The Synthesis of Pyridoquinolines with Dialkylaminopropylamine Side Chains

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Several new pyridoquinolines with dimethylaminopropyl side chains including 4,7-bis(3′-dimethylaminopropylamino)-1,10-phenanthroline (**1**), 4,10-bis(3′-dimethylaminopropylamino)-1,7-phenanthroline (**2**), 4,10-bis(3′-dimethylaminopropylamino)-6-methyl-1,7-phenanthroline (**3**), 4,6-bis(3′-dimethylaminopropylamino)-10-methylpyrido[3,2-*g*]quinoline (**4**) and 4-(3′-dimethylaminopropyl)pyrrolo[*lmn*][4,7]phenanthroline (**5**) have been prepared. The compounds were prepared by a multi-step synthesis which begins with Michael type addition of dimethyl acetylenedicarboxylate or diethyl ethoxymethylenemalonate to the appropriate phenylenediamine. The enamines obtained from the Michael addition were cyclized on heating at elevated temperatures to form the corresponding pyridoquinoline-diester-diones. The diester-diones were saponified decarboxylated and converted into dichloropyridoquinolines which on reaction with dimethylaminopropylamine yielded the title compounds.

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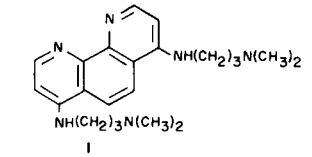
Small molecules which bind to DNA by intercalation are of considerable interest for study of DNA structure and for potential use as chemotherapeutic agents (1). Molecules which bind to DNA by intercalation frequently contain two different regions whose molecular interactions with DNA arise from independent phenomena. These structural elements are a planar aromatic ring which is inserted between the DNA nucleotide base pairs and a cationic side chain which electrostatically interacts with the deoxyribophosphate backbone of DNA (1). Several pyridoquinoline systems with dialkylaminopropylamine side chains have been synthesized as part of a program of synthesis and study of small molecules which bind to DNA (2). The pyridoquinolines reported here provide molecules for biophysical study which have cationic side chains located in different geometric relationships to each other and whose intercalating ring system presents different geometric arrangements (*e.g.*, phenanthrene: anthracene). These systems provide, for the first time, a systematic series of derivatives which can be used to test the importance of the shape of the intercalating ring on the binding constant, as well as the opportunity to investigate the constraints on intercalation caused by side chain protrusion into both the major and minor grooves of DNA. In order to have molecules available to attempt to answer these questions regarding the importance of the molecular topology to intercalator-DNA interactions, we have prepared the following five pyridoquinolines: 4,7-bis(3′-dimethylaminopropylamino)-1,10-phenanthroline (**1**), 4,10-bis(3′-dimethylaminopropylamino)-1,7-phenanthroline (**2**), 4,10-bis(3′-dimethylaminopropylamino)-6-methyl-1,7-methyl-1,7-phenanthroline (**3**), 4,6-bis(3′-dimethylaminopropylamino)-10-methylpyrido[3,2-*g*]quinoline (**4**), and 4(3′-dimethylaminopropyl)pyrrolo[*lmn*][4,7]phenanthroline (**5**).



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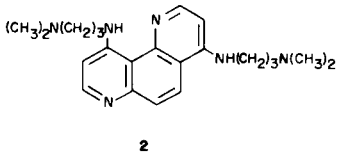

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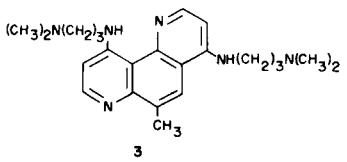

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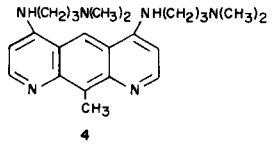

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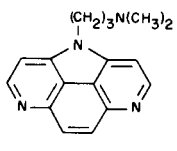

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The synthesis of a number of pyridoquinoline systems is well documented in the literature (3). Many of the synthesis of these and related systems employ phenylenediamines in one of the many variations of the Skraup method (4). However, the recorded chemistry of these systems is not without ambiguity since conflicting reports concerning the direction of ring closure of enamines, derived from the appropriately substituted phenylenediamines, during thermally promoted ring closure have appeared (3a,5).

The synthesis of 4,7-bis(3′-dimethylaminopropylamino)-1,10-phenanthroline (**1**) was patterned after the approach reported by Synder and Freier (6) for the preparation of an analogous 1,10-phenanthroline but differs somewhat in experimental detail. The synthesis is started by condensation of *o*-phenylenediamine with diethyl ethoxymethylenemalonate to produce in good yields *o*-bis(2,2-dicarbethoxylvinylamino)benzene (**6**). Carefully controlled thermally promoted cyclization of **6** in paraffin oil at 245° gave 1,4,7,10-tetrahydro-3,8-dicarboethoxy-1,10-phenan-

throline-4,7-dione (**7**) in excellent yield. Due to the symmetry of the enamine this ring closure is unambiguous. Saponification of the diester 7 gave the corresponding diacid **8**, which was readily decarboxalated to give the 1,10-phenanthroline-4,7-dione (**9**). Treatment of the dione **9** with phosphorus oxychloride yielded 4,7-dichloro-1,10-phenanthroline (**10**). The dichlorocompound **10** was readily converted into the desired *bis*-dimethylaminopropylamino compound **1** by a nucleophilic displacement reaction with 3-dimethylaminopropylamine. A complete assignment of the ^{13}C nmr spectrum of the dichlorocompound **10** has been reported (7) and provides support for the structural assignment of **1**.

