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Synthesis of a New Class of Polydentate Ligands: [Bis(2-imidazolyl)methyl]amino-Thioether-Thiols

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A new class of polydentate bis(imidazole)-thioether-thiol polydentate ligands has been synthesized by the reaction of functionalized primary amines with bis(2-imidazolyl)nitromethane. The molecules contain a bis(2-imidazolyl)methylamino group attached to chains of varying length with thiol (3, 23) and thioether/thiol (7, 11, 15, 19) binding sites.

Introduction

Imidazole is a fundamental ligand type in the synthetic and biological coordination chemistry of metal ions [1, 2]. In the biological context the 4(5)-imidazolyl group has been demonstrated to bind metal ions such as Fe(II,III), Cu(I,II), and Zn(II) in the active sites of a variety of metallobiomolecules [2]. These include, *inter alia*, myoglobin, hemoglobin, hemerythrin, hemocyanin, plastocyanin, azurin, carboxypeptidase, carbonic anhydrase, and superoxide dismutase. There is substantial current interest in the properties of metal ion coordination sites in proteins and enzymes. One method of study of these sites is the synthesis and detailed characterization of low molecular weight representations which contain the same ligand types as present in the native molecule. This has been termed the synthetic analogue approach, whose practices and purposes have been described [2, 3].

In the usual case the imidazolyl group is one of several different protein side chain functionalities coordinated to a metal ion. An especially prominent example of mixed ligand coordination is afforded by the distorted tetrahedral Cu(N(Im)·His)$_2$(S·Cys)(S·Met) site in the electron transfer protein plastocyanin [4]. Application of the synthetic analogue approach to this and other biological coordination units requires the synthesis of suitable polydentate molecules containing the desired set of binding groups. Potentially useful ligands for nitrogen-sulfur coordination have recently been prepared [5, 6]. Our approach to the preparation of bis(imidazolyl), sulfur-containing ligands derives from the work of Joseph *et al.* [7], who demonstrated displacement of the nitro group of bis(2-imidazolyl)nitromethane (*1*, Scheme) by aliphatic primary amines.

In this investigation the reactions of *1* with amines have been substantially elaborated as shown in the Scheme. The syntheses involve reactions of *1* with S-protected aminothiols followed by deprotection of the isolated thioether derivatives to afford the corresponding thiols. The thioether thiols (*4, 12, 16*) and aminothioether thiols (*5, 8, 13, 17*), as well as *20* and *21*, all used as intermediates, have not been previously reported. These reactions have afforded [bis(2-imidazolyl)methyl]amino derivatives of mono- (*2*) and dithioethers (*6, 10, 14, 18*), thiols and thioether thiols (*3, 7, 11, 15, 19*), and thioether and thiol amides (*22, 23*). These molecules contain three, four, or five potential coordination sites. Given the normal affinities of the foregoing metal ions for imidazole *vs.* amine binding, formation of a six-membered chelate ring with the two imidazolyl groups is anticipated. This places the amino nitrogen in an unfavorable position for coordination and disposes the side-chain sulfur atoms and a potential deprotonated amide group in positions suitable for binding. The thiolate anions of *3, 7, 11, 15, 19,* and *23* are expected to be the most effective ligands. They have been designed to be tridentate (*3*) or tetradentate, with the latter having flexible chains of different lengths potentially capable of closing chelate rings of different sizes. The gem-dimethyl groups in *3, 11* and *23* have been introduced as a possible steric impediment to formation of metal-bridged species M-S(R)-M, a frequent behavior of thiolate ligands. The anions of *7, 11, 15,* and *19*

