[Contribution from the Department of Chemistry, Loyola University]

ORGANIC POLYNITRILES. I. γ,γ-DICYANOPIMELONITRILE AND RELATED COMPOUNDS[1]

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Previous work (1) has shown that certain malononitrile derivatives had a retarding effect upon the growth of cancer when given to animals. Malononitrile itself has been reported effective in prolongation of life in mice infected with poliomyelitis virus (2).

Since malononitrile and its derivatives seem to possess interesting potential pharmacological powers, it was decided to investigate derivatives of malononitrile containing two or more nitrile groups.

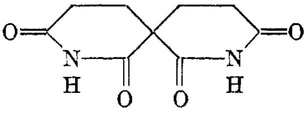
Malononitrile was cyanoethylated to give I, using the technique of Bruson and Reiner (3, 4). It was hoped that by partial hydrolysis preferential action would occur to convert I into a dinitrile diacid, $C_9H_{10}N_2O_4$.

$(NCCH_2CH_2)_2C(CN)_2$ I

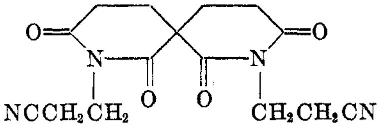
$(NCCH_2CH_2)_2C(CN)(CONH_2)$ II

$(NCCH_2CH_2)_2C(CONH_2)_2$ III

Treatment of I with concentrated hydrochloric acid for 15 minutes did yield a compound whose analysis was as expected, but which did not react with bicarbonate. Since compounds II (4) and III (4) also reacted with concentrated hydrochloric acid to give the same substance, it was assumed to be the spirodiimide (IV). There were indeed two weakly acidic hydrogens in IV and this was shown by further cyanoethylation to give V.



IV



V

The yield of IV from I, II, and III increased as the number of amide groups increased. It is probable that the common intermediate, the tetraamide (VI) is the precursor in the formation of IV in every case. To test this observation, other similar compounds, incapable of tetraamide formation, were prepared. The hydrolysis of compound VII (4) gave only a mono-imide (VIII).

$$(H_2NCOCH_2CH_2)_2C(CONH_2)_2$$

VI

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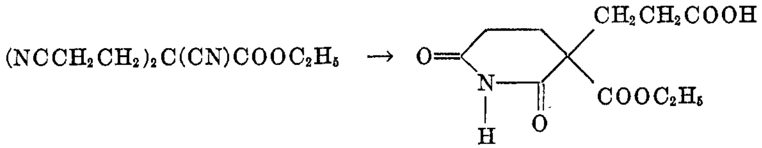
[2] Taken in part from the M.S. thesis of Herman G. Ebner.



VII VIII

Similarly, the hydrolysis of IX gave the diacid diester (X).

$(NCCH_2CH_2)_2C(COOC_2H_5)_2$ IX

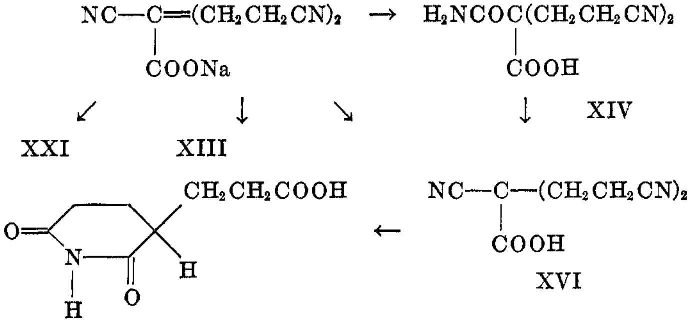
$(HOOCCH_2CH_2)_2C(COOC_2H_5)_2$ X

X was converted into the corresponding diacid chloride (XI) and into the diamide diester (XII), which was undoubtedly the intermediate in the conversion of IX into X. Partial hydrolysis of XII also gave X.

$(ClCOCH_2CH_2)_2C(COOC_2H_5)_2$ XI

$(H_2NCOCH_2CH_2)_2C(COOC_2H_5)_2$ XII

To eliminate any possible nitrile-acid or nitrile-ester interactions in the mechanism of imide formation, hydrolysis reactions on XVI were tried. To obtain XVI, the cyanoethylation of cyanoacetic acid was required. The cyanoethylation of organic acids has not been reported. Satisfactory results were obtained by cyanoethylating the sodium salt of cyanoacetic acid, and the very stable sodium salt (XIII), was obtained.

