388. *Intramolecular Acylation. Part III.* The Preparation and Ring Closure of the α-Methoxyphenylglutaric Acids.*

By D. H. Hey and K. A. Nagdy.

Methods are described for the preparation of α-*o*-, α-*m*-, and α-*p*-methoxyphenylglutaric acid, and a study has been made of the action of cyclising agents on these acids and their acid chlorides. In this manner α-*m*-methoxyphenylglutaric acid and its acid chloride were converted successively into 1 : 2 : 3 : 4-tetrahydro-4-keto-7-methoxy-1-naphthoic, 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-naphthoic, and 7-methoxy-1-naphthoic acid. α-*p*-Methoxyphenylglutaryl chloride was similarly converted into 1 : 2 : 3 : 4-tetrahydro-4-keto-6-methoxy-1-naphthoic acid. Further evidence is produced of the deactivating influence of the nearer carboxyl group in the Friedel–Crafts-type cyclisation of substituted dicarboxylic acids.

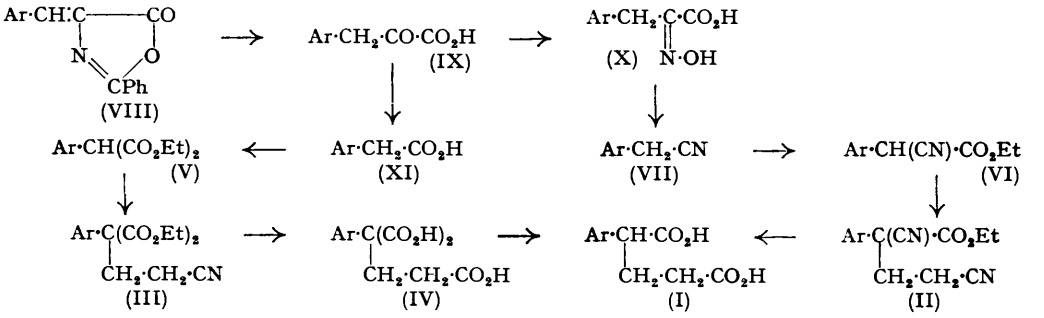
In a previous communication (*J.*, 1950, 1683) a general method for the preparation of α-substituted glutaric acids was described and subsequently (Part II *) a number of these acids were converted by conventional methods into monocarboxylic acids of cyclic ketones. The present communication describes an extension of this work with the three α-methoxyphenylglutaric acids. Experimental work with the β-methoxyphenylglutaric acids was reported in Part I (*J.*, 1949, 3177).

The three isomeric α-methoxyphenylglutaric acids (I) were prepared by the general method referred to above, which involves cyanoethylation of an appropriate malonic or cyanoacetic ester followed by hydrolysis and decarboxylation. Whereas in the unsubstituted series hydrolysis was effected with 48% hydrobromic acid, this reagent, which caused partial demethylation in the present series of compounds, was replaced by aqueous-alcoholic potassium hydroxide. With the cyanoethylated cyanoacetic esters (II) this reagent brought about both hydrolysis and decarboxylation, whereas with the cyanoethylated malonic esters (III) under similar conditions the tricarboxylic acids (IV) were formed, which were subsequently decarboxylated at 180—185°. Similar results were noted when ethyl *m*-methoxyphenylmalonate (V; Ar = *m*-MeO·C_6H_4) and ethyl α-cyano-α-*m*-methoxyphenylacetate (VI; Ar = *m*-MeO·C_6H_4) were subjected to hydrolysis with aqueous-alcoholic potassium hydroxide, the former giving *m*-methoxyphenylmalonic acid and the latter *m*-methoxyphenylacetic acid. These results can be attributed to the greater electron-attracting power of the cyano-group compared with that of the carbethoxy-group, which facilitates the removal of elements of carbon dioxide from the carbon atom to which it is attached.

The three isomeric cyanoacetic esters (VI; Ar = *o*-, *m*-, and *p*-MeO·C_6H_4) were prepared in moderate yield by the condensation of the appropriate methoxybenzyl cyanide

* Part II, *J.*, 1950, 2874.

