I.—α-*iso*PROPYLGLUTACONIC ACID.*

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Amongst the products formed when *d*-Δ^3-carene was oxidised with potassium permanganate in acetone solution was an acid, $C_8H_{12}O_4$, which was probably *cis*-homocaronic acid (I). The acid was, however, somewhat readily attacked by potassium permanganate in alkaline solution and also showed certain other anomalous properties which made it doubtful whether it possessed this constitution. In describing the acid (*J.C.S.*, 1923, **123**, 553) the cyclic structure was only advanced with reserve and it was suggested that the acid might be either α- or β-*iso*propylglutaconic acid (II or III).

CMe_2—$CH{\cdot}CO_2H$ $\quad CO_2H{\cdot}C(CHMe_2){:}CH{\cdot}CH_2{\cdot}CO_2H$ II

CH——$CH_2{\cdot}CO_2H$ $\quad CO_2H{\cdot}CH{:}C(CHMe_2){\cdot}CH_2{\cdot}CO_2H$ III

The syntheses of *cis*- and *trans*-α-iso*propylglutaconic acids* (II) are now recorded together with an account of an unsuccessful attempt to synthesise *cis*-homocaronic acid. β-*iso*Propylglutaconic acid also has been prepared in small quantity and will be described in a future paper. None of the glutaconic acids is identical with the acid obtained from *d*-Δ^3-carene.

α-*iso*Propylglutaconic acid might be synthesised (1) directly by the condensation of ethyl sodiodicarboxyglutaconate with *iso*propyl iodide, (2) and (3) by the removal of a halogen acid from the α or β-monohalogen derivative of ethyl α-*iso*propylglutarate. Only method (3), however, leads to the required acid.

Although α-methylglutaconic acid (Feist and Pomme, *Annalen*, 1909, **370**, 63) and α-ethylglutaconic acid (Gutzeit and Dressel, *Ber.*, 1890, **23**, 182) have been prepared from ethyl sodiodicarboxyglutaconate and the appropriate alkyl iodide, the sole product of the interaction of the sodio-compound and *iso*propyl iodide under the conditions given on p. 209 was ethyl trimesate. The formation of this ester by the condensation of derivatives of ethyl glutaconate, such as ethyl α-formylglutaconate, has been repeatedly observed (von Pechmann, *Annalen*, 1893, **273**, 174; Wislicenus and Bindemann, *ibid.*, 1901, **316**, 34) and presumably ethyl α-*iso*propylglutaconate, which must have been

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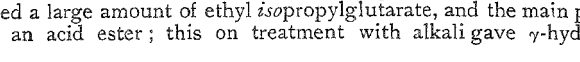
formed as a primary product of the reaction, underwent a similar condensation.

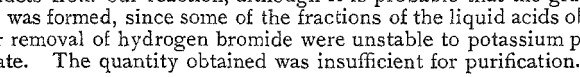
The bromination of α-*iso*propylglutaryl chloride did not proceed smoothly. A bromo-ester of constant boiling point and correct composition could not be isolated. Although a small excess of bromine was used, the reaction mixture, after being poured into alcohol, contained a large amount of ethyl *iso*propylglutarate, and the main product was an acid ester; this on treatment with alkali gave γ-hydroxy-β-



IV; R = H or Et V

methylpentane-γε-dicarboxylic acid, which was isolated as the lactone (V) (compare Fittig and Wolff, *Annalen*, 1895, **288**, 189). This lactone was obtained in an almost theoretical yield on treatment with alkali of the acid products obtained by the esterification of the bromo-acid chloride and it follows, therefore, that it was a tertiary hydrogen atom in the α-*iso*propylglutaryl chloride which had been substituted, yielding α-bromo-α-*iso*propylglutaryl chloride. This result is somewhat remarkable, since it was shown by Ingold (*J.C.S.*, 1925, **127**, 392) that the main product of the bromination of α-methylglutaryl chloride was γ bromo-α-methylglutaryl chloride, only very little of the α-bromo-compound being formed. Apart from α-*iso*propylglutaric acid and the above-mentioned lactone we were not able to isolate any homogeneous products from our reaction, although it is probable that the glutaconic acid was formed, since some of the fractions of the liquid acids obtained after removal of hydrogen bromide were unstable to potassium permanganate. The quantity obtained was insufficient for purification.

