

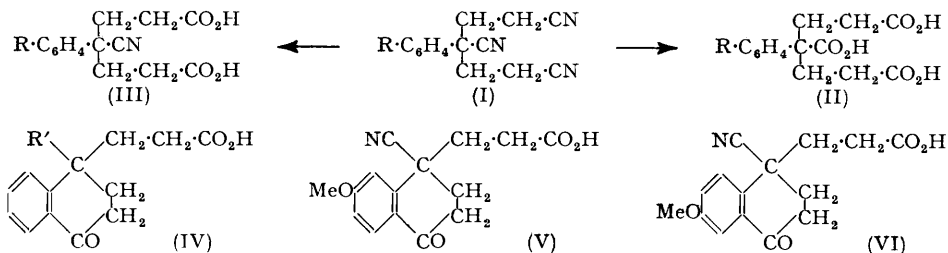
*Intramolecular Acylation. Part IV.\* Preparation and Ring Closure of Some  $\gamma$ -Aryl- $\gamma$ -carboxy- and - $\gamma$ -cyano-pimelic Acids.*

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Methods are described for the preparation of  $\gamma$ -cyano- $\gamma$ -phenylpimelic acid and its *m*- and *p*-methoxy-derivatives. Cyclodehydration of  $\gamma$ -carboxy- $\gamma$ -phenylpimelic acid and of the above cyanophenylpimelic acids affords derivatives of  $\beta$ -(1:2:3:4-tetrahydro-4-oxo-1-naphthyl)propionic acid. The cyclisation of the  $\gamma$ -carboxy-acid provides further evidence of the deactivating influence of the nearer carboxyl group in an aryl-substituted polycarboxylic acid, but no such deactivating influence is found in the cyclisation of the  $\gamma$ -cyano-acids in which the nearer CO<sub>2</sub>H group is replaced by CN.

$\gamma$ -CYANO- $\gamma$ -PHENYLPIMELODINITRILE (I; R = H) was prepared by Bruson and Riener (*J. Amer. Chem. Soc.*, 1943, **65**, 23) from benzyl cyanide and acrylonitrile, and Rubin and Wishinsky (*ibid.*, 1946, **68**, 828) showed that it could be hydrolysed with a mixture of sulphuric and acetic acids to  $\gamma$ -carboxy- $\gamma$ -phenylpimelic acid (II; R = H). The latter workers also reported that hydrolysis with alkali gave  $\gamma$ -carbonyl- $\gamma$ -phenylpimelic acid, but no details were given of the reaction conditions or the concentration of the alkali used. It is now shown that hydrolysis with boiling aqueous-alcoholic potassium hydroxide for seven hours gives  $\gamma$ -cyano- $\gamma$ -phenylpimelic acid (III; R = H), and with the use of substituted benzyl cyanides this constitutes a general method for the preparation of  $\gamma$ -aryl- $\gamma$ -cyanopimelic acids. Horning and Schock (*ibid.*, 1948, **70**, 2945) had previously reported that  $\gamma$ -cyano- $\gamma$ -(2:3-dimethoxyphenyl)pimelic acid could not be obtained by the direct hydrolysis of  $\gamma$ -cyano- $\gamma$ -(2:3-dimethoxyphenyl)pimelodinitrile but was obtained by conversion of the latter into the dimethyl ester followed by alkaline hydrolysis.



The new method has now been applied to the preparation of  $\gamma$ -cyano- $\gamma$ -*m*- and -*p*-methoxyphenylpimelic acids (III; R = *m*-MeO and *p*-MeO) in addition to  $\gamma$ -cyano- $\gamma$ -phenylpimelic acid itself. In the cyanoethylation reaction the *m*- and *p*-methoxybenzyl cyanides reacted less readily than the unsubstituted benzyl cyanides, requiring a longer time and more methanolic potassium hydroxide.

