Heterocyclic Studies: New Heterocyclic Ring Systems from Isomeric Dimethyl Diaminophthalates

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The synthesis and reactions of dimethyl 3,4- and 4,5-diaminophthalate **7** and **9** were investigated. The condensation of these isomeric diaminophthalates and their respective nitroacetamido precursors have been shown to give rise to a variety of five, six and seven membered heterocyclic ring systems. Several new tetraazanthracenes have also been prepared in this sequence.

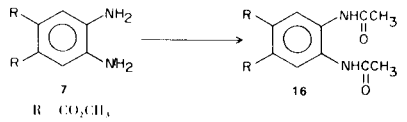
As part of our continuing search for new, polyfunctional aromatic and heteroaromatic systems we have undertaken the synthesis and characterization of the isomeric dimethyl 3,4- and 4,5-diaminophthalates **7** and **9**. These two systems are of particular interest with regard to their potential in the synthesis of thermally stable polymers. The synthesis of these two isomers is summarized in the next paragraph.

Dimethyl 4-nitrophthalate (**1**) was reduced to the corresponding amine **2**, and subsequently converted to the acetamido derivative, **3**, in an overall yield of 56 percent (2,3). Nitration of the amide **3** resulted in a mixture of dimethyl 4-acetamido-5-nitrophthalate (**4**) and dimethyl 4-acetamido-3-nitrophthalate (**5**) which were separated by fractional crystallization. Hydrolysis of the isomeric acetamido derivatives **4** and **5** gave the corresponding nitroamines **6** and **8**, respectively, from which the isomeric diaminophthalates **7** and **9** were obtained by catalytic reduction. The angular diamine **9** was also synthesized by an alternate route starting with the dimethyl 3-nitrophthalate **10**, as follows: compound **10** was reduced to **11**, which was acetylated to **12** and then nitrated to **13** and **14**. Isomer **14** was hydrolyzed and then hydrogenated to given diamine **9**.

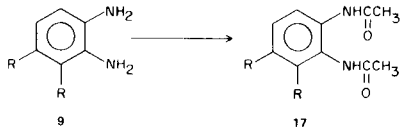
In an effort to fully establish the potential functionality of these new isomeric diaminophthalates, their specific reactivity with regard to cyclization reactions leading to various five, six and seven membered heterocyclic systems, was examined.

Five Membered Ring Systems. Benzimidazoles.

Although the condensation of aryl 1,2-diamines such as *o*-phenylenediamine with acid anhydrides, esters or carboxylic acids usually provides a convenient method for benzimidazole formation (4,5), treatment of both the symmetrical and angular diaminophthalates **7** and **9** with acetic anhydride afforded only the corresponding diacetamido derivatives **16** and **17** respectively. No benzimidazole derivatives were formed under these conditions.



7 R CO_2CH_3 16



9 17

A successful ring closure was achieved, however, by first reducing the 4-acetamido-5-nitro and 4-acetamido-3-nitro systems **4** and **5** to the corresponding aminoacetamido derivatives **20** and **23**. Treatment of **20** with refluxing acetic acid gave the 5,6-dicarbomethoxy-2-methylbenzimidazole acetate (**21**), while conversion to the corresponding tosylate salt **22** could be achieved in molten *p*-toluenesulfonic acid. Each fo these salts could then be converted to the desired benzimidazole free base **18** with aqueous sodium bicarbonate, Scheme I.

A similar cyclization of the 3-amino-4-acetamido isomer **23** was achieved using *p*-toluenesulfonic acid to give the tosylate salt **24**; however, cyclization of **23** in refluxing acetic acid gave the corresponding benzimidazole free base **19** directly. The benzimidazole **19** was also obtained by reducing the dimethyl 3-acetamido-4-nitrophthalate (**14**) to the corresponding 3-acetamido-4-amino species **25** and subsequent cyclization of **25** in acetic acid, Scheme I.

Six and Seven Membered Ring Systems. Condensation Reactions with Diketones.

Aryl *ortho*diamines such as *o*-phenylenediamine reportedly undergo cyclization reactions with a variety of *alpha* (6) and *beta* diketones (7) to give six and seven membered ring systems respectively. Both the symmetrical and angular diaminophthalate isomers **7** and **9** were found to undergo facile condensation with butane-2,3-dione to give the corresponding 5,6- and 6,7-dicarbomethoxy-2,3-dimethylquinoxaline, **26** and **27**, respectively, Scheme II.

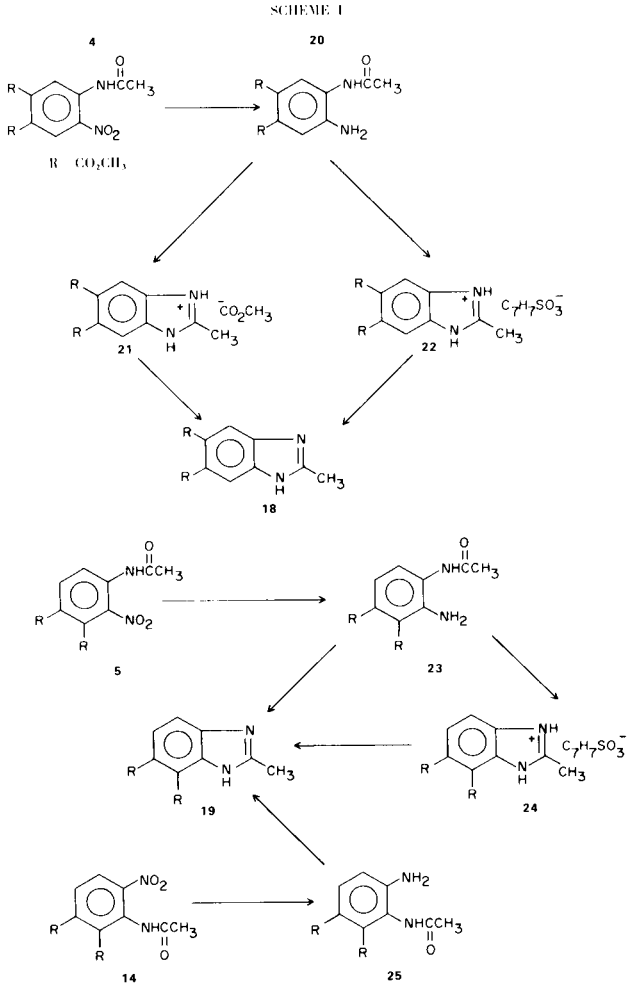
Generally, the conversion of an aryl 1,2-diamino to the corresponding 1,4-dihydroquinoxaline involves condensation with either oxalic acid or ethyl oxalate (8,8a). A similar conversion has been effectively carried out with the two isomeric diaminophthalates **7** and **9** using oxalyl chloride and triethylamine in tetrahydrofuran to give the 6,7- and 5,6-dicarbomethoxy-1,4-dihydroquinoxalines **28** and **29**, respectively, Scheme II.

