Synthesis of Some Benzimidazole- and Benzothiazole-Derived Ligand Systems and Their Precursory Diacids

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Procedures are described for the preparation of various bidentate and linear tetradentate benzimidazoles and benzothiazoles incorporating units such as pyridyl and thioether, and for the preparation of certain thioether dicarboxylic acids precursory to them. Condensations of *ortho*-functinal anilines with carboxylic acids were carried out in polyphosphoric acid or refluxing HCl solution. Syntheses are reported for: $[HO_2C(CH_2)_2S(CH_2)_2]_2X$ (X = O,S), 1,9-bis(benzimidazol-2-yl)-2,5,8-trithianonane, 1,11-bis(*N*-methylbenzimidazol-2-yl)-3,6,9-trithiaundecane, 1,11-bis(2-benzimidazol-2-yl)-6-oxo-3,9-dithiaundecane, 2-(2-pyridyl)benzothiazole, 2,6-bis(benzothiazol-2-yl)pyridine, 2-(2-pyridyl)-*N*-methylbenzimidazole, 2-(2-pyridylmethyl)benzimidazole and 2-(*N*-methyl-2-piperidyl)benzimidazole. The compounds were characterized, where appropriate, by their mass, uv and ^{1}H-nmr spectra.

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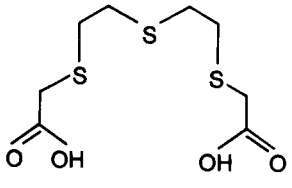
The resurgence of interest in benzimidazole- and benzothiazole-derived chelating agents, generated principally by the work of Thompson *et al.* [1,2] has recently resulted in considerable activity in the chemistry of various benzimidazyl-thioether systems [3-7].

o-Phenylenediamines and *o*-aminothiophenols condense with carboxylic acids and various of their derivatives, to yield benzimidazoles and benzothiazoles. Benzimidazole formation is conveniently effected at elevated temperature in acidic media, such as refluxing hydrochloric acid [8,9]. The pure reactant melt can be an effective alternative when acid-sensitive substituents are present [10]. Those carboxylic acids which are relatively unreactive usually give good yields when polyphosphoric acid is used as the reaction medium for 2-3 hours, at 120-200° [10-12]. In general, we have found that higher temperatures and the reactant melt procedure are better avoided in favour of the Phillips procedure in the case of acids which are susceptible to ready decarboxylation.

Benzothiazole formation, on the other hand, is not readily effected in hydrochloric acid, but polyphosphoric acid [10,13] and the pure reactant melt give good yields. The reaction of the acid with *o*-aminothiophenol is more facile in the latter situation than is its reaction with *o*-phenylenediamine to form the corresponding benzimidazole.



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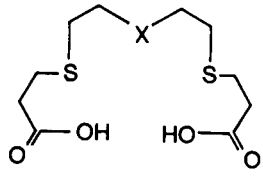

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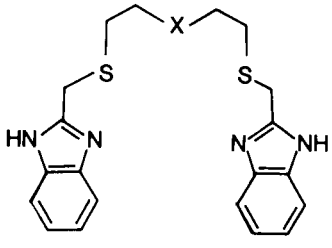

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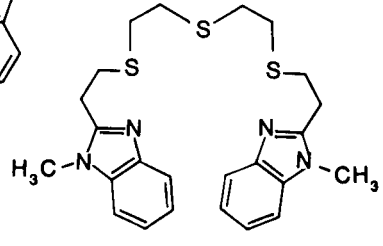
5. X=S



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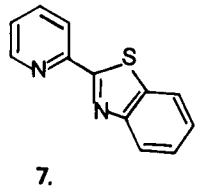

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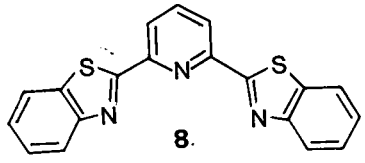

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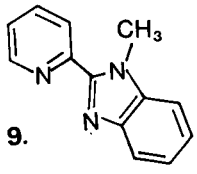

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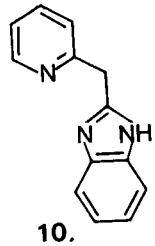

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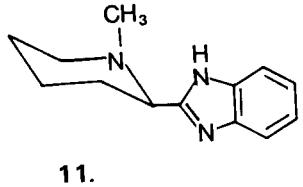


11.