(VII) with ethyl carbonate in presence of sodium (cf. Niederl, Roth, and Plentl, *J. Amer. Chem. Soc.*, 1937, **59**, 1901; Niederl and Roth, *ibid.*, 1938, **60**, 2140; Wallingford, Jones, and Homeyer, *ibid.*, 1942, **64**, 576). The methoxybenzyl cyanides (VII) were prepared in good yield by the condensation of the methoxybenzaldehyde with hippuric acid, hydrolysis of the resulting azlactone (VIII) with 10% aqueous sodium hydroxide, conversion of the pyruvic acid (IX) into its oxime (X), and subsequent dehydration and decarboxylation (cf. Carter, " Organic Reactions," Vol. III, p. 198). For the preparation of ethyl *m*-methoxyphenylmalonate the method of Wallingford, Homeyer, and Jones (*J. Amer. Chem. Soc.*, 1941, **63**, 2056) was used, in which the methoxyphenylacetic ester is condensed with an excess of ethyl carbonate in the presence of sodium ethoxide, but this method failed with the *para*-isomer and was only partly successful with the *ortho*-isomer. The methoxyphenylacetic esters were prepared by the esterification of the acids (XI) obtained by the oxidation of the corresponding pyruvic acids (IX) with alkaline hydrogen peroxide (cf. Carter, *loc. cit.*). Whereas the cyanoethylation of the α-cyano-α-methoxyphenylacetates (VI) with subsequent hydrolysis and decarboxylation gave the α-methoxyphenylglutaric acids in yields of more than 70% with all three isomers, the alternative route by means of the methoxyphenylmalonate (V) gave yields of only 16% in the *ortho*-series and of 18% in the *meta*-series.



(Ar = *o*-, *m*-, and *p*-MeO·C$_6$H$_4$)

Preliminary attempts to cyanoethylate the three α-methoxybenzylmalonic esters with acrylonitrile at 30—35° in presence of methanolic potassium hydroxide failed. These esters were prepared by the condensation of the methoxybenzaldehyde with ethyl malonate in presence of piperidine, followed by reduction of the resulting methoxybenzylidenemalonic ester with Raney nickel.

In order to obtain further information on the influence of both the nuclear methoxyl group and the second carboxyl group on the cyclisation process by means of which ketonic acids are formed, the three isomeric α-methoxyphenylglutaric acids or their acid chlorides were submitted to the action of the conventional cyclising agents. Cyclodehydration occurred readily with α-*m*-methoxyphenylglutaric acid with the common cyclising reagents (anhydrous hydrogen fluoride, 95% sulphuric acid, polyphosphoric acid, stannic chloride), but no keto-acids could be obtained from the *o*- or *p*-acid. Cyclodehydrohalogenation was effective with both stannic chloride and aluminium chloride in the case of α-*m*-methoxyphenylglutaryl chloride, but the yields were low. α-*p*-Methoxyphenylglutaryl chloride was also cyclised with aluminium chloride in nitrobenzene solution at 0°, but only in 10% yield. Ring closure could not be effected with the acid chloride of α-*o*-methoxyphenylgutaric acid. These results are in agreement with expectation because in α-*m*-methoxyphenylglutaric acid the activating effect of the methoxyl group far outweighs the deactivating effect of the carboxyl group, whereas with the *ortho*- and *para*-acids this situation does not exist. Attention was directed to the deactivating influence of a carboxyl group attached to the carbon atom adjacent to the aromatic nucleus by Badger, Campbell, and Cook (*J.*, 1949, 1084) in the cyclisation of αβ-diphenylglutaric acid, and a further example seemed to be provided by the cyclisation of α-phenylglutaric acid to give 1 : 2 : 3 : 4-tetrahydro-4-keto-1-naphthoic acid (Ansell and Hey, *J.*, 1950, 2874). α-Arylglutaric acids may be regarded as carboxy-

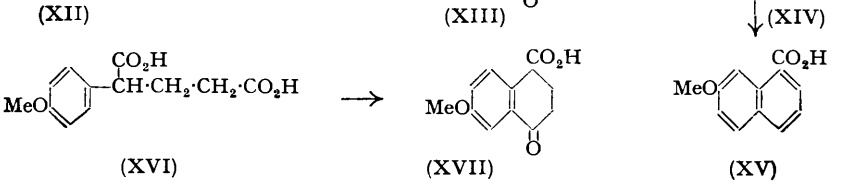
derivatives of γ-arylbutyric acids, and β-arylglutaric acids as carboxymethyl derivatives of β-arylpropionic acids, and a comparison of the yields obtained on cyclodehydration with anhydrous hydrogen fluoride in the two series clearly shows the marked deactivating influence of the second and nearer acidic group (see Table), which is probably present as $Ar{\cdot}CH{\cdot}CO^+$ in the reacting system.