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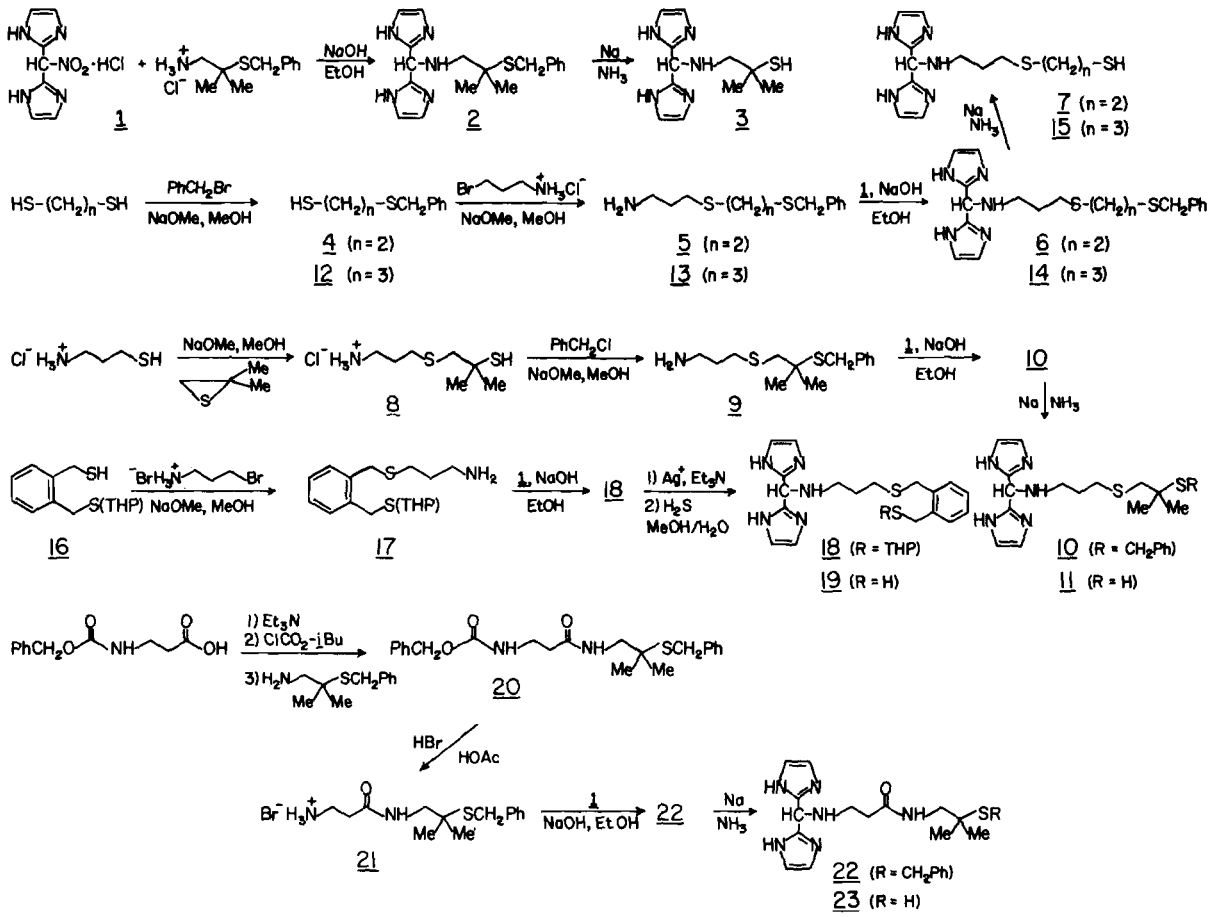

Scheme. Synthesis of bis(imidazolyl)/thioether/thiol polydentate ligands (*3*, *7*, *11*, *15*, *19*, *23*) based on the reactions of bis(2-imidazolyl)nitromethane (*1*) with functionalized primary amines.

contain the set of donor groups equivalent to that in the active site of plastocyanin.

The reactions summarized in the Scheme are capable of extension or modification so as to include other combinations of ligating groups in conjunction with the [bis(2-imidazolyl)methyl] amino moiety. Inasmuch as nucleophiles other than amines displace the nitro group of *1* [7], alternative modes of attachment of functionalized chains to the bis(2-imidazolyl)methine fragment are available. The coordination chemistry of the foregoing ligands remains to be examined in detail. As yet we have been unable to develop the characteristic blue Cu(II) chromophore of plastocyanin with any of the thiolate anions. Some progress has been achieved with another type of bis(imidazolyl) ligand designed for this purpose [5]. However, the demonstration by single crystal X-ray analysis of a bis(imidazolyl) chelate ring in [bis(2-imidazolyl)methane]$CoCl_2$ [8] reveals the potential of an extensive coordination chemistry of molecules containing the bis(2-imidazolyl)methine group. The synthesis of tris(imidazole) ligands and their reactions with divalent metal ions have been described [9, 10].

Experimental

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Proton NMR spectra were recorded on Varian XL-100 and T-60 and a Brüker WM-200 spectrometer; chemical shifts are referenced to Me_4Si in organic solvents and to 2,2-dimethyl-2-silapentane-5-sulfonic acid in aqueous solutions. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan and Galbraith Laboratories, Knoxville, Tennessee. In the following preparations all operations were performed under anaerobic conditions whenever a thiolate anion was generated. Prior to use solvents were distilled from the indicated reagents: acetonitrile, CaH_2; THF, $LiAlH_4$; methanol, $Mg(OMe)_2$; ethanol, $Mg(OEt)_2$. Compounds whose sources are not referenced were commercial samples.