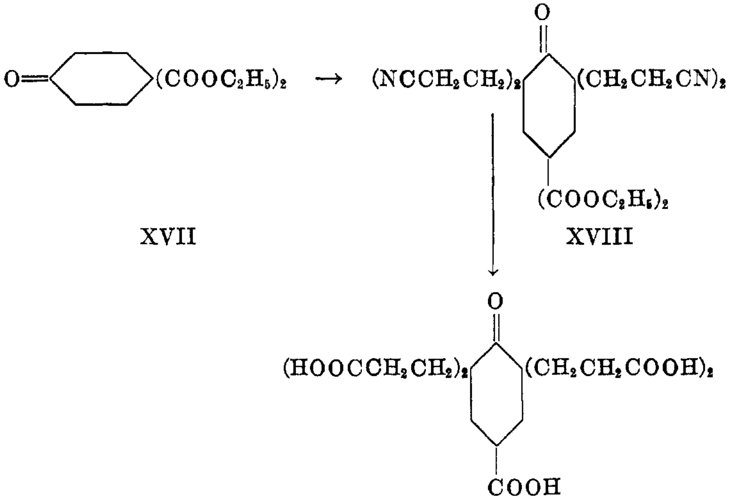


XIII XIV XXI XV XVI

Complete hydrolysis of XIII gave the tricarboxylic acid (XXI) which proved that cyanoethylation was indeed accomplished. Partial hydrolysis of XIII gave the monoimide (XV) proving that a diamide is a necessary precursor for imide formation. In other experiments, it was possible, by gentle hydrolysis of XIII, to get an intermediate compound, presumably XIV. When XIV was heated, dehydration occurred in preference to decarboxylation and the free trinitrile acid, XVI, was obtained. Decarboxylation experiments on XVI were unsuccessful, as the expected trinitrile never was obtained; instead, volatile compounds with a nitrogen base odor, of unknown composition, resulted.

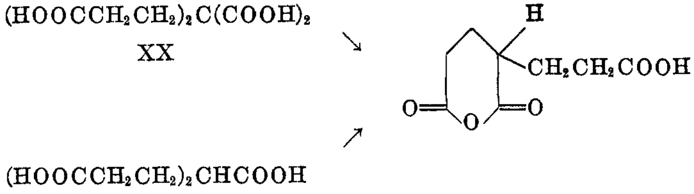
To further prove the structure of X, it was possible to convert X, using BaO or PbO, into the substituted cyclohexanone (XVII).

The cyanoethylation of XVII yielded XVIII. The carbonyl group was very hindered and no simple ketone derivatives could be formed. When refluxing concentrated hydrochloric acid was found not to react with XVIII at a measureable rate, 60% sulfuric acid was resorted to. Under these conditions all four nitrile groups were converted into the corresponding acid groups. In addition, the geminal ester groups were hydrolyzed, and decarboxylation also occurred to give the pentacarboxylic acid (XIX). The complete hydrolysis of I, IV, and X gave either the tetracarboxylic acid (XX) or the tricarboxylic acid (XXI) (5), depending on the method of hydrolysis.



XVII XVIII

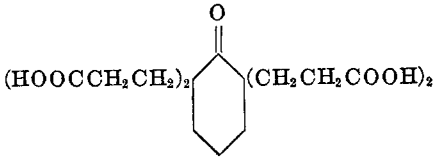
XIX



XX XXI XXII

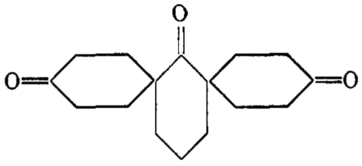
The heating of XX or XXI above the melting point gave the anhydride XXII.

Tetracyanoethyl cyclohexanone (3) was hydrolyzed to the corresponding



XXIII

tetracarboxylic acid (XXIII). Treatment of XXIII with PbO gave the dispirotriketone XXIV. The central ketone group was still quite hindered as only a dioxime could be produced.



XXIV

None of the compounds tested was active against cancer (6).

