Synthesis of Some Novel Derivatives of 1,10-Phenanthroline

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The synthesis is described of a set of new *N*-heterocyclic compounds which are derivatives of 1,10-phenanthroline. The compounds are designed to be general purpose chelating agents which could function as tri-, tetra- or hexadentate ligands with transition metal ions. Fused-ring molecular components have been included in the design of the compounds so that they may function as binding agents to DNA through intercalation. This includes the synthesis of substituted derivatives of pyrazino[2,3-*f*][1,10]phenanthroline and dipyrido[3,2-*a*:2'3'-c]phenazine.

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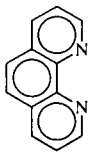
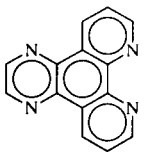
Introduction.

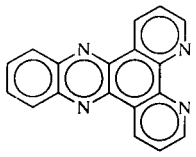
One of the earliest and most extensively studied *N*-heterocyclic chelating agents is the bidentate 1,10-phenanthroline. It, and related *N*-heterocycles, are widely employed as metal-binding components in all aspects of coordination chemistry, and in many of its modern applications to areas such as supramolecular chemistry and bioinorganic chemistry.



1,10-Phenanthroline



Pyrazino[2,3-*f*][1,10]phenanthroline



Dipyrido[3,2-*a*:2',3'-*c*]phenazine

Much interest has been generated by initial reports [1,2] that simple substitution-inert octahedral metal complexes derived from 1,10-phenanthroline are capable of selectively binding DNA through intercalation. This has contributed greatly to the rapid expansion of the field of metal-DNA chemistry [3-5]. For this purpose, ligands have been developed with extended aromatic surface areas, such as dipyrido[3,2-*a*:2'3'-*c*]phenazine [6] and dipyrido[3,2-*f*:-2'3'-*h*]quinoxaline [7-9], which thereby enhances the intercalating capability of their metal complexes. Our goal has been to produce a set of new *N*-heterocyclic ligands derived from 1,10-phenanthroline which may find general use in binding metal ions to DNA. In these derivatives we have sought to increase both the aromatic area available for intercalation and the multidentate character of the ligands by the incorporation of side-chains containing potential metal-ion binding groups in the 2- and 9- positions of the 1,10-phenanthroline structure. The synthesis and spectral characterisation of these products is reported below. An assessment of their metal ion binding properties is under investigation.

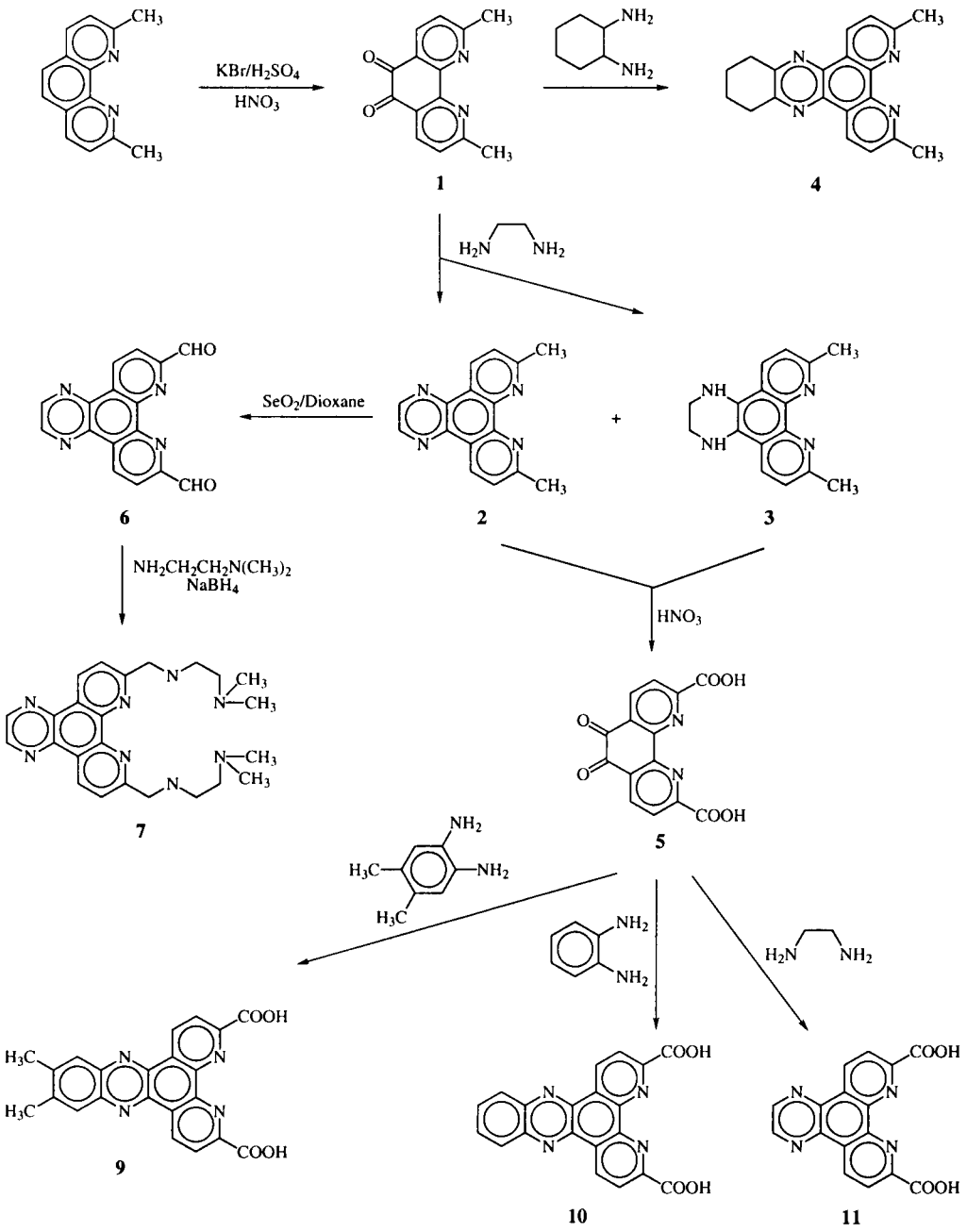
Results and Discussion.

The various compounds isolated (**1-28**) are substitutional derivatives of 1,10-phenanthroline pyrazino[2,3-*f*]-[1,10]phenanthroline or dipyrido[3,2-*a*:2',3'-*c*]phenazine. In general, relatively high yields ranging 40-70% were obtained for the products, which have been characterised by proton nmr and mass spectral methods.