6,6-Bis(2-imidazolyl)-3,3-dimethyl-1-phenyl-5-aza-2-thiahexane (2)

To a mixture of 14.0 g (61.0 mmol) of bis(2-imidazolyl)nitromethane hydrochloride [7] (*1*) and 14.2 g (61.3 mmol) of 4-phenyl-3-thia-2,2-dimethylbutane-1-amine hydrochloride [11] was added 200 ml of ethanol and 60 ml of 3 *M* NaOH. The mixture was stirred at 80 °C for 45 min, during which time a yellow-orange color developed. Solvent was removed in vacuum and the solid white residue was washed with 200 ml of dilute NaOH, water, and ether, and dried under vacuum. This procedure afforded 16.7 g (80%) of product. Recrystallization from hot ethanol yielded a white crystalline solid; m.p. 157.5–160 °C (dec). ^{1}H NMR (60 MHz, dil DCl): δ 7.77 (s, 4H, *Im* (imidazolyl C–H)), 7.37 (s, 5H, Ph), 6.02 (s, 1H, Im_2CH), 5.50 (s, HOD + NH), 3.76 (s, 2H, $PhCH_2$), 2.81 (s, 2H, NCH_2), 1.49 (s, 6H, Me).

Anal. Calcd. for $C_{18}H_{23}N_5S$: C, 63.31; H, 6.79; N, 20.51; S, 9.39. Found: C, 63.33; H, 6.54; N, 20.27; S, 9.56%.

4,4-Bis(2-imidazolyl)-1,1-dimethyl-3-aza-butane-1-thiol (3)

To a suspension of 14.3 g (0.0418 mol) of *2* in liquid ammonia was added with stirring 2.97 g (0.129 mol) of metallic sodium. After the blue color in solution had persisted for 30 min the reaction mixture was quenched with 6.92 g of ammonium chloride. The ammonia was evaporated and the white residue was extracted with 2 × 300 ml of hot THF. After the THF was removed in vacuum the resulting residue was crystallized from methanol–acetonitrile, washed with acetonitrile, and dried under vacuum, affording 7.37 g (70%) of product as a white solid. ^{1}H NMR (60 MHz, dil DCl): δ 7.66 (s, 4H, *Im*), 6.16 (s, 1H, Im_2CH), 5.30 (s, HOD + NH + SH), 2.81 (s, 2H, NCH_2), 1.41 (s, 6H, Me).

4-Phenyl-3-thiabutane-1-thiol (4)

To a suspension of 50.5 g (0.536 mol) of 1,2-ethanedithiol in 100 ml of methanol was added with stirring a solution of 54.0 g (0.354 mol) of NaOMe in 140 ml of methanol. Benzyl bromide (64.7 g, 0.378 mol) in 100 ml of methanol was added dropwise over 1 hr to the vigorously stirred reaction mixture. The mixture was refluxed for 4 hr. Methanol was removed in vacuum and the residue was distributed between 300 ml of 3 *M* NaOH and 200 ml of ether. The aqueous layer was acidified with 300 ml of 6 *M* HCl and extracted with 2 × 200 ml of ether. The latter organic phase was dried (Na_2SO_4) and volatiles were removed by heating the mixture at 60 °C under high vacuum for 4 hr. A slightly yellow oil (32.9 g, 50%) was obtained which was shown to be adequately pure (^{1}H NMR spectrum) for use in the next step.

1-Phenyl-2,5-dithiaoctane-8-amine (5)

To a suspension of 28.2 g (0.153 mol) of *4* in methanol was added with stirring a solution of 16.3 g (0.302 mol) of NaOMe in methanol. A solution of 32.0 g (0.147 mol) of 3-bromopropylamine hydrobromide in methanol was added and the reaction mixture (250 ml total volume) was refluxed for 4 hr. Sodium bromide was removed by filtration and the solvent was evaporated. The oily solid residue was dissolved in 75 ml of ether; this solution was extracted with 50 ml of 2 *M* NaOH. The aqueous phase was washed with several portions of ether and the combined ethereal layers were dried ($MgSO_4$), and the ether was evaporated. The residue was purified by Kügelrohr distillation at 135 °C under high vacuum, affording 17 g (48%) of pure product as a colorless oil.

Anal. Calcd. for $C_{12}H_{19}NS_2$: C, 59.70; H, 7.93; N, 5.80. Found: C, 59.43; H, 8.01; N, 5.54%.