The synthetic scheme used for 4,10-bis(3'-dimethylaminopropylamino)-1,7-phenanthroline (**2**) begins with a Michael type addition of dimethylacetylene dicarboxylate and *m*-phenylenediamine to form *m*-bis(1,2-dicarbomethoxyvinylamine)benzene (**11**). Thermally promoted cyclization of this enamine **11** may be expected to occur in either of two ways to produce the 1,7-phenanthroline system or the pyrido[2,3-*g*]quinoline system. The former has been reported to be the direction of ring closure (3a,5). The ^{13}C nmr spectral results on the dione derived from the 2,8-dicarbomethoxy-1,7-phenanthroline-4,10-dione (**12**) supports the earlier reports *vide infra*. Ring closure of **11** was achieved in good yields by heating in diphenyl ether to form 1,4,7,10-tetrahydro-2,8-dicarbomethoxy-1,7-phenanthroline-4,10-dione (**12**). Hydrolysis of the diester **12** gave the corresponding diacid **13**; no suitable nmr solvent was found for either. Decarboxyalation of **13** gave 1,4,7,10-tetrahydro-1,7-phenanthroline-4,10-dione (**14**). An acceptable ^{13}C nmr spectrum was obtained for **14** in sodium deuteroxide/deuterium oxide and twelve lines were observed as expected for the 1,7-phenanthroline structure. The other isomeric possibility, the linear pyrido[2,3-*g*]quinoline system, would have been expected to give only seven lines. The dione **14** was readily converted by the action of phosphorus oxychloride to 4,10-dichloro-1,7-phenanthroline (**15**) which on reaction with 3-dimethylaminopropylamine gave 4,10-bis-(3'-dimethylaminopropylamino)-1,7-phenanthroline (**2**). The methyl homolog of **2** 4,10-bis(3'-dimethylaminopropylamino)-6-methyl-1,7-phenanthroline (**3**), was synthesized in an analogous manner starting with 2,4-diaminotoluene and diethylethoxymethylene malonate proceeding *via* the intermediates **16-20** analogous to the ones described for preparation of **2**. In this sequence cyclization of both enamine functions with retention of the methyl group can only lead to the 1,7-phenanthroline system. The ^{13}C-nmr results from the intermediates (see experimental section) including 1,10-dichloro-6-methyl-1,7-phenanthroline (7) are consistent with the assigned ring structure.

In order to conveniently synthesize a linear system it was necessary to use a *m*-phenylenediamine with a functional group blocking the site which would lead to angular ring closure. The linear compound synthesized was 4,6-bis(3'-dimethylaminopropylamino)-10-methylpyrido-[3,2-*g*]quinoline (**4**). The synthesis of **4** starts with the Michael type addition of 2,6-diaminotoluene to dimethylacetylene dicarboxylate to form 2,6-bis(1,2-dicarbomethoxyvinylamino)toluene (**21**). The bis-enamine **21** was cyclized at 265° to produce 1,4,6,9-tetrahydro-2,8-dicarbomethoxy-10-methylpyrido[3,2-*g*]quinoline-4,6-dione (**22**). As in the previous routes the diester was saponified to form the diacid **23** which was decarboxalated to yield the corresponding dione **24**. The dione **24** was readily converted into the dichloro compound **25** by the action of phosphorus oxychloride. The target compound, 4,6-bis(3'-dimethylaminopropylamino)-10-methylpyrido[3,2-*g*]-quinoline (**4**) was prepared by reaction of **25** with 3-dimethylaminopropylamine.

The preparation of 4(3'-dimethylaminopropyl)pyrrolo-[*lmn*][4,7]phenanthroline (**5**) was carried out in a manner similar to that reported by Douglas and Kermack for a related pyrrolo[*lmn*][4,7]phenanthroline (8). The first step involved the preparation of *p*-bis(1,2-dicarbomethoxyvinyl amino)benzene (**26**). Thermally promoted cyclization of this bis-enamine could be expected to form either the 4,7-phenanthroline or the pyrido[2,3-*g*]quinoline ring system. An earlier report (5) indicated that the latter was the case; however, more recent x-ray studies (3a) have shown that the 4,7-phenanthroline ring system is formed. The cyclization product 1,4,7,10-tetrahydro-3,8-dicarbomethoxy-4,7-phenanthroline-1,10-dione (**27**) was saponified to form the corresponding diacid **28** which on decarboxalation gave 1,4,7,10-tetrahydro-4,7-phenanthroline-1,10-dione **29**. The dione **29** was converted in the conventional manner to the corresponding dichloro compond **30** which was used as described for the previous compounds to prepare the pyrrolo[*lmn*][4,7]phenanthroline **5**. The fact that the dichloro compound **30** reacted to incorporate only one dialkylamino functionality is further evidence which supports the formation of the 4,7-phenanthroline ring system on thermally induced ring closure of the bis-enamine **26**.

EXPERIMENTAL

All melting points are uncorrected and were determined either on a Thomas-Hoover melting point apparatus (mp >250°) or a Laboratory Services Mel-Temp melting point apparatus (mp >250°). Infrared spectra were determined on a Perkin Elmer-Infrared Spectrophotometer 710B. The ^{1}H nuclear magnetic resonance spectra were recorded on a Varian EM 360 nuclear magnetic resonance spectrometer or a JEOL-FX60Q fourier transform nuclear magnetic resonance spectrometer. Nuclear magnetic resonance spectra of ^{13}C nuclei were recorded on a JEOL-FX60Q fourier transform nuclear magnetic resonance spectrometer. All nuclear magnetic resonance spectra have tetramethylsilane as the internal standard unless otherwise stated.

o-bis(2,2-Dicarbethoxyvinylamino)benzene (**6**).