In their condensation with β-diketones such as acetylacetone, aryl 1,2-diamines generally give rise to the characteristic deeply colored [1,5]benzodiazepinium slats (7,9). The condensation of the isomeric diaminophthalates **7** and **9** with such a reagent was examined and it was noted that the symmetrical isomer **7** underwent a rapid cyclization with acetylacetone to give the purple crystalline 2,4-dimethyl[1,5]benzodiazepinium salt **30**. The angular diamine **9**, however, was resistant to ring closure under these same conditions, Scheme II. This lack of reactivity can presumably be attributed to some degree of steric crowding in the angular isomer which prohibits the essentially planar requirement of diazepine ring formation.

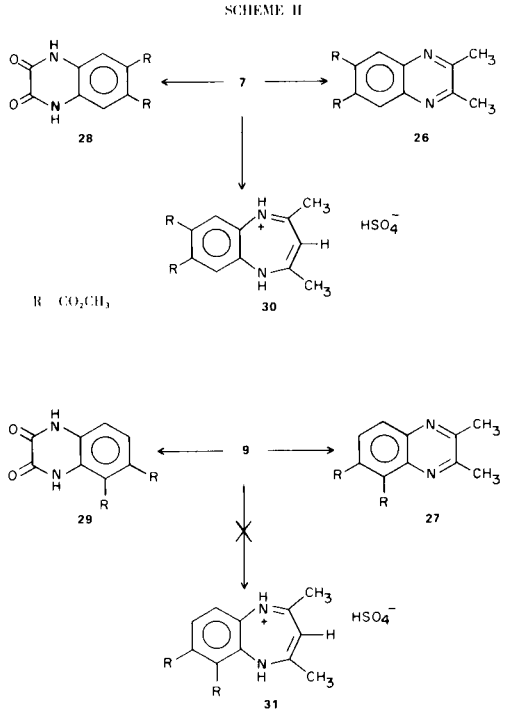
Six Membered Ring Systems. 2,3-Dihydrophthalazines.

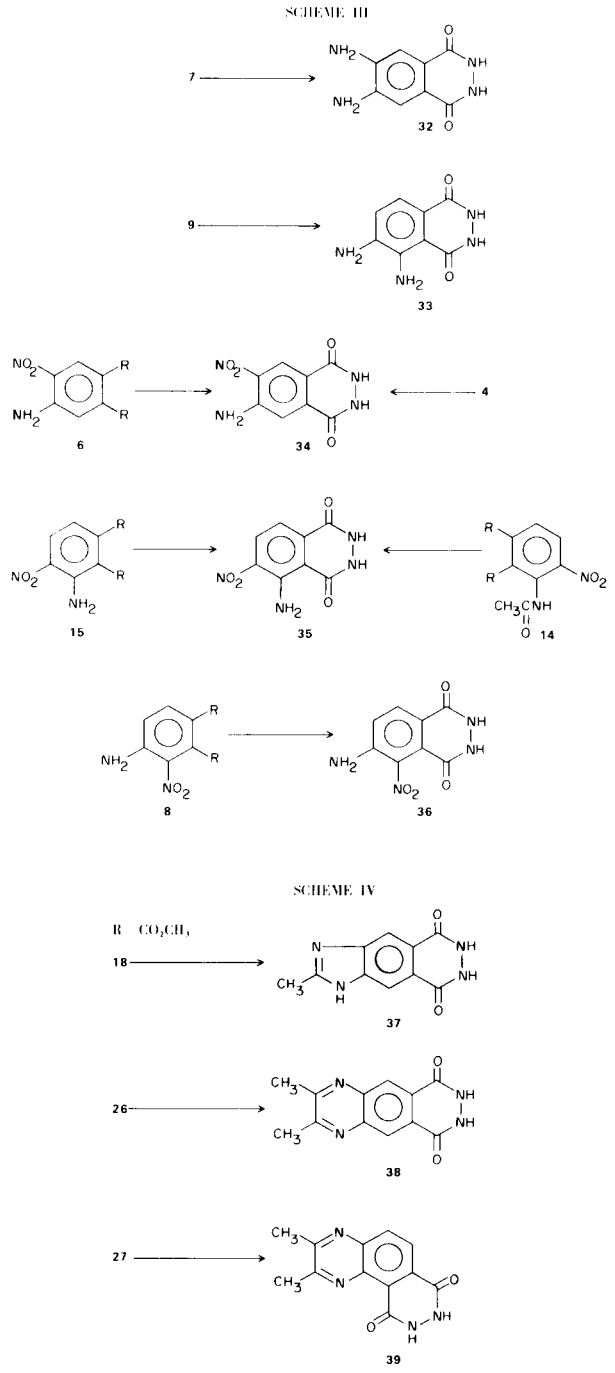
To further demonstrate the excellent functionality and versatility of these new diaminophthalate isomers we have also examined the general reactivity of the ester functions in regards to heterocyclic ring closure. Condensation of the symmetrical diaminophthalate **7** with hydrazine hydrate and triethylamine in methanol gave rise to the corresponding 6,7-diamino-2,3-dihydrophthalazine-1,4-dione (**32**) in 87% yield. Condensation of the unsymmetrical diaminophthalate **9** under the same conditions gave the 5,6-diaminodihydrophthalazine (**33**). Similar conversions were successful with the various nitroaminodimethylphthalates **6**, **15** and **8** to give the corresponding dihydrophthalazines **34**, **35** and **36**, respectively. The 4-acetamido-5-nitrodimethylphthalate (**4**) and the corresponding 3-acetamido-4-nitro isomer **14** underwent a similar condensation with hydrazine hydrate and triethylamine to give the same nitroamino-2,3-dihydrophthalazines **34** and **35** with apparent amide hydrolysis, Scheme III.

SCHEME I



SCHEME II





Fused Ring Systems, Tetraazanthracenes.

Having now tested the general functionality of the two diaminophthalate isomers to give various five, six and seven membered ring systems, we have also sought to examine the synthesis of several representative fused ring systems by extended cyclization fo certain of the above mentioned compounds.