The  $\gamma$ -aryl- $\gamma$ -carboxy- and - $\gamma$ -cyano-pimelic acids thus made available provide suitable compounds from which further information may be obtained on the influence of the nearer CO<sub>2</sub>H or CN group on intramolecular acetylation (cf. Part III, *loc. cit.*). It is known that  $\gamma$ -phenylpimelic acid, which lacks the nearer carboxyl group, can be converted readily into  $\beta$ -(1:2:3:4-tetrahydro-4-oxo-1-naphthyl)propionic acid and a neutral tricyclic diketone (von Braun and Weissbach, *Ber.*, 1931, **64**, 1785; Manske, *J. Amer. Chem. Soc.*, 1931, **53**, 1104). Similar attempts to effect ring closure of  $\gamma$ -carboxy- $\gamma$ -phenylpimelic acid (II; R = H) by the action of aluminium chloride on the acid chloride in carbon disulphide failed to give consistent results. When benzene was used as a solvent a neutral compound, m. p. 137—139°, was obtained in good yield, which formed a 2:4-dinitrophenylhydrazone and a semicarbazone, but its structure has not been determined (cf. Horning and Schock, *J. Amer. Chem. Soc.*, 1948, **70**, 2941, and Johnson and Glenn, *ibid.*, 1949, **71**, 1092). On the other hand, the free  $\gamma$ -carboxy- $\gamma$ -phenylpimelic acid readily underwent cyclodehydration

\* Part III, *J.*, 1953, 1894.

with sulphuric acid in 43% yield and with polyphosphoric acid in 34% yield, to give  $\beta$ -(1-carboxy-1 : 2 : 3 : 4-tetrahydro-4-oxo-1-naphthyl)propionic acid (IV;  $R' = \text{CO}_2\text{H}$ ), which was characterized as the semicarbazone and the 2 : 4-dinitrophenylhydrazone of the half-ester. Esterification of carboxyl groups during the formation of dinitrophenylhydrazones has been previously reported by several workers (cf. Cowley and Schuette, *ibid.*, 1933, 55, 3465; Strain, *ibid.*, 1935, 57, 758; Ansell and Hey, *J.*, 1950, 2874; Reich, Crane, and Sanfilippo, *J. Org. Chem.*, 1953, 18, 822.)

The cyclisation experiments with the  $\alpha$ -methoxyphenylglutaric acids described in Part III (*loc. cit.*) and those recorded above with  $\gamma$ -carboxy- $\gamma$ -phenylpimelic acid have given evidence of the deactivating influence of the nearer carboxyl group on the cyclisation process. This deactivation may be due to the fact that in the reaction medium the nearer carboxyl group would be converted into  $-\text{CO}^+$ . The  $\gamma$ -cyanopimelic acids now made available enable a comparative study to be made on the influence of the cyano-group in similar circumstances. Experiment has now shown that with (III;  $R = \text{H}$ , *m*-MeO, and *p*-MeO) cyclodehydration is effected readily with polyphosphoric acid at  $100^\circ$  in 70, 80, and 67% yield respectively. With the first two acids cyclodehydration is also effected with 95% sulphuric acid under mild conditions in 80 and 67% yield respectively, but with the *p*-methoxy-acid the use of sulphuric acid results in sulphonation. The ease with which the cyclodehydration of the  $\gamma$ -aryl- $\gamma$ -cyanopimelic acids has been effected might suggest that, unlike the carboxyl group, the cyano-group does not change its structure in the reacting system, and become a positive pole.

The cyclisation product from  $\gamma$ -cyano- $\gamma$ -*m*-methoxyphenylpimelic acid (III;  $R = m\text{-MeO}$ ) can be  $\beta$ -(1-cyano-1 : 2 : 3 : 4-tetrahydro-7-methoxy-4-oxo-1-naphthyl)propionic acid (V) or its 5-methoxy-isomer, but oxidation of the product with sodium hypobromite to an oil, which on vacuum-sublimation gave 4-methoxyphthalic anhydride, confirmed its identity as a derivative of 6-methoxytetralone. The cyclisation of (III;  $R = \text{H}$  and *p*-MeO) offers no ambiguity and the products must be (IV;  $R' = \text{CN}$ ) and (VI) respectively, both of which were characterised as 2 : 4-dinitrophenylhydrazones. All attempts to effect the further cyclodehydration of the acid (IV;  $R' = \text{CN}$ ) and its 6- and 7-methoxy-derivatives were unsuccessful.