10,10-Bis(2-imidazolyl)-1-phenyl-9-aza-2,5-dithiadecane (6)

A mixture of 2.29 g (10.4 mmol) of *1* in 10 ml of 2 *M* NaOH and 2.53 g (10.5 mmol) of *5* in 30 ml of ethanol was stirred at 80 °C for 30 min, during which time a yellow color developed. After the mixture was cooled to room temperature, solvent was partially removed in vacuum, causing separation of a white solid which was collected and washed with 10 ml of 2 *M* sodium hydroxide, 10 ml of water (neutral), and 2 × 15 ml of ether. This procedure afforded 3.22 g (80%) of product as a white solid, sufficiently pure for use in the following step. For the analytical sample, a portion of the solid was twice recrystallized from hot isopropanol, washed with water, acetone, and ether, and dried under vacuum.

Anal. Calcd. for $C_{19}H_{25}N_5S_2$: C, 58.88; H, 6.50; N, 18.07; S, 16.55. Found: C, 59.07; H, 6.27; N, 18.08; S, 16.60%.

8,8-Bis(2-imidazolyl)-7-aza-3-thiaoctane-1-thiol (7)

To 200 ml of liquid ammonia was added 8.53 g (22.0 mmol) of *6* followed by small pieces of metallic sodium until a blue color in solution persisted for several min. The reaction mixture was quenched with ammonium chloride, the ammonia was evaporated, and the residue was extracted with the minimum volume of hot THF. Cooling of the THF extract to −20 °C caused separation of a white solid which was collected, washed with small portions of cold THF, and dried in vacuum. This procedure gave 4.41 g (67%) of a white powder; m.p. (sealed tube) 154–157 °C (dec). ^{1}H NMR (200 MHz, CD_2Cl_2): δ 7.02 (s, 4H, *Im*), 5.16 (s, 1H, Im_2CH); 2.71, 2.59 (2t, NCH_2, SCH_2CC), 2.69 (s, SCH_2CH_2S) (combined integral δ 2.71–2.59, 8H); 1.73 (br q, 2H, CCH_2C).

Anal. Calcd. for $C_{12}H_{19}N_5S_2$: C, 48.44; H, 6.44; N, 23.54; S, 21.55. Found: C, 48.32; H, 6.73; N, 23.49; S, 21.40.

1,1-Dimethyl-3-thia-6-aminohexane-1-thiol Hydrochloride (8)

A solution of 8.0 g (58 mmol) of 3-aminopropane-1-thiol hydrochloride [12] in 50 ml of methanol was treated with 3.4 g (63 mmol) of NaOMe in 25 ml of methanol. The mixture was cooled to −60 °C. A solution of 5.3 g (60 mmol) of isobutylene sulfide [13] in 15 ml of methanol was slowly added with vigorous stirring. The mixture was stirred overnight under dinitrogen as it was allowed to warm to room temperature. The mixture was cooled in an ice bath and HCl gas was passed through. After filtration the colorless filtrate was evacuated at 50 °C overnight to give a nearly quantitative yield of product as an amorphous solid. ^{1}H NMR (100 MHz, $CDCl_3$): δ 8.16 (br, NH_3^+), 3.2 (br, NCH_2), 2.80 (m, 4H, CH_2SCH_2), 2.2 (s, 1H, SH), 2.1 (br, m, 2H, CCH_2C), 1.40 (s, 6H, Me). This material was used without further purification; episulfide oligomers were separated after benzylation (*vide infra*).

1-Phenyl-3,3-dimethyl-2,5-dithiaoctane-8-amine (9)

Compound *8* (26.1 g, 0.121 mol) in 200 ml of methanol was added to a solution of 13.1 g (0.242 mol) of NaOMe in methanol. This solution was treated with 15.0 g (0.121 mol) of benzyl chloride in 75 ml of methanol and the mixture was stirred for 48 hr. The reaction mixture filtrate was evaporated and the residue was partitioned between 100 ml of ether and 150 ml of 2 *M* NaOH. The aqueous layer was extracted with 100 ml of ether, 2 × 50 ml of CH_2Cl_2, and 100 ml of ether. The combined organic phases were dried (Na_2SO_4), filtered, and evaporated to give 30.4 g (93%) of the crude amine. The pure product was obtained in ~60% yield by molecular distillation at 130 °C/0.05 mm. ^{1}H NMR (100 MHz, $CDCl_3$): δ 7.28 (m, 5H, Ph), 3.78 (s, 2H, $PhCH_2$), 2.78 (t, 2H, NCH_2; s, 2H, SCH_2CS), 2.60 (t, 2H, SCH_2C), 1.70 (m, 2H, CCH_2C), 1.40 (s, 6H, Me), 1.23 (s, 2H, NH_2).