Condensation of the dicarbomethoxy-2-methylbenzimidazole **18** with hydrazine hydrate and triethylamine in methanol gave the 2,3-dihydro-6,7-(2-methylimidazo)-phthalazindione (**37**). Similarly, the dicarbomethoxydimethylquinoxalines **26** and **27** each underwent facile conversion with hydrazine to the corresponding 2,3-dihydropyridazophthalazindiones **38** and **39**, Scheme IV.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover or Mel-Temp, apparatus and are uncorrected. The ir absorption spectra were recorded on either a Perkin-Elmer Model 137 or a Model 521 spectrophotometer. The nmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as an internal reference. Analyses were performed by M-H-W Laboratories, Garden City, Michigan.

Dimethyl 4-Nitrophthalate (**1**).

A solution of 4-nitrophthalic acid (316 g., 1.5 moles) in methanol (500 ml.) and concentrated sulfuric acid (50 ml.) was heated under reflux for 10 hours. The desired product was recrystallized from methanol (247 g., 69%), m.p. 64-65° (lit. (3) 65°); ν max (chloroform): 1755 (ester C=O), 1550 and 1350 (-NO_2) cm^{-1}.

Dimethyl 4-Aminophthalate (**2**).

A solution of dimethyl 4-nitrophthalate (47.8 g., 0.2 mole) in methanol (300 ml.) was hydrogenated in the presence of 5% platinum on carbon (13 g.) at an initial pressure of 50 psi when the calculated amount of hydrogen was absorbed, the catalyst was removed and the crude aminophthalate **2** was obtained (37 g., 89%), by evaporating the solvent *in vacuo*, and recrystallized from aqueous methanol, m.p. 83-84° (lit. (3) 84°); ν max (potassium bromide): d-3348, 1613 (-NH_2) and 1748 (ester C=O) cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.53; H, 5.24; N, 6.71.

Dimethyl 4-Acetamidophthalate (**3**).

A solution of dimethyl 4-aminophthalate (146.3 g., 0.7 mole) in acetic anhydride (1400 ml.) was stirred for 2 hours at 60-70° and then left overnight. The product was precipitated with methanol, dried and then rinsed with sodium carbonate solution and redried. The product was recrystallized from benzene/methanol (158 g., 90%), m.p. 138-140° (lit. (3) 136.5); ν max (potassium bromide): 3378 (amide NH), 1618 (amide C=O) and 1724 (ester C=O) cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.27; H, 5.15; N, 5.66.

Nitration of Dimethyl 4-Acetamidophthalate.

Dimethyl-4-acetamidophthalate (100.4 g., 0.4 mole) was added to fuming (90%) nitric acid (600 ml.), at 0° to 5°. When the addition was completed (0.5 hour) the solution was stirred for 2.5 hours at 5° to 10°. The reaction mixture was mixed with cold methylene chloride (800 ml.) and shaken with crushed ice. The aqueous layer was separated and extracted further with a fresh amount of cold methylene chloride (200 ml.). The methylene chloride layers were combined, washed with ice water, cold sodium bicarbonate solution, cold water and then dried over magnesium sulfate. The solution was shown by tlc to contain two components which were separated by alternating fractional crystallization of the solid mixture from methanol and carbon tetrachloride. Evaporating the solution to dryness *in vacuo* and crystallizing

the residue from methanol afforded a crystalline solid consisting primarily of one component, which was purified by repeated crystallization from this solvent to give dimethyl 4-acetamido-5-nitrophthalate (**4**), m.p. 123-124.5°. The second component of the reaction product was obtained by evaporation of the initial methanol filtrate and was purified by successive crystallization from carbon tetrachloride to give dimethyl 4-acetamido-3-nitrophthalate (**5**), m.p. 125-127°. The isomeric products **4** and **5** were shown to represent 54% and 46%, respectively, of the total amount of the isolated pure solids (72 g., 61%). The structural assignments for both **4** and **5** were consistent with the ir and nmr spectral data. Compound **4**: ν max (deuteriochloroform): 3333 (amide NH), 1634 (amide C=O), 1745 (ester C=O), 1515 and 1348 (-NO_2) cm^{-1}; δ (potassium bromide): 2.34 (s, 6, acetamide Me), 3.90 and 3.94 (2s, 6, 2 CO_2CH_3), 8.68 and 8.98 (2s, 3-H and 6-H) and br 10.42 (s, 1, -NH-).

Anal. Calcd. for $C_{12}H_{12}N_2O_7$: C, 48.65; H, 4.08; N, 9.46. Found: C, 48.95; H, 4.32; N, 9.37.

Compound **5**: ν max (potassium bromide): 3367 (amide NH), 1613 (amide C=O), 1737 (ester C=O) and 1504, 1351 (NO_2) cm^{-1}; δ (deuteriochloroform): 2.40 (s, 3, acetamido Me), 4.04 and 4.08 (2s, 6, 2 CO_2CH_3), 8.24 and 8.78 (2d, 5-H and 6-H) and br 9.56 (s, 1, NH).

Anal. Calcd. for $C_{12}H_{12}N_2O_7$: C, 48.65; H, 4.08; N, 9.46. Found: C, 48.48; H, 4.03; N, 9.58.

Dimethyl 4,5-Diaminophthalate (**7**).

A solution of dimethyl 4-amino-5-nitrophthalate (20.3 g., 0.08 mole) in methanol (250 ml.) was hydrogenated using 5% platinum on carbon (1 g.) as a catalyst, at room temperature and at an initial hydrogen pressure of 50 psi. When the stoichiometric amount of hydrogen was absorbed (20 minutes), the catalyst was removed and the product was dried *in vacuo* at 25°. The product was then recrystallized from a chloroform/methylene chloride (15.2 g., 90%), m.p. 111.5-113°; ν max (methylene chloride): d-3413, 1634 (-NH_2) and 1730 (ester C=O) cm^{-1}; δ (deuteriochloroform): 3.73 (s, 4, 2 NH_2), 3.83 (s, 6, 2 CO_2CH_3) and 6.99 (s, 2, 3-H and 6-H).

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.39; H, 5.36; N, 12.34.

The hydrochloride salt of compound **7** was prepared and recrystallized from methanol/ether, m.p. 212-214°; ν max (potassium bromide): d-3425, 1631 (-NH_2), br-2591 (-NH_3) and 1715 (ester C=O) cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}ClN_2O_4$: C, 46.07; H, 4.99; N, 10.74. Found: C, 46.10; H, 5.43; N, 10.71.