Cyclisation of α-*m*-methoxyphenylglutaric acid (XII) or its acid chloride can give either 1 : 2 : 3 : 4-tetrahydro-4-keto-5- or -7-methoxy-1-naphthoic acid, but the identity of the product as the latter, *viz.*, (XIII), was confirmed by means of Clemmensen reduction to the known 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-naphthoic acid (XIV), which in turn was dehydrogenated to 7-methoxy-1-naphthoic acid, m. p. 167—168° (XV). Had cyclisation taken place at the *ortho*-position with reference to the methoxyl group this sequence of reactions would have given 5-methoxy-1-naphthoic acid, m. p. 229°. The cyclisation of

Acid	Size of ring	Yield of cyclised product (%)	Reference
γ-Phenylbutyric	6	92	Fieser & Hershberg, *J. Amer. Chem. Soc.*, 1939, **61**, 1272.
α-Phenylglutaric	6	17	Ansell & Hey, *J.*, 1950, 2874.
γ-*m*-Methoxyphenylbutyric	6	85—90 *	Peak & Robinson, *J.*, 1937, 1581.
α-*m*-Methoxyphenylglutaric	6	87	This paper.
γ-*p*-Methoxyphenylbutyric	6	61·5	Campbell & Todd, *J. Amer. Chem. Soc.*, 1942, **64**, 928.
α-*p*-Methoxyphenylglutaric	6	0	This paper.
γ-*o*-Methoxyphenylbutyric	6	55 †	Lockett & Short, *J.*, 1939, 787.
α-*o*-Methoxyphenylglutaric	6	0	This paper.
β-Phenylpropionic	5	73	Fieser & Hershberg, *loc. cit.*
β-Phenylglutaric	5	10·5	Hey & Kohn, *J.*, 1949, 3177.
β-*p*-Methoxyphenylpropionic	5	3	Johnson & Shelberg, "Organic Reactions," Vol. II, 120.
β-*p*-Methoxyphenylglutaric	5	0	Hey & Kohn, *loc. cit.*

* With $SnCl_4$. † With $POCl_3$.

α-*p*-methoxyphenylglutaric acid (XVI) offers no ambiguity and the 6-methoxy acid (XVII) was obtained and characterised as the oxime and semicarbazone.



Experimental

Preparation of the Acids.

α-o-*Methoxyphenylglutaric Acid.*—(*a*) *o*-Methoxybenzaldehyde was converted into *o*-methoxybenzyl alcohol in 72% yield by Davidson and Bogert's method (*J. Amer. Chem. Soc.*, 1935, **57**, 905) and thence into the chloride and cyanide, as described by Niederl and Roth (*loc. cit.*). In an alternative method the azlactone, m. p. 163—166° (from ethyl acetate), was prepared in 70% yield from *o*-methoxybenzaldehyde and hippuric acid by the method of Bergel, Haworth, Morrison, and Rinderknecht (*J.*, 1944, 263), who reported m. p. 154—156° from alcohol; hydrolysis of the azlactone with 10% aqueous sodium hydroxide gave *o*-methoxyphenylpyruvic acid, which was converted into the oxime and treated with acetic anhydride (cf. Niederl and Ziering, *J. Amer. Chem. Soc.*, 1942, **64**, 885) to give *o*-methoxybenzyl cyanide in 36% yield (calc. on *o*-methoxybenzaldehyde). Condensation of *o*-methoxybenzyl cyanide with ethyl carbonate, as described by Niederl and Roth (*loc. cit.*) but with two molecular proportions of ethyl