The synthesis of a set of quinoxaline derivatives based on 2,9-dimethyl-1,10-phenanthroline is depicted in Scheme A. Initial oxidation of 2,9-dimethyl-1,10-phenanthroline with potassium bromide/sulfuric acid/nitric acid gave 2,9-dimethyl-1,10-phenanthroline-5,6-dione **1**, which then was allowed to react with 1,2-diaminoethane under mild conditions to give 7,10-dimethylpyrazino-[2,3-*f*][1,10]phenanthroline **2** as a main product and 7,10-dimethyl-1,2,3,4-tetrahydropyrazino[2,3-*f*][1,10]phenanthroline **3** as a byproduct. Reaction of 1,2-diaminoethane with **1** under reflux produced compound **2** only. By comparison, reaction of *trans*-1,2-diaminocyclohexane with **1** yielded 3,6-dimethyldipyrido[3,2-*a*:2',3'-*c*]phenazine (**4**) as the sole product. An attempt to convert **3** to **2** with manganese dioxide oxidation was unsuccessful. Oxidation of either **2** or **3** with concentrated nitric acid gave the dicarboxylic acid **5** in high yield. However, mild oxidation of **2** with selenium dioxide gave the dialdehyde derivative **6**. This was treated with *N,N*-dimethyl-1,2-diaminoethane followed by reduction to give the potential hexadentate ligand **7**. Reaction of the compound **5** with various 1,2-diamines gave **9**, **10** and **11**. Each are potential tetradentate ligands capable of DNA binding *via* their extended phenanthroline or phenazine components.

The synthesis of a similar set of hydrazino derivatives is shown in Scheme B. 7,10-Dichloropyrazino[2,3-*f*]-[1,10]phenanthroline **12** was prepared by reaction of 1,2-diaminoethane with 2,9-dichloro-1,10-phenanthroline-5,6-

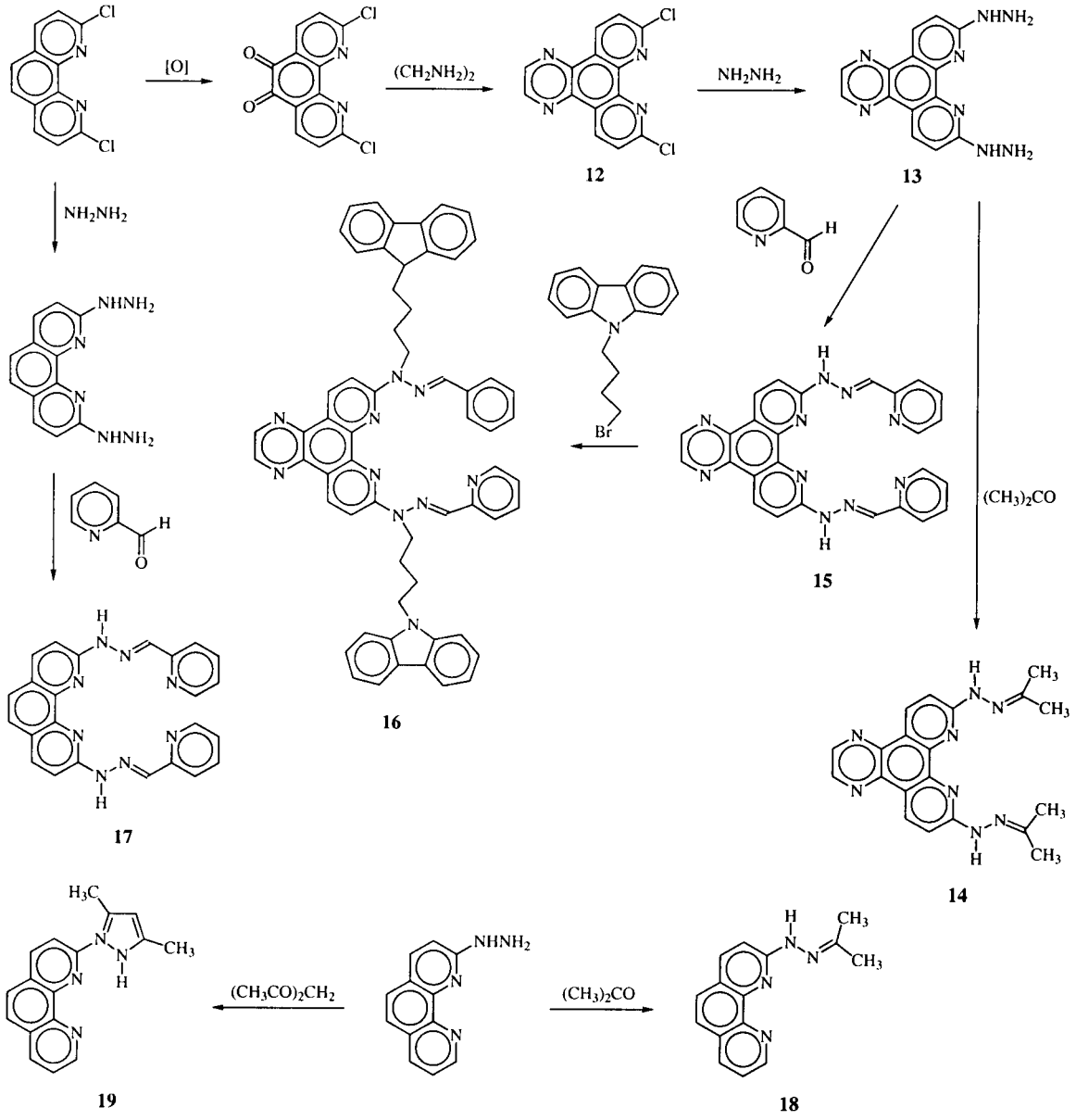
Scheme A



dione. Treatment of **12** with hydrazine hydrate gave the dihydrazino derivative **13**, which when treated with pyridine-2-carboxaldehyde afforded the potential N_6 hexadentate ligand **15**. Compound **17** was synthesised by an analogous method. Alkylation of **15** with bromobutylcarbazole gave **16**, in which both the pyrazinophenanthroline and carbazole fragments are potential intercalators of DNA. However, unfortunately this compound has proved to be highly insoluble in many solvents. The potentially tetradentate compound **14** was isolated unintentionally upon washing **13** with acetone. Its tridentate analogue **18** was obtained by a similar method. The pyrazole derivative **19** was obtained by an analogous reaction involving pentan-2,4-dione.

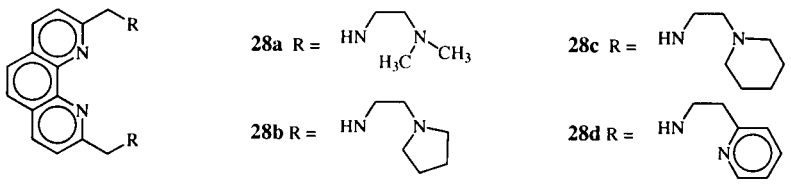
General methods for the synthesis of potential tetra- or hexadentate ligands derived from 1,10-phenanthroline with α-aminoacid sidechains are depicted in Scheme C. Reaction of *S*-alanine ethyl ester hydrochloride with either 1,10-phenanthroline-2-carbonyl chloride or 1,10-phenanthroline-2,9-dicarbonyl chloride gave the ester derivatives **21** and **23**, respectively. Similarly, reaction of glycine- or glutamic acid

