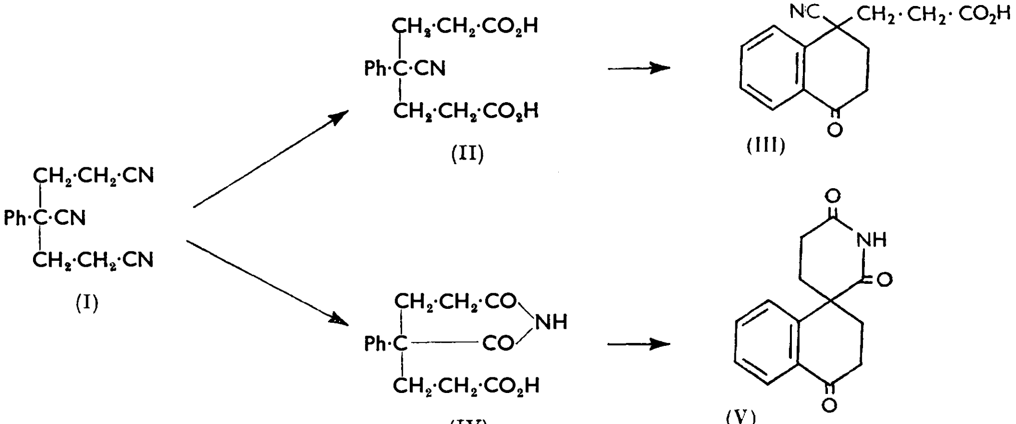
570. *The Hydrolysis of γ-Cyano-γ-phenylpimelodinitrile.*

By J. McDonald Blair and D. H. Hey.

The product obtained on the partial hydrolysis of γ-cyano-γ-phenylpimelodinitrile is shown to be α-2-carboxyethyl-α-phenylglutarimide and not γ-cyano-γ-phenylpimelic acid. Treatment of the imide with aqueous alkali gives γ-carbamoyl-γ-phenylpimelic acid, which, by the action of bromine and sodium methoxide, is converted into a methyl carbamate. Acid hydrolysis of the carbamate gives γ-2-carboxyethyl-γ-phenylbutyrolactone, the constitution of which is established by independent synthesis. Prolonged alkaline hydrolysis of the carbamate gives γ-2-carboxyethyl-γ-phenylbutyrolactam, which with nitrous acid is converted into the corresponding lactone. Short alkaline hydrolysis of γ-cyano-γ-phenylpimelodinitrile gives a diamide-monocarboxylic acid, which on melting appears to give a 1 : 8-naphthyridine.

It was reported by Hey and Nagdy [1] that hydrolysis of γ-cyano-γ-phenylpimelodinitrile (I) and of its *m*- and *p*-methoxy-derivatives with boiling aqueous-alcoholic potassium hydroxide for seven hours, followed by treatment with hydrochloric acid, gave γ-cyano-γ-phenylpimelic acid (II), m. p. 168—170°, and its *m*- and *p*-methoxy-derivatives respectively. It was further reported that the three γ-cyano-γ-phenylpimelic acids underwent cyclodehydration in the presence of polyphosphoric acid at 100° to give β-(1-cyano-1 : 2 : 3 : 4-tetrahydro-4-oxo-1-naphthyl)propionic acid (III), m. p. 200°, and its 7- and 6-methoxy-derivatives, respectively.



Almost simultaneously, Campbell [2] reported that acid hydrolysis of γ-cyano-γ-phenylpimelodinitrile gave α-2-carboxyethyl-α-phenylglutarimide (IV), m. p. 165°, which on cyclodehydration with sulphuric acid gave 1 : 2 : 3 : 4-tetrahydro-4-oxonaphthalene-1-*spiro*-α-glutarimide (V), m. p. 198°. The cyclic imides (IV) and (V) are isomeric with the nitriles (II) and (III) respectively, and the close agreement between the melting points, and between the melting points of the semicarbazones and 2 : 4-dinitrophenylhydrazones of the cyclodehydration products, suggested that the compounds in the two series might be identical. The nitrile formulation was preferred by Hey and Nagdy because it was considered that the relatively hindered tertiary nitrile group would be comparatively resistant to hydrolysis. The cyclic imide formulation was preferred by Campbell because he found that his acid (IV) was monobasic, while his cyclised product (V) was neutral but soluble in strong alkali.

