340. *The Preparation of α-Substituted Glutaric Acids.*

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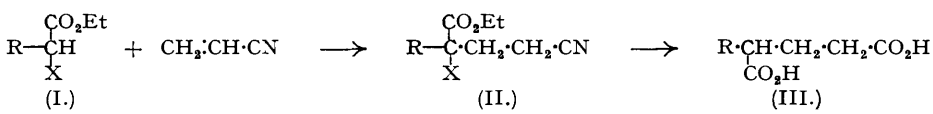
A new general method for the preparation of α-substituted glutaric acids is described. The action of acrylonitrile on a substituted malonic ester or on a substituted cyanoacetic ester gives a cyano-dicarboxylic ester or a dicyano-carboxylic ester respectively, and subsequent hydrolysis and decarboxylation yield an α-substituted glutaric acid. The method is illustrated by the preparation of fourteen such acids, many of which are described for the first time.

One of the general methods for the preparation of α-substituted glutaric acids, a series of which was required for another investigation, consists of the condensation of an ethyl β-halogenopropionate with the sodio-derivative of a monosubstituted malonic ester, cyanoacetic ester, or acetoacetic ester, followed by hydrolysis and, in the first two cases, decarboxylation. This method has been used for the preparation of α-methylglutaric acid (Auwers and Titherley, *Annalen*, 1896, **292**, 209; Ingold, *J.*, 1925, 392), α-ethylglutaric acid (Auwers, *Annalen*, 1896, **292**, 144; Berner and Leonardsen, *ibid.*, 1939, **538**, 39), α-*iso*propylglutaric acid (Heinke and Perkin, *J.*, 1896, **69**, 1507; Arne Fredga, *Arkiv Kemi, Min., Geol.*, 1946, **23**, *B*, No. 2), α-phenylglutaric acid (Fichter and Merckens, *Ber.*, 1901, **34**, 4175), and α-benzylglutaric acid (Braun and Manz, *Annalen*, 1929, **468**, 258). Mellor (*J.*, 1901, **79**, 128) adopted a slightly modified procedure in which he condensed the ethyl β-halogenopropionate with ethyl malonate and alkylated the product. Using this method he prepared α-*n*-propylglutaric acid. An alternative procedure utilises the Michael reaction between the ethyl ester of an α-substituted acrylic acid and ethyl malonate, ethyl cyanoacetate, or ethyl acetoacetate, followed by hydrolysis and, in the first two cases, decarboxylation. Thus, Perkin (*J.*, 1896, **69**, 1490) condensed ethyl malonate with ethyl α-*iso*propylacrylate and then hydrolysed and decarboxylated the resulting ethyl α-*iso*propyl-γ-carbethoxyglutarate to give α-*iso*propylglutaric acid. This procedure may be modified by condensing ethyl malonate with ethyl acrylate and alkylating the product (Arne Fredga, *loc. cit.*).

A new general method has now been developed for the preparation of α-substituted glutaric acids which has advantages over the older methods both in the simplicity of the process and in the accessibility of the starting materials. This method utilised the reaction between acrylonitrile and the esters of monosubstituted malonic or cyanoacetic acids (I), whereby the 2-cyanoethyl group is introduced into the malonic or cyanoacetic ester (Bruson and Riener, *J. Amer. Chem. Soc.*, 1943, **65**, 23; Floyd, *ibid.*, 1949, **71**, 1746). Hydrolysis and decarboxylation of the resulting cyanoethylation product (II) yields the α-substituted glutaric acid (III). During the course of this work Horning and Finelli (*ibid.*, p. 3204) reported the preparation of α-phenylglutaric anhydride from the product obtained on the hydrolysis of the cyanoethylation product resulting from ethyl phenylcyanoacetate.



(I.) (II.) (III.)

(X = CN or CO_2Et).