carbonate, gave ethyl α-cyano-α-*o*-methoxyphenylacetate in 32% yield. To a stirred solution of this ester (3·2 g.) and 30% methanolic potassium hydroxide (1 c.c.) in *tert.*-butyl alcohol (12 c.c.) was added pure acrylonitrile (1 c.c.). The mixture was kept at 30—35° for 3 hr., then diluted with water, neutralised with dilute hydrochloric acid, and extracted with ether. After being washed with water and dried ($MgSO_4$), the extract was heated on the water-bath under reduced pressure. The residual ethyl αγ-dicyano-α-*o*-methoxyphenylbutyrate (4 g.) was boiled under reflux for 6 hr. with a solution of potassium hydroxide (4 g.) in ethyl alcohol (4 c.c.) and water (4 c.c.). The alcohol was removed by distillation and the solution was cooled, diluted with water, washed with ether, acidified, and then extracted with ether. Evaporation of the dried extract left a solid residue, m. p. 162—164°. Recrystallisation from ethylene chloride gave α-o-*methoxyphenylglutaric acid* (2·7 g.), m. p. 164—166° (Found: C, 60·9; H, 6·0. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

(*b*) To an ice-cold solution of *o*-methoxyphenylpyruvic acid [from *o*-methoxybenzaldehyde (100 g.) as outlined in method (*a*)] in 10% aqueous sodium hydroxide (300 c.c.) was added hydrogen peroxide (10-vols.; 500 c.c.) at intervals. After being kept at 0° overnight the solution was acidified and *o*-methoxyphenylacetic acid (44 g.), m. p. 120—123°, separated (cf. Robinson and Zaki, *J.*, 1927, 2411), which was converted into the ethyl ester, b. p. 150°/18 mm., in 80% yield by 5 hr.' boiling under reflux with absolute ethyl alcohol (300 c.c.) and concentrated sulphuric acid (10 c.c.). Ethyl *o*-methoxyphenylacetate (19·4 g.), dry ethyl carbonate (100 c.c.), and sodium ethoxide (from 2·45 g. of sodium) by the method of Wallingford, Homeyer, and Jones (*loc. cit.*) gave crude ethyl *o*-methoxyphenylmalonate (7·2 g.; b. p. 125—140°/0·8 mm.), which was dissolved in *tert.*-butyl alcohol (30 c.c.) to which 30% methanolic potassium hydroxide (2 c.c.) and acrylonitrile (1·8 c.c.) were added. After being stirred for 3 hr. at 30—35° the mixture was diluted with water, neutralised with dilute hydrochloric acid, and extracted with ether. Evaporation of the dried extract gave crude ethyl α-2-cyanoethyl-α-o-methoxyphenylmalonate (8 g.), which was boiled under reflux for 6 hr. with a solution of potassium hydroxide (8 g.) in ethyl alcohol (8 c.c.) and water (8 c.c.). After removal of the alcohol the solution was cooled, diluted with water, washed with ether, acidified, and then extracted with ether. Evaporation of the ethereal extract left α-carboxy-α-*o*-methoxyphenylglutaric acid as an oil, which was decarboxylated at 180—185° (bath-temp.) for 1 hr. The cooled product was boiled with water for 15 min., cooled, and extracted with ether. Evaporation of the dried extract gave α-*o*-methoxyphenylglutaric acid, which after three crystallisations from ethylene chloride had m. p. 164—166° (1 g.) alone and on admixture with the acid prepared by method (*a*).

α-m-*Methoxyphenylglutaric Acid.*—(*a*) The azlactone (m. p. 108°; 50 g.) prepared from *m*-methoxybenzaldehyde and hippuric acid (Pschorr, *Annalen*, 1912, **391**, 44) gave *m*-methoxyphenylpyruvic acid (20 g.; m. p. 150°), which was converted successively into the oxime (20 g.; m. p. 140°) and *m*-methoxybenzyl cyanide (7 g.; b. p. 100°/4·6 × 10^{-3} mm.). Condensation of the cyanide (6·3 g.) with dry ethyl carbonate (15 c.c.) and powdered sodium (0·9 g.) in dry ether (20 c.c.) by Niederl and Roth's method (*loc. cit.*) gave ethyl α-cyano-α-*m*-methoxyphenylacetate (4·9 g.; b. p. 120—125°/5 × 10^{-3} mm.). Hydrolysis of a portion of this ester with boiling aqueous-alcoholic potassium hydroxide gave *m*-methoxyphenylacetic acid, m. p. 68—69°. Ethyl α-cyano-α-*m*-methoxyphenylacetate (3·7 g.) and acrylonitrile (1·2 c.c.) by the method described above for the corresponding *o*-isomeride gave ethyl αγ-dicyano-α-*m*-methoxyphenylbutyrate as a viscous oil (4·6 g.), and on hydrolysis α-m-*methoxyphenylglutaric acid* (2·9 g.) in plates, m. p. 121—122° after crystallisation from ether–light petroleum (b. p. 40—60°) (Found: C, 60·5; H, 6·0. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