Ethyl β-*chloro*-α-iso*propylglutarate* (VIII) was readily prepared by the reactions indicated in the following scheme :—



VI VII VIII $CO_2Et{\cdot}CHPr\beta{\cdot}CHCl{\cdot}CH_2{\cdot}CO_2Et \longrightarrow$ II.

Ethyl α-iso*propylacetonedicarboxylate* (VI) was obtained in an excellent yield when ethyl potassioacetonedicarboxylate was treated with *iso*propyl iodide in alcoholic solution. It could not be reduced catalytically to the *hydroxy-ester* (VII), which could only be prepared by prolonged reduction with a large excess of sodium amalgam. The preparation of the chloro-ester and its conversion into the glutaconic acid (II) were readily carried out under conditions similar to those used by Perkin and Tattersall (*J.C.S.*, 1905, **87**, 362). Separation of

the *cis*- and *trans*-forms of the acid was effected by means of acetyl chloride (Thole and Thorpe, *J.C.S.*, 1911, **99**, 2227).

For the synthesis of homocaronic acid the most ready method appeared to be that represented by the scheme :

$$CMe_2\langle\begin{matrix}CH\cdot CO_2Na\\ |\\ CH\cdot CO_2Me\end{matrix}\rightarrow CMe_2\langle\begin{matrix}CH-CO\\ |\\ CH-CH_2\end{matrix}\rangle O\rightarrow CMe_2\langle\begin{matrix}CH\cdot CO_2H\\ |\\ CH\cdot CH_2\cdot CN\end{matrix}\rightarrow \text{I.}$$

IX X XI

When sodium methyl caronate (IX) was reduced with sodium and alcohol, a small quantity of a neutral oil was obtained. This was not

XII $\begin{matrix}CH\cdot CMe_2\cdot CH_2\cdot CH_2\\ |\qquad\qquad\qquad |\\ CO\text{———————}O\end{matrix}$ $\qquad$ $\begin{matrix}CH_2\cdot CMe_2\cdot CH_2\cdot CH_2\\ |\qquad\qquad\qquad\quad |\\ CO_2H\qquad\qquad CO_2H\end{matrix}$ XIII

(X), but the lactone of δ-hydroxy-ββ-dimethylvaleric acid (XII) (Blanc, *Bull. Soc. chim.*, 1905, **33**, 897), since on treatment with potassium cyanide at 275°, followed by hydrolysis of the resulting nitrile, it gave ββ-dimethyladipic acid (XIII). The reduction of the ester group had therefore been accompanied by fission of the *cyclo*propane ring. Further experiments on the synthesis of homocaronic acid are in progress.

EXPERIMENTAL

The Condensation of Ethyl Sodiodicarboxyglutaconate and iso*Propyl Iodide : Ethyl Trimesate.*—A mixture of the dry sodio-derivative (7gms.) alcohol (10 c.c.), and *iso*propyl iodide (4 gms.) was heated in a sealed tube at 140–160° for 4 hours. Considerable pressure was developed and the liquid contained a colourless solid. This was collected and well washed with alcohol ; it proved to be a mixture of ethyl trimesate and sodium carbonate. The filtrate, after removal of the alcohol, was dissolved in ether to remove inorganic matter, the ether evaporated, and the residual oil distilled under diminished pressure (17 mm.); about half passed over at 100–110°, and the remainder at 205–225°. The higher-boiling fraction slowly crystallised in needles, m.p. 125–127° (after draining on porous porcelain), 132–133° (constant ; after recrystallisation from alcohol). The substance was identified, by analysis (Found : C, 61·3 ; H, 6·3. Calc. : C, 61·2 ; H, 6·1 per cent.) and by direct comparison with an authentic specimen, as ethyl trimesate. The lower-boiling oil was a mixture and owing to the small quantity available was not further examined.