Diethyl ethoxymethylenemalonate (85.6 g, 0.396 mole) and *o*-phenylenediamine (20.0 g, 0.185 mole) were rapidly heated (45 minutes) to and maintained at 80° for one hour. The mixture was allowed to cool to room temperature and the semi solid mass was poured into methanol (375 ml). The solid was collected and recrystallized twice from cyclohexane to yield 66.4 g (80%), mp 94-95°, lit (6) mp 94-95°. ^{13}C nmr (deuteriochloroform): 168.1, 164.9, 152.9, 131.4, 126.0, 119.5, 95.3, 60.1, 59.7, 14.0, and 13.9 ppm.

1,4,7,10-Tetrahydro-3,8-dicarboethoxy-1,10-phenanthroline-4,7-dione (**7**).

To 350 ml of paraffin oil at the temperature of 245 ±5° was added **6** (20 g, 0.045 mole). The reaction mixture temperature was held at 245 ±5° for thirty minutes, (longer time results in charring), cooled to 85°, poured into 400 ml of petroleum ether (90-120°) and allowed to stand for several hours. The solid was filtered, washed with copious amounts of acetone, followed by several portions (100 ml) of ethyl ether, and dried to yield 14.3 g (90%) of **7** mp 265-266°, lit (6) mp 264-265°; ^{13}C nmr (DMSO-d_6): 169.1, 166.0, 146.6, 137.7, 124.7, 120.1, 110.3, 60.9, and 14.2 ppm.

1,4,7,10-Tetrahydro-3,8-dicarboxy-1,10-phenanthroline-4,7-dione (**8**).

1,4,7,10-Tetrahydro-3,8-dicarboethoxy-1,10-phenanthroline-4,7-dione (**7**) (13 g, 0.036 mole), suspended in a 10% potassium hydroxide solution (600 ml), was allowed to reflux overnight, treated with charcoal, filtered, acidified and the *p*H of the solution was adjusted to 2 with 4 *M* hydrochloric acid. The resulting solid was filtered, washed two times each with water, acetone, and ethyl ether. The compound was dried, dissolved in a 5% potassium hydroxide and subjected again to the charcoal, acidification, and washing treatment described above. The product was dried to yield 9.3 g (85%), mp 305-311° dec, lit (6) mp 300-310°. No crystallization solvent was found and the sample was used directly in the next step; ^{13}C nmr (DMSO-d_6): 175.1, 168.4, 148.4, 141.5, 125.0, 118.7, and 109.6 ppm.

1,4,7,10-Tetrahydro-1,10-phenanthroline-4,7-dione (**9**).

1,4,7,10-Tetrahydro-3,8-dicarboxy-1,10-phenanthroline-4,7-dione (**8**) (9 g, 0.03 mole) in 300 ml of paraffin oil was rapidly heated (20 minutes) to 320-325° and held at this temperature for one hour. The system was flushed with nitrogen at 30 minute intervals. The reaction mixture was cooled to 75° and poured into 200 ml of petroleum ether (90-120°) and allowed to stand for several hours. The solution was filtered and washed with several portions of acetone and dried. The solid was dissolved in an 8% potassium hydroxide solution, treated with charcoal, filtered, and the pH adjusted with concentrated hydrochloric acid to a *p*H of 3. The solid was filtered, washed with copious amounts of water, several portions (50 ml) of chloroform, and dried to yield 5.7 g (90%) of **9** mp 471-474° dec; lit (6) mp 475° dec. ^{13}C nmr (DMSO-d_6): 175.4, 142.9, 139.1, 125.6, 116.1, and 110.1 ppm.

4,7-Dichloro-1,10-phenanthroline (**10**).

The 1,10-phenanthroline-4,7-dione (**9**) (5.5 g, 0.026 mole) and phosphorus oxychloride (50 ml) were heated under reflux for six hours and allowed to cool. The reaction mixture was added dropwise to a stirred mixture of concentrated ammonium hydroxide and ice. Care was taken to keep the solution cold and basic. After the hydrolysis was complete, the solution was filtered, the solid was washed with two 100 ml portions of *p*-dioxane and water. The product was crystallized once from ethanol and then from methanol, to yield 6 g (93%) of **10**, mp 250-251°, lit (6) mp 249-250°; ^{13}C nmr (deuteriochloroform): 150.1, 146.9, 142.7, 126.7, 123.7, and 123.0 ppm.

4,7-Bis-(3'-dimethylaminopropylamino)-1,10-phenanthroline (**1**).

4,7-Dichloro-1,10-phenanthroline (**10**) (3.0 g 0.012 mole) and 40 ml of 3-diethylaminopropylamine were heated (oil bath) at 140-150° for four hours and allowed to cool to room temperature. The solution was added to 75 ml of a 4% sodium hydroxide solution, stirred, extracted with three portions of chloroform (175 ml). The combined portions of chloroform were removed under reduced pressure and a light brown precipitate appeared. The solid was recrystallized once from ethyl ether:chloroform (1:1) and then from *n*-heptane to yield 4.1 g (89%) of **1**, mp 236-238° dec; ^{13}C nmr (deuteriochloroform): 150.4, 146.6, 117.2, 116.1, 100.5, 59.1, 45.5, 43.8, and 24.9 ppm.

