2SO_4 . $\text{K} = 31.53$.

$\text{C}_7\text{H}_9\text{O}_4\text{NK}_2$ requires $\text{K} = 31.32$ per cent.

This salt, when its solution in water was acidified and extracted with ether, yielded a solid substance, which was not further purified but directly treated with concentrated hydrochloric acid. On boiling, a considerable quantity of carbon dioxide was evolved, which ceased after the heating had been continued for 1 hour. The solution was then extracted with ether, and the ethereal solution shaken three times with a dilute solution of sodium carbonate. On evaporating the ether, a solid remained which separated from hot water in long needles and melted at 173° , evidently consisting of *$\alpha\alpha'$ -dimethylglutarimide*, $\text{CH}_2 \begin{array}{c} \text{CH}(\text{CH}_3) \cdot \text{CO} \\ \text{CH}(\text{CH}_3) \cdot \text{CO} \end{array} \text{NH}$ (Auwers and Thorpe, *Annalen*, 1895, 285, 315). On analysis:

0.1885 gave 16.4 c.c. nitrogen at 17° and 749 mm. $\text{N} = 9.96$.

$\text{C}_7\text{H}_{11}\text{O}_2\text{N}$ requires $\text{N} = 9.93$ per cent.

The imide on heating for 2 hours with 50 per cent. sulphuric acid is completely hydrolysed, yielding *cis- $\alpha\alpha'$ -dimethylglutaric acid*, which separated from water in needles and melted at $127-128^\circ$. On analysis:

0.2237 gave 0.4295 CO_2 and 0.1172 H_2O . $\text{C} = 52.38$; $\text{H} = 7.47$.

$\text{C}_7\text{H}_{12}\text{O}_4$ requires $\text{C} = 52.50$; $\text{H} = 7.50$ per cent.

On treatment with acetyl chloride, the acid yielded an anhydride which separated from light petroleum or ethyl acetate in plates and melted at $94-95^\circ$. On analysis:

0.1950 gave 0.4212 CO_2 and 0.1223 H_2O . $\text{C} = 58.91$; $\text{H} = 7.00$.

$\text{C}_7\text{H}_{10}\text{O}_3$ requires $\text{C} = 58.89$; $\text{H} = 6.97$ per cent.

The sodium carbonate washings from the ether extract of the product of hydrolysis of the cyano-ester gave nearly pure *trans-aa'*-dimethylglutaric acid on acidifying and extracting with ether. The acid separated from hot water in needles and melted at 141° . On analysis:

0.2170 gave 0.4171 CO_2 and 0.1503 H_2O . $\text{C} = 52.49$; $\text{H} = 7.63$.

$\text{C}_7\text{H}_{12}\text{O}_4$ requires $\text{C} = 52.50$; $\text{H} = 7.50$ per cent.

The acid gave no anhydride on treatment with acetyl chloride

THE OWENS COLLEGE,
MANCHESTER.