The reactions of *o*-substituted anilines with thioamides and selenoamides also provide synthetic pathways to benzimidazoles and benzothiazoles, under conditions mild enough to ensure the survival of other reactive substituents [14-16]. However, the procedures usually add steps to the overall syntheses, and often result in considerably lesser yields. The last is also true of the Willgerodt reaction, involving oxidative coupling of anilines with picolines using elemental sulfur, whereafter chromatographic separation is usually required [17,18,19].

Of the compounds described herein, some have been reported previously in the literature, but we offer either greatly improved yield (*e.g.* **8**) and greater synthetic convenience (*e.g.* **7**) or more complete characterization of compounds reported in relatively inaccessible literature (*e.g.* **3**). Compounds **2, 4, 5, 6, 9, 10** and **11** are novel.

EXPERIMENTAL

Nuclear magnetic resonance spectra were obtained at ambient temperature on a JEOL FX90Q (90 MHz) FT instrument, chemical shifts being quoted with respect to tetramethylsilane (nonaqueous samples) or trimethylsilylpropionate (aqueous samples) as internal standards. The nmr spectra are reported as: δ - value (multiplicity, integral, coupling constant, assignment). The uv spectra are reported as: wavelength in nm (molar absorptivity in ℓ mole^{-1}cm^{-1}). Mass spectra were recorded on a Finnigan-4000 GC-MS, with the data for the lower mass fragments truncated below m/e = 46 and 4% intensity. The uv spectra were obtained using a Perkin-Elmer 320 spectrophotometer. Melting points are uncorrected. Microanalyses (C,H,N,S) were performed by Canadian Microanalytical Service Ltd. (Vancouver) and Galbraith Laboratories. Reagents were used for syntheses as received from Sigma, Aldrich and Eastman Kodak (*N*-methyl-*o*-phenylenediamine dihydrochloride).

2,5,8-Trithianonane-1,9-dicarboxylic Acid (**1**) (Diethylenetrithiodiacetic Acid).

This compound was prepared from bis(2-mercaptoethyl) sulfide and iodoacetic acid, in a manner similar to its 13-carbon analogue **2**, and to the synthesis by Ford *et al.* [20], yield, 56% of white prismatic crystals, mp 109° (lit 114° [20], 109° [21], 110° [22]); ms: (m/e) 270 (M$^+$, 2%), 178 (29%), 152 (18%), 132 (16%), 119 (100%), 105 (24%), 73 (54%), 60 (31%); nmr: (deuterium oxide/potassium carbonate): 2.84 (s, 8, S-CH$_2$-CH$_2$-S), 3.25 (s, 4, S-CH$_2$-COOH).

3,6,9-Trithiaundecane-1,11-dicarboxylic Acid (**2**) (Diethylenetrithiodipropionic Acid).

This compound was prepared by treating bis(2-mercaptoethyl) sulfide (10 g, 65 mmoles) in 80% ethanol (150 ml) under nitrogen with sodium borohydride (0.25 g, 6.5 mmoles), followed by addition of pellet potassium hydroxide (16.8 g of 87%, 260 mmoles). Bromopropionic acid (20.7 g, 97%, 131 mmoles) in ethanol (100 ml), was added over 15 minutes. After having been stirred overnight, the solution was evaporated to dryness. The residue was dissolved in water and ether-extracted at *p*H 7 to remove impurities. The solution was acidified with sulfuric acid (6*M*) to a *p*H of 1.5, and the very bulky precipitate was filtered off and recrystallized from water (3 ℓ required) to give the white flaky crystals, yield, 11 g (56%) after drying *in vacuo* over phosphorus(V) oxide, mp 165°; ms: (m/e) 298 (M$^+$, 12%), 192 (10%), 166 (13%), 132 (100%), 119 (18%), 105 (75%), 89 (28%), 73 (22%), 61 (42%); nmr (deuterium oxide/potassium carbonate): 2.48 (d, 4, -CH$_2$-COOH, J = 5.9 Hz), 2.73 (d, 4, -CH$_2$-S, J = 7.1 Hz), 2.83 (s, 8, S-CH$_2$-CH$_2$-S).

Anal. Calcd. for $C_{10}H_{14}O_4S_3$: C, 40.2; H, 6.08. Found: C, 40.2; H, 6.06.

6-Oxo-3,9-dithiaundecane-1,11-dicarboxylic Acid (**3**) [23].