Anal. Calcd. for $C_{22}H_{32}N_6$: C, 69.44; H, 8.48; N, 22.08. Found: C, 69.18; H, 8.53; N, 21.98.

m-bis(1,2-Dicarbomethoxyvinylamino)benzene (**11**).

m-Phenylenediamine 33 g (0.3 mole) dissolved in 300 ml methanol was treated dropwise with a dimethylacetylene dicarboxylate (85.24 g 0.6 mole) in 100 ml methanol, allowed to stand for 2 hours, poured into 1200 ml of boiling methanol, stirred for 30 minutes, filtered and allowed to cool until yellow needles formed. The product was filtered, recrystallized twice from methanol and dried to yield 106 g (84%), mp 146-147°, lit (5) mp 147°; ^{13}C nmr (deuteriochloroform): 169.3, 164.1, 147.3, 141.2, 129.4, 116.5, 113.3, 94.4, 52.7, and 51.1 ppm.

Anal. Calcd. (9) for $C_{18}H_{20}N_2O_8$: C, 55.10; H, 5.14; N, 7.14. Found: C, 55.16; H, 5.17; N, 7.08.

1,4,7,10-Tetrahydro-2,8-dicarbomethoxy-1,7-phenanthroline-4,10-dione (**12**).

A mixture of **11** (30 g, 0.076 mole) in 350 ml of diphenyl ether, under a nitrogen atmosphere, was rapidly raised (30 minutes) to 250-255°. The mixture was maintained at this temperature for 30 minutes, filtered and the precipitate washed three times each with petroleum ether (90-120°), acetone and ethyl ether. A suitable crystallization solvent was not found, however, the crystals obtained from the above treatment were analytically pure, yield 23.3 g (93%) of **12**, mp 274-275°, lit (5) mp 273.5°; ^{13}C nmr: no suitable nmr solvent was found.

Anal. Calcd. for $C_{16}H_{12}N_2O_6$: C, 58.54; H, 3.68; N, 8.58. Found: C, 58.66; H, 3.73; N, 8.47.

1,4,7,10-Tetrahydro-2,8-dicarboxy-1,7-phenanthroline-4,10-dione (**13**).

The 2,8-dicarbomethoxypyrido[2,3-*g*]quinoline-4,10-dione (**12**) (15.0 g, 0.046 mole) was added to 550 ml of 6*M* hydrochloric acid, (attempted hydrolysis with a 6*M* potassium hydroxide solution produced an insoluble salt) refluxed for twenty-four hours, filtered, washed three times each with acetone, *p*-dioxane and methylene chloride. The product **13** was dried under vacuum at 100° yielding 13.7 g (99%), mp 340-343°. lit (3a) mp >320. No suitable recrystallization or nmr solvent was found and the compound was used directly in the next step.

1,4,7,10-Tetrahydro-1,7-phenanthroline-4,10-dione (**14**).

The 2,8-dicarboxy-1,7-phenanthroline-4,10-dione (**13**) (15 g, 0.05 mole) in 375 ml of paraffin oil, under a nitrogen atmosphere, was rapidly raised (30 minutes) to 330° and maintained at that temperature for 6 hours. The system was flushed with nitrogen at 1.5 hour intervals since constant nitrogen flow facilitated sublimation. The reaction mixture was allowed to cool to 80° and poured into 500 ml of petroleum ether (90-120°). The mixture was filtered, washed with several portions of a acetone:*p*-dioxane (8:1) and dried. The product was suspended in a 10% sodium hydroxide solution, treated with charcoal, filtered and the pH was adjusted to approximately 2 with 6 *M* hydrochloric acid. The solid was collected by filtration, washed with copious amounts of water; followed by several portions (100 ml) of *p*-dioxane and dried to yield 9.4 g (89%) of the pyrido[2,3-*g*]quinoline-4,10-dione **14**, mp 390-391°, lit (10) mp 390. No recrystallization solvent was found; therefore the material was used directly in the next step; ^{13}C nmr (sodium deuteroxide in deuterium oxide, *p*-dioxane as reference): 177.6, 176.4, 151.9, 151.7, 141.8, 138.1, 124.6, 124.1, 119.1, 112.9, 112.3, and 110.9 ppm.

4,10-Dichloro-1,7-phenanthroline (**15**).

The 1,7-phenanthroline-4,10-dione (**14**) (10 g, 0.047 mole) in 50 ml of phosphorus oxychloride was allowed to reflux for one hour after which time 2 drops of water were added and the reaction mixture was allowed to reflux for an additional two hours. The reaction mixture was added dropwise to a mixture of ammonium hydroxide and ice and precautions were taken to keep the solution basic and cold. After completion of addi-

tion the solution was filtered, the solid was washed with three portions (200 ml) each of water, dioxane, and toluene. The compound was recrystallized once from ethanol and then from methylene chloride to yield 11.5 g (98%) of **15** mp 155-157, lit (11) mp 156°; ^{13}C nmr (deuteriochloroform): 151.5, 149.9, 147.3, 146.6, 143.0, 141.8, 130.2, 125.6, 125.2, 124.8, 123.1, and 122.2 ppm.

4,10-Bis(3'-dimethylaminopropylamino)-1,7-phenanthroline (**2**).