EXPERIMENTAL (7)

γ,γ-Dicyanopimelonitrile (I). This compound was prepared by the method of Bruson and Reiner (4). From 50 g. of malononitrile in 100 g. of dioxane, using 15 ml. of Triton B, and 80.3 g. of acrylonitrile there were obtained 120 g. (95%) of I; colorless crystals from ethanol, m.p. 92°.

Anal. Calc'd for $C_9H_8N_4$: C, 62.77; H, 4.68.

Found: C, 63.00; H, 4.50.

1,3,7,9-Tetraketo-2,8-diazaspiro[5·5]hendecane (IV). Compound I (10 g.) was refluxed with 20 ml. of concentrated hydrochloric acid. After ten minutes, crystals began to form, and after 15 minutes the mixture became almost solid. After cooling, the mixture was filtered, and the white solid was recrystallized from water; 2.8 g. (23%), m.p. 283°.

Anal. Calc'd for $C_9H_{10}N_2O_4$: N, 13.33. Found: N, 13.30.

Compound IV was also prepared in the same manner in a 43% yield from γ-carbamyl-γ-cyanopimelonitrile (II) (4) and in a 48% yield from γ,γ-dicarbamyl-pimelonitrile (III) (4).

1,3,7,9-Tetraketo-2,8-di(β-cyanoethyl)-2,8-diazaspiro[5·5]hendecane (V). Using the method of Galat (8), 21 g. of IV, 140 ml. of acrylonitrile, and 15 ml. of Triton B gave 11 g. (35%) of white crystals (from 1:1 ethanol water) m.p. 122°.

Anal. Calc'd for $C_{15}H_{16}N_4O_4$: N, 17.71. Found: N, 17.60.

γ,γ-Dicarbethoxypimelic acid (X). A solution of 257 g. of IX (4) and 400 ml. of concentrated hydrochloric acid was refluxed. After 20 minutes, crystals began to form, and, after an additional five minutes of refluxing, the mixture was cooled and filtered. The solid was washed carefully with ice-water to remove the ammonium chloride, and the residue was recrystallized from water, 167 g. (57%) m.p. 122°

Anal. Calc'd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.63; Neut. equiv., 152.

Found: C, 51.25; H, 6.73; Neut. equiv., 151.

When 0.5 g. of XII and 1 ml. of concentrated hydrochloric acid were refluxed for ten minutes, 0.3 g. of X was formed.

γ,γ-Dicarbethoxypimelamide (XII). A solution of 5 g. of X and 5 g. of thionyl chloride was refluxed for 15 minutes. The solution of crude XI then was cooled and was poured gradually into 20 ml. of ice-cold concentrated ammonium hydroxide. The resulting crystals were washed with ice-water. Recrystallization from ethanol gave white crystals, 2.8 g. (56%), m.p. 135.5°.

Anal. Calc'd for $C_{13}H_{22}N_2O_6$: C, 51.64; H, 7.34; N, 9.29.

Found: C, 51.68; H, 7.29; N, 9.11.

α-Carbethoxy-α-(β-carboxyethyl)glutarimide (VIII). A solution of 10 g. of VII (4) and 20 ml. of concentrated hydrochloric acid was refluxed for ten minutes. After cooling, the crystals of ammonium chloride were filtered off, and the resulting clear solution was let stand at 5° for 15 hours. The white crystals which formed were removed by filtration and were recrystallized from water, 4 g. (35%), m.p. 122°.

Anal. Calc'd for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.45; Neut. equiv., 257.

Found: C, 51.55; H, 5.68; N, 5.75; Neut. equiv., 262.

The *p*K of the acid was 4.35.

Sodium γ-cyanopimelonitrile-γ-carboxylate (XIII). To a solution of 127.5 g. of cyanoacetic acid (1.5 moles) in 60 ml. of water was added 60 g. of sodium hydroxide (1.5 moles) and 2 g. of excess base slowly and with cooling. To the resultant solution, 200 ml. (3 moles) of acrylonitrile was added dropwise over a period of one hour. Vigorous stirring and good cooling was required to maintain the reaction temperature at less than 35°. A golden color developed in the course of the reaction. After the addition was completed, stirring was continued for two hours and the reaction mixture was allowed to stand overnight. Crystals appeared and were removed by filtration to give 207 g. of material. The filtrate was evaporated to dryness under a vacuum and 102 g. of additional solid was obtained. The white crystals slowly decomposed upon heating and upon standing for several days at room temperature began to turn brown. The compound was insoluble in organic solvents. Ignition left a basic ash. The total yield was 309 g. (96%) of the sodium salt of the cyanoethylation adduct of sodium cyanoacetate.