This compound was prepared by a similar procedure, from bis(2-mercaptoethyl) ether (2.76 g, 20 mmoles) and bromopropionic acid (6.1 g, 40 mmoles). The product was recrystallized from water and vacuum-desiccated to a white powder (3.2 g, 40% yield), mp 130-132°; ms: (m/e, no parent ion observed) 133 (51%), 132 (71%), 105 (100%), 89 (29%), 73 (44%), 61 (81%), 60 (68%), 55 (40%); nmr (deuterium oxide/potassium carbonate): 2.48 (t, 4, J = 6.1 Hz, -CH$_2$-COOH), 2.80 (t, 8, J = 6.3 Hz, -CH$_2$-S-CH$_2$-), 3.74 (t, 4, J = 6.3 Hz, -CH$_2$-O-CH$_2$-).

Anal. Calcd. for $C_{10}H_{18}S_2O_5$: C, 42.5; H, 6.43; S, 22.7; O, 28.3. Found: C, 42.5; H, 6.32; S, 23.0 (remainder, 28.3).

1,9-Bis(benzimidazol-2-yl)-2,5,8-trithianonane (**4**).

2,5,8-Trithianonane-1,9-dicarboxylic acid (**1**) (2.7 g, 10 mmoles) was stirred in the molten state with *o*-phenylenediamine (2.0 g, 20 mmoles) at 120° for 3 hours. When cool, the blue product was recrystallized from aqueous acetonitrile (charcoal) and dried *in vacuo* over phosphorus(V) oxide to give a white powdery product, yield, 70%, mp 185°; ms: (m/e) 177 (10%), 144 (100%), 132 (20%), 118 (60%), 90 (20%), 77 (20%), 64 (60%), 52 (20%); nmr (DMSO-d$_6$): 2.74 (s, 8, S-CH$_2$-CH$_2$-S), 3.97 (s, 4, -CH$_2$-Bzim), 7.13 (q, 4, J = 3.1 Hz, Bzim-5,6), 7.51 (q, 4, J = 3.1 Hz, Bzim-4,7); uv (methanol): 285 (sh, 15000), 275 (17500), 250 (14000).

Anal. Calcd. for $C_{20}H_{22}N_4S_3 \cdot 1/2H_2O$: C, 56.7; H, 5.43; N, 13.2. Found: C, 57.1; H, 5.43; N, 13.2.

1,9-Bis(2-benzimidazol-2-yl)-5-oxo-2,8-dithianonane (**5**).

To bis(2-mercaptoethyl)ether (2.76 g, 20 mmoles) in 90% ethanol (100 ml) under nitrogen was added sodium borohydride (0.08 g, 2 mmoles) and, after 30 minutes, potassium hydroxide (8 ml of 10*M*). This was followed by slow addition of 2-chloromethylbenzimidazole (6.66 g, 40 mmoles) in ethanol (150 ml). The mixture was stirred overnight under nitrogen, refluxed briefly, then (rotary) evaporated to dryness. The resulting brown gum was dispersed in 100 ml of hot water, the *p*H was adjusted to 7 (dilute hydrochloric acid) and the solution was cooled, to give a grey gum, which was dried and recrystallized twice from acetonitrile to give a chalky white solid (1.2 g, 15%), mp 150-154°; ms: (m/e, no parent peak observed) 267 (4%), 235 (4%), 224 (4%), 191 (4%), 164 (21%), 132 (83%), 131 (83%), 119 (67%), 118 (31%), 104 (21%), 89 (58%), 77 (52%), 73 (58%), 61 (79%), 60 (52%), 47 (75%), 46 (100%); nmr (DMSO-d$_6$): 2.68 (t, 4, J = 6.9 Hz, CH$_2$O), 3.49 (t, 4, J = 6.5 Hz, -CH$_2$-S), 3.92 (s, 4, S-CH$_2$-Bzim), 7.15 (m, 4, Bzim-5,6), 7.45 (m, 4, Bzim-4,7); uv (methanol): 285 (sh, 14200), 275 (16200), 250 (13800).

Anal. Calcd. for $C_{22}H_{22}N_4OS_2$: C, 60.3; H, 5.56; N, 14.1. Found: C, 60.0; H, 5.92; N, 13.9.

1,11-Bis(*N*-methylbenzimidazol-2-yl)-3,6,9-trithiaundecane (**6**).