10,10-Bis(2-imidazolyl)-3,3-dimethyl-1-phenyl-9-aza-2,5-dithiadecane (10)

A solution of 6.5 g (24 mmol) of *9* in 75 ml of ethanol was combined with 5.5 g (25 mmol) of *1* and 24 ml of 2 *M* NaOH. The mixture was heated at 80 °C for 75 min during which time it developed a yellow color. After the mixture was cooled to room temperature it was evaporated to near-dryness. The residue was treated with 25 ml of 2 *M* NaOH and extracted with 3 × 75 ml of chloroform. The combined extracts were washed (25 ml of 2 *M* NaOH, 2 × 25 ml of water), dried (Na_2SO_4), filtered, and concentrated to a volume of 25 ml. Dilution to 100 ml with n-hexane followed by cooling to −20 °C gave the crude product as an off-white solid (74%). Recrystallization from isopropanol afforded 5.56 g (57%) of pure product; m.p. 132–134 °C. ^{1}H NMR ($CDCl_3$): δ 7.25 (m, 5H, Ph), 6.99 (s, 4H, *Im*), 5.14 (s, 1H, Im_2CH), 3.76 (s, 2H, CH_2Ph), 2.78 (m, 6H, NCH_2, CH_2SCH_2), 1.70 (m, 2H, CCH_2C), 1.39 (s, 6H, Me).

Anal. Calcd. for $C_{21}H_{29}N_5S_2$: C, 60.68; H, 7.03; N, 16.85. Found: C, 60.66; H, 6.85; N, 17.03%.

8,8-Bis(2-imidazolyl)-1,1-dimethyl-7-aza-3-thiaoctane-1-thiol (11)

A solution of 5.35 g (12.9 mmol) of *10* in 250 ml of liquid ammonia was treated with 0.66 g (29 mmol) of metallic sodium in small pieces until a blue color in solution persisted for several min. After the reaction mixture was quenched with ammonium chloride and the solvent removed, a ^{1}H NMR spectrum indicated that deprotection was not complete. The reaction was repeated, affording after solvent removal a slightly pink solid. This material was recrystallized from hot acetonitrile to give 2.45 g (58%) of pure product; m.p. (sealed tube) 147 °C (dec). ^{1}H NMR (CD_3OD): δ 6.99 (s, 4H, *Im*), 5.07 (s, 1H, Im_2CH), 2.76 (s, 2H, SCH_2CS), 2.61 (m, 4H, NCH_2CCH_2S), 1.75 (m, 2H, CCH_2C), 1.38 (s, 6H, Me).

Anal. Calcd. for $C_{14}H_{23}N_5S_2$: C, 51.66; H, 7.12; N, 21.52; S, 19.70. Found: C, 51.73; H, 6.91; N, 21.60; S, 19.58%.

5-Phenyl-4-thiapentane-1-thiol (12)

To a solution of 64.7 g (0.598 mol) of propane-1,3-dithiol in 110 ml of methanol was added a solution of 22.8 g (0.422 mol) of NaOMe in 150 ml of methanol. After the mixture was stirred for several min, a solution of 71.9 g (0.420 mol) of benzyl bromide in 110 ml of methanol was added dropwise over a 50-min period. The reaction mixture was refluxed for 4 hr. Removal of solvent gave a yellow oil and white solid. The oil was taken up in ether; this solution was filtered and extracted with 300 ml of 6 *M* NaOH, and the aqueous layer was treated with 300 ml of 6 *M* HCl. The oil which separated was extracted with 3 × 150 ml of ether. The latter organic fractions were combined, dried (Na_2SO_4), and the solvent was evaporated. The residue was distilled (short path); the fraction with b.p. 95–97 °C/~0.1 torr afforded 30.6 g (37%) of product. ^{1}H NMR (60 MHz, CCl_4): δ 7.16 (s, 5H, Ph), 3.58 (s, $PhCH_2$), 2.40 (t, 4H, SCH_2), 1.70 (m, 2H, CCH_2C), 1.13 (t, 1H, SH).

Anal. Calcd. for $C_{10}H_{14}S_2$: C, 60.56; H, 7.11; S, 32.33. Found: C, 60.54; H, 7.09; S, 32.57%.

1-Phenyl-2,6-dithianonane-9-amine (13)

To a suspension of 28.0 g (0.141 mol) of *12* in 180 ml of methanol was added with stirring a solu-

tion of 15.5 g (0.285 mol) of NaOMe in methanol. A solution of 30.9 g (0.141 mol) of 3-bromopropylamine hydrobromide in 120 ml of methanol was added over 40 min, and the reaction mixture was refluxed for 4 hr. After methanol was removed the residue was distributed between 100 ml of 3 *M* NaOH and 200 ml of ether. The aqueous layer was separated and extracted with 100 ml of ether. The combined ether layers were dried (Na_2SO_4) and evaporated to give a residue that was distilled in high vacuum (Kügelrohr, ~150 °C), affording 34.0 g (94%) of product as a colorless oil. ^{1}H NMR (60 MHz, CCl_4): δ 7.19 (s, 5H, Ph), 3.61 (s, 2H, $PhCH_2$), 2.45 (m, 8H, SCH_2, NCH_2), 1.61 (m, 4H, CCH_2C), 0.93 (s, 2H, NH_2).