Scheme B

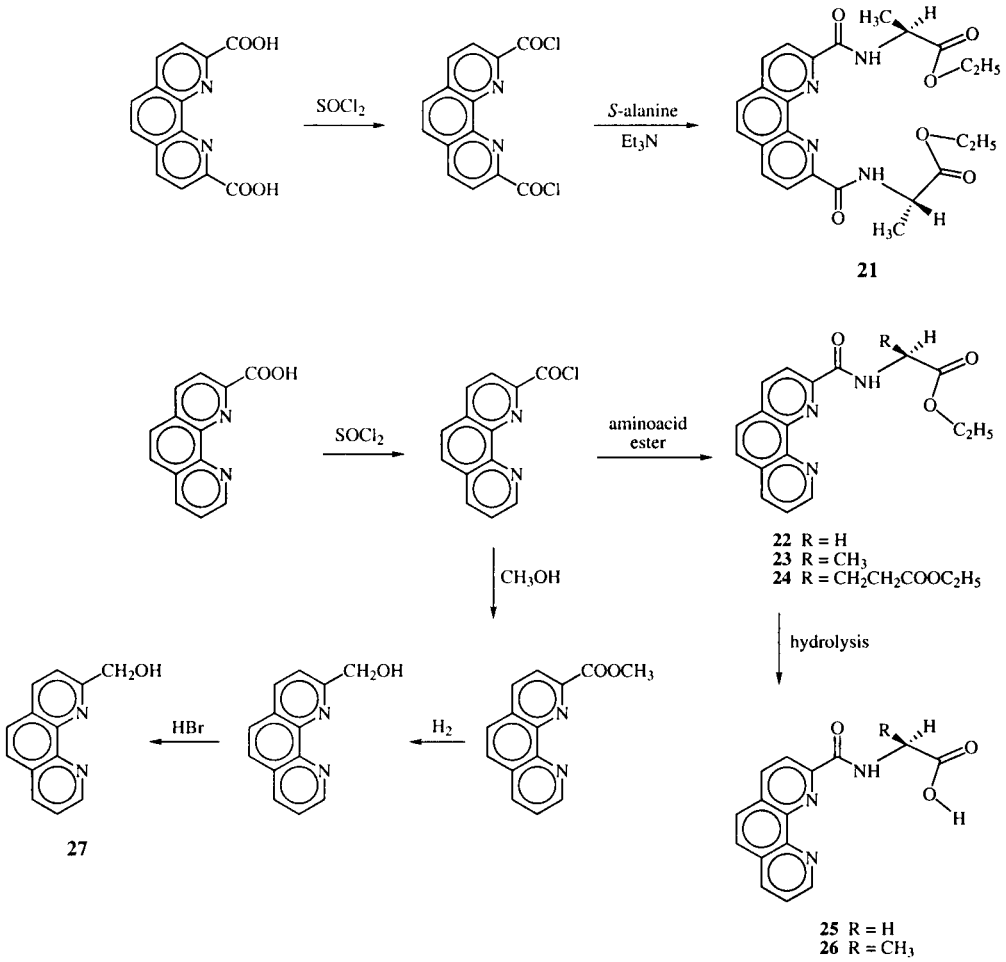


ester hydrochlorides afforded the esterified compounds **22** and **24**. Such compounds could provide a means of linking the 1,10-phenanthroline moiety to oligo- or polypeptides. Simple hydrolysis gave the compounds **25** and **26**. Compound **27** may be utilised as a general polyamine ligand synthetic precursor by reaction with any chosen amine.

A further set of potential N_6 hexadentate ligands also was synthesised. Compounds **28a-d** were obtained by templating 1,10-phenanthroline-2,9-dicarboxaldehyde with magnesium chloride prior to reaction with the corresponding amines. This was followed by reduction with sodium borohydride.



Scheme C



EXPERIMENTAL

The ^{1}H nmr spectra were recorded on a Varian 400 XL instrument and electrospray mass spectra were obtained on a Fison's Quattro-II triple-quadrupole mass spectrometer. Elemental analyses were determined in the Microanalytical Laboratory of the School of Chemistry, University of New South Wales. Carbazole, sodium borohydride, triethylamine, 1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline, pyridine-2-carboxaldehyde, *trans*-1,2-diaminocyclohexane, protected amino acids and the amine precursors used to synthesise the compounds **28a-d** were purchased from the Sigma-Aldrich Chemical Company and used as obtained. Thionyl chloride and hydrazine hydrate were purchased from Crown Scientific Pty Ltd (Australia). Chloroform, dichloromethane, dioxane and methanol were used in anhydrous forms throughout. The synthetic precursors 2,9-dichloro-1,10-phenanthroline-5,6-dione [10], 2,9-dichloro-1,10-phenanthroline [11], 2,9-dihydrazino-1,10-phenanthroline [12], 1,10-phenanthroline-2,9-dicarboxaldehyde [13], 1,10-phenanthroline-2,9-dicarboxylic acid [13], 1,10-phenanthroline-2-carboxylic acid [14] and 2-hydroxymethyl-1,10-phenanthroline [15] were prepared according to literature methods. Previously unreported spectral data for some of these compounds are given below.

2-Hydroxymethyl-1,10-phenanthroline.

This compound had ms: m/z 212 (M^++2), 211 (M^++1); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.08 (dd, 1H, J_1 = 1.5 Hz, J_2 = 3.8 Hz), 8.44 (m, 2H), 7.90 (m, 3H), 7.72 (dd, 1 H, J_1 = 4.5, J_2 = 6.5 Hz), 5.41 (br, H-O), 4.89 (s, 2H).

1,10-Phenanthroline-2-carboxylic Acid.

This compound had ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.12 (dd, 1H, J_1 = 1.9 Hz, J_2 = 4.8 Hz), 8.66 (d, 1H, J = 8.3 Hz), 8.55 (dd, 1H, J_1 = 1.8 Hz, J_2 = 8.0 Hz), 8.37 (d, 1H, J = 8.3 Hz), 8.15 (d, 1H, J = 9.0 Hz), 8.07 (d, 1H, J = 9.0 Hz), 7.83 (dd, 1H, J_1 = 7.4 Hz, J_2 = 8. 0 Hz).

2,9-Dichloro-1,10-phenanthroline.

This compound had ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.60 (d, 2H, J = 8.6 Hz), 8.09 (s, 2H), 7.87 (d, 2H, J = 8.6 Hz).

2,9-Dihydrazino-1,10-phenanthroline.

This compound had ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.91 (d, 2H, J = 9.1 Hz), 7.35 (s, 2H), 7.0 (d, 2H, J = 9.2 Hz).

2,9-Dimethyl-1,10-phenanthroline-5,6-dione (**1**).

A round-bottom flask containing 2,9-dimethyl-1,10-phenanthroline (3.35 g, 16 mmoles) and potassium bromide (19.0 g, 160

mmoles) was cooled in an ice bath. Concentrated sulfuric acid (60 ml) was added dropwise while stirring followed by slow addition of concentrated nitric acid (30 ml). After all of the 2,9-dimethyl-1,10-phenanthroline had dissolved in the acid medium the reaction mixture was heated under reflux in an oil bath at 80° for 3 hours, then cooled to room temperature and the solution poured slowly into deionized water (800 ml). The resulting yellow solution was carefully neutralized with sodium bicarbonate and extracted with chloroform. The extracts were washed with water and then dried over anhydrous magnesium sulfate. The chloroform was removed under reduced pressure to leave a yellow residue which was recrystallized from dioxane to yield 3.5 g (78%) of **1** in a crystalline monohydrate form; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.5 (d, 2H, J = 8.0 Hz), 7.51 (d, 2H, J = 8.0 Hz), 2.66 (s, 6H); ms: m/z 238 (M^+), 210 (M^++2 -2CH_3).