γ-Carbamyl-γ-carboxypimelonitrile (XIV). To a solution of 10 g. of XIII in 10 ml. of water was added 10 ml. of a concentrated solution of hydrochloric acid. The temperature was maintained below 20°. A precipitate was obtained which amounted to 5.3 g. This compound was recrystallized from acetone-petroleum ether, to give white crystals, m.p. 167°. The crystals liberated carbon dioxide from a solution of sodium bicarbonate but could not be titrated. Ignition left a basic residue. It was probably the sodium salt of γ-carbamyl-γ-carboxypimelonitrile. A solution of 5 g. of this compound in 15 ml. of water was further acidified with 10 ml. of concentrated hydrochloric acid and was extracted with three 50-ml. portions of diethyl ether. The ethereal solution was concentrated to 30 ml. on a steam-bath and 50 ml. of petroleum ether was added. An oil separated which crystallized upon scratching with a glass rod. The white needle-like crystals amounted to 3.4 g. and were recrystallized from ether-petroleum ether, m.p. 49–50°.

Anal. Calc'd for $C_9H_{11}N_3O_3$: C, 51.68; H, 5.30; N, 20.10.

Found: C, 51.51; H, 5.57; N, 20.01.

γ-Cyanopimelonitrile-γ-carboxylate (XVI). In an attempt to decarboxylate XIV, 2 g. of XIV was placed in a sublimation apparatus and distilled at 200–250° at a pressure of 10 mm. The oil obtained was trapped by placing an indentation in the tube at the point at which condensation took place. The oil was crystallized from 95% ethanol and 0.9 g. of a white crystalline solid was obtained, m.p. 134–135° (45% yield).

Anal. Calc'd for $C_9H_9N_3O_2$: C, 56.55; H, 4.75; N, 21.98.

Found: C, 56.87; H, 4.67; N, 21.27.

Three further distillations increased the nitrogen content to 23%, indicating decarboxylation at a very slow rate.

β-(α-Glutarimide)propionic acid (XV). A mixture of 10 g. of XIII and 30 ml. of concentrated hydrochloric acid was heated under reflux for one hour. A large volume of carbon dioxide was evolved at the initiation of heating and this evolution slowly diminished in amount until the hydrolysis was stopped. When the solution was cooled, 5.3 g. of a white solid precipitated out and was filtered. The precipitate was mostly inorganic salts. The filtrate was taken to dryness and the white residue was recrystallized from water to give white needles, 5.5 g., m.p. 125°.

Anal. Calc'd for $C_8H_{11}NO_4$: C, 51.91; H, 5.94; N, 7.56.

Found: C, 51.38; H, 5.96; N, 7.86.

γ-Carboxypimelic acid (XXI). A solution of 10 g. of XIII and 100 ml. of 6 *N* hydrochloric acid solution was heated under reflux for one hour. Upon cooling, approximately 3 g. of sodium chloride and ammonium chloride crystallized out and was separated. The solution was evaporated to dryness under a vacuum and the white solid residue was recrystallized from ether-petroleum ether, m.p. 117°, 7.4 g. This material did not depress the m.p. of a sample prepared from I.

4,4-Dicarbethoxycyclohexanone (XVII). A mixture of 30.4 g. of X and 4.5 g. of lead oxide was ground together and then was heated gently and then more vigorously until all the lead oxide had dissolved, leaving a clear orange solution. The solution then was vacuum-distilled as water and carbon dioxide were evolved. A liquid was collected, boiling in the range of 100–170° at 5 mm. This was fractionally distilled and a colorless liquid, b.p. 175° at 0.5 mm. was obtained; 4.7 g. (20%); n_D^{25}, 1.4549; d_4^{25} 1.1213.

Anal. Calc'd for $C_{12}H_{18}O_5$; C, 59.47; H, 7.49; M_R, 58.73.

Found: C, 59.16; H, 7.71; M_R, 58.82.

The *semicarbazone* melted at 178°.

