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Displacement reactions of 2-chloro- and 2,9-dichloro-1,10-phenanthroline: synthesis of a sulfur-bridged bis-1,10-phenanthroline macrocycle and a 2,2′-amino-substituted-bis-1,10-phenanthroline

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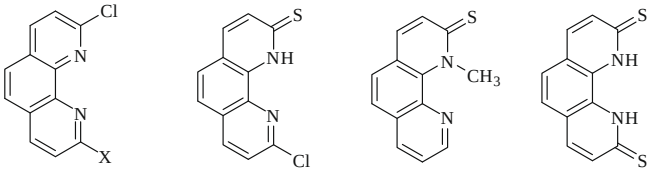
2-Amino- and 2,9-diamino-substituted 1,10-phenanthrolines
Amino-substituted-2,2′-bis-1,10-phenanthroline

ABSTRACT

The synthesis and structural assignments of 9-chloro-1,1-phenanthroline-2(1*H*)-thione and 1,10-dihydro-1,10-phenanthroline-2,9-dithione have been accomplished. The sulfur-bridged bis-1,10-phenanthroline macrocycle was readily prepared by heating the thione or equimolar amounts of the dithione and 2,9-dichloro-1,10-phenanthroline in diphenyl ether. Displacements of 2-chloro- or 2,9-dichloro-1,10-phenanthroline with *N*,*N*-dimethylethylenediamine afforded the corresponding amine and diamino analogues. An amino-substituted-2,2′-bis-1,10-phenanthroline has been prepared.

Our interest in the synthesis of analogues with 1,10-phenanthroline pharmacophores is based on their potential applications as inhibitors of telomerase, an enzyme found in cancer cells which controls the continuous growth of the tumor.[1,2] In particular, we wish to evaluate the ability of metal-binding ligands such as heteroatom-bridged macrocycles to stabilize the G-quadruplex structure of telomeric DNA and interfere with the action of telomerase. Porphyrins (tetradentate nitrogen ligands) have been shown to act as telomerase inhibitors,[3] and a platinum-1,10-phenanthroline complex has demonstrated telomerase inhibition.[4]

A mixture of **1a**[5] and thiourea in refluxing ethanol led to **2**[6,7] in reasonable yields. The formulation as **2**, rather than the tautomeric form, is based on NMR comparisons with **3**, a non-tautomerizable model. The ^{13}C NMR for the C=S in **2** appears at 186.1 ppm (DMSO-d_6), while that for **3**[8] is at 185.1 ppm ($CDCl_3$). Treatment of **1a** with NaSH hydrate in DMF at 130–135 °C for 3 h followed by acidification readily led to **4**.[9] A previous preparation of **4** has been reported, and the authors proposed the thione form on one side when the ^{1}H NMR was run in $CDCl_3$ and the dithiol tautomer in DMSO-d_6[10]



1 a, X = Cl
b, X = H

2

3

4

The structure as **4**, rather than the tautomeric forms, was established by an NMR comparison with **5a** which cannot undergo tautomerism. Analogue **5a**[11] was prepared by treatment of **5b**[12] with Lawesson's reagent, and it exhibits a ^{13}C NMR C=S absorption (DMSO-d_6) at 183.6 ppm, while **4** exhibits a similar absorption at 182.4 ppm. In addition, **4** and **5a** exhibit similar ^{1}H NMR absorptions.

The metal-free macrocycle **6** has been prepared by thermolysis of **2** in dimethyl acetamide in the presence of DBU.[13] A Na^+ complex of **6** was prepared by heating **2** with NaOH in *N*,*N*-DMA.[14] Thermolysis of **1a** with H_2S at 170 °C afforded **6** (presumably as a salt).[15] We have found that heating a solution of equimolar molar amounts of **1a** and **4** in diphenyl ether led to the precipitation of

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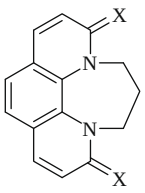
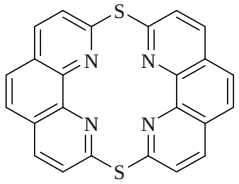
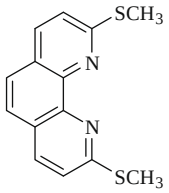
the sulfur macrocycle **6** (as the hydrochloride salt), which was readily isolated as a lemon-yellow solid.[16] The structure was clearly established by ^{1}H NMR and ^{13}C NMR data obtained in CF_3COOD. The macrocycle **6** could also be prepared by thermolysis of **2** in diphenyl ether.[17]



5 a, X = S
b, X = O



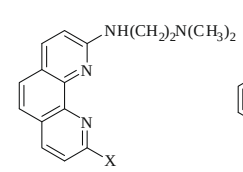
6



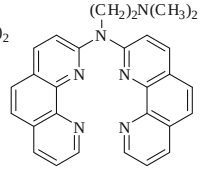
7

As a model for NMR comparison, the 2,9-bis-(methylthio)-[1,10]-phenanthroline (**7**)[18] was prepared by treatment of **1a** with sodium thiomethoxide. A comparison of the chemical shifts in the ^{1}H NMR spectra of **6** with those of **7** (both in CF_3COOD) showed an upfield shift for the d,s,d pattern of about 0.3 ppm for **7** of each absorption in **6**.