Anal. Calcd. for $C_{14}H_{10}N_2O_2 \cdot H_2O$: C, 65.6; H, 4.7; N, 10.9. Found: C, 66.0; H, 4.7; N, 10.3.

7,10-Dimethylpyrazino[2,3-*f*][1,10]phenanthroline (**2**) and 7,10-Dimethyl-1,2,3,4-tetrahydropyrazino[2,3-*f*][1,10]phenanthroline (**3**).

To a solution of dione compound **1** (3.7 g, 14 mmoles) in absolute ethanol (200 ml) was added 1,2-diaminoethane (1.0 g, 16 mmoles). The reaction solution was heated gently for 16 hours at 50°, then concentrated under reduced pressure to 100 ml and allowed to stand at room temperature for 3-4 hours. The orange precipitate which formed was filtered and recrystallized from ethanol to yield 0.63 g (17%) of compound **3**; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.23 (d, 2H, J = 8.6 Hz), 7.40 (d, 2H, J = 8.5 Hz), 5.58 (br, 2 NH), 3.39 (t, 4H, J = 1.9 Hz), 2.69 (s, 6H); ms: m/z 265 (M^++ 1), 264 (M^+), 263 (M^+- 1).

Anal. Calcd. for $C_{16}H_{16}N_4$: C, 72.7; H, 6.1; N, 21.2. Found: C, 72.3; H, 6.2; N, 21.0.

The filtrate was concentrated under reduced pressure to 30 ml and was allowed to stand overnight. The solid which formed was filtered and recrystallized from methanol to yield 1.8 g (50%) of compound **2**; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.30 (d, 2H, J = 8.3 Hz), 9.10 (s, 2H), 7.76 (d, 2H, J = 8.3 Hz), 2.84 (s, 6H); ms: m/z 261 (M^++1), 260 (M^+), 259 (M^+-1).

Anal. Calcd. for $C_{16}H_{12}N_4$: C, 73.8; H, 4.6; N, 21.5. Found: C, 73.6; H, 4.7; N, 21.5.

3,6-Dimethyl-10,11,12,13-tetrahydrodipyrido[3,2-*a*:2',3'-*c*]-phenazine (**4**).

To a solution of **1** (3.07 g, 12 mmoles) in absolute ethanol (150 ml) was added *trans*-1,2-diaminocyclohexane (1.37 g, 12 mmoles) and the mixture refluxed for 5 hours. The solution was allowed to cool and the precipitate which formed then was filtered. The filtrate was decolourized with activated charcoal, ethanol was removed by rotary evaporation and then methanol was added to prompt precipitation of a pale yellow solid, which then was filtered. The combined solid fractions were recrystallized from methanol to give 2.7 g (76%) of compound **4**; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.23 (d, 2H, J = 8.2 Hz), 7.72 (d, 2H, J = 8.3 Hz), 3.18 (br m, 4H), 2.85 (s, 6H), 2.04 (br m, 4H); ms: m/z 318 (M^++4), 317 (M^++3), 315 (M^++1), 239.

Anal. Calcd. for $C_{20}H_{18}N_4 \cdot 0.5H_2O$: C, 74.3; H, 5.9; N, 17.3. Found: C, 74.0; H, 6.2; N, 17.2.

1,10-Phenanthroline-5,6-dione-2,9-dicarboxylic Acid (**5**).

To compound **2** (3.7 g, 14 mmoles) in crude form was added slowly concentrated nitric acid (50 ml). The resulting solution was refluxed for 3 hours, cooled to room temperature and then poured over crushed ice. The yellow precipitate was filtered, washed with ice cold water (10 ml) and recrystallized from methanol to yield 3.8 g (78%) of **5**; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.60 (d, 2H, J = 8.1 Hz), 8.21 (d, 2H, J = 8.1 Hz), 13.70 (br, 2H); ms: m/z 298 (M^+), 297 (M^+-1), 254 (M^+-COO), 253 (M^+-COOH), 209 (M^++1 -2COOH).

Anal. Calcd. for $C_{14}H_6N_2O_6 \cdot 2H_2O$: C, 50.3; H, 3.0; N, 8.4. Found: C, 50.2; H, 3.8; N, 9.0.

Pyrazino[2,3-*f*][1,10]phenanthroline-3,6-dicarboxaldehyde (**6**).

Compound **2** (2.6 g, 10.0 mmoles) and selenium dioxide (5.0 g) in dioxane (100 ml) were heated under reflux for 4 hours then the mixture was filtered through celite. The dioxane was removed under reduced pressure and the residue recrystallized from ethanol to yield 1.58 g (55%) of **6**; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 10.40 (s, 2H), 9.65 (d, 2H, J = 8.4 Hz), 9.23 (s, 2H), 8.42 (d, 2H, J = 8.3 Hz); ms: m/z 290 (M^++2), 289 (M^++1). Prolonged reflux for 24 hours afforded the monocarboxaldehyde monocarboxylic acid; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 10.34 (s, 1H), 9.53 (m, 2H), 9.16 (m, 2H), 8.47 (dd, 2H, J_1 = 5.0 Hz, J_2 = 8.4 Hz), 8.34 (dd, 2H, J_1 = 1.6 Hz, J_2 = 8.3 Hz).

3,6-Bis(*N',N'*-dimethylaminoethyl-*N*-aminomethyl)pyrazino-[2,3-*f*][1,10]phenanthroline (**7**).

Compound **6** (1.58 g, 5.5 mmoles) and dry magnesium chloride (0.42 g) were suspended in dry methanol (100 ml) under nitrogen with constant stirring until all solid had dissolved. To this was added *N,N*-dimethylaminoethylamine (0.92 ml, 11.0 mmoles) and stirring was continued for 48 hours at 25°. The mixture was refluxed for 0.5 hour and then cooled to 0° while sodium borohydride (4.0 g) was added during 0.5 hour. After 24 hours of stirring at room temperature, deionized water (50 ml) was added and the mixture was concentrated under reduced pressure to half volume. The mixture was extracted by dichloromethane until the extracts were colourless. These were combined, washed with water, dried over magnesium sulfate and the solvent removed to yield 1.1 g (40%) of **7** as a red solid; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.36 (d, 2H, J = 8.5 Hz), 9.03 (s, 2H), 7.93 (d, 2H, J = 8.5 Hz), 4.18 (s, 4H), 2.75 (t, 4H, J = 6.5 Hz), 2.42 (t, 4H, J = 6.5 Hz), 2.15 (s, 12H); ms: m/z 434 (M^++2), 433 (M^++ 1).