Anal. Calcd. for $C_{13}H_{21}NS_2$: C, 61.13; H, 8.29; N, 5.48; S, 25.10. Found: C, 60.98; H, 8.19; N, 5.45; S, 24.97%.

11,11-Bis(2-imidazolyl)-1-phenyl-10-aza-2,6-dithiaundecane (14)

A mixture of 4.23 g (19.7 mmol) of *1* in 19 ml of 2.2 *M* NaOH and 5.03 g (19.7 mmol) of *13* in 60 ml of ethanol was stirred at 75–85 °C for 30 min, during which time a yellow color developed. The white solid remaining after solvent removal was treated with 80 ml of 2 *M* NaOH and 80 ml of dichloromethane. The aqueous layer was extracted with 2 × 50 ml of dichloromethane. The organic fractions were combined, washed with 100 ml of 2 *M* NaOH, and dried (Na_2SO_4). Volume reduction to ~10 ml and addition of ether gave an off-white solid, which was washed with ether and dried in vacuum (5.84 g). This material was recrystallized from hot isopropanol, washed with cold isopropanol and ether, and dried in vacuum. The product (3.46 g, 44%) was obtained as a white solid; m.p. (sealed tube, N_2), 137–138 °C (dec). ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.21 (s, 5H, Ph), 6.96 (s, 4H, *Im*), 5.46 (s, 1H, *Im*$_2$CH), 3.65 (s, $PhCH_2$), 2.44 (m, 8H, NCH_2, SCH_2), 1.69 (m, 4H, CCH_2C).

Anal. Calcd. for $C_{20}H_{27}N_5S_2$: C, 59.82; H, 6.78; N, 17.44. Found: C, 59.75; H, 6.61; N, 17.43%.

9,9-Bis(2-imidazolyl)-8-aza-4-thianonane-1-thiol (15)

To a suspension of 8.70 g (21.7 mmol) of *14* in 300 ml of liquid ammonia was added with stirring 1.60 g (70 mmol) of metallic sodium in small pieces. At the end of the addition a blue color persisted for ~5 min. After the reaction mixture was quenched with 3.73 g of NH_4Cl and ammonia was evaporated, the residue was extracted with 300 ml of hot THF. A slightly pinkish solid separated after volume reduction of the extract to 200 ml and cooling to –20 °C. This material was washed with cold THF and dried in vacuum (4.34 g, 64%). A 0.300-g portion of this solid was recrystallized from methanol/acetonitrile to give 0.172 g of pure product as a white solid after it was washed with acetonitrile and dried in vacuum; m.p. (sealed tube) 153–157 °C (dec). ^{1}H NMR (60 MHz, dil DCl, ext. Me_4Si): δ 7.71 (s, 4H, *Im*), 6.48 (s, 1H, *Im*$_2$CH), 5.24 (HOD + SH + NH), 3.09 (t, 2H, NCH_2), 2.73 (m, 6H, SCH_2), 1.99 (m, 4H, CCH_2C).

Anal. Calcd. for $C_{13}H_{21}N_5S_2$: C, 50.13; H, 6.80; N, 22.48; S, 20.59. Found: C, 50.10; H, 6.79; N, 22.38; S, 20.47%.

S-tetrahydropyranyl-o-xylene-α,α′-dithiol (16)

To a solution of 17.1 g (0.100 mol) of *o*-xylene-α,α′-dithiol [14] and 4 drops of ether saturated with dry HCl in 250 ml of dichloromethane was added 8.41 g (0.100 mol) of dihydropyran in 60 ml of dichloromethane. The reaction mixture was refluxed for 2.5 hr and stirred overnight at room temperature. Evaporation of solvent gave 23.9 g of an oil which was shown by tlc to contain the unreacted dithiol as well as the mono- and di-THP ethers (THP = tetrahydropyranyl). Pure mono-THF ether as a colorless oil was typically obtained in ~45% yield after chromatography on silica gel eluting with petroleum ether/dichloromethane. An analytical sample was obtained by Kügelrohr distillation at 150 °C. ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.20 (s, 4H, Ar), 4.72 (t, br, 1H, SCHO); 3.90, 3.86 (s, d, $ArCH_2$); 3.2–4.4 (m, OCH_2) (combined integral δ 3.2–4.4, 6H), 1.85 (t, 1H, SH), 1.64 (m, br, 6H, CCH_2C).