Bromination of α-iso*Propylglutaryl Chloride.*—α-*iso*Propylglutaric acid was most conveniently prepared by the hydrolysis with 50 per

cent. sulphuric acid of *ethyl α-cyano-iso*propylglutarate, which was obtained in an excellent yield under the following conditions: Ethyl *iso*propylcyanoacetate (38 gms.) was added to a solution of sodium (5·6 gms.) in alcohol (75 c.c.) and to the mixture, cooled in salt and ice, ethyl β-iodopropionate (63·7 gms.) was gradually added, care being taken that the temperature did not rise above 0°. After remaining at 0° for 5 hours, the reaction mixture was kept at room temperature overnight and finally heated on the water-bath for 1 hour. The condensation product was separated in the usual manner and distilled under diminished pressure, practically the whole distilling at 195°/32 mm. (yield, 75 per cent.) (Found: N, 5·7. $C_{15}H_{21}O_4N$ requires N, 5·5 per cent.). It was a somewhat viscid, yellow oil with a faint but unpleasant smell.

α-*iso*Propylglutaric acid (45 gms.) was mixed with phosphorus pentachloride (110 gms.) and, after the formation of the acid chloride was complete, dry bromine (44 gms.) was gradually added; the mixture was then heated on the water-bath for 24 hours, only the slight excess of bromine remaining unabsorbed. The acid chloride was poured into well-cooled alcohol and next day ice was added. The heavy oil precipitated was dissolved in ether, and the ethereal solution was well washed with sodium carbonate solution (A), dried, and evaporated. After repeated fractionation under diminished pressure (30 mm.), four fractions were separated: (i) 130–145°, (ii) 145–165°, (iii) 165–180°, and (iv) 180–210°. Fractions (i) and (ii) contained only traces of bromine, and fractions (iii) and (iv), which were small in quantity, contained 13·5 and 23·3 per cent. of bromine respectively ($C_{12}H_{21}O_4Br$ requires Br, 27·5 per cent.).

Fractions (i) and (ii) were examined separately and gave identical products. After hydrolysis with alcoholic potassium hydroxide solution and separation of the organic acid in the usual manner, an oil was obtained which partly crystallised on keeping. It was converted through the sparingly soluble copper salt into pure α-*iso*propylglutaric acid.

Fraction (iii) was boiled with an excess of freshly distilled diethylaniline. The ester obtained distilled mainly at 155–165°/36 mm.; a small amount of an oil boiled above this temperature. From the main fraction, only α-*iso*propylglutaric acid could be separated after hydrolysis.

Fraction (iv) when treated in a similar manner gave an oil, b. p. 170–200°/30 mm. This gave on hydrolysis a liquid acid which was unstable to potassium permanganate in alkaline solution but was insufficient in quantity for investigation.

The sodium carbonate solution (A) on acidification deposited an oil which, after extraction with ether and drying in a vacuum, contained Br, 18·3 per cent. The oil was added to an excess of boiling alcoholic potassium hydroxide solution, the alcohol removed, and the alkaline solution acidified and extracted with ether. On removal of the ether an oil was obtained which crystallised completely on keeping. It was purified by slow evaporation of its benzene solution, crystallising in prisms, m. p. 65–67°. Its identity with the lactone (V) of γ-hydroxy-β-methylpentane-γα-dicarboxylic acid was confirmed by analysis (Found: C, 56·1; H, 7·1; *M*, 171·9. Calc.: C, 55·8; H, 7·0 per cent.; *M*, 172).