Dimethyl 4-Amino-3-nitrophthalate (**8**).

Dimethyl 4-acetamido-3-nitrophthalate (14.8 g., 0.05 mole) was dissolved in concentrated sulfuric acid (90 ml.) and the reaction was continued for 30 minutes at room temperature. The crude product (11.4 g., 90%) was precipitated by pouring onto an ice-water mixture, m.p. 122-124°. This was then recrystallized from benzene, m.p. 122.5-124°; ν max (potassium bromide) d-3460, 1631 (-NH_2), 1745 (ester C=O), 1529 and 1350 (-NO_2) cm^{-1}; δ (deuteriochloroform): 3.88 and 4.02 (2s, 6, 2 CO_2CH_3), 6.22 (s, 2, NH_2), 6.88 and 7.90 (2d, 5-H and 6-H).

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.64; H, 4.24; N, 10.89.

Dimethyl 3,4-Diaminophthalate (**9**).

Dimethyl 4-amino-3-nitrophthalate (12.7 g., 0.05 mole) in methanol (150 ml.) was hydrogenated with 5% platinum on carbon (1.2 g.) as described for the preparation of compound **7**. The dry product was obtained as a viscous light brown liquid (11 g., 98%), which could not be crystallized form the more common organic solvents; ν max (film) d-3448, 1621 (-NH_2) and 1718 (ester C=O) cm^{-1}; δ (deuteriochloroform): br 3.39 (s, 4, 2 NH_2), 3.81 and 3.86 (2s, 6, 2 CO_2CH_3), 6.66 and 7.17 (2d, 5 and 6-H). The hydrochloride salt of compound **9** was prepared and recrystallized from methanol/ether 186-189° dec. After several recrystallizations, the salt decomposition temperature did not change and a small amount of impurity was always associated with the desired hydrochloride. This impurity was detected by tlc (using a 1:3 mixture of methanol and chloroform) as a minor spot having a lower Rf value than the major product. This salt was examined by ir, ν max (potassium bromide) d-3413, 1631 (-NH_2), br-2632 (-NH_3) and 1733 (ester C=O) cm^{-1}. A monopicrate of compound **9** was prepared and recrystallized from methanol, m.p. 167-169°.

Anal. Calcd. for $C_{16}H_{15}N_5O_{11}$: C, 42.39; H, 3.33; N, 15.45. Found: C, 42.16; H, 3.22; N, 14.84.

Dimethyl 3-Nitrophthalate (**10**).

A solution of 3-nitrophthalic acid (147.7 g., 0.7 mole) in methanol (600 ml.) and concentrated sulfuric acid (400 ml.) was refluxed for 15 hours and refrigerated overnight. The product was precipitated by pouring the solution onto stirred ice water, filtered, rinsed with cold water and allowed to air dry, then recrystallized from methanol (299 g., 73%), m.p. 68-69°. (Lit. (10) 67-69°); ν max (potassium bromide): 1748 (ester C=O), 1543 and 1359 (-NO_2) cm^{-1}.

Dimethyl 3-Aminophthalate (**11**).

Hydrogenation of dimethyl 3-nitrophthalate (48.5 g., 0.19 mole) in methanol (300 ml.) was achieved in the usual manner in the presence of 5% platinum on carbon (1.5 g.). The mixture was filtered and the product was isolated by evaporating the solvent *in vacuo* at 25-35° to give a yellow oil in an almost quantitative yield (42 g.); ν max (film) d-3448, 1618 (-NH_2) and 1730 (ester C=O) cm^{-1}. The hydrochloride salt of compound **11** was prepared and recrystallized from methanol/ether, m.p. 173-174° dec., (lit. (10) 172-174°.

Dimethyl 3-Acetamidophthalate (**12**).

To a solution of dimethyl 3-aminophthalate (104.5 g., 0.5 mole) and dry triethylamine (53.5 g., 0.53 mole) in anhydrous ether (1000 ml.) at about 0°, a solution of acetyl chloride (41.6 g., 0.53 mole) in anhydrous ether (300 ml.) was added slowly while stirring (40 minutes) and the mixture was then refluxed for one hour. The volatile components of the reaction mixture were evaporated, the residue was extracted with water and dried by entraining water with benzene, to give a yellow solid (98 g., 78%) which was crystallized from benzene/light petroleum, m.p. 93-94° (lit. (10) 92-93°); ν max (potassium bromide): 3279 (amide NH), 1618 (amide C=O) and 1724 (ester C=O) cm^{-1}.

Nitration of Dimethyl 3-Acetamidophthalate.

Dimethyl 3-acetamidophthalate (15.1 g., 0.06 mole) was nitrated using fuming (90%) nitric acid (100 ml.) following a procedure similar to the one previously reported for the nitration of compound **3**. The crude product (12.5 g.) was shown by tlc to consist of two major components, which were separated by alternating fractional crystallization from methanol and carbon tetrachloride and identified as *dimethyl 3-acetamido-6-nitrophthalate* (**13**) and *dimethyl-3-acetamido-4-nitrophthalate* (**14**). Compound **13** was recrystallized from methanol, m.p. 125.5-127°;

ν max (potassium bromide): 3356 (amide NH) 1610 (amide C=O), 1739 (ester C=O) 1534 and 1350 (-NO_2) cm^{-1}; δ (deuteriochloroform): 2.26 (s, 3, acetamido Me), 3.88 and 3.94 (2s, 6, 2 CO_2CH_3), 8.20 and 8.86 (2d, 4 and 5-H) and br 10.42 (s, 1, NH).

Anal. Calcd. for $C_{12}H_{12}N_2O_7$: C, 48.65; H, 4.08; N, 9.46. Found: C, 48.42; H, 4.20; N, 9.41.

Compound **14** was recrystallized from carbon tetrachloride / methylene chloride as needles, m.p. 150-152°; ν max (potassium bromide) 3333 (amide NH), 1610 (amide C=O), 1724 (ester C=O) 1536 and 1362 (-NO_2) cm^{-1}; δ (deuteriochloroform): 2.16 (3H, s, acetamido Me), 3.88 and 3.90 (6H, 2s, 2 CO_2CH_3), 7.75 and 8.06 (2d, 5 and 4-H) and br 8.56 (s, NH).

Anal. Calcd. for $C_{12}H_{12}N_2O_7$: C, 48.65; H, 4.08; N, 9.46. Found: C, 48.30; H, 4.34; N, 9.38.