Anal. Calc'd for $C_{13}H_{21}N_3O_5$: N, 14.04. Found: N, 13.88.

2,2,6,6-Tetra(β-cyanoethyl)-4,4-dicarbethoxycyclohexanone (XVIII). By the method of Bruson and Reiner (3), 19.2 g. of XVII, 15 ml. of dioxane, 8 ml. of Triton B, and 17 g. of acrylonitrile gave a solid which was recrystallized from ethylene glycol monomethyl ether; 4.85 g. (19%), m.p. 205°.

Anal. Calc'd for $C_{24}H_{30}N_4O_5$: N, 12.33. Found: N, 12.13.

It was not possible to prepare any simple ketone derivative.

2,2,6,6-Tetra(β-carboxyethyl)-4-carboxycyclohexanone (XIX). A solution of 5 g. of XVIII in 50 ml. of 50% sulfuric acid was refluxed for 15 minutes. After diluting with 20 ml. of water and cooling the solution to 5°, white crystals formed. After filtration and recrystallization from water, white crystals were obtained; 4.7 g. (99%), m.p. 244°.

Anal. Calc'd for $C_{19}H_{26}O_{11}$: C, 53.02; H, 6.09.

Found: C, 52.72; H, 6.27.

γ,γ-Dicarboxypimelic acid (XX). (*A*). *From* X. A solution of 4 g. of X in 10% sodium hydroxide was refluxed for three hours, then acidified, and evaporated to dryness. The residue was extracted with ether in a Soxhlet to give 2 g. of XX, m.p. 187°.

(*B*). *From* IV. Five g. of IV was treated as in method *A* to give 2.5 g. of XX, m.p. 185°.

γ-Carboxypimelic acid (XXI). (*A*). *From* I. A solution of 10 g. of I in 60 ml. of 1:1 hydrochloric acid was refluxed. The solution was evaporated to dryness, and the solid was extracted with ether in a Soxhlet apparatus to give 3 g. of XXI, m.p. 117°.

α-(β-Carboxyethyl)glutaric anhydride (XXII). (*A*). Compound XX (0.5 g.) was sublimed in a vacuum to give 0.3 g. of XXII, m.p. 103° (9).

Anal. Calc'd for $C_8H_{10}O_5$: C, 51.62; H, 5.38.

Found: C, 51.25; H, 5.74.

(*B*). Compound XXI (0.80 g.) was sublimed in a vacuum to give 0.65 g. of XXII, m.p. 103°.

2,2,6,6-Tetra-(β-carboxyethyl)cyclohexanone (XXIII). A solution of 100 g. of tetracyanoethyl cyclohexanone (3) in 300 ml. of concentrated hydrochloric acid was refluxed for one hour. After cooling, the precipitate was filtered, washed with ice-water, and the solid was recrystallized from water to give 110 g. (89%), m.p. 180° (10).

3,13,16-Triketo-dispiro[5·3·5·1]hexadecane (XXIV). A mixture of 38.6 g. of XXIII and 4.5 g. of lead oxide was ground together and treated in the manner as described in the formation of XVII. A liquid slowly distilled over from the reaction flask, and eventually solidified. Recrystallization from ethanol gave 0.51 g. (2%), m.p. 167°.

Anal. Calc'd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45.

Found: C, 73.19; H, 8.17.

The dioxime melted at 235°.

Anal. Calc'd for $C_{16}H_{24}N_2O_3$: N, 9.58. Found: N, 9.41.

SUMMARY

The cyanoethyl derivatives of malononitrile, cyanoacetamide, and malonamide all produced the spiro-diimide, IV, by acid hydrolysis. Synthetic evidence is

given to prove that a diamide is a necessary precursor to imide formation. The first example of cyanoethylation of a sodium salt is reported.

Chicago 26, Illinois

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(6) Bio-tests were performed at the Midwest Research Institute.

(7) Microanalyses by Micro-Tech Labs., Skokie, Illinois.

(8) Galat, *J. Am. Chem. Soc.*, **67**, 1415 (1945).

(9) We are indebted to Miss Miriam Gruber for the preparation of this compound.

(10) Bruson and Reiner (Ref. 3) used alkaline hydrolysis for five hours and got a 75% yield of product, m.p. 180°.