Ethyl α-iso*Propylacetonedicarboxylate* (VI).—A mixture of ethyl potassioacetonedicarboxylate (32 gms.), alcohol (50 c.c.), and *iso*propyl iodide (23 gms.) was heated on the water-bath for 6 hours. After addition of water the *ester* was separated by ether and distilled under diminished pressure, the bulk passing over at 141–143°/9 mm. (yield, 60 per cent.). For analysis it was redistilled; b. p. 142–143°/9 mm. (Found: C, 59·0; H, 8·3. $C_{12}H_{20}O_5$ requires C, 59·0; H, 8·2 per cent.). The ester is a colourless oil of pleasant odour and gives with ferric chloride a deep red coloration. Its hydrolysis with alcoholic potassium hydroxide gives α-iso*propylacetonedicarboxylic acid*, which crystallises from ether in needles, decomp., 153°, and gradually decomposes on keeping (Found: C, 50·7; H, 6·6. $C_8H_{12}O_5$ requires C, 51·1; H, 6·4 per cent.).

Ethyl β-Hydroxy-α-iso*propylglutarate* (VII).—The preceding keto-ester (80 gms.) was dissolved in alcohol (200 c.c.) and, after the addition of water until the solution was just turbid, sodium amalgam (5 kg.; 2½ per cent.) was gradually added, the solution being vigorously stirred and a rapid stream of carbon dioxide passed through it. When the reduction was complete (6 days), the alcohol was removed in steam, the unhydrolysed ester (8 gms.) separated by ether, and the alkaline solution evaporated on the water-bath. The dry residue of salts was heated with alcohol and an excess of sulphuric acid on the water-bath for 10–12 hours, giving *ethyl β-hydroxy*-α-iso*propylglutarate*, b. p. 145–146°/10 mm. (Found: C, 58·1; H, 9·0. $C_{12}H_{22}O_5$ requires C, 58·5; H, 8·9 per cent.), as a somewhat viscid oil which gave no colour with ferric chloride. The hydroxy-acid obtained by hydrolysis could not be crystallised.

Ethyl β-Chloro-α-iso*propylglutarate.*—To the well-cooled hydroxy-ester (13 gms.), phosphorus pentachloride (11·5 gms.) was gradually added. It slowly dissolved and on allowing the temperature to rise hydrogen chloride was evolved; reaction was complete at 50° after 30 minutes. The cooled mixture was poured on ice, the chloro-ester

separated by ether, and the ethereal solution washed with sodium carbonate solution, dried, and evaporated. The ester had a penetrating smell and was analysed after being kept for some days in a vacuum (Found : Cl, 12·2. $C_{12}H_{21}O_4Cl$ requires Cl, 13·4 per cent.).

Ethyl α-iso*Propylglutaconate.*—The chloro-ester (19 gms.) was mixed with freshly distilled diethylaniline (50 gms.) and heated at 180–190° for 12 hours. The cooled mixture was poured on ice and dilute hydrochloric acid, the oil dissolved in ether, and the ethereal extract well washed with dilute hydrochloric acid and with sodium carbonate solution, dried, and evaporated. After two distillations an oil was obtained, b. p. 148–150°/15 mm. As the ester contained traces of chlorine, it was not analysed.

cis- *and* trans-α-iso*Propylglutaconic Acids* (II).—The ester (24 gms.) was hydrolysed with methyl-alcoholic potassium hydroxide and after removal of the alcohol the acid was separated from the acidified solution by repeated extraction with ether ; on removal of the solvent, an oil was obtained which partly solidified on keeping (yield 16 gms.). The crude acid, m. p. 80–100°, was a mixture of the *cis-* and *trans-*forms, which were separated by treatment with acetyl chloride.

The acid (26 gms.) was mixed with acetyl chloride (100 gms.) and heated on the water-bath until all evolution of hydrogen chloride ceased (8 hours). The excess of acetyl chloride was removed under diminished pressure, and the deep red reaction mixture poured into an ice-cold solution of sodium bicarbonate. The neutral oil (A) was extracted with ether, the alkaline solution being reserved.