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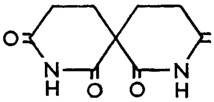
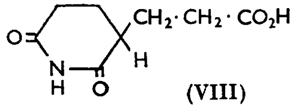
[1] Hey and Nagdy, *J.*, 1954, 1204.
[2] Campbell, *J.*, 1954, 1377.

Rubin and Wishinsky[3] had earlier reported that hydrolysis with alkali, or acid hydrolysis for less than 20 hours, converted γ-cyano-γ-phenylpimelodinitrile into γ-carbamoyl-γ-phenylpimelic acid (VI). In addition, Horning and Shock[4] prepared γ-cyano-γ-(2 : 3-dimethoxyphenyl)pimelic acid from the corresponding trinitrile by a two-stage hydrolysis, having found that direct alkaline hydrolysis failed to give the desired product. The trinitrile was converted with methanol and hydrogen chloride into a dimethyl ester, which on hydrolysis with aqueous alkali yielded the monocyano-dicarboxylic acid. Prolonged hydrolysis of γ-cyano-γ-phenylpimelodinitrile with either acid or alkali gave γ-carboxy-γ-phenylpimelic acid.[2,3]

Mariella, Clutter, and Ebner[5] hydrolysed γγ-dicyanopimelodinitrile, γ-carbamoyl-γ-cyanopimelodinitrile, γγ-dicarbamoylpimelodinitrile, and γ-carboxy-γ-cyanopimelodinitrile, among other compounds, by refluxing them for 15 minutes with concentrated hydrochloric acid. The first three compounds gave *spiro*-αα′-diglutarimide (VII), and the last gave α-2-carboxyethylglutarimide (VIII), from which it was suggested that a diamide is a necessary precursor to imide formation.


(VII)


(VIII)

A repetition of the hydrolysis of γ-cyano-γ-phenylpimelodinitrile as described by Campbell,[2] using 65% sulphuric acid under reflux, gave only a dark viscous oil, but by limiting the temperature to 95—100° a clean product of m. p. 167—169° was obtained in 81% yield. A mixed melting point with the product of m. p. 168—169° prepared by Hey and Nagdy's method showed no depression, and both compounds were monobasic. The infrared spectra of the two compounds were identical, and showed the absence of the nitrile group. It is therefore concluded that both compounds are α-2-carboxyethyl-α-phenylglutarimide (IV). The infrared spectra of the corresponding compounds obtained by the hydrolysis of the *m*- and *p*-methoxy-derivatives of γ-cyano-γ-phenylpimelodinitrile, and of the three cyclodehydration products, also showed the absence of the nitrile group. The latter must also therefore be represented by the imide structures.

The imide ring of α-2-carboxyethyl-α-phenylglutarimide (IV) was opened by alkali, to give γ-carbamoyl-γ-phenylpimelic acid (VI), m. p. 177—178°, which at 179° was converted back into the cyclic imide. This acid had been prepared previously by Rubin and Wishinsky,[3] who reported m. p. 182—183°. Treatment of the monoamide-dicarboxylic acid (VI) with concentrated hydrochloric acid also regenerates α-2-carboxyethyl-α-phenylglutarimide (IV), showing that a diamide is not an essential precursor to imide formation, as Mariella, Clutter, and Ebner suggested it was.[5] The location of the carbamoyl group at the γ-carbon atom was demonstrated by partial degradation and synthesis.

The action of bromine in the presence of sodium methoxide on γ-carbamoyl-γ-phenylpimelic acid (VI) gave the methyl carbamate (IX), acid hydrolysis of which gave γ-2-carboxyethyl-γ-phenylbutyrolactone (X). The lactone ring of this compound was opened with alkali to give the hydroxy-acid, which was stable to alkaline permanganate, confirming the tertiary nature of the hydroxyl group. The identity of the lactone (X) was confirmed by its synthesis from phenylmagnesium bromide and diethyl γ-oxopimelate (XI). Prolonged hydrolysis of the methyl carbamate (IX) with alkali followed by acidification gave γ-2-carboxyethyl-γ-phenyl-γ-butyrolactam (XII), which was stable to acid hydrolysis, proving that acid hydrolysis of the methyl carbamate does not proceed through the lactam. Nitrous acid converted the lactam into the lactone (X).