This compound was synthesized by the Phillips condensation of *N*-methyl-*o*-phenylenediamine (1.95 g, 10 mmoles) and 3,6,9-trithiaundecane-1,11-dicarboxylic acid, **2** (1.5 g, 5 mmoles) in 4*M* hydrochloric acid (100 ml, 48 hours reflux). The deep blue solution was filtered, cooled to room temperature and its *p*H was adjusted to 8 with 5*M* aqueous ammonia. The precipitated pink solid was filtered off, washed with water and recrystallized from tetrahydrofuran (after charcoaling) by the addition of cold water to the ice-cold solution. The product was dried over potassium hydroxide *in vacuo*. Drying the compound in the air, or over phosphorus(V) oxide causes the crystals to form a gum, yield, 30%, mp 97-99°; ms: (m/e) 240 (17%), 160 (82%), 149 (23%), 129 (58%), 115 (100%), 104 (23%), 91 (30%), 77 (47%), 60 (47%); nmr (deuteriochloroform): 2.75 (d, J = 3.4 Hz, S-CH$_2$-CH$_2$-S), 3.16 (s, S-CH$_2$-CH$_2$-Bzim), 3.75 (s, -CH$_3$), 7.4 (m, Bzim-5,6 and chloroform), 7.8 (m, Bzim-4,7); uv (methanol): 285 (12300), 275 (14500), 250 (13500).

Anal. Calcd. for $C_{24}H_{30}S_3N_4$: C, 61.3; H, 6.38; N, 11.9. Found: C, 61.1; H, 6.27; N, 12.3.

2-(2-Pyridyl)benzothiazole (**7**) [14,19,24].

To pyridine-2-carboxylic acid (6.2 g, 50 mmoles) in hot polyphosphoric acid (40 ml) was added *o*-aminothiophenol (6.2 g, 50 mmoles). The reac-

tion mixture was stirred at 180° for 2 hours, then poured into an ice/water slurry. The solution was made basic with potassium hydroxide, and the precipitated product was filtered off and dried. After recrystallization from methanol (charcoal), it yielded 7.0 g (70%) of colorless prisms. The product can also be purified by vacuum sublimation (155°, 1 Torr), mp 131° (lit 132 [14], 133-135 [19]); ms: (m/e) 212 (M^+, 100%), 186 (8%), 108 (23%), 82 (18%), 78 (22%), 69 (43%), 63 (20%), 58 (13%), 51 (33%); nmr (deuteriochloroform): 7.4 (m, Bthz and Pyr-β), 8.1 (m, Bthz), 8.5 (d, J = 7.7 Hz, Pyr-γ), 8.66 (d, J = 3.6 Hz, Pyr-α); uv (dichloromethane): 325 (sh, 14300), 310 (20000), 250 (6500).

Anal. Calcd. for $C_{12}H_8N_2S$: C, 67.9; H, 3.80; N, 13.2; S, 15.1. Found: C, 67.8; H, 3.77; N, 13.3; remainder, 15.1.

2,6-Bis(benzothiazol-2-yl)pyridine (**8**) [25].

To pyridine-2,6-dicarboxylic acid (8.7 g, 52 mmoles) in polyphosphoric acid (40 ml, 180°) was added *o*-aminothiophenol (12.5 g, 100 mmoles). The reaction mixture was stirred for 2-½ hours, poured into ice/water and neutralized with potassium hydroxide. The yellow precipitate was filtered off, dried, recrystallized from pyridine (charcoal) and washed with methanol. After drying it *in vacuo* to give phosphorus(V) oxide, the yield of product was 11.8 g (66%) of shiny cream platelets, mp >220° (lit [25] 273-275°). The mass spectrum agrees with that reported peviously [22]. The compound is insufficiently soluble for nmr; uv (dichloromethane): 345 (sh, 27500), 330 (32500), 300 (sh, 23000), 255 (14400).

2-(2-Pyridyl)-*N*-methylbenzimidazole (**9**).

