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CYCLIZATION OF THE REACTION PRODUCTS OF *p*-PHENYLENEDIAMINE WITH MALEIC ACID

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Treatment of p-phenylenediamine with maleic acid and its diethyl ester gave di- and tetracarboxylic amino acids and their esters. A benzene derivative having an α-alanine and an aspartic acid residue has been prepared. The cyclization of aminocarboxylic acids to imidazole and pyrimidine derivatives has been carried out.

Keywords: acrylic acid, hydropyrimidinedione, carboxymethylimidazolidinedione, carboxymethyl-imidazolidinethione, maleic acid, *p*-phenylenediamine.

N-Substituted amino acids are convenient compounds for the preparation of heterocyclic systems. The action of urea, cyanates, or thiocyanates on N-aryl-α-alanine gives substituted hydropyrimidinediones or their thio analogs [1] but N-arylaspartic acids give imidazolidinedione derivatives under these conditions [2].

In this work we have carried out the reaction of *p*-phenylenediamine with maleic acid and its ester and studied the cyclization reactions of the aminocarboxylic acids obtained with urea and potassium thiocyanate. Depending on reaction time, heating *p*-phenylenediamine with diethyl maleate gives the products of mono- or diaddition. The sole product obtained in modest yield (33%) after heating for 6 h was diethyl N-(4-aminophenyl)aspartate (**2**), but after 16 h the tetraethyl ester **3** could also be obtained *via* column chromatography along with compound **2**. The ^{1}H NMR spectra of compounds **2** and **3** show singlets at 1.07 and 2.7 ppm corresponding to the methyl and methylene fragments of the ester groups. The overlapping signals for the aliphatic $CHCH_2$ part of the aspartic acids were observed at 3.9-4.3 ppm.

Basic hydrolysis of the esters **2** and **3** and subsequent acidification of the hydrolysate with acetic acid gave the di- (**4**) and tetracarboxylic (**5**) acids.

The N-(4-aminophenyl)aspartic acid (**4**) was also prepared by the reduction of N-(4-nitrophenyl)aspartic acid which was synthesized by treating *p*-nitroaniline with maleic acid and by a direct synthesis from *p*-phenylenediamine and maleic acid. The patent [3] reports that *p*-phenylenediamine forms the corresponding amide with maleic acid and undergoes hydrolysis to give the acid **4**. When the amine **1** was heated with maleic acid in water for 6 h we were unable to observe formation of the amide but the acid **4** was separated from the reaction mixture upon cooling.

N-[4-(2-Carboxyethylamino)phenyl]aspartic acid (**6**) was synthesized from the amino acid **4** by heating with acrylic acid in dilute acetic acid. The ^{1}H NMR spectrum of the tricarboxylic acid **6**, when compared with the spectrum of compound **4**, shows additional signals for the methylene groups of the aliphatic part of