The isomeric products **13** and **14** represented 60% and 40% of the total weight of the isolated pure solids (10.6 g., 60%) respectively.

Dimethyl 3-Amino-4-nitrophthalate (**15**).

Dimethyl 3-acetamido-4-nitrophthalate (2.4 g., 0.081 mole) was dissolved in concentrated sulfuric acid (15 ml.) and the reaction was continued for 30 minutes at room temperature. The solution was poured onto an ice water mixture and the product (1.9 g., 94%) was separated and crystallized from carbon tetrachloride, m.p. 85-86.5°; ν max (potassium bromide) d-3448, 1623 (-NH_2), 1757 and 1730 (2 ester C=O) 1504 and 1342 (-NO_2) cm^{-1}; δ (D_6MSO): 4.00 and 4.03 (2s, 6, 2 CO_2CH_3), 7.27 and 8.43 (2d, 5 and 4-H) and 7.95 (s, 2, NH_2).

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.10; H, 3.97; N, 10.90.

Reduction of Dimethyl 3-Amino-4-nitrophthalate.

Dimethyl 3-amino-4-nitrophthalate (**15**) (1.27 g., 5 mmoles) in methanol (60 ml.) was hydrogenated in the presence of 5% platinum on carbon (0.2 g.), in the usual manner, and the product was obtained as a yellowish brown oil, in an almost quantitative yield. This was shown to be identical with dimethyl 3,4-diaminophthalate (**9**) as verified by tlc, ir and nmr spectral data. The picrate and hydrochloride salts of this product were found to be identical with those arising from compound **9** by a comparison of their melting and mixed melting points.

Dimethyl 4,5-Diacetamidophthalate (**16**).

A solution of dimethyl 4,5-diaminophthalate (0.45 g., 0.002 mole) in acetic anhydride (15 ml.) was heated for 30 minutes on a water bath (80-90°). Upon cooling, compound **16** crystallized from solution; it was separated and then recrystallized from chloroform/carbon tetrachloride (0.57 g., 93%) m.p. 203-204°; ν max (potassium bromide) 3300 (amide NH), 1733 (ester C=O) and 1661 (amide C=O) cm^{-1}; δ (D_6MSO): 2.14 (6H, s, 2 acetamido Me), 3.80 (6H, s, 2 CO_2CH_3), 8.7 (2H, s, 3- and 6-H), 9.6 (2s, 2, acetamido-NH).

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.66; H, 5.25; N, 9.13.

Dimethyl 3,4-Diacetamidophthalate (**17**).

Dimethyl 3,4-diaminophthalate (0.45 g., 0.002 mole) was reacted with acetic anhydride (15 ml.) to give compound **17** under the same condition employed in the preparation of compound **16**. The product was recrystallized from ethanol (0.55 g., 90%) m.p. 242-244°; ν max (potassium bromide) 3333 (amide -NH-), d-1724 (ester C=O), and 1672 (amide C=O) cm^{-1}; δ (D_6MSO): 2.03 and 2.14 (2s, 6, 2 acetamide-Me) 2.70 and 2.82 (2s, 6, 2-CO_2CH_3), 7.75 and 8.20 (2d, 5-H and 6-H) and br 9.30 (s, 2, 2 acetamido -NH-).

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.78; H, 5.23; N, 8.79.

Dimethyl 4-Acetamido-5-aminophthalate (**20**).

Dimethyl 4-acetamido-5-nitrophthalate (**4**) (8.9 g., 0.03 mole) in methanol (120 ml.) was hydrogenated as usual in the presence of 5% Pt on carbon (0.9 g.). The desired product, **20**, was isolated and crystallized from methanol (7.3 g., 91%) m.p. 157-159°; ν max (potassium bromide): d-3448, 1619 (-NH_2), 3311 (amide NH), 1727 (ester C=O) and 1667 (amide C=O) cm^{-1}; δ (D_6MSO): 2.10 (s, 3, acetamido Me), 2.76 and 2.80 (2s, 6, 2-CO_2CH_3), 5.95 (s, 2, NH_2), 6.90 and 7.90 (2s, 6-H and 4-H) and 9.20 (s, 1, acetamido NH).

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 53.92; H, 5.37; N, 10.36.

5,6-Dicarbomethoxy-2-methylbenzimidazole (**18**).

Method A.

Dimethyl 4-acetamido-5-aminophthalate (**20**) (1.33 g., 0.005 mole) was mixed with *p*-toluenesulfonic acid monohydrate (1.55 g., 0.009 mole) and then heated to melt. Benzene (20 ml.) was dropped on the melt and allowed to evaporate over a period of 10 minutes. The solid product was cooled, washed with benzene, and then crystallized from methanol (1.8 g., 86%), m.p. 244-245°. It was identified as the *p*-toluenesulfonic acid salt of 5,6-dicarbomethoxy-3-methylbenzimidazole (**22**); ν max (potassium bromide): 2717, 2632 (-NH), 1739 (ester C=O), 1667 (-C=N-), 1637 (aromatic C=N), 1149, 1033 and 678 (tosylic -SO_3) cm^{-1}; δ (D_6MSO): 2.29 (s, 3, tosylic Me), 2.82 (s, 3, 2-Me), 3.86 (s, 6, 2-CO_2CH_3), 7.14 (d, 2, tosylic 3 and 5-H) 7.55 (d, 2, tosylic 2 and 6-H), 8.12 (s, 2, 2-H and 6-H) and br 10.25 (s, 2, 2NH).

Anal. Calcd. for $C_{19}H_{20}N_2O_7S$: C, 54.27; H, 4.75; N, 6.66. Found: C, 54.05; H, 4.49; N, 6.45.

Adding sodium bicarbonate (1.5 g., 0.012 mole) to a cold solution of compound **22** (3 g., 0.007 mole) in water (20 ml.) and stirring for 5 minutes yielded most of the expected free base **18**. This was crystallized from benzene m.p. 149-151°; ν max (potassium bromide): 3448 (-NH), 1724 (ester C=O) and 1634 (aromatic C=N) cm^{-1}; δ (D_6MSO): 2.58 (s, 3, 2-Me), 3.87 (s, 6H, 2-CO_2CH_3), 7.89 (s, 2, 4- and 7-H) and br 12.7 (s, 1, NH).

Anal. Calcd. for $C_{23}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.05; H, 4.80; N, 11.10.

Method B.