#### EXPERIMENTAL

$\gamma$ -Cyano- $\gamma$ -phenylpimelodinitrile, m. p.  $70\text{--}71^\circ$ , was prepared from benzyl cyanide and acrylonitrile by Bruson and Riener's method (*loc. cit.*) and hydrolysed with a mixture of sulphuric and acetic acids, to give  $\gamma$ -carboxy- $\gamma$ -phenylpimelic acid, m. p.  $153\text{--}154^\circ$ , as described by Rubín and Wishinsky (*loc. cit.*).

$\gamma$ -Cyano- $\gamma$ -phenylpimelic Acid.— $\gamma$ -Cyano- $\gamma$ -phenylpimelodinitrile (1 g.) was boiled under reflux for 7 hr. with a solution of potassium hydroxide (1 g.) in a mixture of alcohol (2.5 c.c.) and water (2.5 c.c.). The alcohol was distilled off and water (10 c.c.) was added, followed by concentrated hydrochloric acid (20 c.c.). Ether extracted only a small quantity of oil (*ca.* 0.1 g.). The acid solution was evaporated almost to dryness and placed in the refrigerator for 24 hr. The precipitate was collected and washed with ice-cold water to remove sodium chloride. The insoluble residue on crystallisation from alcohol gave  $\gamma$ -cyano- $\gamma$ -phenylpimelic acid (0.5 g.) in prisms, m. p.  $168\text{--}170^\circ$  (Found: C, 64.3; H, 5.6; N, 5.3.  $\text{C}_{14}\text{H}_{15}\text{O}_4\text{N}$  requires C, 64.3; H, 5.7; N, 5.3%).

$\gamma$ -Cyano- $\gamma$ -*m*-methoxyphenylpimelic Acid.—A solution of acrylonitrile (4.9 c.c.) in *tert.*-butyl alcohol (5 c.c.) was added dropwise during  $4\frac{1}{2}$  hr. to a stirred solution of *m*-methoxybenzyl cyanide (5.3 g.) in *tert.*-butyl alcohol (10 c.c.) and 30% methanolic potassium hydroxide (1 c.c.) at  $20\text{--}25^\circ$ . After being stirred for 24 hr. at room temperature it was neutralised with dilute hydrochloric acid, diluted with ethyl alcohol (10 c.c.), and kept in the refrigerator for 2 days. The trinitrile which had separated was collected and crystallisation from alcohol gave  $\gamma$ -cyano- $\gamma$ -*m*-methoxyphenylpimelodinitrile (7 g.) in prisms, m. p.  $73\text{--}74^\circ$  (Found: C, 70.9; H, 5.8.  $\text{C}_{15}\text{H}_{15}\text{ON}_3$  requires C, 71.1; H, 5.9%). Hydrolysis of  $\gamma$ -cyano- $\gamma$ -*m*-methoxyphenylpimelodinitrile (1 g.) with aqueous-alcoholic potassium hydroxide, as described above, gave  $\gamma$ -cyano- $\gamma$ -*m*-methoxyphenylpimelic acid (0.5 g.), which separated from alcohol-light petroleum (b. p.  $40\text{--}60^\circ$ ) as a microcrystalline powder, m. p.  $159\text{--}161^\circ$  (Found: C, 62.5; H, 5.7; N, 4.8.  $\text{C}_{15}\text{H}_{17}\text{O}_5\text{N}$  requires C, 61.8; H, 5.8; N, 4.8%).

$\gamma$ -Cyano- $\gamma$ -*p*-methoxyphenylpimelic Acid.—In similar manner *p*-methoxybenzyl cyanide

(3.4 g.) and acrylonitrile (3 c.c.) gave  $\gamma$ -cyano- $\gamma$ -*p*-methoxyphenylpimelodinitrile (4.0 g.), which separated from alcohol in prisms, m. p. 83—83.5° (Found: C, 71.3; H, 5.8; N, 16.8%). Hydrolysis of the trinitrile (1 g.) with aqueous-alcoholic potassium hydroxide, as described above, gave  $\gamma$ -cyano- $\gamma$ -*p*-methoxyphenylpimelic acid (0.5 g.), which after crystallisation from alcohol melted at 156—158° after softening at 148° (Found: C, 61.2; H, 5.9; N, 4.75%).