Using this method the following acids (III) have been prepared: α-methyl- (R = Me), α-ethyl- (R = Et), α-*n*-propyl- (R = Pr^n), α-*iso*propyl- (R = Pr^i), α-*n*-butyl- (R = Bu^n), α-phenyl- (R = Ph), α-benzyl- (R = Ph·CH_2), α-2-phenylethyl- (R = Ph·CH_2·CH_2), α-1-naphthyl- (R = 1-$C_{10}H_7$), α-1-naphthylmethyl- (R = 1-$C_{10}H_7$·CH_2), α-(2-1′-naphthylethyl)- (R = 1-$C_{10}H_7$·CH_2·CH_2), α-2-naphthyl- (R = 2-$C_{10}H_7$), α-2-naphthylmethyl (R = 2-$C_{10}H_7$·CH_2), and α-(2-2′-naphthylethyl)-glutaric acid (R = 2-$C_{10}H_7$·CH_2·CH_2). The initial malonic or cyanoacetic esters were prepared by published methods with the exception of ethyl 2-naphthylmalonate (I; X = CO_2Et, R = 2-$C_{10}H_7$) and 2-2′-naphthylethylmalonate (I; X = CO_2Et; R = 2-$C_{10}H_7$·CH_2·CH_2). The former was prepared from ethyl oxalate and ethyl 2-naphthyl-

acetate, which gave ethyl 2-naphthyloxaloacetate from which carbon monoxide was eliminated by heating the ester with powdered glass at 175° under reduced pressure. Ethyl 2-2′-naphthylethylmalonate was prepared by the standard method using ethyl malonate and 2-2′-naphthylethyl bromide. In several cases the intermediate cyano-dicarboxylic esters or dicyano-carboxylic esters (II) were isolated in pure form, but in other cases hydrolysis was effected on the crude product.

Experimental.

α-Methylglutaric Acid.—Acrylonitrile (10·6 g.) was added to a stirred solution of ethyl methylmalonate (Weiner, *Org. Synth.*, Coll. Vol. II, p. 279) (34·8 g.) and 30% methanolic potassium hydroxide (1·0 g.) in *tert.*-butyl alcohol (50 g.). The reaction mixture was kept at 30—35° during the addition, and then stirred for a further 3 hours. The solution was neutralised with 2N-hydrochloric acid, diluted with water, and extracted with ether. Evaporation of the dried extract left *ethyl methyl-2-cyanoethylmalonate* (44·0 g.), b. p. 110°/0·04 mm. (Found: C, 57·7; H, 7·4; N, 6·4. $C_{11}H_{17}O_4N$ requires C, 58·2; H, 7·5; N, 6·2%). The ester (10·0 g.) was boiled under reflux with 48% hydrobromic acid (140 c.c.) for 8 hours, and the solution then evaporated almost to dryness under reduced pressure. Sufficient water was added to dissolve the ammonium bromide, and the mixture was extracted with ether. Evaporation of the dried extract left α-methylglutaric acid as an oil (6·2 g.), which solidified when kept. Recrystallisation from benzene gave the pure acid in small needles, m. p. 77—78°. Auwers (*loc. cit.*) records m. p. 77—78° for this acid.

α-Ethylglutaric Acid.—Ethyl ethyl-2-cyanoethylmalonate (5·0 g.), prepared by the method of Bruson and Riener (*loc. cit.*) using *tert.*-butyl alcohol in place of dioxan and 30% methanolic potassium hydroxide in place of trimethylbenzylammonium hydroxide, was hydrolysed by boiling it under reflux with 48% hydrobromic acid (20 c.c.) for 8 hours. The reaction mixture was extracted as for α-methylglutaric acid. Evaporation of the ethereal extract left α-ethylglutaric acid (3·0 g.) as an oil, which when cooled and scratched solidified. Recrystallisation from ice-cold benzene–light petroleum (b. p. 40—60°) gave the pure acid, m. p. 58—60°. Berner and Leonardsen (*loc. cit.*) record m. p. 60—61°.