During the alkaline hydrolysis of γ-cyano-γ-phenylpimelodinitrile under Hey and

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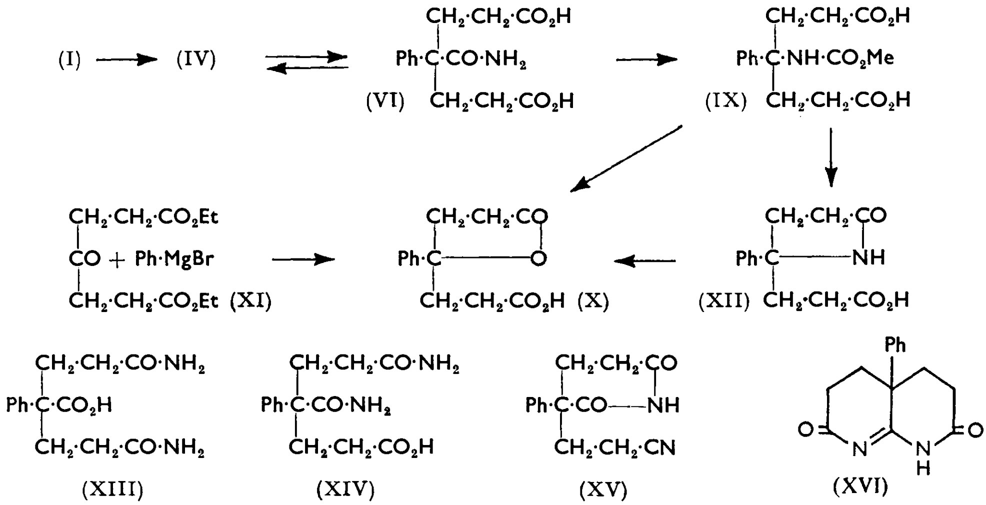
[3] Rubin and Wishinsky, *J. Amer. Chem. Soc.*, 1946, **68**, 828.

[4] Horning and Shock, *ibid.*, 1948, **70**, 2945.

[5] Mariella, Clutter, and Ebner, *J. Org. Chem.*, 1955, **20**, 1702.

Nagdy's conditions, it was observed that evolution of ammonia was practically complete within 30 minutes, and that if the reaction was arrested at this stage, the product was a diamide-monocarboxylic acid, for which two structures, (XIII) and (XIV), are possible. The same diamide-monocarboxylic acid was also isolated after 7 hours' alkaline hydrolysis when the cold reaction mixture was made just acid. The precipitated diamide-monocarboxylic acid dissolved in excess of acid, and subsequent evaporation left α-2-carboxyethyl-α-phenylglutarimide (IV). Attempts to effect alkaline hydrolysis under milder conditions gave only mixtures. The diamide-monocarboxylic acid loses two molecular proportions of water on melting. Loss of the first molecule of water must give a glutarimide structure, but loss of the second molecule of water can give either the nitrile-imide (XV), or more probably the 1 : 8-naphthyridine (XVI). The infrared absorption spectrum of the product shows that the nitrile group is absent, but that bands associated with :NH, C=O, and cyclic –C=N– are present. The naphthyridine structure is therefore preferred. The sequence of reactions used to establish the structure of the monoamide-dicarboxylic acid was also applied to the diamide-monocarboxylic acid, but the Hofmann degradation gave an oil, which solidified but resisted purification.