3,6-Bis(pyrrolidinoethylaminomethyl)pyrazino[2,3-*f*]-[1,10]phenanthroline (**8**).

This compound was prepared by a method similar to that used in preparation of compound **7**. Compound **6** (1.2 g, 4.2 mmoles), magnesium chloride (0.4 g), *N*-pyrrolidylaminoethane (1.0 ml, 8.4 mmoles) and sodium borohydride (2.0 g) gave compound **8** as a thick oil in (20%) yield; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.36 (d, 2H, J = 8.5 Hz), 9.08 (s, 2H), 7.97 (d, 2H, J = 8.5 Hz), 4.18 (s, 4H), 2.77 (t, 4H, J = 6.4 Hz), 2.61 (t, 4H, J = 6.4 Hz), 2.5 (br, 4H), 1.67 (br, 4H).

2,3-Dimethylpyrido[3,2-*a*:2'3'-*c*]phenazine-3,6-dicarboxylic Acid (**8**).

A 1:1 mixture of 1,2-diamino-4,5-dimethylbenzene (0.75 g, 5.5 mmoles) and compound **5** (1.83 g, 5.5 mmoles) in absolute ethanol was refluxed for 72 hours. The reaction mixture was allowed to cool and the precipitate which had formed was filtered and recrystallized from ethanol to yield 1.2 g (66%) of **9**; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.67 (d, 2H, J = 8.5 Hz), 8.52 (d, 2H, J = 8.5), 8.14 (s, 2H), 2.62 (s, 6H).

Anal. Calcd. for $C_{22}H_{14}N_4O_4 \cdot 3H_2O$: C, 58.4; H, 4.5; N, 12.4. Found: C, 59.1; H, 4.6; N, 12.6.

Pyrido[3,2-*a*:2',3'-*c*]phenazine-3,6-dicarboxylic Acid (**10**).

A mixture of compound **5** (3.67 g, 10 mmoles) and 1,2-diaminobenzene (1.08 g, 10 mmoles) in absolute ethanol (200 ml) was refluxed for 24 hours. The mixture was cooled slowly and the precipitate which formed was filtered and recrystallized from a large excess of methanol or water to yield 3.0 g (81%) of **10**; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.70 (d, 2H, J = 8.5 Hz), 8.53 (d, 2H, J = 8.5 Hz), 8.42 (dd, 2H, J_1 = 5.9 Hz, J_2 = 3.5 Hz), 8.09 (dd, 2H, J_1 = 5.9, J_2 = 3.5 Hz); ms: m/z 369 (M^+-1), 368 (M^+-2), 324 (M^+-CO_2), 281 (M^++1-2CO_2).

Anal. Calcd. for $C_{20}H_{10}N_4O_4 \cdot 3H_2O$: C, 56.6; H, 3.8; N, 13.2. Found: C, 56.0; H, 3.7; N, 13.8.

Pyrazino[2,3-*f*][1,10]phenanthroline-7,10-dicarboxylic Acid (**11**).

A mixture of compound **5** (2.94 g, 8 mmoles) and 1,2-diaminoethane (0.49 g, 8 mmoles) in absolute ethanol (200 ml) was refluxed for 72 hours and then was allowed to cool. The solid product which formed was filtered, washed with ethanol and recrystallized twice from methanol or water to yield 2.0 g (78%) of **11**; ms: m/z 321 (M^++1), 320 (M^+), 275 (M^+ -CO_2).

Anal. Calcd. for $C_{16}H_8N_4O_4$: C, 60.0; H, 2.5. Found: C, 59.7; H, 4.0.

7,10-Dichloropyrazino[2,3-*f*][1,10]phenanthroline (**12**).

To a solution of 2,9-dichlorophenanthroline-5,6-dione (4.53 g, 16.2 mmoles) in absolute ethanol (200 ml) was added 1,2-diaminoethane (1.44 g, 24 mmoles) and the reaction mixture refluxed for 3 hours. The solution was reduced to 50 ml and the solid product which formed was filtered, washed with ethanol (10 ml), acetone (3 x 10 ml) and recrystallized from dmf/ethanol to yield 3.5 g (72%) of compound **12** as a pale yellow powder in trihydrate form; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.4 (d, 2H, J = 8.5 Hz), 9.15 (s, 2H), 7.99 (d, 2H, J = 8.6 Hz); ms: m/z 303 (M^++2), 301 (M^+).

Anal. Calcd. for $C_{14}H_6Cl_2N_4 \cdot 3H_2O$: C, 47.3; H, 3.4; N, 15.8. Found: C, 47.3; H, 3.2; N, 16.7.

7,10-Dihydrazinopyrazino[2,3-*f*][1,10]phenanthroline (**13**).

A mixture of compound **12** (3.55 g, 10 mmoles) in degassed hydrazine hydrate (40 ml) was refluxed under nitrogen for 6 hours and then was allowed to cool to room temperature. The solid which formed was filtered, washed with chloroform (2 x 5 ml) and recrystallized from dimethylformamide to yield 2.3 g (79%) of **13**; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.97 (d, 2H, J = 9.1 Hz), 8.78 (s, 2H), 7.19 (d, 2H, J = 9.0 Hz); ir (potassium bromide): 3359, 3272, 3152, 3050, 2938, 1599, 1612; ms: m/z 299 (M^++3), 297 (M^++1), 295 (M^+-1).

7,10-Bis(pyrrolidinoethylaminomethyl)pyrazino[2,3-*f*][1,10]phenanthroline (**14**).

The solid **13** (2 g) was washed with acetone (2 x 5 ml) to give 1.8 g of the off-white solid **14**; ^{1}H nmr (35° C, perdeuteriomethanol-deuteriochloroform 1:1): δ d 9.21 (d, 2H, J = 8.8 Hz), 8.76 (s, 2H), 7.73 (d, 2H, J = 8.9 Hz), 2.08 (s, 6H), 2.00 (s, 6H); ms: m/z 374 (M^++2), 373 (M^++1), 303 (M^++1-NHN=C(CH_3)$_2$).

Anal. Calcd. for $C_{20}H_{20}N_8 \cdot 0.5H_2O$: C, 63.0; H, 5.5; N, 29.4. Found: C, 63.7; H, 5.3; N, 29.2.

Bis[7,10-(*N*-2'-pyridylmethylidenehydrazino)]pyrazino[2,3-*f*]-[1,10]phenanthroline (**15**).

To a suspension of compound **13** (1.14 g, 3.9 mmoles) in dry methanol (300 ml) was added pyridine-2-carboxaldehyde (0.74 ml, 7.8 mmoles) and the mixture stirred for 3 days at 50°. The resulting gelatinous product was concentrated under reduced pressure leaving a yellow residue which was recrystallized from acetonitrile/dimethylformamide to yield 1.3 g (71%) of **15**; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.26 (d, 2H, J = 8.1 Hz), 8.92 (s, 2H), 8.59 (d, 2H, J = 4.8 Hz), 8.32 (m, 4H), 8.08 (br d, 2H, J = 8.0 Hz), 7.9 (m, 4H), 7.36 (t, 2H, J = 12.0 Hz); ms: m/z 472 (M^++2), 471 (M^++1), 392 (M^+-C_6H_4N), 391 (M^+-C_6H_3N), 210, 209.