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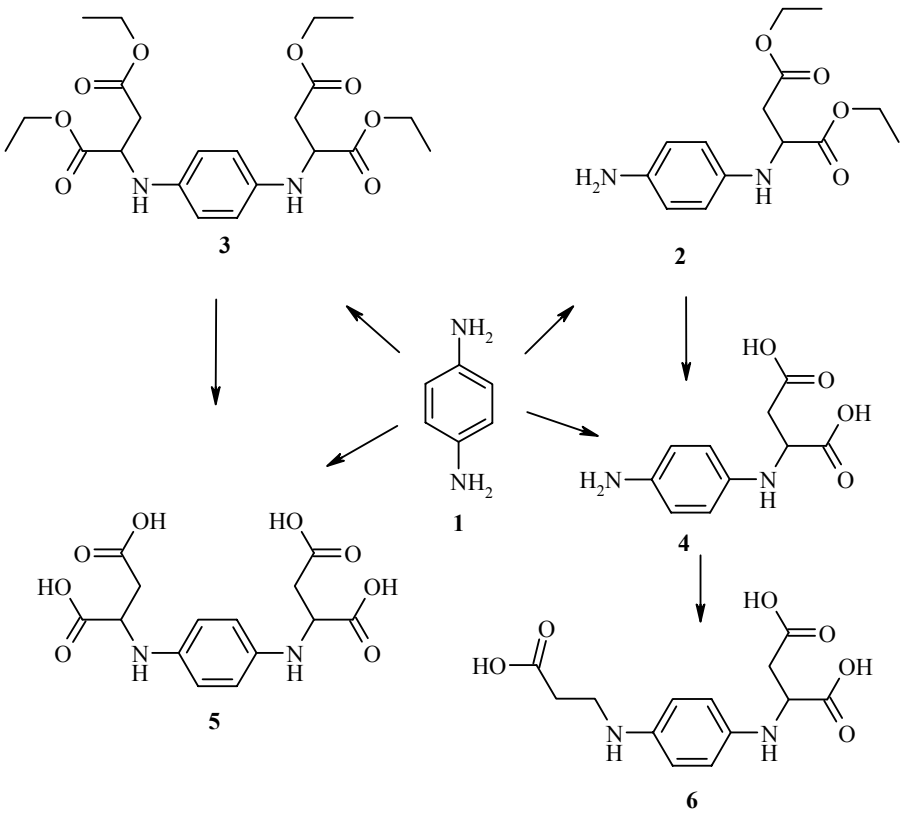
α-alanine. Heating of the tricarboxylic acid **6** with urea in acetic acid and subsequent addition of HCl gives the 1,4-bis[2,4-(1H,3H))-dioxohexahydropyrimidin-1-yl]benzene (**7**), i.e. the α-alanine and the aspartic acid residues form the same heterocyclic system. This is explained by the fact that N-substituted β-alanine with urea in acid medium forms N-carbamoyl β-alanine which is cyclized to the dihydropyrimidinedione. Under the same conditions, N-substituted aspartic acid forms a ureidosuccinic acid derivative [4] which cyclises to the corresponding 5-carboxymethylhydantoin derivative or an orotic acid derivative which undergoes decarboxylation in these conditions to give the dihydropyrimidinedione.

Scheme 1

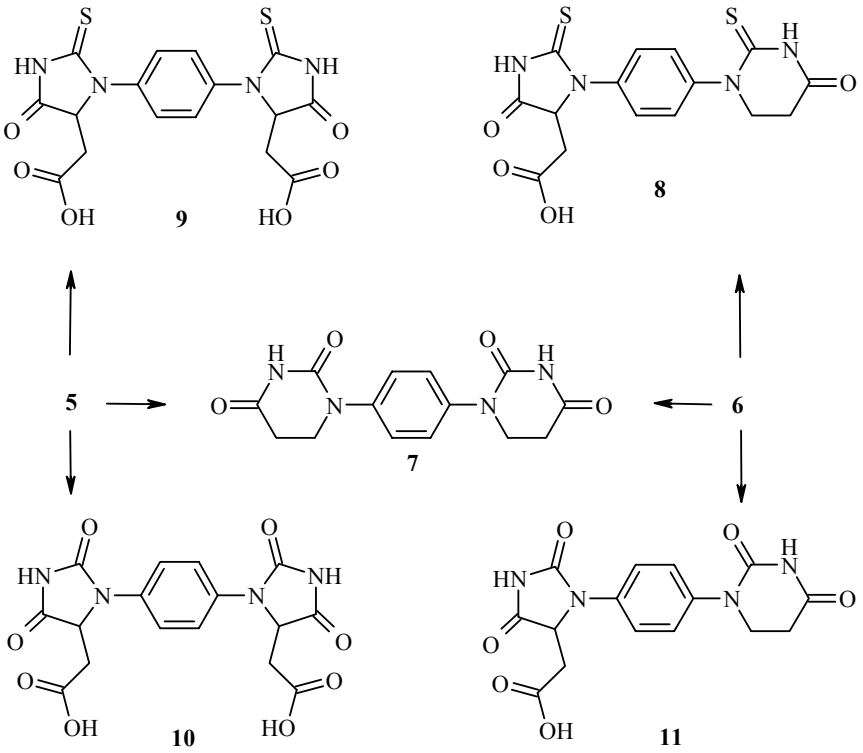


Compound **7** was also obtained along with compound **10** from the aspartic acid dimer **5** by heating the latter with urea. The bisdihydrouracil derivative is difficultly soluble whereas the 1,4-bis(2,4-dioxo-5-carboxymethylimidazolidin-1-yl)benzene (**10**) is soluble in water.