N-Methyl-*o*-phenylenediamine (9.4 g, 77 mmoles, prepared from the dihydrochloride) and pyridine-2-carboxylic acid (98.2 g, 75 mmoles) were stirred in polyphosphoric acid at 160-180° for 2 hours, after which the purple melt was added to 500 ml ice/water and neutralized with aqueous sodium hydroxide to give a purple oil. This oil eventually crystallized, was filtered off and flash-distilled *in vacuo* to give a yellow crystalline, air-sensitive product (4.4 g, 28%), mp 53-56°; ms: (m/e) 210 (12%), 209 (M^+, 60%), 208 (100%), 131 (30%), 104 (20%), 78 (30%), 77 (27%), 51 (36%); nmr (deuteriochloroform): 4.19 (s, 3, -CH_3), 7.3 (m, 4, Bzim-5,6 and Pyr-β), 7.8 (m, 2, Bzim-4,7), 8.34 (d, 1, J = 7.7 Hz, Pyr-γ), 8.60 (s, 1, Pyr-α); uv (methanol): 300 (19200), 240 (sh, 11000).

Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.6; H, 5.30: N, 20.1. Found: C, 74.9; H, 5.19; N, 20.2.

2-(2-Pyridylmethyl)benzimidazole (**10**).

2-Pyridylacetic acid hydrochloride (9.5 g, 55 mmoles) and *o*-phenylenediamine (5.40 g, 50 mmoles) were refluxed for 24 hours in 4*M* hydrochloric acid (50 ml). The resulting green solution was made basic with potassium hydroxide (*p*H 9) and gave a dark brown solid, which was recrystallized from acetonitrile and dried over phosphorus(V) oxide to give straw-coloured needles (3.54 g, 34%), mp 161-164°; ms: (m/e) 223 (17%), 209 (M^+, 100%), 208 (96%), 195 (25%), 131 (30%), 104 (30%), 90 (28%), 79 (32%), 78 (100%), 77 (37%), 65 (62%), 64 (43%), 63 (49%), 52 (53%), 51 (78%), 50 (20%); nmr (deuteriochloroform): 4.45 (s, 3, -CH_2-), 7.2 (m, 4, Bzim-5,6 and Pyr-β), 7.5 (m, 3, Bzim-4,7 and Pyr-γ), 8.47 (d, 1, J = 4.0 Hz, Pyr-α); uv (methanol): 325 (6700), 260 (sh, 8800), 255 (9400), 225 (9400).

Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.6; H, 5.30; N, 20.1. Found: C, 75.0; H, 5.42; N, 20.3.

2-(*N*-Methyl-2-piperidyl)benzimidazole (**11**).

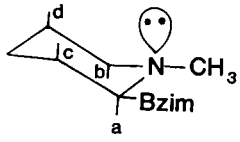
Ethyl *N*-methylpipecolinate (6.06 g, 50 mmoles) and *o*-phenylenediamine (5.40 g, 50 mmoles) were stirred in 50 ml of polyphosphoric acid at 160° for 2 hours. The purple melt was poured into 500 ml of ice/water and made basic with potassium hydroxide. Cooling, filtering and drying over phosphorus(V) oxide gave a light purple powder which was recrystallized from chloroform, yield, 0.40 g, (8%), mp approximately 245° dec; ms: (m/e) 215 (M^+, 8%), 158 (20%), 145 (100%), 132 (30%), 119 (8%), 98 (8%), 92 (10%), 77 (8%), 70 (20%), 65 (12%), 55 (8%); nmr (deuteriochloroform): 1.7 (m, 7, piperidyl-3,6), 2.12 (s, 3, -CH_3), 3.03 (d, 1, J = 11.7 Hz, Pip-6), 3.40 (q, 1, J = 10.8 Hz, Pip-2); uv (methanol): 280 (5450), 275 (5900), 245 (5500).

Anal. Calcd. for $C_{13}H_{16}N_3 \cdot 0.75H_2O$: C, 68.2; H, 8.15; N, 18.4. Found: C, 68.5; H, 7.96; N, 18.1.

Conclusion.

The ultraviolet spectra of the heterocycles are mostly dominated by the $\pi \rightarrow \pi^*$ transitions of the benzimidazole or benzothiazole moieties, which occur in the 230-290 nm region [26]. However, in compounds **7**, **8** and **9**, conjugation with the pyridyl unit is presumably the cause for the added absorption in the 300-340 nm region. A band of this appearance is also present in the methylene-bidged **10**.

The ^{1}H-nmr spectrum suggests that the solution conformation of **11** is principally that shown below.



The protons *a* and *c* are thus both axial (J = 10.8 Hz), while *b* is *trans* to the axially disposed piperidyl nitrogen lone pair, and axially akin to *d* (J = 11.7 Hz).

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