Anal. Calcd. for $C_{26}H_{18}N_{10} \cdot 4H_2O$: C, 57.8; H, 4.5; N, 25.9. Found: C, 57.7; H, 4.5; N, 25.0.

Bis[7,10-*N*{-4-(9-carbazolyl)butyl}-(*N*'-2'-pyridylmethylidene-hydrazino)]pyrazino[2,3-*f*][1,10]phenanthroline (**16**).

To compound **15** (1.75 g, 3.2 mmoles) in dry dimethylformamide (20 ml) was added sodium hydride (0.16 g, 6.5 mmoles). The mixture was stirred at 90° for 8 hours followed by the addition of 9-(4-bromobutyl)carbazole (1.96 g, 6.5 mmoles). The dark solution was stirred for 3 days at 90°, cooled to room temperature and filtered. The filtrate was poured into water (100 ml) and extracted with chloroform (50 ml). The extracts were washed with water (3 x 50 ml), dried over sodium sulfate and reduced to dryness. The residue was recrystallized twice from a large excess of ethanol/charcoal to yield 1.9 g, (64%) of **16** as a yellow crystals. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.17 (d, 2H, J = 8.9 Hz), 8.92 (s, 2H), 8.68 (d, 2H, J = 4.7 Hz), 8.12 (m, 4H), 8.02 (d, 4H, J = 7.5 Hz), 7.91 (t, 2H, J = 7.5 Hz), 7.81 (s, 2H), 7.39 (t, 2H, J = 6.3 Hz), 7.32 (d, 4H, J = 7.6 Hz), 7.21 (t, 4H, J = 7.6 Hz), 7.06 (t, 4H, J = 7.7 Hz), 4.29 (br, 4H), 4.1 (br, 4H), 1.68 (br, 8H); ms: m/z 913 (M^++1), 693 (M^++2 -butylcarbazole), 692 (M^++1 -butylcarbazole), 457 (M^{+2} +2)/2, 391, 251, 239.

Anal. Calcd. for $C_{58}H_{48}N_{12} \cdot 2H_2O$: C, 73.4; H, 5.5; N, 17.7. Found: C, 73.9; H, 5.3; N, 17.9.

Bis[2,9-(*N*-2'-pyridylmethylidenehydrazino)][1,10]phenanthroline (**17**).

A mixture of 2,9-dihydrazino-1,10-phenanthroline (1.0 g, 4.2 mmoles) and pyridine-2-carboxaldehyde (0.8 ml, 8.4 mmoles) in dry methanol (300 ml) was stirred for 3 days until all hydrazine had dissolved and an orange solution was obtained. The solvent was removed and the residue was recrystallized from chloroform to yield 1.22 g (71%) of compound **17** as a yellow powder. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 11.3 (br, 2H), 8.57 (d, 2H, J = 4.6 Hz), 8.26 (m, 4H), 8.05 (d, 2H, J = 8.2 Hz), 7.82 (m, 4H), 7.61 (s, 2H), 7.32 (t, 2H, J = 6.1 Hz); ms: m/z 420 (M^++2), 419 (M^++1), 300 (M^++2 - $C_5H_5NCHNHNH$).

Anal. Calcd. for $C_{24}H_{18}N_8 \cdot 2.5H_2O$: C, 62.2; H, 5.0; 24.2. Found: C, 61.9; H, 4.9; N, 22.7.

2-Isopropylidenehydrazino[1,10]phenanthroline (**18**).

A mixture of 2-chloro-1,10-phenanthroline (5.0 g, 23.4 mmoles) and degassed hydrazine hydrate (25 ml) was refluxed for 2 hours under nitrogen then allowed to cool. The white solid which formed was filtered, washed with chloroform (5 ml) and recrystallized from ethanol/acetone (1:1, 5 ml) to yield 4.5 g (77%) of **18**. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.7 (dd, 1H, J_1 = 1.8 Hz, J_2 = 4.1 Hz), 8.38 (dd, 1H, J_1 = 1.5 Hz, J_2 = 8.2 Hz),

8.22 (br, 1H), 7.7 (m, 4H), 2.99 (s, 6H); ms: m/z 252 (M^++2), 251 (M^++1).

Anal. Calcd. for $C_{15}H_{14}N_4$: C, 71.9; H, 5.6; N, 22.4 Found: C, 71.3; H, 5.8; N, 22.0.

2-[*N*-(3,5-Dimethylpyrazole)][1,10]phenanthroline (**19**).

A mixture of 2-hydrazino[1,10]phenanthroline (2.0 g, 8.5 mmoles) and acetylacetone (0.86 g, 8.5 mmoles) was stirred in dry methanol (50 ml) for 24 hours followed by refluxing for 1 hour. The solvent. was removed on a rotary evaporator and the residue recrystallized from chloroform/activated charcoal to give 1.3 g (48%) of **19** as a white microcrystalline powder. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ d: 9.12 (dd, 1H, J_1 = 1.6 Hz, J_2 = 4.0 Hz), 8.57 (d, 1H, J = 9.1 Hz), 8.47 (dd, 1H, J_1 = 1.6 Hz, J_2 = 7.9 Hz), 8.24 (d, 1H, J = 9.1 Hz), 7.97 (m, 2H), 7.75 (dd, 1H, J_1 = 3.8 Hz, J_2 = 7.1 Hz), 6.20 (s, 1H), 3.00 (s, 3H), 2.26 (s, 3H).

2-Hydrazino[1,10]phenanthroline (**20**).

A mixture of 2-chloro[1,10]phenanthroline (17 g, 79 mmoles) and degassed hydrazine hydrate (85%, 60 ml) was refluxed under nitrogen for 1 hour. The mixture was cooled, filtered and the precipitate which formed was suspended in water, then extracted into chloroform. The chloroform was evaporated and the residue triturated with ethylacetate (20 ml). The precipitated solid was filtered, washed with ethylacetate (5 ml) and recrystallized from ethanol to yield 11.0 g (66%) of **20**. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.97 (dd, 1H, J_1 = 1.8 Hz, J_2 = 3.8 Hz), 8.32 (dd, 1H, J_1 = 1.7 Hz, J_2 = 7.9 Hz), 8.12 (br, 1H-N), 8.05 (d, 1H, J = 8.5 Hz), 7.73 (d, 1H, J = 8.9 Hz), 7.6 (dd, 1H, J_1 = 4.1 Hz, J_2 = 8.4), 7.57 (d, 1H, J = 8.9 Hz), 7.12 (d, 1H, J = 8.5 Hz), 4.47 (s, H_2N).

Bis(*N,N*-(*S*)-alanyl ethyl ester)[1,10]phenanthroline-2,9-dicarboxamide (**21**).