Anal. Calcd. for $C_{13}H_{18}OS_2$: C, 61.37; H, 7.13; S, 25.21. Found: C, 61.52; H, 7.14; S, 25.20%.

S-THP,S′-(3-aminopropyl)-o-xylene-α,α′-dithiol (17)

A solution of 9.27 g (36.4 mmol) of *16* in 50 ml of methanol was treated with 3.9 g (70 mmol) of NaOMe in 50 ml of methanol followed by 7.50 g (34.3 mmol) of 3-bromopropylamine hydrobromide in 30 ml of methanol. The volume of the reaction mixture was reduced to 80 ml and the solution was refluxed for 4 hr. The residue after solvent evaporation was partitioned between 100 ml of ether and 50 ml of 3 *M* NaOH. The ether layer was extracted with an additional 50 ml portion of 3 *M* NaOH and dried (Na_2SO_4). Evaporation of the ether followed by Kügelrohr distillation of the residue at 160–170 °C afforded 9.93 g (93%) of pure product as a colorless oil. ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.20 (s, 4H, Ar), 4.72 (t, br, 1H, SCHO); 3.95, 3.87 (2s, $ArCH_2$), 3.2–4.4 (m, OCH_2) (combined integral δ 3.2–4.4, 6H), 2.62 (m, 4H, SCH_2C, NCH_2), 1.67 (br, 8H, CCH_2C), 1.06 (s, NH_2).

Anal. Calcd. for $C_{16}H_{25}NOS_2$: C, 61.69; H, 8.09; N, 4.50; S, 20.59. Found: C, 61.06; H, 7.88; N, 4.26; S, 19.89%.

S-THP,S'-[5,5'-bis(2-imidazolyl)-4-aza-1-pentyl]-o-xylene-α,α'-dithiol (18)

A mixture of 4.42 g (19.2 mmol) of *1* in 20 ml of 2 *M* NaOH and 6.00 g (19.3 mmol) of *17* in 60 ml of ethanol was stirred at 80 °C for 30 min. Removal of the solvent under vacuum yielded an oily solid which was taken up in 100 ml of 2 *M* NaOH and extracted with 3 × 60 ml of dichloromethane. The combined organic layers were washed with 2 *M* NaOH and dried (Na_2SO_4). The volume of solution was reduced to 10 ml and a slightly pinkish precipitate was obtained by addition of ether with stirring. The solid was collected, washed with ether, and dried under vacuum, affording 5.87 g (67%) of product. ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.11 (m, 4H, Ar), 6.91 (s, 4H, *Im*), 5.36 (s, 1H, Im_2CH), 4.67 (t, br, 1H, SCHO); 3.89, 3.74 (2s, $ArCH_2$); 3.2–4.4 (m, CH_2O) (combined integral δ 3.2–4.4, 6H), 2.53 (m, 4H, SCH_2C, NCH_2), 1.61 (br, 8H, CCH_2C).

Anal. Calcd. for $C_{23}H_{31}N_5OS_2$: C, 60.36; H, 6.83; N, 15.30. Found: C, 60.01; H, 6.83; N, 15.59%.

S-[5,5'-bis(2-imidazolyl)-4-aza-1-pentyl]-o-xylene-α,α'-dithiol (19)

To a solution of 0.247 g (1.45 mmol) of silver nitrate in 23 ml of 20:3 v/v methanol/water was slowly added 0.600 g (1.31 mmol) of *18* in 5 ml of methanol. A precipitate formed initially but redissolved after being stirred for several hr. Addition of triethylamine caused the separation of a white solid, which was collected and washed with 1:1:20 v/v triethylamine/methanol/water and THF, and dried under vacuum to yield 0.385 g of a slightly brownish solid, presumed to be a silver complex. This material was suspended in 15 ml of methanol and hydrogen sulfide was bubbled through for 15 min, causing the precipitation of a black solid. After the mixture was filtered through Celite the filtrate was taken to dryness, affording 0.170 g (35%) of product as a slightly yellow solid. ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.53 (br, ~4H, SH, NH), 7.20 (m, 4H, Ar), 7.00 (s, 4H, *Im*), 5.46 (s, 1H, Im_2CH), 3.81, 3.75 (2s, 4H, $ArCH_2$), 2.55 (m, 4H, SCH_2C, NCH_2), 1.63 (m, 2H, CCH_2C).

Anal. Calcd. for $C_{18}H_{23}N_5S_2$: C, 57.88; H, 6.21; N, 18.75. Found: C, 57.10; H, 6.22; N, 17.81%.