4,10-Dichloro-1,7-phenanthroline (**15**) (3 g, 0.012 mole) and 30 ml of 3-dimethylaminopropylamine were heated with an oil bath at 165-175° for four hours. The mixture was allowed to cool to room temperature and added with stirring to 100 ml of a 10% aqueous sodium hydroxide solution. The mixture was extracted with three portions (250 ml) of ethyl ether. The combined portions of ethyl ether solution were evaporated under reduced pressure to yield a brown oil. The oil was dissolved in 100 ml of methanol, treated with charcoal, filtered and the methanol removed under reduced pressure to yield a brown oil which was added to 20 ml of a boiling petroleum ether (90-120°):benzene (5:1). The mixture was filtered and the volume reduced by one-third. The solution was cooled to room temperature, placed in an ice bath and after two hours cream colored flakes were collected, washed with cold benzene and dried to yield 3.65 g (80%) of **2** mp 141.0-142.5°; ^{13}C nmr (deuteriochloroform): 154.5, 150.8, 150.4, 149.9, 148.6, 146.7, 127.3, 120.1, 113.7, 112.6, 110.5, 99.0, 59.3, 57.5, 45.5, 44.0, 40.8, 27.1, and 24.9 ppm.

Anal. Calcd. for $C_{22}H_{32}N_6$: C, 69.44; H, 8.48; N, 22.08. Found: C, 69.21; H, 8.53; N, 21.99.

2,4-Bis(2,2-dicarbethoxyvinylamino)toluene (**16**).

A mixture of 2,4-diaminotoluene (15.0 g, 0.123 mole) and diethyl ethoxymethylenemalonate (53.1 g, 0.246 mole) was rapidly heated (30 minutes) to 80° and held at this temperature until a solid white cake formed. The solid mass was dissolved into 1200 ml of hot methanol, filtered, allowed to crystallize, and collected. The solid was recrystallized first from methanol and then from n-heptane. A yield of 53.5 g (94%) of mp 144-146° was obtained; ^{13}C nmr (deuteriochloroform): 169.0, 168.9, 165.4, 165.2, 151.5, 151.2, 139.0, 138.7, 132.4, 123.4, 112.5, 104.5, 94.7, 93.8, 60.4, 60.1, 16.8, 14.3, and 14.2 ppm.

Anal. Calcd. for $C_{23}H_{30}N_2O_8$: C, 59.73; H, 6.54; N, 6.06. Found: C, 59.82; H, 6.58; N, 5.98.

1,4,7,10-Tetrahydro-2,8-dicarboethoxy-6-methyl-1,7-phenanthroline-4,10-dione (**17**).

Paraffin oil (500 ml) was heated to 260°, at this temperature 30 g (0.065 mole) of 2,4-bis(2,2-dicarbethoxyvinylamino)toluene qas quickly added and the solution was held at 250 ±5° for 20 minutes (longer time periods resulted in charring). The solution was allowed to cool to 80°, and poured into 300 ml of hexane. The mixture was allowed to stand at 50° for two hours and the resulting solid was filtered, washed with three 150 ml portions of hexane and two 100 ml portions of *p*-dioxane. The product was triturated using acetone (50°), filtered, and crystallized from dimethylformamide twice. A yield of 17 g (81%) of **17** mp 294-298°, was obtained. ^{13}C nmr (DMSO-d_6): 176.6, 171.5, 164.2, 163.6, 143.8, 141.0, 138.0, 129.7, 122.8, 122.2, 113.0, 112.7, 112.2, 59.7, 59.3, 16.8, and 13.9 ppm.

Anal. Calcd. for $C_{19}H_{18}N_2O_6{\cdot}\frac{1}{2}H_2O$: C, 60.16; H, 5.05. Found: C, 60.43; H, 4.96.

1,4,7,10-Tetrahydro-2,8-dicarboxy-6-methyl-1,7-phenanthroline-4,10-dione (**18**).

A mixture of 500 ml of 6*M* hydrochloric acid and 16 g (0.05 mole) of **17** was heated at reflux overnight. The resulting solid was filtered, washed with copious amounts of water and after drying yielded 15.1 g (96%) of 2,8-dicarboxy-6-methyl-1,7-phenanthroline-4,10-dione, mp >400°. No crystallization solvent was found and the compound was used directly in the next step; ^{13}C nmr (sodium deuterioxide in deuterium oxide, *p*-dioxane as reference): 176.4, 176.0, 174.5, 171.7, 153.2, 151.9, 151.7, 140.8, 140.1, 132.8, 124.8, 120.8, 120.6, 120.3, and 19.2 ppm.

1,4,7,10-Tetrahydro-6-methyl-1,7-phenanthroline-4,10-dione (**19**).

Paraffin oil (400 ml) was heated to 330° and 14.0 g (0.045 mole) of **18** was added, the temperature of the mixture was held constant at 320°, under nitrogen, for two hours. The mixture was allowed to cool to 80° and was poured into 400 ml of hexane. The mixture was allowed to stand (50°) for two hours, filtered, washed with copious amounts of acetone, three 100 ml portions of methylene chloride and dried to yield 8.3 g (81%) of the 6-methyl-1,7-phenanthroline-4,10-dione, mp >400°. No recrystallization solvent was found and the compound was used directly in the next step; ^{13}C nmr: (sodium deuterioxide in deuterium oxide, *p*-dioxane as reference): 177.1, 176.7, 151.4, 151.1, 140.8, 137.5, 132.5, 123.0, 118.8, 112.7, 112.4, 110.6, and 19.5 ppm.