Dimethyl 4-acetamido-5-aminophthaalte (**20**) (2.13 g., 0.008 mole) was dissolved in acetic acid (20 ml.) and heated with xylene (20 ml.), part of the solvent (25 ml.) was distilled during the first hour, the mixture was then refluxed for a second hour. The crude product, precipitated upon adding *n*-hexane to the cold reaction mixture, was crystallized from benzene (2.1 g., 85%), m.p. 132-134°, and was identified as the acetic acid salt of 5,6-dicarbomethoxy-3-methylbenzimidazole (21); ν max (potassium bromide): 1727 (ester C=O) and 1637 (aromatic C=N) cm^{-1}; δ (deuteriochloroform): 2.11 (s, 3, acetic Me), 2.58 (s, 3, 2-Me) 3.91 (s, 6, 2-CO_2CH_3), 7.84 (s, 2, 4- and 7-H) and br 10.44 (s, 2, 2NH, or NH and COOH).

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 8.91. Found: C, 54.69; H, 5.03; N, 8.91.

The free base **18** was obtained from salt **21** in 82% yield, following the same procedure for its formation from salt **22**.

Dimethyl 4-Acetamido-3-aminophthalate (**23**).

Dimethyl 4-acetamido-3-nitrophthalate (5.92 g., 0.02 mole) in methanol (80 ml.) was hydrogenated in the usual manner in the presence of Pt over carbon (1.5 g.). The desired product was isolated and crystallized from carbon tetrachloride/methylene chloride (4.4 g., 83%), m.p. 107-108.5°, ν max (potassium bromide): d-3448; 1631 (-NH_2), 3333 (amide NH), d-1724 (ester C=O) and 1695 (amide C=O) cm^{-1}; δ (D_6MSO): 2.03 (s, 3, acetamido-Me), 3.72 and 3.74 (2s, 6, 2-CO_2CH_3), br 5.60* (s, 2, -NH_2), 6.94 and 7.83 (2d, 5- and 6-H) and 9.24 (s, 1, acetamido-NH).

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 53.86; H, 5.14; N, 10.37.

4,5-Dicarbomethoxy-2-methylbenzimidazole (**19**).

Method A.

The same procedure described above for the preparation of compound **18** in method A was used to prepare compound **24**. Dimethyl 4-acetamido-3-aminophthalate (1.33 g., 0.005 mole) and *p*-toluenesulfonic acid monohydrate (1.55 g., 0.009 mole) in the presence of benzene (20 ml.) gave the *p*-toluenesulfonic acid salt **24**. The salt was recrystallized from methanol (1.7 g., 81%), m.p. 232-233°; ν max (potassium bromide) 2747, 2646 (C=NH), d-1739 (ester C=O), 1669 (-C=N-), 1637 (aromatic C=N), 1145, 1034 and 680 (tosylic-SO_3) cm^{-1}; δ (D_6MSO): 2.29 (s, 3, tosylic-Me), 2.82 (s, 3, 2-Me), 3.88 and 3.98 (2s, 6, 2-CO_2CH_3), 7.14 (d, 2, tosylic 3- and 5-H), 7.56 (d, 2, 2- and 6-H) 7.92 and 8.00 (2s, 6- and 7-H) and br 10.10 (s, 2, 2-NH).

Anal. Calcd. for $C_{19}H_{20}N_2O_7S$: C, 54.27; H, 4.79; N, 6.66. Found: C, 54.39; H, 4.75; N, 6.35.

The free base **19** was obtained in 85% yield by treating the salt **24** with sodium bicarbonate. This was crystallized from water and dried *in vacuo*, m.p. 116-118°; ν max (potassium bromide): 3448 (-NH-), d-1736 (ester C=O) and 1626 (aromatic C=N) cm^{-1}; δ (deuteriochloroform) 2.66 (s, 3H, 2-Me), 3.96 (s, 6, 2-CO_2CH_3) 7.30 (s, 1, NH), 7.49 and 7.80 (2d, 4- and 6-H).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.24; H, 4.84; N, 11.18.

Method B.

Following the same procedure employed to prepare the salt **21** dimethyl 4-acetamido-3-aminophthalate (**23**) (2.13 g., 0.008 mole) and acetic acid (20 ml.) in xylene (20 ml.) yielded the free 4,5-dicarbomethoxy-2-methylbenzimidazole (**19**) (1.8 g., 91%).

General Procedure for the Preparation fo the 1,4-Dihydroquinoxaline-2,3-diones.

The 1,4-dihydroquinoxaline-2,3-diones were prepared by using oxalyl chloride (0.011 mole) in dry tetrahydrofuran (25 ml.) containing triethylamine (5 ml.). The addition was completed in 10 minutes; during this period cooling was necessary to retain the temperature below 20°. The reaction was continued by stirring at room temperature for one hour. The volatile components were then distilled under reduced pressure and the residue was washed with cold water and then dried *in vacuo*.

6,7-Dicarbomethoxy-1,4-dihydroquinoxaline-2,3-dione (**28**).

Dimethyl 4,5-diaminophthalate (**1**) (2.24 g.) and oxalyl chloride (1.39 g.) gave **28**, which was crystallized from methanol (1.95 g., 70%), m.p. 285-286°; ν max (potassium bromide): 3247, 1626 (amide NH), 1730 (ester C=O), 1709 sh-1698 (amide C=O) cm^{-1}; δ (D_6MSO): 3.88 (s, 6, 2 CO_2CH_3), 7.47 (s, 2, 5- and 8-H).

Anal. Calcd. for $C_{12}H_{10}N_2O_6$: C, 51.81; H, 3.62; N, 10.07. Found: C, 51.56; H, 3.78; N, 9.71.

The precise location of a two protons peak due to the two -NH- groups in **28** was difficult to interpret from the diffused integration curve. This could be due to the low solubility of the product in D_6MSO.

5,6-Dicarbomethoxy-1,4-dihydroquinoxaline-2,3-dione (**29**).

Dimethyl 3,4-diaminophthalate (**9**) (2.24 g.) and oxalyl chloride (1.39 g.) gave **29**, which was crystallized with difficulty from acetic acid (1.9 g., 68%), m.p. 264-265° dec.; ν max (potassium bromide): br-3400-2500 with sh 3206 (amide NH), 1730 (ester C=O) 1709, 1695 (amide C=O) and 1610 (amide NH) cm^{-1}; δ (D_6MSO): 3.83 and 3.92 (2s, 6, 2 CO_2CH_3), 7.33 and 7.67 (2d, 8- and 7-H).