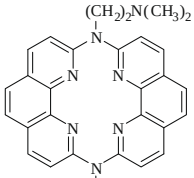
We then turned our attention to the preparation of nitrogen-substituted bis-1,10-phenanthrolines. Upon refluxing **1b** or **1a** in *N*,*N*-dimethylethylenediamine, the corresponding mono- and disubstituted-1,10-phenanthrolines **8a**[19] or **8b**[20] were readily obtained in high yields.



8 a, X = H
b, X = $NH(CH_2)_2N(CH_3)_2$



9



10

Initial attempts to prepare **9** by thermolysis of **8a** with **1b** in diphenyl ether or in DMF in the presence of K_2CO_3 at 150 °C were unsuccessful. However, treatment of **8a** with NaH in DMF followed by addition of **1b** and refluxing led to the amino-substituted bis-2,2′-1,10-phenanthroline **9**.[21] Attempts to prepare the amino-bis-1,10-phenanthroline macrocycle **10** by thermolysis of **8b** with **1a** in diphenyl ether or in DMF, K_2CO_3 have been unsuccessful. Efforts to prepare **10** are currently being pursued.

The sulfur macrocycle (HCl salt) **6**, **8a**, **8b** and **9** are being evaluated for their anti-telomerase activities, and the results will be reported on completion of the assays.