α-n-Propylglutaric Acid.—Ethyl n-propyl-2-cyanoethylmalonate (18·5 g.) was prepared as was ethyl methyl-2-cyanoethylmalonate from ethyl *n*-propylmalonate (15·1 g.) (Backer and Toxopeus, *Rec. Trav. chim.*, 1926, **45**, 895), acrylonitrile (4·0 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (2·0 g.). It separated from ice-cold alcohol in colourless prisms, m. p. 31—32° (Found: C, 61·7; H, 8·1. $C_{13}H_{21}O_4N$ requires C, 61·2; H, 8·2%). This ester (5·0 g.) was hydrolysed by boiling it under reflux with 48% hydrobromic acid (20 c.c.) for 8 hours. The reaction mixture was then extracted as for α-methylglutaric acid. Evaporation of the ethereal extract left *α-n-propylglutaric acid* (3·6 g.) as an oil, which readily solidified. Recrystallisation from water gave the pure acid in small colourless needles, m. p. 69·5—70·5°. Mellor (*loc. cit.*) records m. p. 66—68°.

*α-iso**Propylglutaric Acid.—Ethyl** iso**propyl-2-cyanoethylcyanoacetate* (40·2 g.), b. p. 125°/0·035 mm., was prepared as for ethyl methyl-2-cyanoethylmalonate from ethyl *iso*propylcyanoacetate (31·0 g.), acrylonitrile (10·6 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (1·0 g.) (Found: C, 63·8; H, 7·8; N, 13·6. $C_{11}H_{16}O_2N_2$ requires C, 63·5; H, 7·7; N, 13·6%). It (10·0 g.) was hydrolysed by boiling 48% hydrobromic acid (40 c.c.) (8 hours), and the reaction mixture then extracted as for α-methylglutaric acid. Evaporation of the ethereal extract left *α-iso*propylglutaric acid (8·1 g.) as an oil, which readily solidified. Recrystallisation from water gave the pure acid as small colourless needles, m. p. 94—95°. Perkin (*J.*, 1896, **69**, 1495) records m. p. 94—95°.

α-n-Butylglutaric Acid.—Ethyl *n*-butyl-2-cyanoethylmalonate (10 g.), prepared by the method of Bruson and Riener (*loc. cit.*) using *tert.*-butyl alcohol and 30% methanolic potassium hydroxide in place of dioxan and trimethylbenzylammonium hydroxide, was hydrolysed by boiling 48% hydrobromic acid (40 c.c.) (8 hours), and the reaction mixture was then extracted as for α-methylglutaric acid. Evaporation of the ethereal extract left *α-n-butylglutaric acid* (5·9 g.) as an oil which solidified on storage in an evacuated desiccator over sulphuric acid for several days. Recrystallisation from benzene gave the pure acid, m. p. 40° (Found: C, 57·2; H, 8·4. $C_9H_{16}O_4$ requires C, 57·6; H, 8·5%).

α-Phenylglutaric Acid.—Ethyl phenyl-2-cyanoethylmalonate was prepared as for ethyl methyl-2-cyanoethylmalonate from ethyl phenylmalonate (23·6 g.), acrylonitrile (5·3 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (2·0 g.). Evaporation of the ethereal extract left the ester (26·2 g.) as an oil, which when cooled and scratched solidified. Recrystallisation from ice-cold alcohol gave the pure compound as colourless prisms, m. p. 37° (Found: C, 66·6; H, 6·2. $C_{18}H_{19}O_4N$ requires C, 66·4; H, 6·2%). It (19·5 g.) was hydrolysed and worked up as above, α-phenylglutaric acid being obtained (13·8 g.) as an oil, which on storage with occasional cooling and scratching solidified. Recrystallisation from ice-cold benzene–light petroleum (b. p. 40—60°) gave the pure acid in small colourless needles, m. p. 82—84°. Fichter and Merckens (*loc. cit.*) record m. p. 82°.