(*b*) The azlactone (50 g.) from *m*-methoxybenzaldehyde was converted into *m*-methoxyphenylpyruvic acid (20 g.) and then into *m*-methoxyphenylacetic acid (15·5 g.), m. p. 68—69°, and its ethyl ester (14·8 g.), b. p. 90°/1·27 × 10^{-2} mm. as described in the previous example. By the method of Wallingford, Homeyer, and Jones (*loc. cit.*), ethyl *m*-methoxyphenylacetate (26 g.) and dry ethyl carbonate (110 c.c.) in the presence of sodium ethoxide (from 3·2 g. of sodium) gave ethyl *m*-methoxyphenylmalonate (23·5 g.), b. p. 128—132°/0·35 mm. A portion on hydrolysis with aqueous alcoholic potassium hydroxide gave m-*methoxyphenylmalonic acid* in prisms, m. p. 116—117° (decomp.) (from chloroform) (Found: C, 57·0; H, 5·1. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%). By the method described above ethyl *m*-methoxyphenylmalonate (13·3 g.), 30% methanolic potassium hydroxide (2 c.c.), and acrylonitrile (3·3 c.c.) in *tert.*-butyl alcohol (50 c.c.) at 30—35° for 3 hr. gave ethyl α-2-cyanoethyl-α-*m*-methoxyphenylmalonate (15·8 g.), which was hydrolysed as above to α-carboxy-α-*m*-methoxyphenylglutaric acid, an oil, which in turn was decarboxylated at 180—185° for 1 hr. α-*m*-Methoxyphenylglutaric acid (2·1 g.) was obtained in

plates, m. p. 121—122°, from ether–light petroleum (b. p. 40—60°) alone and on admixture with the acid prepared by method (*a*).

α-p-*Methoxyphenylglutaric Acid.*—The azlactone (m. p. 156—158°; 50 g.), prepared in 80% yield from *p*-methoxybenzaldehyde and hippuric acid (Dakin, *J. Biol. Chem.*, 1910, **8**, 17), was converted successively into *p*-methoxyphenylpyruvic acid, m. p. 184° (23 g.), its oxime, m. p. 159° (22 g.), and *p*-methoxybenzyl cyanide, b. p. 92°/1·5 × 10^{-2} mm. (11 g.), identical with a specimen prepared by the methylation of *p*-hydroxybenzyl cyanide (Meisenheimer and Weibezahn, *Ber.*, 1921, **54**, 3200). The *p*-methoxybenzyl cyanide (13·2 g.), dry ethyl carbonate (12 c.c.), and sodium (2·1 g.) in dry ether (30 c.c.), by the method of Niederl, Roth, and Plentl (*loc. cit.*), gave ethyl α-cyano-α-*p*-methoxyphenylacetate, b. p. 132—135°/8·16 × 10^{-3} mm. (10·7 g.). By the method outlined above this ester (9·5 g.) with 30% methanolic potassium hydroxide (2 c.c.) and acrylonitrile (2·9 c.c.) in *tert.*-butyl alcohol (25 c.c.) at 30—35° gave ethyl αγ-dicyano-α-*p*-methoxyphenylbutyrate (11·6 g.) as a viscous oil, which after hydrolysis with aqueous-alcoholic potassium hydroxide as above gave α-p-*methoxyphenylglutaric acid* (8 g.), m. p. 137—138°, in needles from ether–light petroleum (b. p. 40—60°) (Found: C, 60·8; H, 6·0. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