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References and notes

1. Davis, J. T. *Angew. Chem., Int. Ed.* **2004**, *43*, 668.
2. Tan, J.-H.; Gu, L-Q.; Wu, J.-W. *Mini-Rev. Med. Chem.* **2008**, *8*, 1163.
3. Maraval, A.; Franco, S.; Vialas, C.; Pratviel, G.; Blasco, M. A.; Meunier, B. *Org. Biomol. Chem.* **2003**, *1*, 921.
4. Reed, J. E.; Neidle, S.; Vilar, R. *Chem. Commun.* **2007**, 4366.
5. Krapcho, A. P.; Lanza, J. B. *Org. Prep. Proced. Int.* **2007**, *39*, 603.
6. Hirai, M.; Shinozuka, K.; Sawai, H.; Ogawa, S. *Chem. Lett.* **1992**, 2023. Treatment of **1a** with thiourea is reported to afford **2** without the benefit of any experimental details or spectra data to support this structure.
7. A mixture of **1a** (210 mg, 0.84 mmol), thiourea (130 mg, 1.70 mmol), and ethyl alcohol (9 mL) was refluxed for 3 h, and the ethanol was removed by rotary evaporation. The residue was heated with CH_2Cl_2 (40 mL) and the insoluble material was removed by filtration. The filtrate was concentrated by rotary evaporation to yield **2** as a yellow solid (74 mg, 34%). Recrystallization from CH_2Cl_2 led to beautiful yellow needle-like crystals; mp >310 °C (yellow to orange color change). ^{1}H NMR ($CDCl_3$): δ 12.04 (br s, 0.5H), 8.16 (d, J = 8.5 Hz, 1H), 7.65 (m, 4H), 7.56 (d, J = 8.5 Hz, 1H).^{1}H NMR (DMSO-d_6) δ 12.32 (br s), 8.60 (d, J = 9.0 Hz), 8.06 (d, J = 9.0 Hz), 7.91 (m, 2H), 7.87 (d, J = 8.5 Hz), 7.54 (d, J = 9.0 Hz). ^{13}C NMR (DMSO-d_6): δ 186.1, 155.5, 145.9, 140.6, 140.5, 139.8, 139.4, 132.7, 131.3, 130.5, 128.5, 127.4. Anal. Calcd for $C_{12}H_7ClN_2S$: C, 58.42; H, 2.86; N, 11.35. Found: C, 58.31; H, 2.82; 11.25.
8. Krapcho, A. P.; Sparapani, S.; Boxer, M. *Tetrahedron Lett.* **2007**, *48*, 5593.
9. A mixture of **1a** (0.114 mg, 0.45 mmol) and $NaSH{\cdot}H_2O$ (0.200 g) in DMF (2 mL), which formed a bright green mixture, was heated in an oil bath (130–135 °C) for 3.5 h. After standing overnight, a yellow precipitate formed in a dark red-orange liquid. The DMF was removed under reduced pressure on a water aspirator to leave a yellow-orange solid. Water (3 mL) was added followed by acetic acid (2 mL, 2 M), which led to a bright yellow solid. The product was collected by filtration, heated in chloroform, and some insoluble material was removed by filtration from the hot chloroform. On concentration of the filtrate, **4** was obtained as an orange solid (84 mg, 74%); mp 193–197 °C (lit. mp[10] 217 °C). ^{1}H NMR (DMSO-d_6) δ 10.91 (br s, 0.5H), 7.91 (d, J = 9.05 Hz, 2H), 7.67 (s, 2H), 7.41 (d, J = 9.05 Hz, 2H); addition of D_2O leads to disappearance of NH absorption at 10.91. ^{1}H NMR (CF_3COOD) δ 8.72 (d, J = 9.0 Hz, 2H), 8.24 (s, 2H), 8.08 (d, J = 8.5 Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 182.4, 135.1, 133.5, 126.8, 123.6, 123.5.
10. Hunziker, M.; Hauser, U. *Heterocycles* **1982**, *19*, 2131. Prepared under rather drastic conditions by heating **1a** with excess KSH in ethanol in a sealed Teflon cup at 140 °C for 23 h.
11. Unpublished results. Prepared by treatment of **5b** with Lawesson's reagent in THF. ^{13}C NMR (DMSO-d_6) δ 183.6, 134.3, 133.0, 132.1, 126.1, 125.5, 53.2, 24.5; ^{1}H NMR (DMSO-d_6) δ 7.93 (d, J = 9.0 Hz, 2H), 7.82 (s, 2H), 7.63 (d, J = 9.0 Hz, 2H), 4.62 (br s, 4H), 2.53 (m, 2H). Anal. Calcd for $C_{15}H_{12}N_2S_2$: C, 63.35; H, 4.25; N, 9.85. Found: 63.01; H, 4.00; N, 9.54. The protons adjacent to the nitrogen were broadened by the quadrupole of ^{14}N, and appeared only if the ^{14}N symmetry was increased by raising the temperature. Since these protons relax very fast the accurate integration required a short acquisition time.
12. Yamada, M.; Nakamura, Y.; Kuroda, S.; Shimao, I. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2710.
13. Hirai, M.; Kazuo, S.; Hiroaki, O.; Ogawa, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1147. Attempts to repeat their preparation of the metal-free macrocyclic **6b** by heating **2**, DBN (200 mL) in DMA (10 mL) 1 h at 80 °C in our hands was unsuccessful..
14. Hirai, M.; Shinozuka, K.; Ogawa, S.; Sawai, H. *Chem. Lett.* **1996**, 1113.
15. Wang, W.-J.; Sengul, A.; Luo, C.-F.; Kao, H.-C.; Cheng, Y.-H. *Tetrahedron Lett.* **2003**, *44*, 7099. The mono-protonated salt was prepared by slow diffusion of ether into a TFA solution of **6**. The ^{1}H NMR (CF_3CO_2D) was incorrectly assigned as 9.20 (d, J = 8.7 Hz, 4H), 8.61 (d, J = 8.7 Hz, 4H), 8.44 (s, 4H). The 8.61 peak is a singlet, while the 8.44 peak is a doublet.
16. A mixture of **4** (50 mg, 0.20 mmol) and **1a** (50 mg, 0.20 mmol) in diphenyl ether (3 mL) was placed in an oil bath, and the bath was gradually heated to 130 °C (1 h) and held at this temperature for 1.5 h. The initial orange solution deposited a yellow solid over this period. The mixture was cooled, and the product was collected by filtration, washed thoroughly with ether, and dried to yield **6** as a lemon-yellow solid (89 mg, 94%, for mono HCl salt), mp >260 °C. ^{1}H NMR (CF_3CO_2D) δ 9.05 (d, J = 8.8 Hz, 4H), 8.48 (s, 4H), 8.30 (J = 8.8 Hz, 4H); ^{1}H NMR (CF_3CO_2D) δ 159.2, 145.6, 138.2, 130.0, 131.7, 128.2.
17. A mixture of **2** (26 mg, 0.10 mmol) in diphenyl ether 99% (1 mL) was heated at 165–172 °C for 4 h. An orange solution formed, followed by the precipitation of a yellow solid. The suspension was cooled to room temperature, the solid was collected by filtration and was thoroughly washed with ether to afford **6** (15 mg, 62%).
18. A mixture of **1a** (46 mg, 0.18 mmol) in DMF (0.5 mL) was treated with sodium thiomethoxide (63 mg, 0.090 mmol) and was stirred at rt (20 h). Water was added, and the white product was collected by filtration, washed thoroughly with water, and dried to afford **7** (43 mg, 88%); mp 183–184 °C (lit. mp[10] 192 °C) (from acetone): ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 8.4 Hz, 2H), 7.62 (s, 2H), 7.44 (d, J = 8.4 Hz, 2H), 2.91 (s, 6H); ^{1}H NMR (DMSO-d_6) δ 8.26 (d, J = 8.4 Hz, 2H), 7.84 (s, 2H), 7.62 (J = 8.4 Hz, 2H), 2.81 (s, 6H); ^{1}H NMR (CF_3COOD) δ 8.71 (d, J = 9.1 Hz, 2H), 8.18 (s, 2H), 8.01 (d, J = 8.6 Hz, 2H), 3.02 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 160.0, 144.9, 135.3, 126.1, 124.7, 124.7, 122.1, 12.8.
19. A mixture of **1b** (1.18 g, 5.5 mmol) and *N*,*N*-dimethylethylenediamine (2.0 mL, 18 mmol) was refluxed for 19 h. The excess amine was removed by distillation under water aspirator pressure, and the residue was placed under vacuum pump pressure overnight. Treatment of the residue with aqueous KOH yielded an oil which was extracted into CH_2Cl_2. After drying over sodium sulfate and removal of the solvent, the brown solid was triturated with hexane and collected to afford **8a** as a yellow solid (1.28 g, 87%); mp 123–125 °C; ^{1}H NMR δ 9.09 (dd, J = 1.8, 4.3 Hz, 1H), 8.16 (dd, J = 1.8, 8.1 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.62 (d, 8.7 Hz, 1H), 7.52 (dd, J = 4.3, 8.1 Hz, 1H); 7.46 (d, J = 8.7 Hz, 1H); 6.85 (d, J = 8.8 Hz. 1H), 5.90 (br s, 1H), 3.60 (m, 2H), 2.62 (t, J = 6.2 Hz, 2H), 2.29 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 157.9; 149.2; 146.0; 145.0; 137.6; 135.7; 129.2; 126.5; 122.1; 122.0; 120.8; 57.8; 45.0; 39.6. Anal. Calcd for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found; C, 72.10; H, 6.60; N, 20.95.