3-(Benzyloxycarbonyl)amino-N-[1-(4-phenyl-3-thia-2,2-dimethyl)butyl]propionamide (20)

This compound was prepared by the mixed anhydride coupling method previously employed (but not described) for the synthesis of the related N(1-phenyl-2-thiabutyl)propionamide [15]. A solution of 32.0 g (0.143 mol) of Z-β-Ala·OH (prepared by the method for Z-Gly·OH [16], m.p. 104–105 °C, lit. [17] 106 °C) and 15 ml of triethylamine in 350 ml of dry 6:1 v/v toluene–chloroform was cooled to −10 °C. Isobutylchloroformate (18.6 ml, 0.143 mol) was added over 5 min and the reaction mixture was stirred for 20 min at −10 °C. 4-Phenyl-3-thia-2,2-dimethylbutane-1-amine [11] (27.9 g, 0.143 mol) was slowly added with stirring. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The mixture was washed with water (400 ml), 3% $NaHCO_3$ solution (2 × 400 ml), saturated NaCl solution (3 × 400 ml), and the organic phase was dried (Na_2SO_4). Volume reduction to 250 ml followed by addition of ~1500 ml of petroleum ether caused separation of 40.1 g (70%) of product as a white solid. This material was used without further purification in the following step. A portion of the solid was recrystallized from ethyl acetate/petroleum ether; m.p. 77–78 °C.

Anal. Calcd. for $C_{22}H_{28}N_2O_3S$: C, 65.97; H, 7.05; N, 6.99. Found: C, 65.69; H, 7.13; N, 6.93%.

3-Amino-N-[1-(4-phenyl-3-thia-2,2-dimethyl)butyl]-propionamide Hydrobromide (21)

The benzyloxycarbonyl group was removed from *20* (74.4 g, 0.186 mol) by the standard hydrogen bromide/glacial acetic acid method [18]. Ether (600 ml) was added and the reaction mixture was kept at −20 °C overnight. The oily material which separated was triturated until a solid formed. The solid was recrystallized from ethanol; a second crop was obtained from the filtrate by addition of ether and storage overnight at −20 °C. This procedure gave 46.4 g (72%) of product; m.p. 128–129 °C.

Anal. Calcd. for $C_{14}H_{23}BrN_2OS$: C, 48.41; H, 6.67; N, 8.07. Found: C, 48.31; H, 6.73; N, 8.14%.

3-[Bis(2-imidazolyl)methyl]amino-N-[1-(4-phenyl-3-thia-2,2-dimethyl)butyl]propionamide (22)

A mixture of 4.59 g (20.9 mmol) of *1* in 40 ml of 2 *M* NaOH and 7.29 g (21.0 mmol) of *21* in 40 ml of ethanol was heated at 80 °C for 30 min. Removal of ethanol in vacuum left an oily residue which was taken up in two 50-ml portions of chloroform. The combined chloroform solution was washed with 25 ml of 2 *M* NaOH and 2 × 25 ml of water (neutral), and was dried (Na_2SO_4). Volume reduction followed by addition of petroleum ether caused separation of a solid. After storage at −20 °C overnight the solid was collected, washed with ether, and dried under vacuum; 5.16 g (65%) of product was obtained as a white solid; m.p. 127–128 °C (dec).

Anal. Calcd. for $C_{21}H_{28}N_6OS$: C, 61.13; H, 6.80; N, 20.37. Found: C, 60.91; H, 7.05; N, 20.30%.

3-[Bis(2-imidazolyl)methyl]amino-N-[1-(2-methyl-2-mercapto)propyl]propionamide (23)

The benzyl group was removed from 7.44 g (18.1 mmol) of *22* with use of the procedure for deprotection of *6*. The THF extract was reduced in volume until the appearance of cloudiness and was then maintained at −20 °C overnight. The white solid

that separated was collected and dried under vacuum, affording 3.60 g (62%) of product. Melting points of different preparations occurred in the 138–150 °C range; the highest value was 149–150 °C. ^{1}H NMR (200 MHz, CD_2Cl_2): δ 7.01 (s, 4H, *Im*), 5.12 (s, 1H, Im_2CH), 3.39 (d, 2H, CH_2NCO), 3.05 (t, 2H, CH_2CO), 2.47 (t, 2H, NCH_2), 1.35 (s, 6H, Me).

Anal. Calcd. for $C_{14}H_{22}N_6OS$: C, 52.15; H, 6.88; N, 26.07; S, 9.94. Found: C, 51.66; H, 6.69; N, 25.45; S, 9.61%.

Ellman thiol group assays [19] of *3, 7, 11, 15, 19,* and *23* gave >92% thiol content. These compounds should be manipulated and stored under anaerobic conditions.

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