Heating the tricarboxylic acid **6** with potassium thiocyanate in acetic acid and subsequent addition of hydrochloric acid gave compound **8** which has thiohydantoin and thiodihydrouracil residues in its structure. Under analogous conditions, the tetracarboxylic acid **5** and thiocyanate give the derivative **9** which has two carboxymethylthiohydantoin substituents (Scheme 2).

The ^{1}H NMR spectrum of compound **7** shows triplets at 2.7 and 3.6 ppm characteristic of dihydropyrimidinediones, corresponding to the two methylene groups. The spectra of the imidazole derivatives **9** and **10** show multiplets for the methylene groups at 3.1-3.6 and triplets for the methine groups near 5 ppm.

Scheme 2



EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker AW-80 (80 MHz) and JEOL FX-100 (100 MHz) instruments with HMDS as internal standard. Monitoring of the reaction course and the purity of the compounds obtained was carried out by TLC on Silufol 254 and Silufol UV-254 plates.

Diethyl N-(4-Aminophenyl)aspartate (2) and Diethyl N-[4-(1,2-Bisethoxycarbonylethylamino)-phenyl]aspartate (3). A mixture of amine **1** (10.8 g, 100 mmol), diethyl maleate (34.4 g, 200 mmol), and acetic acid (50 ml) was refluxed for 16 h. The liquid fractions were distilled in vacuo to give an oily mass (21.2 g). Passage of 1 g of this mass through a 100/250 grade silica gel column, eluting with acetone and hexane (1:1), gave fractions with R_f 0.64 and 0.47. The solvent was distilled off and the fraction with R_f 0.64 was crystallized from hexane to give the diethyl ester **2** (0.4 g, 30%); mp 47-48°C. Found, %: C 59.62; H 7.20; N 9.83. $C_{14}H_{20}N_2O_4$. Calculated, %: C 60.01; H 7.14; N 10.00.

The fraction with R_f 0.47 gave 0.4 g (20%) of the tetraethyl ester **3** as a viscous oil. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 1.04 (6H, t, J = 7, $2CH_3$); 1.06 (6H, t, J = 7, $2CH_3$); 2.73 (4H, d, J = 4.2, $2CH\underline{CH_2}$); 3.7-4.2 (10H, m, 2CH, $4CH_2$); 6.3 (4H, s, ArH). Found, %: C 58.51; H 7.32; N 6.39. $C_{22}H_{32}N_2O_8$. Calculated, %: C 58.40; H 7.07; N 6.19.

N-(4-Aminophenyl)aspartic Acid (4). A. A mixture of *p*-phenylenediamine (10.8 g, 100 mmol), maleic acid (5.8 g, 50 mmol), and water (200 ml) was refluxed for 20 h, NaOH (45%, 50 ml) was added, and the heating was continued for a further 6 h. The cooled reaction mixture was neutralized with acetic acid to pH 6. The crystals formed were filtered off and washed with water, alcohol, and ether. Yield of 17.66 g (79%); mp 230-231.5°C.

B. A mixture of ester **2** (28.0 g, 100 mmol), water (100 ml), ethanol (20 ml), and NaOH (25 g, 625 mmol) was refluxed for 2 h. After cooling, the reaction mixture was treated with acetic acid to pH 6 and the precipitated compound was filtered, washed with water, alcohol, and ether to give a yield of 20.16 g (90%).

C. N-(4-Nitrophenyl)aspartic acid (25.4 g, 100 mmol) was dissolved in 10% ammonia (180 ml) and $Na_2S_2O_4$ was added to the disappearance of the yellow color in the solution. The reaction mixture was then filtered and the filtrate was diluted with water (200 ml) and neutralized with acetic acid to pH 6. The crystals formed were filtered off and washed with water, alcohol and ether to give a yield of 9.5 g (42%).