20. A mixture of **1a** (200 mg, 0.77 mmol) and *N*,*N*-dimethylethylenediamine (4 mL) was refluxed for 22 h. Workup as described for **8a** led to the product **8b** as an off- white solid (200 mg, 72%); recrystallized from cold ethyl acetate, mp 65–67 °C. ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 8.7 Hz, 2H); 7.31 (s, 2H); 6.75 (d, J = 8.7 Hz, 2H); 5.64 (br s, 2H); 3.68 (m, 4H); 2.61 (t, J = 6.1 Hz, 4H); 2.30 (s, 12H). ^{13}C NMR ($CDCl_3$) δ 157.1; 144.1; 137.4; 123.0; 121.3; 110.6; 58.3; 45.2; 39.2. Anal. Calcd for $C_{20}H_{28}N_6$: C, 68.15; H, 8.01; N, 23.84. Found: C, 68.01; H, 7.89; N, 23.85.
21. The amine **8a** (370 mg, 1.4 mmol) in DMF (2.5 mL) was treated with NaH (110 mg, 2.8 mmol) and after gas evolution ceased, **1b** (300 mg, 1.4 mmol) was added and the mixture was stirred at rt for 0.25 h, heated to 150 °C over 1.5 h, and then refluxed for 2 h. The cooled mixture was poured over ice and a light brown oily solid was collected by filtration. This material was taken up in acetonitrile and the light brown solid was collected by filtration (175 mg, 28%). This solid on dissolving in ethyl acetate and filtration to remove some insoluble material led to **9** as yellow crystals, mp 175–177 °C. ^{1}H NMR ($CDCl_3$) δ 9.15 (dd, J = 1.5, 4.5 Hz, 2H), 8.23 (dd, J = 1.5, 8.5 Hz, 2H), 8.08 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H); 7.64 (m, 2H), 7.61 (dd, J = 4.5, 8.5 Hz, 2H), 5.10 (t, J = 7.5 Hz, 2H), 2.92 (t, 7.5 Hz, 2H), 2.42 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 156.2; 149.7; 145.6; 145.3; 137.4; 136.1; 129.2; 126.1; 124.8; 124.0; 122.7; 116.4; 56.9; 47.6; 45.5. Anal. Calcd for $C_{28}H_{24}N_6$: C, 75.65; H, 5.44; N, 18.91. Found: C, 75.55; H, 5.34; N, 18.76.