o-, m-, and p-*Methoxybenzylmalonic Acids.*—These acids were prepared from dry ethyl malonate (12 c.c.), the appropriate methoxybenzaldehyde (10 g.), and piperidine (2 c.c.) by setting the mixture aside for 2 days and then boiling it under reflux for 12 hr. The cold mixture was diluted with ether (100 c.c.), washed successively with water, dilute sulphuric acid, and water, dried ($MgSO_4$), and distilled under reduced pressure. The resulting methoxybenzylidenemalonic esters were hydrogenated in alcohol at room temperature over Raney nickel and then hydrolysed to the methoxybenzylmalonic acids with aqueous-alcoholic potassium hydroxide. The following compounds were obtained: *ethyl* o-*methoxybenzylidenemalonate*, needles, m. p. 49·5—50·5° (from alcohol) (Found: C, 64·5; H, 6·4. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·4%); o-*methoxybenzylmalonic acid*, m. p. 140° [from ether–light petroleum (b. p. 40—60°)] (Found: C, 59·1; H, 5·3. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·3%); ethyl *m*-methoxybenzylidenemalonate, b. p. 160°/3 × 10^{-3} mm.; m-*methoxybenzylmalonic acid*, m. p. 100—102° [from ether-light petroleum (b. p. 40—60°)] (Found: C, 58·7; H, 5·5%); ethyl *p*-methoxybenzylidenemalonate, m. p. 38—40° (cf. Marckwald, *Ber.*, 1898, **31**, 2594); ethyl *p*-methoxybenzylmalonate, b. p. 122—123°/6·85 × 10^{-3} mm. (cf. Bowden and Adkins, *J. Amer. Chem. Soc.*, 1940, **62**, 2422); and p-*methoxybenzylmalonic acid*, m. p. 119—120° [from ether–light petroleum (b. p. 40—60°)] (Found: C, 59·4; H, 5·4%).

Ring Closure Experiments.

(a) *Cyclodehydration.*—(i) A mixture of anhydrous hydrogen fluoride (*ca.* 50 c.c.) and α-*m*-methoxyphenylglutaric acid (0·5 g.) in a "Polythene" beaker was left for 24 hr. in the open under shelter, after which ice-cold water was added. The separated solid was extracted with ether and the ethereal extract washed with aqueous sodium carbonate. The alkaline extract was acidified and extracted with ether. Evaporation of the solvent from the dried extract left 1 : 2 : 3 : 4-*tetrahydro*-4-*keto*-7-*methoxy*-1-*naphthoic acid* (0·4 g.), long needles, m. p. 155° [from ether–light petroleum (b. p. 40—60°)] (Found: C, 65·2; H, 5·6. $C_{12}H_{12}O_4$ requires C, 65·45; H, 5·45%). The *semicarbazone* separated from alcohol in long needles, m. p. 221—222° (Found: C, 56·9; H, 5·6. $C_{13}H_{15}O_4N_3$ requires C, 56·3; H, 5·4%). A mixture of amalgamated zinc turnings (2 g.), water (2 c.c.), concentrated hydrochloric acid (3 c.c.), toluene (5 c.c.), acetic acid (0·2 c.c.), and the keto-acid (0·4 g.) was boiled under reflux for 30 hr., during which a further quantity of hydrochloric acid (4 c.c.) was added in portions. The toluene layer was then collected and when cold 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-naphthoic acid (0·2 g.) gradually separated in colourless prisms, m. p. 137—138° (cf. Fieser and Holmes, *J. Amer. Chem. Soc.*, 1936, **58**, 2319). When this acid (0·15 g.) was heated at 220—240° for ½ hr. with sulphur (0·5 g.) dehydrogenation was effected, and digestion of the cold mixture with aqueous sodium carbonate extracted the acid. The alkaline solution was acidified and extracted with ether. Evaporation of the dried extract gave 7-methoxy-1-naphthoic acid, which after crystallisation from dilute alcohol and then twice from hexane was obtained in needles, m. p. 166—167° (cf. Davies, Heilbron, and Irving, *J.*, 1932, 2715, and Fieser and Holmes, *loc. cit.*).

(ii—iv) 1 : 2 : 3 : 4-Tetrahydro-1-keto-7-methoxy-1-naphthoic acid, m. p. 154°, was obtained in yields of 0·10 g., 0·11 g., and 0·11 g. respectively when α-*m*-methoxyphenylglutaric acid (0·2 g.) was (*a*) stirred with 95% sulphuric acid (2 c.c.) for 1 hr. at 0° and a second hour at 20°, (*b*) stirred at 100° for 15 min. with polyphosphoric acid (2 c.c.), and (*c*) stirred at 120° for 20 min. with stannic chloride (2 c.c.).