EXPERIMENTAL

Hydrolysis of γ-Cyano-γ-phenylpimelodinitrile by Hey and Nagdy's Method.—A mixture of γ-cyano-γ-phenylpimelodinitrile (6 g.), potassium hydroxide (6 g.), ethanol (15 c.c.), and water (15 c.c.) was boiled under reflux for 7 hr. Ammonia was rapidly evolved during the first 30 min. After removal of the ethanol by distillation, water (100 c.c.) and concentrated hydrochloric acid (200 c.c.) were added and the solution evaporated almost to dryness. On addition of water (50 c.c.) an oil separated, which solidified. Recrystallisation from water gave α-2-carboxyethyl-α-phenylglutarimide (4·3 g.), m. p. 168—169°. Titration with alkali gave an equivalent of 264. α-2-Carboxyethyl-α-phenylglutarimide requires an equivalent of 261.

Hydrolysis of γ-Cyano-γ-phenylpimelodinitrile by Campbell's Method.—When a mixture of γ-cyano-γ-phenylpimelodinitrile (9 g.), concentrated sulphuric acid (30 c.c.), and water (30 c.c.) was boiled under reflux for 6 hr., the solution became very dark and a black viscous oil separated when the mixture was added to crushed ice. No pure product could be isolated. When a similar mixture was heated on a steam-bath for 6 hr., and then added to crushed ice, a colourless crystalline product was obtained. Recrystallisation from water gave γ-2-carboxyethyl-α-phenylglutarimide (8·4 g.), m. p. 167—169°. Titration with alkali gave an equivalent of 258. A mixed m. p. with the product obtained by Hey and Nagdy's method showed no depression.

γ-Carbamoyl-γ-phenylpimelic Acid.—α-2-Carboxyethyl-α-phenylglutarimide (12 g.) was dissolved in an excess of 2N-aqueous sodium hydroxide, warmed slightly, and left for several days. Acidification deposited a crystalline solid which was filtered off, washed with cold water, and dried, to give γ-carbamoyl-γ-phenylpimelic acid (11·2 g.), m. p. 171—173°. Several recrystallisations from water gave needles, m. p. 177—178°, decomp. 179° (Found: C, 60·2; H, 6·45; N, 4·6. Calc. for $C_{14}H_{17}O_5N$: C, 60·2; H, 6·1; N, 5·0%). Titration with alkali gave an equivalent of 136; γ-carbamoyl-γ-phenylpimelic acid requires an equivalent of 139. Rubin and Wishinsky [3] reported m. p. 182—183° for this compound. A portion of the monoamide-dicarboxylic acid (0·52 g.) was melted in a test-tube, and kept molten until decomposition was complete. Water condensed in the upper part of the tube. The product was dissolved in boiling water and, on cooling, crystals separated. These were filtered off and recrystallised from water to give α-2-carboxyethyl-α-phenylglutarimide (0·32 g.), m. p. 165—168°. A mixed m. p. with an authentic sample of the imide showed no depression. A second portion of the monoamide-dicarboxylic acid (1 g.) was boiled under reflux for 3 hr. with concentrated hydrochloric acid (10 c.c.). After 1 hr., crystals began to separate. The mixture was cooled and diluted a little, and the product was filtered off and dried at 100°. α-2-Carboxyethyl-α-phenylglutarimide (0·8 g.), m. p. 168—170°, was obtained. A mixed m. p. with the starting material was depressed. A mixed m. p. with an authentic sample of the imide was undepressed.

Degradation of γ-Carbamoyl-γ-phenylpimelic Acid (cf. Wallis and Lane [6]).—The monoamide dicarboxylic acid (5 g.) was dissolved in a solution of sodium (1·7 g.) in anhydrous methanol (50 c.c.), and the whole cooled in ice. Bromine (3 g.) was slowly added with stirring, after which the mixture was heated on the steam-bath for 15 min. When cold, acetic acid was added until the mixture was just acid. Most of the methanol was distilled off, and water (30 c.c.) was added, followed by concentrated hydrochloric acid until precipitation was complete. *γ-Methoxycarbonylamino-γ-phenylpimelic acid* (4·5 g.) separated from water in needles, m. p. 192—193° (Found: C, 58·1; H, 6·15; N, 4·7%; equiv., 154. $C_{15}H_{19}O_6N$ requires C, 58·2; H, 6·15; N, 4·5; equiv., 154·5).