Anal. Calcd. for $C_{12}H_{10}N_2O_6$: C, 51.81; H, 3.62; N, 10.07. Found: C, 51.52; H, 3.53; N, 9.55.

General Method for the Preparation of the 2,3-Dimethylquinoxalines.

The 2,3-dimethylquinoxalines were prepared by reacting the diamines (0.01 mole) with butane-2,3-dione (0.011) mole in refluxing absolute ethanol (30 ml.) for 3 hours. The ethanol was evaporated under reduced pressure and the residue was purified as specific below in the following prepositions.

6,7-Dicarbomethoxy-2,3-dimethylquinoxaline (**26**).

Dimethyl 4,5-diaminophthalate (**7**) (2.24 g.) and butane-2,3-dione (0.95 g.) gave the quinoxaline **26**, which was crystallized from benzene/*n*-hexane (2.3 g., 85%), m.p. 159-161°; ν max (potassium bromide): 1721 (ester C=O), 1592, 1575, 1515 and 1451 (stretching vibrations of the ring -C=C and -C=N-) cm^{-1}; δ (D_6MSO): 2.72 (s, 6, 2- and 3-Me), 3.93 (s, 6, 2 CO_2CH_3), 8.21 (s, 2, 5- and 8-H).

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.61; H, 5.05; N, 10.01.

5,6-Dicarbomethoxy-2,3-dimethylquinoxaline (**27**).

Dimethyl 3,4-diaminophthalate (**9**) (2.24 g.) and butane-2,3-dione (0.95 g.) gave the quinoxaline **27** which was crystallized from benzene/*n*-hexane (2.1 g., 78%), m.p. 153-154°; ν max (potassium bromide): 1754, 1730 (ester C=O), 1616, 1580, 1505 and 1460 (stretching vibrations of the ring-C=C- and -C=N- cm^{-1}; δ (D_6MSO): 2.67 (s, 6, 2- and 3-Me), 3.92 and 3.96 (2s, 6, 2 CO_2CH_3), 8.14 (s, 2, 7- and 8-H).

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.59; H, 5.18; N, 10.16.

General Procedure for the Preparation of the Benzodiazepines.

The substituted benzodiazepinium bisulfates were prepared by stirring pentane-2,4-dione (0.011 mole) with a warm solution of the diamine (0.01 mole) in ethanol (40 ml.) for 5 minutes at 50°; then concentrated sulfuric acid (1 ml.) was added and the reaction was continued at that temperature for 20 minutes. The mixture was left to cool and a small amount of ether was added for the complete precipitation of the product.

7,8-Dicarbomethoxy-2,4-dimethyl-[1,5]-benzodiazepinium bisulfate **30**.

Dimethyl-4,5-diaminophthalate **7** (2.24 g.), pentane-2,4-dion (1.1 g.) and H_2SO_4 gave a purple product which was crystallized from ethanol (3.6 g., 86%), m.p. 236-237° (d); ν max (potassium bromide): 1733 (ester C=O) 3300, 3226, 1656, 1603, 1565 and 1429 cm^{-1}; δ (D_6MSO): 1.82 (s, 6, Me) 3.86 (s, 6, -CO_2CH_3), 4.39 (s, 1, vinyl), 6.99 (s, 2, 4 and 6H).

Anal. Calcd. for $C_{15}H_{18}N_2O_8S$: C, 46.63; H, 4.69; N, 7.25. Found: C, 46.33; H, 4.78; N, 7.03.

Attempted Preparation of 6,7-Dicarbomethoxy-2,4-dimethyl-1,5-diazepinium Bisulfate (**31**).

Dimethyl 3,4-diaminophthalate (**9**) (2.24 g.), pentane 2,4-dione (1.1 g.) and sulfuric acid resulted in a red solution which, upon the addition of ether, gave a brown oil. This was shown to be a mixture of different products. One of the major components of the mixture was identified as the sulfate of dimethyl 3,4-diaminophthalate.

General Procedure for the Preparation of Functional and Fused Phthalazines.

A solution of the aromatic *o*-dimethyl ester in methanol was treated with a mixture of hydrazine hydrate (85% solution) and triethylamine. The reaction was continued under reflux for 2 hours, and the product was left to cool overnight. Isolation and purification of the crude products are discussed below for each specific case.

6,7-Diamino-2,3-dihydrophthalazine-1,4-dione (**32**).

Dimethyl 4,5-diaminophthalate (7) (1.1 g., 0.005 mole) was reacted with hydrazine hydrate (3 ml.) in the presence of triethylamine (3 ml.) in methanol (20 ml.). The product was precipitated by concentrating the resulting solution and then triturating it with a mixture of benzene/methanol. The product was crystallized from *N,N'*-dimethylacetamide/acetic acid (0.85 g., 87%), m.p. 407°; ν max (potassium bromide): broad band between 3400 and 2000 with two shoulders at 3413, 3333 (-NH_2) and a peak at 3257 (lactam NH), 1667 (lactam C=O) and 1634 (-NH_2) cm^{-1}; δ (D_6MSO): br 5.63 (s, 6, $2NH_2$ and 2NH), 7.18 (s, 2, 5- and 8-H).

Anal. Calcd. for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 49.96; H, 4.14; N, 29.30.

5,6-Diamino-2,3-dihydrophthalazine-1,4-dione (**33**).

Dimethyl 3,4-diaminophthalate (**9**) (0.55 g., 0.005 mole) was reacted with hydrazine hdyrate (1.5 ml.) in the presence of thiethylamine (1.5 ml.) in methanol (10 ml.). The solution was concentrated *in vacuo* and triturated with hot benzene/methanol. Upon cooling, a yellow solid precipitated, m.p. 74°; ν max (potassium bromide): 3250 br (NH, NH_2), 1670 sh (lactam C=O) cm^{-1}; δ (D_6MSO): br, 6.15 (s, 6, $2NH_2$ and 2NH), 6.9 (d, 1, J = 8 cps, 8H), 7.14 (d, 1, J = 8 cps, 7H).

Anal. Calcd. for $C_8H_8N_4O_2 \cdot H_2O$: C, 45.71; H, 4.80; N, 26.65. Found: C, 45.20; H, 4.66; N, 27.09.

6-Amino-2,3-dihydro-7-nitrophthalazine-1,4-dione (**34**).