Cyclodehydration failed with both α-*o*- and α-*p*-methoxyphenylglutaric acid and (*a*) anhydrous hydrogen fluoride, (*b*) 85% and 95% sulphuric acid at 0°, (*c*) polyphosphoric acid at 100°, and (*d*) stannic chloride at 120°, and with α-*m*-methoxyphenylglutaric acid and cold 85% sulphuric acid.

(b) *Cyclohydrohalogenation.*—(i) A mixture of α-*m*-methoxyphenylglutaric acid (0·1 g.) and phosphorus pentachloride (0·2 g.) in dry benzene (5 c.c.) was kept at room temperature for 1 hr. and then boiled for 5 min. on the water-bath. After the removal of benzene, phosphorus oxychloride, and phosphorus pentachloride under reduced pressure the residual α-*m*-methoxyphenylglutaryl chloride was dissolved in benzene (3 c.c.) and cooled, and a solution of stannic chloride (0·2 c.c.) in benzene (2 c.c.) added. The mixture was shaken, kept at 0° for 15 min., and then decomposed with ice and hydrochloric acid. The product was extracted with ether, and the extract was washed successively with dilute hydrochloric acid, water, and aqueous sodium carbonate. The alkaline solution was acidified and extracted with ether, evaporation of which left an oil, which was heated in ethyl alcohol (5 c.c.) at 70° for 1 hr. with a solution of semicarbazide hydrochloride (0·1 g.) in water (1 c.c.) and pyridine (0·1 c.c.). Next morning the semicarbazone (20 mg.), m. p. 221—222°, of 1 : 2 : 3 : 4-tetrahydro-4-keto-7-methoxy-1-naphthoic acid separated in long needles. Hydrolysis with dilute hydrochloric acid gave the free acid (13 mg.), which separated from ether–light petroleum (b. p. 40—60°) in long needles, m. p. 155° alone and on admixture with the compound prepared from α-*m*-methoxyphenylglutaric acid and anhydrous hydrogen fluoride.

(ii) Anhydrous aluminium chloride (0·4 g.) was added to a solution of α-*m*-methoxyphenylglutaryl chloride (from 0·3 g. acid) in nitrobenzene (5 c.c.) at room temperature. After 15 min. the mixture was stirred at 60—70° for 15 min. and then decomposed with ice and hydrochloric acid. The nitrobenzene was removed with steam, and the residue was extracted with ether. Working up as usual and crystallisation (charcoal) from ether–light petroleum (b. p. 40—60°) gave 1 : 2 : 3 : 4-tetrahydro-4-keto-7-methoxy-1-naphthoic acid (85 mg.) as needles, m. p. 155°, identical with the product obtained by method (i).

(iii) Anhydrous aluminium chloride (1·3 g.) was added to a solution of α-*p*-methoxyphenylglutaryl chloride (from 1·0 g. of acid) in nitrobenzene (15 c.c.) at 0°. After ½ hr. the mixture was added to ice and concentrated hydrochloric acid, and treated as in the preceding example. Purification of the product with charcoal and two crystallisations from ether–light petroleum (b. p. 40—60°) gave 1 : 2 : 3 : 4-*tetrahydro*-4-*keto*-6-*methoxy*-1-*naphthoic acid* (90 mg.) in plates, m. p. 115° (Found : C, 65·5; H, 5·4. $C_{12}H_{12}O_4$ requires C, 65·45; H, 5·45%). The *oxime* separated from ethylene chloride in platelets, m. p. 202° (Found : N, 5·5. $C_{12}H_{13}O_4N$ requires N, 5·95%), and the *semicarbazone* from alcohol in needles, m. p. 255° (Found : N, 14·0. $C_{13}H_{15}O_4N_3$ requires N, 15·1%).

Cyclodehydrohalogenation failed with α-*o*-methoxyphenylglutaryl chloride and (*a*) stannic chloride in benzene, (*b*) aluminium chloride in carbon disulphide, and (*c*) aluminium chloride in nitrobenzene, with α-*m*-methoxyphenylglutaryl chloride and aluminium chloride in carbon disulphide, and with α-*p*-methoxyphenylglutaryl chloride and (*a*) stannic chloride in benzene and (*b*) aluminium chloride in carbon disulphide.

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