D. A solution of the amine **1** (5.4 g, 50 mmol) and maleic acid (5.8 g, 50 mmol) in water (100 ml) was refluxed for 6 h. After cooling, the crystals formed were filtered off and washed with water, alcohol, and ether. Yield 10.0 g (89%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.55 (2H, d, *J* = 5, CH_2); 3.9 (1H, t, *J* = 5, CH); 6.4 (4H, dd, *J* = 7.3; *J* = 2, ArH); 6.6-7.2 (2H, br. s, NH_2). Found, %: C 53.18; H 5.62; N 12.44. $C_{10}H_{12}N_2O_4$. Calculated, %: C 53.57; H 5.36; N 12.28. A mixed sample of the substance **4** prepared by the methods A-D did not show a depression of melting point.

N-[4-(1,2-Dicarboxyethyl)amino]phenylaspartic Acid (5). Compound **1** (5.04 g, 50 mmol) and maleic acid (11.6 g, 100 mmol) in water (100 ml) was refluxed for 6 h. The mixture was cooled and the precipitate was filtered off and washed with water and acetone. Yield 5.52 g (53%); mp 203-204°C (ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.54 (4H, d, *J* = 5, $2CH_2$); 3.9 (2H, t, *J* = 5, 2CH); 6.47 (4H, s, ArH); 6.6-7.38 (4H, br. s, 4OH). Found, %: C 49.81; H 4.98; N 8.38. $C_{14}H_{16}N_2O_8$. Calculated, %: C 49.41; H 4.70; N 8.23.

N-[4-(2-Carboxyethyl)amino]phenylaspartic Acid (6). A mixture of the aspartic acid **4** (2.24 g, 10 mmol), acrylic acid (0.75 ml, 11 mmol), and 60% acetic acid (50 ml) was refluxed for 4 h. The liquid fractions were distilled in vacuo and the remaining viscous mass was treated with acetone, whereupon it crystallized. The crystals were filtered off, crystallized from a mixture of acetic acid and acetone (1:5), and washed with alcohol. Yield 2 g (67%); mp 97-98.5°C. ^{1}H NMR spectrum (CF_3COOH), δ, ppm (*J*, Hz); 2.55 (2H, t, *J* = 6, $COCH_2$); 2.87-3.25 (2H, m, CH_2); 3.42-3.85 (2H, m, NCH_2); 4.45-4.75 (1H, m, CH); 6.0-7.75 (4H, ArH). Found, %; C 52.48; H 5.08; N 9.45. $C_{13}H_{16}N_2O_6$. Calculated, %: C 52.70; H 5.40; N 9.46.

1,4-Bis[2,4-(1H,3H)-dioxohexahydropyrimidin-1-yl]benzene (7). A mixture of the tricarboxylic acid **6** (14.8 g, 50 mmol) and urea (12 g, 200 mmol) in acetic acid (100 ml) was refluxed for 8 h, HCl (30 ml) was added, and refluxing was continued for a further 2 h. The reaction mixture was cooled and the crystals were filtered off and washed with refluxing acetic acid and acetone. Yield 6.75 g (45%); mp 320°C. According to the study [5] the mp is 320°C. ^{1}H NMR spectrum (CF_3COOH), δ, ppm (*J*, Hz): 2.7 (4H, t, *J* = 5, $COCH_2$); 3.67 (4H, t, *J* = 5, NCH_2); 7.07 (4H, s, ArH). Found, %: C 55.36; H 4.82; N 18.58. $C_{14}H_{14}N_4O_4$. Calculated, %: C 55.63; H 4.63; N 18.54.

1-[4-(Hexahydro-4-oxo-2-thioxopyrimidin-1-yl)phenyl]-4-oxo-2-thioxo-5-imidazolidineacetic Acid (8). A mixture of the acid **6** (19.8 g, 50 mmol), acetic acid (70 ml), and potassium thiocyanate (20 g, 200 mmol) was refluxed for 10 h, conc. HCl (15 ml) was added, and the refluxing was continued for a further 2 h. The reaction mixture was cooled, diluted with water (200 ml), and the crystals formed were filtered off. Yield 12.5 g (66%); mp 210-211°C (ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.55 (2H, d, *J* = 4, $CH\underline{CH_2}$); 2.8 (2H, t, *J* = 5, $COCH_2$); 3.93 (2H, t, *J* = 5, NCH_2); 5.02 (1H, t, *J* = 4, CH); 7.47 (4H, s, ArH); 11.23 (1H, s, NH); 12.1-12.5 (1H, br. s, NH). Found, %: C 47.92; H 4.07; N 14.71. $C_{15}H_{14}N_4O_4S_2$. Calculated, %: C 47.62; H 3.70; N 14.81.