Dimethyl 4-amino-5-nitrophthalate (**6**) (1.9 g., 0.0075 mole), hydrazine hydrate (3 ml.) and triethylamine (3 ml.) in ethanol (40 ml.) were reacted to give compound **34**. The crude product was crystallized from *N,N'*-dimethylacetamide/acetic acid 91.5 g., (90%), m.p. 382° (d); ν max (potassium bromide): broad band at 3500-2500 with a distinct doublet at 3460 (-NH_2) and a peak at 3226 (lactam NH), 1667 (lactam C=O), 1629 (NH_2), 1513 and 1361 (NO_2) cm^{-1}; δ (D_6MSO): 7.61 (s, 1, 4H), 7.87 (s, 2, NH_2), 8.75 (s, 1, 8H).

Anal. Calcd. for $C_8H_6N_4O_4$: C, 43.25; H, 2.72; N, 25.22. Found: C, 43.26; H, 2.74; N, 25.11.

5-Amino-2,3-dihydro-6-nitrophthalazine-1,4-dione (**35**).

Reacting dimethyl 3-amino-4-nitrophthalate (**15**) (2.2 g., 0.009 mole) with hydrazine hydrate (5 ml.) in methanol (50 ml.) containing triethylamine (5 ml.) yielded a product which was soluble in the reaction mixture. This was concentrated and the product was precipitated by adding acetic acid (10 ml.) to the residue. The product was crystallized from DMF/benzene and was identified as compound **35** (1.6 g., 80%), m.p. 342° (d); ν max (potassium bromide) broad band between 3500 and 2500 with a doublet at 3472 (NH_2) and a peak at 3300 (lactam NH), 1664 (lactum C=O), 1634 (NH_2), 1511 and 1364 (NO_2) cm^{-1}; ν (D_6MSO): br 6.68 (s, 4, -NH_2 and 2NH), 7.02 and 8.42 (2d, 8- and 7-H).

Anal. Calcd. for $C_8H_6N_4O_4$: C, 43.25; H, 2.72; N, 25.22. Found: C, 43.20; H, 2.94; N, 24.96.

Compound **35** was shown to be identical with the reaction product of dimethyl 3-acetamido-4-nitrophthalate (**14**) (2.65 g., 0.009 mole) with hydrazine hydrate (5 ml.) in the presence of triethylamine (5 ml.) in methanol (50 ml.). The product was precipitated by adding acetic acid and then crystallized from DMF/benzene (1.5 g., 75%), m.p. 342° dec. It revealed an identical spectra with that of an authentic sample of compound **35** and their mixed m.p. was the same as those of the mixed samples.

6-Amino-2,3-dihydro-5-nitrophthalazine-1,4-dione (**36**).

Dimethyl 4-amino-3-nitrophthalate (**8**) (1.8 g., 0.007 mole), and hydrazine hydrate (3 ml.) in methanol (40 ml.) to yield compound **36**.

The crude product was separated after stirring the cold reaction mixture with acetic acid (20 ml.) and was then crystallized from *N,N'*-dimethylacetamide/acetic acid (1.3 g., 84%), m.p. 348° dec., ν max (potassium bromide) broad band at 3500-2000 with a distinct doublet at 3460 (NH_2) and a peak at 3279 (lactam NH), 1650 (lactam C=O), 1620 (NH_2), 1493 and 1361 (NO_2) cm^{-1}; δ (D_6MSO): br 6.62 (s, 4, NH_2 and 2NH), 7.32 and 7.90 (2d, 7- and 8-H).

Anal. Calcd. for $C_8H_6N_4O_4$: C, 43.25; H, 2.72; N, 25.22. Found: C, 43.24; H, 2.70; N, 25.20.

2,3-Dihydro-7-methylimidazo[4,5-*g*]phthalazine-1,4-dione (**37**).

5,6-Dicarbomethoxy-3-methylbenzimidazole (**17**) (1.5 g., 0.006 mole), and hydrazine hydrate (3 ml.) were reacted in the presence of triethylamine (3 ml.) in methanol (30 ml.) to give compound **37**, which precipitated during reflux. After cooling the crude produce was separated and purified by digestion in warm DMAc, and was insoluble in the more common organic solvents (1.1 g., 85%), m.p. 375°; ν max (potassium bromide): broad band at 3500-2000 with distinct peaks at 3322 (imidazole NH) and 3226 (lactam NH), 1664 (lactam C=O) and 1634 (aromatic C=N) cm^{-1}; δ (D_6MSO): 2.67 (s, 3, 2-Me), br, 6.75 (s, 3, 3 NH) and 7.91 (s, 2, 8- and 9-H).

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.55; H, 3.77; N, 25.64.

2,3-Dihydro-7,8-dimethylpyrazino[2,3-*g*]phthalazine-1,4-dione (**38**).

6,7-Dicarbomethoxy-2,3-dimethylquinoxaline (**26**) (0.55 g., 0.002 mole) was reacted with hydrazine hydrate (2 ml.) in the presence of triethylamine (2 ml.) in methanol (30 ml.) yielding compound **38** upon cooling the reaction mixture. The crude product was crystallized from *N,N'*-dimethylacetamide/acetic acid (0.42 g., 86%), m.p. 383° dec.; ν max (potassium bromide): complex multiplet at 3500-2000, 1667 (lactam C=O), 1634 (aromatic C=N), 1587, 1563, 1493 and 1471 (quinoxaline ring vibrations) cm^{-1}; δ (D_6MSO): 2.74 (s, 6, 2- and 3-Me), br 6.04 (s, 2, 2NH) and 8.48 (s, 2, 9- and 10-H).

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 58.89; H, 4.17; N, 22.72.

2,3-Dihydro-8,9-dimethylpyrazino[2,3-*f*]phthalazine-1,4-dione (**39**).

5,6-Dicarbomethoxy-2,3-dimethylquinosaline (**27**) (0.55 g., 0.002 mole) was reacted with hydrazine hydrate (2 ml.) in the presence of triethylamine (2 ml.) in methanol (30 ml.), to give compound **39** upon cooling the reaction mixture, m.p. 365° dec., ν max (potassium bromide): broad band at 3500-2500 with a distinct peak at 3195 (lactam NH), 1667 (lactam C=O), 1634 (aromatic C=N), 1585, 1563, 1508 and 1484 (quinoxaline ring vibrations) cm^{-1}; δ (D_6MSO): 2.82 (s, 6, 2 and 3-Me), 8.30 and 8.32 (2s, 9- and 10-H) and br 8.68 (s, 2, 2NH).

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.75; H, 4.04; N, 23.15.

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