The ethereal solution of (A) gave on removal of the solvent a deep red oil having a pungent smell and evidently consisting of the chloro-anhydride. On treatment with potassium hydroxide solution it rapidly dissolved and a sparingly soluble *potassium* salt was deposited in colourless leaflets which became green, brown, and finally red. It was recrystallised from alcohol (Found : K, 19·7. $C_8H_9O_3K$ requires K, 20·3 per cent.). When an aqueous solution of the potassium salt was acidified with dilute acetic acid an oil was deposited which could not be induced to crystallise and probably consisted of the hydroxy-anhydride. The oil in neutral solution gave with silver nitrate a black precipitate, and, as has been previously observed in similar cases, in alkaline solution it became deep red on keeping.

For the preparation of the *cis*-modification of the acid the above-mentioned potassium salt was dissolved in water and digested with an excess of potassium hydroxide solution. From the acidified solution, repeated extraction with ether removed the acid, which was obtained

as an oil and rapidly crystallised. It was recrystallised from cold dilute hydrochloric acid (Found: C. 55·4; H, 7·3; *M*, 173. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0 per cent. *M*, 172).

cis-α-iso*Propylglutaconic acid* separated from hydrochloric acid in small plates, m. p. 101°, softening slightly at 95°. The acid was readily soluble in water, chloroform, and benzene, more sparingly soluble in light petroleum. The calcium and barium salts are readily soluble in water, but an aqueous solution of the acid gave on addition of copper acetate a sparingly soluble copper salt. In acetic acid solution the acid does not take up bromine, but its alkaline solution immediately decolorises potassium permanganate.

The sodium bicarbonate solution, from which the chloroanhydride had been separated, was acidified, and the acid extracted with ether. On evaporation of the ether an oil remained which on keeping partly solidified. After draining on porous porcelain the acid was purified by crystallisation from either water or chloroform (Found: C, 56·2; H, 7·0. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0 per cent.).

trans-α-iso*Propylglutaconic acid* separated from chloroform in feathery needles, m. p. 132°. It was somewhat sparingly soluble in cold water, chloroform, and benzene, readily soluble in these solvents when hot, and very sparingly soluble in light petroleum. The barium salt crystallised from water in small plates. The acid resembles the *cis*-form in its behaviour towards bromine and potassium permanganate.

Reduction of the Monomethyl Ester of Caronic Acid.—For the preparation of the monomethyl ester, caronic anhydride (7 gms.) was added all at once to a solution of sodium (1·15 gms.) in methyl alcohol (50 c.c.). After removal of the alcohol the sodium salt was dissolved in water and the solution acidified; an oil then separated which crystallised on scratching. It separated from benzene-ligroin in short prisms, m. p. 108–110° (Found: C, 55·6; H, 7·1. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0 per cent.).

For the reduction of the acid ester the sodium salt (30 gms.) was dissolved in alcohol (350 c.c.) and added as rapidly as possible to sodium (36 gms.), kept in a boiling water-bath. Owing to the separation of the sodium salt the whole mass became pasty. The alcohol was removed in steam, the aqueous solution acidified and repeatedly extracted with ether, and the ether dried and evaporated. The crystalline residue was distilled in steam, a small quantity of an oil passing over. This was extracted with ether and after the removal of the solvent the residual oil (2 gms.) was distilled; b. p. 137°/43

mm., 232–235/685 mm. On cooling in ice-salt the distillate crystallised, but it melted at room temperature and was evidently not quite pure. The lactone was converted into the dibasic acid by the method of Blanc (*loc. cit.*) and this acid was identified as $\beta\beta$-dimethyladipic acid by its m. p. (86°) and by analysis (Found: C, 55·0; H, 8·3. Calc.: C, 55·1; H, 8·0 per cent.).

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