Hydrolysis of the methyl carbamate (5 g.) under reflux for 18 hr. with potassium hydroxide (4 g.) in water (30 c.c.) gave, on neutralisation to Congo-red and cooling to 0°, *γ-2-carboxyethyl-γ-phenyl-γ-butyrolactam* (2 g.), which crystallised from water in plates, m. p. 169—171° (Found: C, 67·15; H, 6·6; N, 6·4%; equiv., 233. $C_{13}H_{15}O_3N$ requires C, 66·95; H, 6·4; N, 6·0%; equiv., 233).

After a similar hydrolysis of the methyl carbamate (4 g.), the mixture was cooled to 0°, then acidified to Congo-red, and a solution of sodium nitrite (2 g.) in concentrated hydrochloric acid (3 c.c.) and water (10 c.c.), cooled to 0°, was immediately added. The blue colour of the nitrous acid disappeared. The solution was left at room temperature overnight, then warmed and then cooled; crystals of *γ-2-carboxyethyl-γ-phenyl-γ-butyrolactone* (*ca.* 1 g.) separated. Recrystallisation from water gave plates, m. p. 118—119° (Found: C, 66·3; H, 6·0%; equiv., 235. $C_{13}H_{14}O_4$ requires C, 66·6; H, 6·0%; equiv., 234).

Hydrolysis of the methyl carbamate (1 g.) by boiling concentrated hydrochloric acid (5 c.c.) and water (5 c.c.) for 2 hr. gave, after dilution, an oil which solidified. Recrystallisation from water gave γ-2-carboxyethyl-γ-phenyl-γ-butyrolactone (0·7 g.) in plates, m. p. 118—119°. A mixed m. p. with the previous specimen was undepressed.

γ-2-Carboxyethyl-γ-phenyl-γ-butyrolactam was recovered practically unchanged after 16 hours' refluxing with concentrated hydrochloric acid. The m. p. had dropped to 164—166°, but a mixed m. p. with the starting material was 170—171°.

The lactone-acid (1 g.) was heated on the steam-bath with potassium hydroxide (1·3 g.) in water (20 c.c.) for 16 hr., by which time it was assumed that hydrolysis would be practically complete. After cooling, the silica was precipitated with carbon dioxide and filtered off. Water (20 c.c.) and potassium permanganate (2·2 g.) were added, and the mixture was heated on the steam-bath until the colour was discharged. The precipitated manganese dioxide was filtered off and washed with water. The combined filtrate and washings were acidified with concentrated hydrochloric acid. Unchanged γ-2-carboxyethyl-γ-phenylbutyrolactone (0·5 g.) separated, having m. p. and mixed m. p. 117—118°.

Synthesis of γ-2-Carboxyethyl-γ-phenyl-γ-butyrolactone.—Hydrogen chloride was bubbled into a solution of furfurylacrylic acid (23 g.), prepared by Johnson's method,[7] in a mixture of ethanol (77 c.c.) and water (3 c.c.) until it was saturated. After being boiled on the steam-bath for 20 min., the solution was cooled and re-saturated with hydrogen chloride. The solution

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[6] Wallis and Lane, " Organic Reactions," Vol. III, p. 283.

[7] Johnson, *Org. Synth.*, **20**, 55.

was then evaporated on the steam-bath as far as possible, and the residue shaken successively with sodium hydrogen carbonate solution and water, and finally distilled under a vacuum. *Diethyl γ-oxopimelate* (27 g.) (cf. Marckwald [8]) was collected in the fraction, b. p. 175—185°/17 mm. A small portion was redistilled, and collected at 176—180°/14 mm. (Found: C, 57·5; H, 8·0. $C_{11}H_{18}O_5$ requires C, 57·4; H, 7·8%). A Grignard solution, prepared from bromobenzene (14 g.) and magnesium (2·2 g.) in a mixture of ether (22 c.c.) and benzene (22 c.c.), was added dropwise during 1 hr. to a stirred solution of the crude diethyl γ-oxopimelate (20 g.) in benzene (80 c.c.) cooled in a freezing mixture. After 1 hr. at room temperature the mixture was decomposed with ice and dilute sulphuric acid. The layers were separated. The aqueous layer was washed with benzene, and the washings were added to the organic portion. The solvents were removed by distillation, and the residue was boiled under reflux with 60 c.c. of aqueous-alcoholic (1 : 1) sodium hydroxide solution (containing 10 g.) for 15 hr. Water and benzene were added and the layers separated. The aqueous layer was evaporated to about 100 c.c. Charcoal was added and the solution was boiled, cooled, and filtered. On acidification of the filtrate with concentrated hydrochloric acid, an oil separated which crystallised. It was filtered off and dissolved in boiling benzene, and the solution was boiled with charcoal, filtered hot, and cooled. The product was precipitated with light petroleum (b. p. 60—80°). After two further recrystallisations from water and benzene–light petroleum, γ-2-carboxyethyl-γ-phenylbutyrolactone (3 g.) was obtained, having m. p. 118—119°. A mixed melting point with a specimen of the acid hydrolysis product of the methyl carbamate was 118—120°. The infrared spectra of the two specimens were identical.