To [1,10]phenanthroline-2,9-dicarboxylic acid (2.45 g, 9.1 mmoles) was added thionyl chloride (80 ml) and the mixture refluxed for 6 hours. The solution was concentrated under reduced pressure to 10 ml then benzene (50 ml) was added, which then was removed also under reduced pressure. To the residue was added *S*-alanine ethyl ester hydrochloride (2.79 g, 18.3 mmoles) in dry dichloromethane (100 ml) followed by the addition of triethylamine (4.0 g). The solution was stirred for 72 hours at room temperature, poured into sodium bicarbonate/deionized water (200 ml) and the organic layer separated and washed with water. The extracts were dried over magnesium sulfate and concentrated under reduced pressure to leave a white solid which was recrystallized from ethanol/ethyl acetate to yield 3.2 g (76%) of **21**. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.6 (d, 2HN, J = 7.1 Hz), 8.76 (d, 2H, J = 8.2 Hz), 8.44 (d, 2H, J = 8.1 Hz), 8.20 (s, 2H), 4.64 (p, 2H, J = 7.2 Hz), 4.17 (dd, 4H, J_1 = 2.6 Hz, J_2 = 7.2 Hz), 1.6 (d, 6H, J = 7.3 Hz), 1.29 (t, 6H, J = 7.2 Hz); ms: m/z 468 (M^++2), 467 (M^++1).

Anal. Calcd. for $C_{24}H_{26}N_4O_6 \cdot H_2O$: C, 59.5; H, 5.8; N, 11.6. Found: C, 59.8; H, 5.9; N, 11.7.

N-Glycinyl ethyl ester[1,10]phenanthroline-2-carboxamide (**22**).

This compound was prepared by a method similar to that used in the preparation of compound **21**, except for the use of dichloromethane/chloroform (2:1) for extraction. Reaction of [1,10]phenanthroline-2-carboxylic acid (3.05 g, 12.5 mmoles), glycine ethyl ester hydrochloride (1.75 g, 12.5 mmoles) and triethylamine (7 ml) gave compound **22** which was recrystallized from ethyl acetate to yield 2.0 g (53%). ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.20 (m, 2H), 8.70 (d, 1H, J = 8.2 Hz), 8.57 (dd, 1H, J_1 = 7.9 Hz, J_2 = 8.2 Hz), 8.41 (d, 1H, J = 8.2 Hz), 8.10 (m, 2H), 7.84 (dd, 1H, J_1 = 7.8 Hz, J_2 = 6.7 Hz), 4.26 (d, 2H, J = 6.4 Hz), 4.18 (q, 2H, J = 7.0 Hz), 1.24 (t, 3H, J = 7.0 Hz); ms: m/z 311 (M^++2), 310 (M^++1), 280 (M^+-C_2H_5).

Anal. Calcd. for $C_{17}H_{15}N_3O_3 \cdot H_2O$: C, 62.4; H, 5.2; N, 12.8. Found: C, 61.8; H, 5.3; N, 12.4.

N-(*S*)-Alanyl ethyl ester[1,10]phenanthroline-2-carboxamide (**23**).

This compound was prepared by a method sirmilar to that used in the preparation of the compound **21**. Reaction of [1,10]phenanthroline-2-carboxylic acid (4.48 g, 20 mmoles), *S*-alanine ethyl ester hydrochloride (3.0 g, 20 mmoles) and triethylamine (7 ml) gave 2.5 g (40%) of compound **21** as a thick oil. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.24 (d, HN, J = 7.6 Hz), 9.20 (dd, 1H, J_1 = 1.7 Hz, J_2 = 3.9 Hz), 8.7 (d, 1H, J = 8.1 Hz), 8.55 (dd, 1H, J_1 = 1.7 Hz, J_2 = 8.0 Hz), 8.41 (d, 1H, J = 8.2 Hz), 8.10 (dd, 2H, J_1 = 8.8 Hz), 8.65 (d, 1H, J_2 = 8.9 Hz), 7.86 (dd, 1H, J_1 = 8.2, J_2 = 7.1 Hz), 4.72 (p, 1H, J = 7.2 Hz), 4.21 (d t, 2H, J_1 = 3.0 Hz, J_2 = 7.0 Hz), 1.60 (d, 3H, J = 7.2 Hz), 1.26 (t, 3H, J = 7.0 Hz); ms: m/z 325 (M^++2), 324 (M^++1).

N-(*S*)-α-Glutamyl ethyl ester[1,10]phenanthroline-2-carboxamide (**24**).

This compound was prepared by a method similar to that for **21**. [1,10]phenanthroline-2-carboxylic acid (3.05 g, 12.5 mmoles), *S*-glutamic ethyl ester hydrochloride (2.82 g, 12.5 mmoles) and triethylamine (7 ml) gave 3.0 g of the compound **24** as a thick oil. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.19 (m, HN + 1H), 8.70 (d, 1H, J = 8.2), 8.55 (dd, 1H, J_1 = 8.0 Hz, J_2 = 8.2 Hz), 8.45 (d, 1H, J = 8.2 Hz), 8.11 (d, 1H, J = 9.0 Hz), 8.07 (d, 1H, J = 9.0 Hz), 7.85 (dd, 1H, J_1 = 7.2 Hz, J_2 = 8.1 Hz), 4.72 (m, 1H), 4.17 (m, 4), 2.32 (m, 4H), 1.20 (m, 6H); ms: m/z 409 (M^+), 381 (M^++1 -C_2H_5), 380 (M^+-C_2H_5), 352 (M^++1 -$2C_2H_5$), 249 (M^+-$CH_2COOC_2H_5$ -$COOC_2H_5$).

N-Glycyl[1,10]phenanthroline-2-carboxamide (**25**).

A mixture of compound **22** (2.06 g, 6.2 mmoles) and potassium hydroxide (2.8 g, 50 mmoles) was refluxed in ethanol (200 ml) for 2 hours. The solvent was stripped off leaving an oily residue to which water (20 ml) was added to assist precipitation. The white solid (**25**) which formed was filtered, washed with water and air-dried; yield: 1.3 g (75%); ^{1}H nmr (benzene-d_6): δ 9.70 (br, 1H), 9.18 (dd, 1H, J_1 = 4.0 Hz, J_2 = 1.8 Hz), 8.66 (br, 1H + deutrated benzene signal), 8.32 (d, 1H, J = 8.3 Hz), 8.16 (dd, 1H, J_1 = 1.7 Hz, J_2 = 3.7 Hz), 7.77 (m, 2H), 7.22 (br, 1H + deutrated benzene), 4.60 (d, 2H, J = 6.0 Hz); ms: m/z 281 (M^+), 280 (M^+-1), 238 (M^+-COOH).

Anal. Calcd. for $C_{15}H_{11}N_3O_3 \cdot 3H_2O$: C, 53.7; H, 5.1; N, 12.5. Found: C, 53.7; H, 4.0; N, 12.0.

N-(*S*)-alanyl[1,10]phenanthroline-2-carboxamide (**26**).