*Cyclisation of  $\gamma$ -Carboxy- $\gamma$ -phenylpimelic Acid.*—A solution of  $\gamma$ -carboxy- $\gamma$ -phenylpimelic acid (2 g.) in 95% sulphuric acid (20 c.c.) was stirred for 30 min. at 0° and then for 4 hr. at room temperature. After being warmed for 5 min. on the steam-bath it was added to ice and extracted with ether. The extract was washed with aqueous sodium carbonate, the pink alkaline solution was acidified and extracted with ether, and the extract was washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation left a yellow oil (1.4 g.), which solidified. Recrystallisation from ether-light petroleum (b. p. 40—60°) gave  $\beta$ -(1-carboxy-1 : 2 : 3 : 4-tetrahydro-4-oxo-1-naphthyl)propionic acid (0.8 g.), m. p. 167—168° (Found: C, 64.65; H, 5.65. C<sub>14</sub>H<sub>14</sub>O<sub>5</sub> requires C, 64.1; H, 5.35%). The semicarbazone crystallised from alcohol-pyridine in needles, m. p. 225° (decomp.) (Found: N, 12.7. C<sub>15</sub>H<sub>17</sub>O<sub>5</sub>N<sub>3</sub> requires N, 13.15%). Treatment with 2 : 4-dinitrophenylhydrazine in concentrated sulphuric acid and alcohol (cf. Brady, J., 1931, 756) gave the 2 : 4-dinitrophenylhydrazone of ethyl  $\beta$ -(1-carboxy-1 : 2 : 3 : 4-tetrahydro-4-oxo-1-naphthyl)propionate, which separated from benzene-ethyl acetate as a microcrystalline powder, m. p. 233—234° (Found: C, 55.8; H, 5.1; N, 11.5. C<sub>22</sub>H<sub>22</sub>O<sub>8</sub>N<sub>4</sub> requires C, 56.1; H, 4.6; N, 11.9%). A similar cyclisation was effected in 34% yield by polyphosphoric acid at 100° for 1 hr. An attempt to effect the cyclisation through dehydrohalogenation of the acid chloride with (a) stannic chloride in benzene at 0° and (b) aluminium chloride in boiling carbon disulphide failed. With aluminium chloride in benzene (cf. Johnson and Glenn, *loc. cit.*) a neutral compound (2.5 g. from 5.6 g. of acid) was obtained in shining scales, m. p. 137—139° (from alcohol) (Found: C, 80.35; 81.1; H, 5.5; 6.0%). It gave a semicarbazone, m. p. 241—243° (crude), and a 2 : 4-dinitrophenylhydrazone, m. p. 233—235° after recrystallisation from chloroform-light petroleum (b. p. 40—60°).

*Cyclisation of  $\gamma$ -Cyano- $\gamma$ -phenylpimelic Acid.*—By the method outlined above  $\gamma$ -cyano- $\gamma$ -phenylpimelic acid (1 g.) and 95% sulphuric acid (10 c.c.) gave a white precipitate on decomposition with ice. Recrystallisation from alcohol gave  $\beta$ -(1-cyano-1 : 2 : 3 : 4-tetrahydro-4-oxo-1-naphthyl)propionic acid (0.75 g., 80%) in long needles, m. p. 200° (Found: C, 69.0; H, 5.3; N, 5.95. C<sub>14</sub>H<sub>13</sub>O<sub>3</sub>N requires C, 69.2; H, 5.35; N, 5.8%). A similar cyclisation was effected in 70% yield with polyphosphoric acid at 100° for 2 hr. The semicarbazone melted at 255° (decomp.), but because of its insolubility could not be recrystallised. The 2 : 4-dinitrophenylhydrazone, prepared by Brady's method, separated from nitrobenzene in orange crystals, m. p. 289—290° (Found: C, 56.7; H, 4.1. C<sub>20</sub>H<sub>17</sub>O<sub>6</sub>N<sub>5</sub> requires C, 56.7; H, 4.0%). Attempts to effect cyclodehydrohalogenation of the acid chloride with (a) stannic chloride in benzene, (b) aluminium chloride in carbon disulphide, and (c) aluminium chloride in nitrobenzene, failed. Attempts to effect the further cyclodehydration of the 4-cyanopropionic acid with 95% sulphuric acid at 100° and 130° and polyphosphoric acid at 160° also failed.