Short Alkaline Hydrolysis of γ-Cyano-γ-phenylpimelodinitrile.—A mixture of γ-cyano-γ-phenylpimelodinitrile (6 g.) and potassium hydroxide (4 g.) in ethanol (15 c.c.) and water (15 c.c.) was boiled under reflux for 35 min. The alcohol was removed under reduced pressure, and concentrated hydrochloric acid was added to the residual solution until Congo-red paper was just not turned blue. The crystalline product was collected, washed with cold water, and dried (5·1 g.; m. p. 191—196° with decomp.). After several recrystallisations from water, the diamide-monocarboxylic acid was obtained in needles, m. p. 204—206° (decomp.) [Found, (*a*) after drying *in vacuo* over concentrated sulphuric acid at room temperature: C, 57·7; H, 6·5; N, 9·9. $C_{14}H_{18}O_4N_2,\frac{3}{4}H_2O$ requires C, 57·6; H, 6·7; N, 9·6. (*b*) After drying *in vacuo* over P_2O_5 at 75°; C, 59·5; H, 6·7; N, 10·0. $C_{14}H_{18}O_4N_2,\frac{1}{4}H_2O$ requires C, 59·5; H, 6·55; N, 9·9%]. Difficulty was found in drying specimens for analysis without decomposition. Titration of sample (*b*) with alkali gave an equivalent of 276·5. The diamide-monocarboxylic acid requires an equivalent of 278. When the diamide-monocarboxylic acid was heated at 200° until gas evolution ceased, a loss in weight of 12·4% was recorded. This corresponds very nearly to 2 mols. of water; a little ammonia was also evolved. When cold, the mixture set to a yellow resin, which was dissolved in boiling ethanol. After filtration and cooling, a crystalline product was obtained in 80% yield which crystallised from ethanol-ether in cubes, m. p. 201—203° (Found: C, 69·6; H, 6·15; N, 11·5. $C_{14}H_{14}O_2N_2$ requires C, 69·5; H, 5·8; N, 11·6%). Titration with alkali, which was slow, gave an equivalent of 252. The *naphthyridine* structure, with allowance for opening of the imide ring, requires 242. A solution of the diamide-monocarboxylic acid (5 g.) in 2N-sodium hydroxide (35 c.c.) was slowly added to a stirred solution of bromine (6 g.) in 2N-sodium hydroxide (45 c.c.), cooled in freezing mixture. The temperature was kept below 0°. A gas was slowly evolved and stirring was continued for a further 30 min. The mixture was then heated on the steam-bath for about 30 min., cooled, acidified with concentrated hydrochloric acid, and extracted with ether. The ether was removed and the residue was dissolved in saturated sodium hydrogen carbonate solution. This solution was washed with ether, warmed with charcoal, filtered, acidified with concentrated hydrochloric acid, and extracted with ether. On evaporation of the ether and drying in a desiccator, an oil was left which crystallised and had m. p. 144—146° (γ-carboxy-γ-phenylpimelic acid melts at 154°) (Found: C, 58·0; H, 5·6; equiv., 107. Calc. for $C_{14}H_{16}O_6$: C, 60·0; H, 5·7%; equiv., 93).

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[8] Marckwald, *Ber.*, 1887, **20**, 2811.