α-Benzylglutaric Acid.—Ethyl benzylmalonate (Marvel, *Org. Synth.*, 1941, **21**, 99) was condensed with acrylonitrile according to the procedure of Bruson (*loc. cit.*), using *tert.*-butyl alcohol and 30% methanolic potassium hydroxide in place of dioxan and trimethylbenzylammonium hydroxide. The resulting ethyl benzyl-2-cyanoethylmalonate (17·5 g.) was hydrolysed by boiling it under reflux with 48% hydrobromic acid (120 c.c.) for 8 hours and then extracted as for α-methylglutaric acid. Evaporation of the ethereal extract left α-benzylglutaric acid (18·2 g.) as an oil, which readily solidified. Recrystallisation from benzene gave the pure acid in small colourless needles, m. p. 77—78°. Braun and Manz (*loc. cit.*) record m. p. 76°.

α-(2-Phenylethyl)glutaric Acid.—Ethyl 2-phenylethyl-2′-cyanoethylmalonate was prepared, as for ethyl methyl-2-cyanoethylmalonate, from ethyl 2-phenylethylmalonate (71·7 g.) (Rupe, *Annalen*, 1913, **395**, 114), acrylonitrile (14·5 g.), *tert.*-butyl alcohol (100 g.), and 30% methanolic potassium hydroxide (6·0 g.). Evaporation of the ethereal extract left the malonate (83·2 g.) as a viscous liquid, b. p. 168—170°/0·03 mm. This compound (30·0 g.), hydrolysed as above, gave *α-(2-phenylethyl)glutaric acid*

(21·3 g.) as an oil, which readily solidified. Recrystallisation from benzene gave the pure acid in small colourless needles, m. p. 86—87° (Found : C, 66·0; H, 6·7. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

α-1-Naphthylglutaric Acid.—*Ethyl 1-naphthyl-2′-cyanoethylmalonate* was prepared as above from ethyl 1-naphthylmalonate (21·4 g.) (Blicke and Feldkamp, *J. Amer. Chem. Soc.*, 1944, **66**, 1088), acrylonitrile (4·0 g.), *tert.*-butyl alcohol (75 g.), and 30% methanolic potassium hydroxide (2·0 g.). Evaporation of the ethereal extract left the malonate (22·7 g.) as an oil, which when scratched with ice-cold light petroleum (b. p. 40—60°) solidified. Recrystallisation from alcohol gave the pure compound in colourless prisms, m. p. 82·5—83·5° (Found : C, 70·6; H, 6·1. $C_{20}H_{21}O_4N$ requires C, 70·8; H, 6·2%). This ester (23·0 g.) was hydrolysed by boiling it under reflux with potassium hydroxide (23·0 g.) in alcohol (23 c.c.) and water (18 c.c.). After about 2 hours a considerable amount of solid had separated and water (18 c.c.) was added. Boiling under reflux was continued for a further 4 hours, and the alcohol then distilled off. The residual solution was cooled, diluted with water, and extracted with ether, and the aqueous layer acidified and extracted with ether again. Evaporation of the dried ethereal extract left α-carboxy-α-1-naphthylglutaric acid as an oil, which was decarboxylated by heating at 180—185° for 1 hour (bath-temperature). After cooling, the product was boiled with water for 15 minutes and extracted with ether. Evaporation of the dried ethereal solution left *α-1-naphthylglutaric acid* (16·1 g.) as an oil, which readily solidified. Recrystallisation from benzene–light petroleum (b. p. 40—60°) gave the pure acid in small needles, m. p. 122—124° (Found : C, 70·1; H, 5·4. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