*Cyclisation of  $\gamma$ -Cyano- $\gamma$ -*m*-methoxyphenylpimelic Acid.*— $\gamma$ -Cyano- $\gamma$ -*m*-methoxyphenylpimelic acid (0.4 g.) in 95% sulphuric acid (4 c.c.) was stirred at 0° for 1 hr. and at room temperature for 2 hr., and then added to ice. Recrystallisation of the white precipitate from alcohol containing a little water gave  $\beta$ -(1-cyano-1 : 2 : 3 : 4-tetrahydro-7-methoxy-4-oxo-1-naphthyl)propionic acid (0.25 g., 67%) in small needles, m. p. 213—214° (Found: C, 65.6; H, 5.4; N, 5.1. C<sub>15</sub>H<sub>15</sub>O<sub>4</sub>N requires C, 65.9; H, 5.5; N, 5.1%). This acid was also obtained in 80% yield by cyclodehydration with polyphosphoric acid at 100° for 45 min. The 2 : 4-dinitrophenylhydrazone, prepared as above, separated from nitrobenzene in red crystals, m. p. 294° (decomp.) (Found: C, 55.4; H, 4.4; N, 15.0. C<sub>21</sub>H<sub>19</sub>O<sub>7</sub>N<sub>5</sub> requires C, 55.6; H, 4.2; N, 15.45%). Attempted cyclodehydrohalogenation of the acid chloride with aluminium chloride, in both carbon disulphide and nitrobenzene, failed. Attempted further cyclodehydration of the 4-cyano-acid with polyphosphoric acid at 170° failed.

*Oxidation of  $\beta$ -(1-Cyano-1 : 2 : 3 : 4-tetrahydro-7-methoxy-4-oxo-1-naphthyl)propionic Acid* (cf. Ruzicka and Waldmann, *Helv. Chim. Acta*, 1932, 15, 914).—The keto-acid (0.1 g.) was added to a solution of bromine (0.2 g.) in aqueous sodium hydroxide (0.6 g. in 10 c.c.), and the mixture warmed on the steam-bath for 15 min. and left at room temperature for 24 hr. The orange-coloured solution was decolorised with sulphur dioxide, further acidified with hydrochloric acid, and boiled to remove sulphur dioxide. When cold, the solution was extracted with ether. Evaporation of the solvent left a residue, which on sublimation at 180°/0.32 mm. gave 4-methoxyphthalic anhydride, m. p. 94°, both alone and on admixture with an authentic specimen prepared

from 6-methoxytetral-1-one by oxidation with potassium permanganate as described by Attwood, Stevenson, and Thorpe (*J.*, 1923, 123, 1764).

*Cyclisation of  $\gamma$ -Cyano- $\gamma$ -p-methoxyphenylpimelic Acid.*— $\gamma$ -Cyano- $\gamma$ -p-methoxyphenylpimelic acid (0.4 g.) was stirred with polyphosphoric acid (5 c.c.) for 1 hr. at 100° and the mixture was then added to ice. Crystallisation of the white precipitate from alcohol gave  $\beta$ -(1-cyano-1:2:3:4-tetrahydro-6-methoxy-4-oxo-1-naphthyl)propionic acid (0.25 g., 67%) in small needles, m. p. 213—214° (Found: C, 65.83; H, 6.05; N, 5.1.  $C_{15}H_{15}O_4N$  requires C, 65.9; H, 5.5; N, 5.1%). The m. p. is identical with that of the corresponding 7-methoxy-compound: a mixed m. p. shows a big depression. The 2:4-dinitrophenylhydrazone, prepared as above, separated from nitrobenzene in orange crystals, m. p. 300—302° (Found: C, 55.7; H, 4.75; N, 15.4.  $C_{21}H_{19}O_7N_5$  requires C, 55.6; H, 4.2; N, 15.45%). An attempted cyclodehydration with 95% sulphuric acid at room temperature gave a clear solution on addition to ice, probably owing to sulphonation. The further cyclodehydration of the cyano-acid with 95% sulphuric acid at room temperature and polyphosphoric acid at 150° failed.

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