1,10-Dichloro-6-methyl-1,7-phenanthroline (**20**).

The 6-methyl-1,7-phenanthroline-4,10-dione (8.0 g, 0.035 mole) and 60 ml of phosphorus oxychloride were heated at reflux for two hours and allowed to cool to 50°. The mixture was hydrolyzed by dropwise addition to a stirred mixture of ammonium hydroxide and ice during which care was taken to keep the solution cold and basic. The hydrolyzed solution was filtered and washed with two 200 portions of *p*-dioxane. The product was recrystallized twice from ethanol to yield 5.5 g (60%), mp 155-157°; ^{13}C nmr (deuteriochloroform): 149.2, 146.6, 125.8, 122.5, 143.3, 141.2, 138.0, 124.4, 151.3, 146.2, 124.9, and 123.1 ppm.

Anal. Calcd. for $C_{13}H_8Cl_2N_2$: C, 59.34; H, 3.06; N, 10.65. Found: C, 59.26; H, 3.11; N, 10.64.

4,10-Bis-(3'-dimethylaminopropylamino)-6-methyl-1,7-phenanthroline (**3**).

6-Methyl-1,10-dichloropyrido-1,7-phenanthroline (**20**) (4 g, 0.015 mole) and 35 ml of 3-diethylaminopropylamine were heated with an oil bath at 165-170° for eight hours. The reaction mixture was allowed to cool to room temperature and 100 ml of 10% sodium hydroxide solution added, and the mixture was stirred for two hours. The basic mixture was extracted with 250 ml of ethyl ether. The ether was removed under reduced pressure to yield a brown oil. The oil was dissolved in 100 ml of methanol, treated with charcoal, filtered, and the methanol removed under reduced pressure to obtain a brown oil. The oil was suspended in 50 ml of water and crystals appeared. The precipitate was collected washed with cold water. The solid on standing becomes an oil (2.0 g, 34%); ^{13}C nmr (deuteriochloroform): 154.9, 150.2, 149.9, 149.1, 147.9, 146.1, 133.8, 120.1, 113.4, 112.1, 100.7, 98.9, 59.1, 57.4, 45.3, 43.8, 40.6, 20.3 and 14.0 ppm.

Anal. Calcd. for $C_{23}H_{34}N_6$: C, 70.01; H, 8.69; N, 21.30. Found: C, 69.84; H, 8.70; N, 21.22.

2,6-Bis(1,2-dicarbomethoxyvinylamino)toluene (**21**).

A solution of 2,6-diaminotoluene (33 g, 0.3 mole) dissolved in 350 ml methanol:chloroform (10:1) was treated dropwise with dimethyl acetylenedicarboxylate (85.2 g, 0.6 mole) in 100 ml methanol and allowed to stand overnight. The resulting precipitate was filtered, crystallized twice from a methylene chloride:chloroform (10:1), to yield 116 g (95%) of **21**, mp 190.5-192.5°, lit (3a) mp 190-195°; ^{13}C nmr (deuteriochloroform): 169.8, 164.2, 148.7, 139.8, 125.7, 124.0, 118.7, 93.1, 52.5, 51.1, and 12.3 ppm.

Anal. Calcd. (12) for $C_{19}H_{22}N_2O_8$: C, 56.16; H, 5.46; N, 6.89. Found: C, 56.11; H, 5.50; N, 6.85.

1,4,6,9-Tetrahydro-2,8-dicarbomethoxy-10-methylpyrido[3,2-*g*]quinoline-4,6-dione (**22**).

2,6-bis(1,2-Dicarbomethoxyvinylamino)toluene (**21**) (40 g, 0.098 mole) in 500 ml of diphenyl ether, under a nitrogen atmosphere, was heated rapidly (30 minutes) to 260-265° and maintained at that temperature for 45 minutes. The reaction mixture was cooled to room temperature, poured into 500 ml of petroleum ether (90-120°), stirred well, filtered, and washed three times each with petroleum ether, chloroform, and carbon tetrachloride. A crystallization solvent was not found; however, the compound was analytically pure after the above washing procedure. A yield of 31.2 g (93%) of **22** was obtained, mp 290-291°, lit (3a) mp

291-292.5°; ^{13}C nmr (CF_3CO_2H, *p*-dioxane as reference): 178.9, 161.1, 145.1, 139.6, 125.5, 121.8, 118.7, 107.0, and 56.0 ppm.

Anal. Calcd. (12) for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18. Found: C, 59.80; H, 4.19; N, 8.12.

1,4,6,9-Tetrahydro-2,8-dicarboxy-10-methylpyrido[3,2-*g*]quinoline-4,6-dione (**23**).

1,4,6,9-Tetrahydro-2,8-dicarbomethoxy-10-methylpyrido[3,2-*g*]quinoline-4,6-dione (**22**) (30 g, 0.088 mole) and 600 ml of 7% potassium hydroxide were heated under reflux overnight. The mixture was treated with charcoal, filtered, and the pH was adjusted to 2 with 6 *M* hydrochloric acid. The solid acid was filtered, washed three times each with acetone, *p*-dioxane, and chloroform. The compound was dried, dissolved in a 10% potassium hydroxide solution, and the *p*H was adjusted to 2 with 6 *M* hydrochloric acid. The resulting solid was filtered, washed with copious amounts of water and three times with chloroform. The product was dried to yield 26.6 g (94%) of (**23**). No crystallization solvent was found and the material was used directly in the next step, mp >450°; ^{13}C nmr (sodium deuteroxide in deuterium oxide, *p*-dioxane as reference): 179.3; 171.7, 153.3, 143.2, 123.3, 122.7, 119.2, 105.6, and 11.7 ppm.