1-[-4-(5-Carboxymethyl)-4-oxo-2-thioxoimidazolidin-1-yl]phenyl-4-oxo-2-thioxo-5-imidazolidine-acetic Acid (9). A mixture of the acid **5** (6.8 g, 20 mmol), potassium thiocyanate (3.84 g, 60 mmol) and 70% acetic acid (70 ml) was refluxed for 8 h, hydrochloric acid (20 ml) was added, and heating was continued for a further 2 h. The reaction mixture was cooled, neutralized with sodium carbonate, and the crystals formed were filtered off and washed with water and acetone. Yield 5.1 g (60%); mp 221-222.5°C (ethanol–water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.21 (4H, d, *J* = 5, $2CH_2$); 4.92 (2H, t, *J* = 5, 2CH); 6.91 (4H, s, ArH); 9.81 (2H, s, 2NH). Found, %: C 45.72; H 3.41; N 13.49. $C_{16}H_{14}N_4O_6S_2$. Calculated, %: C 47.62; H 3.70; N 14.81.

1,4-Bis[2,4-(1H,3H)-dioxohexahydropyrimidin-1-yl]benzene (7) and 1,4-Bis(5-carboxymethyl-2,4-dioxoimidazolidin-1-yl)benzene (10). A mixture of the acid **5**, (3.4 g, 10 mmol), urea (5 g, 88 mmol), and acetic acid (50 ml) was refluxed for 16 h. HCl (15 ml) was added to the reaction mixture and refluxing was continued for a further 30 min. The mixture was cooled and poured into water (200 ml). The precipitated crystalline compound **7** was filtered off. Yield 1.55 g (45%); mp 320°C. A mixed sample of compound **7** with that prepared from the tricarboxylic acid **6** did not give a depression of melting point. The filtrate obtained after the removal of compound **7** was evaporated in vacuo and the residue was refluxed in acetone, filtered, and the acetone evaporated to give the acid **10** (0.92 g, 27%); mp 254-255.5°C (water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.67 (4H, d, *J* = 5, $2CH_2$); 4.21 (2H, d, *J* = 5, 2CH); 6.9 (4H, s, ArH); 11.3 (2H, s, NH). Found, %: C 50.04; H 3.71; N 14.53. $C_{16}H_{14}N_4O_8$. Calculated, %: C 49.23; H 3.59; N 14.36.

1-[4-(5-Carboxymethyl-2,4-dioxoimidazolidin-1-yl)phenyl]dihydropyrimidin-2,4-(1H,3H)-dione (11). A mixture of the tricarboxylic acid **6** (5.92 g, 20 mmol), sodium isocyanate (5.2 g, 80 mmol), and acetic acid (40 ml) was refluxed for 4 h. The reaction mixture was cooled and poured into acetone (200 ml). The precipitated NaCl was separated and the filtrate was evaporated to dryness in vacuo. The oily mass was treated with water (20 ml) and allowed to stand for 20 h at 6°C. The crystals formed were filtered off. Yield 4.4 g (64%); mp 291-292.5°C (ethanol–water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.51 (2H, d, *J* = 5, $CH\underline{CH_2}$); 2.82 (2H, t, *J* = 7, $COCH_2$); 3.94 (2H, t, *J* = 7, NCH_2); 5.13 (1H, t, *J* = 5, CH); 7.43 (1H, s, NH); 7.48 (4H, s, ArH); 11.5 (1H, br. s, NH). Found, %: C 55.62; H 4.42. $C_{15}H_{14}N_4O_6$. Calculated, %: C 52.02; H 4.05.

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