α-(1-Naphthylmethyl)glutaric Acid.—Ethyl 1-naphthylmethyl-2′-cyanoethylmalonate was prepared as above from ethyl 1-naphthylmethylmalonate (30 g.) (Fieser and Gates, *J. Amer. Chem. Soc.*, 1940, **62**, 2338), acrylonitrile (5·3 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (2·0 g.). Evaporation of the ethereal extract left ethyl 1-naphthylmethyl-2′-cyanoethylmalonate (33·3 g.) as a viscous liquid, b. p. 156—158°/0·003 mm. This (57·0 g.) was hydrolysed by boiling it under reflux with potassium hydroxide (57 g.) in alcohol (57 c.c.) and water (48 c.c.). Treatment as in the preceding case then gave *α-1-naphthylmethylglutaric acid* (37·5 g.) as an oil, which readily solidified. Recrystallisation from toluene gave the pure acid in small needles, m. p. 144—146° (Found : C, 70·6; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

α-(2-1′-Naphthylethyl)glutaric Acid.—Ethyl 2-1′-naphthylethyl-2″-cyanoethylmalonate was prepared as above from ethyl 2-1′-naphthylethylmalonate (34·5 g.) (Bachmann, Gregg, and Pratt, *J. Amer. Chem. Soc.*, 1943, **65**, 2314), acrylonitrile (6·0 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (2·0 g.). Evaporation of the ethereal extract left the ether (38·1 g.) as a viscous liquid. It (10·2 g.) was hydrolysed with a boiling solution of potassium hydroxide (10·0 g.) in alcohol (10 c.c.) and water (8 c.c.). The reaction product was extracted and decarboxylated as for α-1-naphthylglutaric acid. The decarboxylated product solidified when boiled with water and was filtered off. Recrystallisation from ethyl acetate–benzene (equal volumes) gave *α-(2-1′-naphthylethyl)glutaric acid* (6·5 g.) in small needles, m. p. 171—173° (Found : C, 71·2; H, 6·2. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

α-2-Naphthylglutaric Acid.—Ethyl oxalate (19·0 g.) was added to a stirred solution of sodium ethoxide, prepared from absolute alcohol (60 c.c.) and sodium (3·0 g.), followed after a few minutes' stirring by ethyl 2-naphthylacetate (28·8 g.) (Wislicenus and Elvert, *Ber.*, 1916, **49**, 2827) in absolute alcohol (20 c.c.). The solution was heated under reflux for 30 minutes, solid beginning to separate. The mixture was then cooled to 0°, the solid product removed from the flask with the aid of ether, filtered off, washed with ether, and then mixed with water (200 c.c.). When most of it had dissolved, ether (100 c.c.) was added and the solution made just acid to litmus with 20% sulphuric acid. The ethereal layer was separated and the aqueous layer extracted with ether. After the removal of the ether from the dried extracts (Na_2SO_4) the residue of ethyl 2-naphthyloxaloacetate was mixed with powdered glass (4·0 g.) and heated under 15 mm. pressure until the bath temperature reached 175°, where it was kept for 1 hour, after which time evolution of carbon monoxide had ceased. It was then distilled to give *ethyl 2-naphthylmalonate* (16·0 g.), b. p. 168—172°/0·5 mm., which immediately solidified. Recrystallisation from light petroleum (b. p. 60—80°) gave the pure ester in stout needles, m. p. 99—100° (Found : C, 71·1; H, 6·0. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%). The ethyl 2-naphthylmalonate (5·0 g.) was dissolved in *tert.*-butyl alcohol (20 g.) with heating, and the solution then cooled with stirring to 30°, thus yielding a fine suspension. 30% Methanolic potassium hydroxide (1·0 g.) was added, followed by acrylonitrile (2·0 g.). The ethyl 2-naphthylmalonate dissolved and the temperature of the solution rose and was allowed to reach a maximum of 40°. After a further 3 hours' stirring, the solution was extracted as for ethyl methyl-2-cyanoethylmalonate. Evaporation of the ethereal extract left ethyl 2-naphthyl-2-cyanoethylmalonate (5·5 g.) as a viscous liquid, b. p. 170—175°/0·03 mm. This compound (4·5 g.) was hydrolysed by boiling it under reflux with a solution of potassium hydroxide (4·5 g.) in alcohol (5 c.c.) and water (5 c.c.). After about 2 hours a considerable amount of solid had separated and water (5 c.c.) was added, and heating continued for a further 4 hours. The reaction product was then extracted as for α-1-naphthylglutaric acid. After boiling of the decarboxylated product with water the oily acid solidified on cooling and was filtered off. Recrystallisation from water gave *α-2-naphthylglutaric acid* (3·0 g.) in small needles, m. p. 109—110° (Found : C, 69·6; H, 5·7. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