A solution of compound **22** (1.0 g, 3.1 mmoles) and sodium hydroxide (0.35 g) was refluxed in ethanol (95%, 25 ml) for 2 hours. The volume was reduced to 5 ml, then ethyl acetate was added and the solid which formed was filtered, and washed with ethyl acetate to give **26** as an off-white solid; yield: 0.7 g (79%) ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.20 (br, 2H), 8.65 (d, 1H, J = 8.2 Hz), 8.53 (dd, 1H, J_1 = 2.0 Hz, J_2 = 7.9 Hz), 8.38 (d, 1H, J =

8.2 Hz), 8.03 (m, 2H), 7.8 (m, 2H), 4.13 (p, 1H, J = 6.9 Hz), 1.38 (d, 3H, J = 6.8 Hz); ms: m/z 295 (M^+), 294 (M^+-1), 251 (M^+-COO), 250 (M^+-COOH).

2-Bromomethyl[1,10]phenanthroline (**27**).

A mixture of 2-hydroxymethyl[1,10]phenanthroline (1.8 g, 8.5 mmoles) and 48% hydrobromic acid/acetic acid (1:1, 50 ml) was refluxed for 3 hours. The cooled mixture was neutralized by slow addition of 10% sodium bicarbonate solution, and the solid filtered off. This was washed with water and recrystallized from dilute ethanol to yield 1.3 g, (56%) of **28** as a white powder. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.30 (dd, 1H, J_1 = 1.7 Hz, J_2 = 5.1 Hz), 9.22 (d, 1H, J = 8.4 Hz), 8.76 (d, 1H, J = 8.3 Hz), 8.30 (m, 3H), 8.15 (d, 1H, J = 8.4 Hz), 5.06 (s, 2H); ms: m/z 276 (M^++3), 275 (M^++2), 274 (M^++1), 273 (M^+).

General procedure for the preparation of **28a-d.**

Both [1,10]phenanthroline-2,9-dicarboxaldehyde (1.0 g, 4.2 mmoles) and dry magnesium chloride were suspended in dry methanol (70 ml). With constant stirring under nitrogen the respective amine (8.4 mmoles) was added slowly and stirring then continued for 48 hours at 25°. The mixture was refluxed for 0.5 hour, cooled and sodium borohydride was added during 0.5 hour at 0°. After a further 24 hours stirring at room temperature deionized water was added (50 ml) and the solution was concentrated under reduced pressure to half volume. The mixture was extracted by either chloroform or dichloromethane until clear and the extracts washed with water, dried over magnesium sulfate and the solvent removed to give a red oil. Any unreacted amine was removed under 5 mm Hg vacuum at 50°. The desired products were obtained by flash chromatography on activity-3 silica gel using chloroform/methanol (21:1) and were dried over diphorphorus pentaoxide to give thick oils in 60-70% yield.

2,9-Di(5-methyl-2,5-diazahex[1,10]phenanthroline (**28a**).

This compound was prepared by the above general procedure. Reaction of 1,10-phenanthroline-2,9-dicarboxaldehyde (1.0 g, 4.2 mmoles), magnesium chloride (0.40 g, 8.4 mmoles), *N,N*-dimethyl-1,2-diaminoethane (0.74 g, 8.4 mmoles) and sodium borohydride (0.95 g, 25.3 mmoles) gave the compound **28a** as a thick yellow oil. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.40 (d, 2H, J = 8.2 Hz), 7.90 (s, 2H), 7.82 (d, 2H, J = 8.1 Hz), 4.13 (s, 4H), 2.70 (t, 4H, J = 6.5 Hz), 2.40 (t, 4H, J = 6.4 Hz), 2.15 (s, 12H); ms: m/z 382 (M^++2), 381 (M^++1), 309 (M^++1- $Me_2NCH_2CH_2$), 265, 207.

2,9-Di{4-(*N*-pyrrolidinyl)-2-azabut[1,10]phenanthroline (**28b**).

This compound was prepared by reaction of [1,10]phenanthroline-2,9-dicarboxaldehyde (1.0 g, 4.2 mmoles), magnesium chloride (0.40 g, 4.2 mmoles), 1-(2-aminoethyl)pyrrolidine (0.96 g, 8.4 mmoles) and sodium borohydride (0.95 g, 25.3 mmoles), giving the compound **28b** as a brown semi-solid; yield: 0.85 g (47%). ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.42 (d, 2H, J = 8.3 Hz), 7.91 (s, 2H), 7.83 (d, 2H, J = 8.4 Hz), 4.14 (s, 4H), 2.72 (t, 4H, J = 6.6 Hz), 2.56 (t, 4H, J = 6.6 Hz), 2.41 (br, 8H), 1.65 (br, 8H); ms: m/z 433 (M^++1), 432 (M^+), 431 (M^+-1), 405 (M^+-CH_2CH_3), 217 (M^{+2}/2+1), 224.

Anal. Calcd. for $C_{26}H_{36}N_6$•2.5H_2O: C, 65.4; H, 8.7; N, 17.6. Found: C, 65.4; H, 8.7; N, 17.3.

2,9-Di(4-(*N*-piperidinyl)-2-azabut[1,10]phenanthroline (**28c**).

This compound was prepared by the general procedure by using[1,10]phenanthroline-2,9-dicarboxaldehyde (1.0 g, 4.2 mmoles), magnesium chloride (0.4 g, 4.2 mmoles), 1-(2-aminoethyl)piperidine (1.07 g, 8.4 mmoles) and sodium borohydride (0.95 g, 25.3 mmoles) to give 1.1 g (57%) of compound **28c** as a yellow thick oil. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.40 (d, 2H, J = 8.5 Hz), 7.89 (s, 2H), 7.81 (d, 2H, J = 8.6 Hz), 4.13 (s, 4H), 2.72 (t, 4H, J = 6.4 Hz), 2.41 (t, 4H, J = 6.5 Hz), 2.34-2.23 (m, 8H), 1.50-1.28 (m, 12H); ms: m/z 462 (M^++2), 376 (M^+-$N(CH_2)_5$), 347 (M^+-$CH_2CH_2N(CH_2)_5$), 222, 208, 194, 180 ($phen^+$).

2,9-Di{4-(2-pyridyl)-2-azabut}[1,10]phenanthroline (**28d**).

Reaction of [1,10]phenanthroline-2,9-dicarboxaldehyde (1.0 g, 4.2 mmoles), magnesium chloride (0.4 g, 4.2 mmoles), 2-aminoethylpyridine (1.02 g, 8.4 mmoles) and sodium borohydride, (0.95 g, 25.3 mmoles) gave the compound **28d** as a yellow thick oil; yield: 1.2 g, (64%). ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.46 (d, 2H, J = 4.8 Hz), 8.4 (d, 2H, J = 8.1 Hz), 7.90 (s, 2H), 7.79 (d, 2H, J = 8.2 Hz), 7.66 (t, 2H, J = 7.7 Hz), 7.28 (d, 2H, J = 8.3 Hz), 7.17 (t, 2H, J = 6.0 Hz), 4.16 (s, 2H), 2.99 (m, 8H); ms: m/z 449 (M^++1), 447 (M^+-1), 356 (M^+-$CH_2C_5H_4N$), 344, 343, 225 (M^++1)/2, 224 (M^+-1)/2, 176, 106 ($CH_2CH_2C_5H_4N^+$).

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