1,4,6,9-Tetrahydro-10-methylpyrido[3,2-*g*]quinoline-4,6-dione (**24**).

1,4,6,9-Tetrahydro-2,8-dicarboxy-10-methylpyrido[3,2-*g*]quinoline-4,6-dione (**23**) (15 g, 0.048 mole) in 325 ml of paraffin oil was rapidly heated (45 minutes) to 338 ±5° and held at this temperature for 3 hours, during which time it was flushed with nitrogen at 30 minute intervals. The reaction mixture was poured into 700 ml of petroleum ether (90-120°), and allowed to stand. The solution was filtered, washed with several portions of *p*-dioxane, and dried. The solid was dissolved in a 15% sodium hydroxide solution, treated with charcoal, filtered, and the pH was adjusted to 2 with concentrated hydrochloric acid. The solid was washed with copious amounts of *p*-dioxane, followed by several 200 ml portions of water and to yield 9.7 g (89%) of **24** mp 340-344° dec. No crystallization solvent was found and the product was used directly in the next step; ^{13}C nmr (sodium deuteroxide in deuterium oxide; *p*-dioxane as reference): 176.3, 153.1, 146.6, 126.3, 124.3, 118.2, 105.8, and 13.0 ppm.

4,6-Dichloro-10-methylpyrido[3,2-*g*]quinoline (**25**).

The 10-methylpyrido[3,2-*g*]quinoline-4,6-dione (**24**) (8.0 g, 0.35 mole) and 60 ml of phosphorus oxychloride were heated under reflux for two hours. The mixture was cooled to 50° and added dropwise to a stirred mixture of ammonium hydroxide and ice; care was taken to keep the solution cold and basic. The product was filtered and washed with three 200 ml portions of water, dioxane and *p*-xylene. The compound was recrystallized first from a ethyl ether:chloroform (1:1), second from petroleum ether (90-120°) and third from cyclohexane to yield 7.4 g (80%) of light yellow needles of 4,6-dichloro-10-methylpyrido[2,3-*g*]quinoline (**25**), mp 202-204°C; ^{13}C nmr (deuteriochloroform): 149.9, 145.4, 142.9, 137.7, 124.6, 120.7, 118.1, and 12.9 ppm.

Anal. Calcd. for $C_{13}H_8Cl_2N_2$: C, 59.34; H, 3.06; N, 10.65. Found: C, 59.30; H, 3.08; N, 10.66.

4,6-Bis-(3'-dimethylaminopropylamino)-10-methylpyrido[3,2-*g*]quinoline (**4**).

4,6-dichloro-10-methylpyrido[3,2-*g*]quinoline (**25**) (3 g, 0.011 mole) and 45 ml of 3-dimethylaminopropylamine were heated with an oil bath at 165-175° for two hours, allowed to cool to room temperature, and added to 100 ml of a 5% potassium hydroxide solution. The mixture was extracted with three 250 ml portions of chloroform. The combined fractions of chloroform were removed under reduced pressure to leave an orange oil. The oil was dissolved in 100 ml of isopropyl alcohol, treated with charcoal, filtered and the isopropyl alcohol removed under reduced pressure to yield an orange oil. The orange oil was added dropwise to 50 ml of a boiling petroleum ether (90-120°):benzene (10:1), filtered, the volume reduced by one-fourth, and allowed to cool to room temperature. Cooling in an ice bath produced orange flakes after approximately six hours. The solid was washed with cold toluene, and dried to yield 3.9 g (91%) of **4** mp 76-78°; ^{13}C nmr (deuteriochloroform): 151.2, 150.2, 145.5, 133.8, 117.3, 109.4, 96.2, and 13.1 ppm.

Anal. Calcd. for $C_{23}H_{34}N_6 \cdot \frac{1}{2}H_2O$: C, 68.45; H, 8.74; N, 20.82. Found: C, 68.16; H, 8.87; N, 21.00.

p-bis(1,2-Dicarbomethoxyvinylamino)benzene (**26**).

Dimethyl acetylene dicarboxylate (85.2 g, 0.6 mole) in 100 ml methanol was added dropwise to *p*-phenylenediamine (33 g, 0.3 mole) dissolved in 330 ml of methanol and the resulting mixture was allowed to stand overnight. The solid which separated was filtered and recrystallized twice from methanol to yield 100 g of **26** (85%) mp 129° (lit (5) mp 129-130°); ^{13}C nmr (deuteriochloroform): 169.4, 164.2, 147.7, 136.6, 121.5, 93.3, 52.6, and 51.0 ppm.

1,4,7,10-Tetrahydro-3,8-dicarbomethoxy-4,7-phenanthroline-1,10-dione (**27**).