α-(2-Naphthylmethyl)glutaric Acid.—Ethyl 2-naphthylmethyl-2′-cyanoethylmalonate was prepared as above from ethyl 2-naphthylmethylmalonate (27·6 g.) (Mayer and Sieglitz, *Ber.*, 1922, **55**, 1855), acrylonitrile (4·9 g.), *tert.*-butyl alcohol (50 g.), and 30% methanolic potassium hydroxide (2·0 g.). Evaporation of the ethereal extract left ethyl 2-naphthylmethyl-2′-cyanoethylmalonate (30·8 g.). The ester (28·0 g.) was hydrolysed by a boiling solution of potassium hydroxide (28·0 g.) in alcohol (28 c.c.) and water (23 c.c.) (6 hours). The reaction product was then extracted and decarboxylated as for α-1-naphthylglutaric acid. Evaporation of the ethereal extract left *α-(2-naphthylmethyl)glutaric acid* (27·6 g.) as an oil which readily solidified. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave the pure acid in small needles, m. p. 124—125° (Found : C, 70·9; H, 5·7. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

α-(2-2′-Naphthylethyl)glutaric Acid.—Absolute alcohol (37 c.c.) was added slowly to a suspension of powdered sodium (3·5 g.) in dry benzene (11 c.c.). After the mixture had been heated under reflux

for a short time all the sodium had reacted, and ethyl malonate (37 c.c.) was added, followed after 30 minutes' heating by 2-2'-naphthylethyl bromide (25·0 g.) (Karrer, Geiger, Ruegger, and Schwab, *Helv. Chim. Acta*, 1940, **23**, 586) in benzene (40 c.c.). The reaction mixture was kept warm on a water-bath overnight and then boiled under reflux for 1½ hours. After cooling the mixture was diluted with water and neutralised with 2N-hydrochloric acid, the benzene layer separated, and the aqueous layer extracted with ether. After drying of the combined extracts (Na_2SO_4), the solvents were removed and the residual oil was distilled to give ethyl malonate (14·6 g.), b. p. 85—88°/10 mm., and *ethyl 2-2'-naphthylethylmalonate* (28·5 g.), b. p. 197—202°/0·2 mm. (Found: C, 72·0; H, 7·4. $C_{19}H_{12}O_4$ requires C, 72·6; H, 7·0%). This ester (25·0 g.) was condensed with acrylonitrile (4·2 g.) in *tert.*-butyl alcohol (50 g.) in the presence of 30% methanolic potassium hydroxide (2·0 g.) as for ethyl methyl-2-cyanoethylmalonate. Evaporation of the ethereal extract gave ethyl 2-2'-naphthylethyl-2''-cyanoethylmalonate (28·0 g.) as a viscous liquid. The latter compound (28·0 g.) was hydrolysed by heating it under reflux with potassium hydroxide (28·0 g.) in alcohol (28 c.c.) and water (25 c.c.) for 6 hours. The reaction product was extracted as for α-1-naphthylglutaric acid. Evaporation of the ethereal extract gave a solid which was decarboxylated at 200—205° (bath-temperature) (45 minutes). After cooling, it was boiled with water for 15 minutes and extracted with ether. Evaporation of the dried ethereal solution gave *α-(2-2'-naphthylethyl)glutaric acid* (19·9 g.) as an oil, which readily solidified. Recrystallisation from benzene gave the pure acid in small needles, m. p. 117—119° (Found: C, 71·3; H, 6·4. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

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