The enamine **26** (20 g, 0.051 mole) was added to 300 ml of diphenyl ether under a nitrogen atmosphere and the mixture was rapidly heated (*ca* 30 minutes) to 248 ±5° and this temperature was maintained for one hour; after ten minutes orange-yellow flakes precipitated. The reaction mixture was allowed to cool to room temperature, filtered, and the orange-yellow filter cake was washed with three portions of petroleum ether (90-110°) and two protions of acetone. A suitable recrystallization solvent was not found. A yield of 16.4 g (98%) of **27**, mp 262-263° dec, was obtained (lit (5) mp 263-264°); ^{13}C nmr (trifluoroacetic acid; *p*-dioxane as reference): 179.3, 162.0, 142.7, 139.5, 129.7, 120.8, 115.5, and 55.8 ppm.

Anal. Calcd. (9) for $C_{16}H_{12}N_2O_6$: C, 58.54; H, 3.68; N, 8.53. Found: C, 58.66; H, 3.73; N, 8.47.

1,4,7,10-Tetrahydro-3,8-dicarboxy-4,7-phenanthroline-1,10-dione (**28**).

A mixture of the dione **27** (15.0 g, 0.046 mole) and 400 ml of an aqueous solution of 6*M* potassium hydroxide was heated under reflux for 24 hours. The solution was filtered hot and the filter cake washed twice with acetone and ethyl ether. The resulting solid was dissolved in a sodium hydroxide solution (4%) and treated with charcoal. The basic solution was filtered and the p*H* was adjusted to 2 with concentrated hydrochloric acid. The mixture was filtered, the cake washed twice each with water acetone and ethyl ether to yield 13.2 g (96%) of **28**. A suitable recrystallization solvent was not found; therefore the compound was used directly in the next step, lit (3a) mp >320°, observed mp >410°; ^{13}C nmr (sodium deuteroxide in deuterium oxide; *p*-dioxane as reference): 174.1, 169.1, 155.0, 149.9, 132.6, 119.7, and 111.1 ppm.

1,4,7,10-Tetrahydro-4,7-phenanthroline-1,10-dione (**29**).

A mixture of **28** (11 g, 0.037 mole) in 250 ml paraffin oil, under a nitrogen atmosphere, was rapidly heated (45 minutes) in an oil bath to 360° and maintained there for 8 hours. The reaction mixture was flushed with nitrogen at one hour intervals since constant nitrogen flow facilitates sublimation of the product. The reaction mixture was cooled to 70° and quickly filtered, washed three times with petroleum ether (90-110°) and the filter cake was suspended in 350 ml sodium hydroxide solution (4%) and treated with charcoal. The basic solution was filtered and adjusted to *p*H 2 with concentrated hydrochloric acid. The solid was filtered, washed twice with a dilute hydrochloric acid solution, acetone, and petroleum ether (30-60°), respectively, to yield **29** (89%), mp 389-392° dec. No recrystallization solvent was found and the compound was used directly in the next step; ^{13}C nmr (sodium deuteroxide in deuterium oxide; *p*-dioxane as reference): 167.8, 149.1, 131.1, 119.0 and 111.4 ppm (the fully coupled spectrum shows that the signal at 149.1 represents 2 carbon resonances).

1,10-Dichloro-4,7-phenanthroline (**30**).

The dione **29** (7.0 g, 0.033 mole) was added to 30 ml of phosphorus oxychloride and the mixture was heated under reflux for thirty minutes at which time three drops of water were added and reflux was continued for

six additional hours. The reaction mixture was added dropwise to a rapidly stirred mixture of ammonium hydroxide and ice; care was taken to keep the solution cold basic. The solution was filtered, washed with copious amounts of water and dried. The compound was crystallized once from ethanol and then from a two:one methylene chloride: chloroform solution, which afford 8.1 g (98%) of 1,10-dichloro-4,7-phenanthroline (**30**), mp 232-234°C, lit (8) mp 237-238°C; ^{13}C nmr (deuteriochloroform): 150.8, 149.7, 172.9, 132.3, and 122.5 ppm (the fully coupled spectrum shows that 132.2 represents 2 carbon resonances).

Anal. Calcd. for $C_{12}H_6Cl_2H_2$: C, 57.86; H, 2.43; N, 11.24. Found: C, 57.72; H, 2.48; N, 11.20.

4-(3'-Dimethylaminopropyl)pyrrolo[*lmn*][4,7]phenanthroline (**5**).

1,10-dichloropyrido[2,3-*f*]quinoline (**30**) (1.0 g, 0.004 mole) and 30 ml of 3-dimethylaminopropylamine were heated with an oil bath at 165-170° for eight hours. The reaction mixture was allowed to cool to room temperature, 100 ml of 10% sodium hydroxide solution added, and the mixture stirred for one hour. The mixture was extracted with 250 ml of ethyl ether (phase separation occurred after two days), the ethyl ether layer was separated and the volatiles were removed under vacuum to yield a brown oil. The oil was dissolved in methanol (100 ml), treated with charcoal, filtered and the methanol removed under reduced pressure to obtain a brown oil. The brown oil was added to 20 ml of hot petroleum ether (90-120°):benzene (8:1) solution, filtered, the volume was reduced by one-fourth, allowed to cool to room temperature, placed in an ice bath and after 4 hours creamy-white crystals were collected, washed with cold benzene and dried to yield 1.0 g (87%) of **5**, mp 108.5-110°; ^{13}C nmr (deuteriochloroform): 150.0, 145.3, 147.5, 130.6, 116.8, 102.6, 55.8, 45.3, 42.7 and 27.7 ppm.

Anal. Calcd. for $C_{17}H_{18}N_4 \cdot H_2O$: C, 68.90; H, 6.80; N, 18.90. Found: C, 68.94; H, 6.82; N, 18.88.

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