Synthesis of Some Benzimidazole-, Pyridine- and Imidazole-Derived Chelating Agents

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Procedures are described for the preparation of various bidentate and potentially tridentate chelating agents. These incorporate pyridyl, benzimidazole, imidazole or phenolic moieties. Phillips condensations of carboxylic acids with *o*-phenylenediamines were carried out in 4 *M* hydrochloric acid. Syntheses are reported for 2,6-bis(*N'*-methylimidazol-2'-ylthiomethyl)pyridine, 2,6-bis(benzimidazol-2'-ylthiomethyl)pyridine, 2-(4'-piperidyl)benzimidazole, 2-(3'-piperidyl)benzimidazole, 2-(3-*N'*-methylpiperidyl)benzimidazole, 2-(3-*N'*-methylpiperidyl)-*N*-methylbenzimidazole, 2-(2'-hydroxybenzyl)benzimidazole and 2-(2'-hydroxybenzyl)-*N*-methylbenzimidazole. The compounds were characterized where appropriate by their mass, uv, and ^{1}H-nmr spectra. 2-(2'-Hydroxybenzyl)benzimidazole hydrochloride acts as a gelling agent in aqueous solution.

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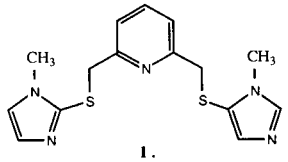
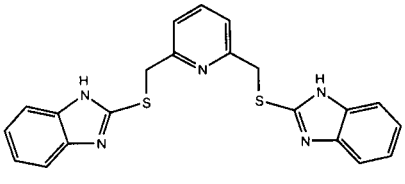
Introduction.

The compounds here are of interest primarily for their use as oligodentate imidazole, benzimidazole, or phenolate donor ligands for transition metal complexes. This work is a logical extension of our earlier work on benzimidazole- and benzothiazole-containing ligands, some with thioether linkages [1, 2, 3, 4].

The benzimidazole derivatives were prepared by condensing *o*-phenylenediamine with the appropriate carboxylic acid to give the desired product. Reaction is effected at elevated temperature in acidic medium, in this case aqueous hydrochloric acid [5,6]. This method is an effective, one-step process which is easily carried out. The formation of **1** and **2** is a simple nucleophilic displacement of halide by thiol or thiolate ion to give the thioether linkage.



1.



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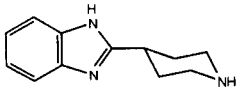

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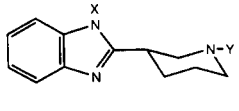
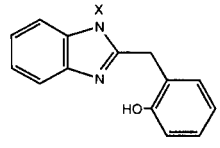


4. X=H, Y=H
5. X=H, Y=CH_3
6. X=CH_3, Y=CH_3



7. X=H
8. X=CH_3

EXPERIMENTAL

Nuclear magnetic resonance spectra were obtained at ambient temperature on a JEOL FX90Q (90 MHz) FT or Bruker Aspect 2000 (250 MHz) FT instrument, chemical shifts being quoted with respect to tetramethylsilane as internal standard. The ^{1}H nmr spectra are reported as: δ - value (multiplicity, integral, coupling constant, assignment). The proton assignments for compound **5** were made on the basis of ^{1}H decoupling experiments. The uv spectra, obtained using a Perkin-Elmer Lambda-3B spectrophotometer, 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 = 58 and 4% intensity. Melting points are uncorrected. Microanalyses (C, H, N, S) were performed by Canadian Microanalytical Service Ltd. (Vancouver). Reagents were used for syntheses as received from Sigma, Aldrich and Eastman Kodak (*N*-methyl-*o*-phenylenediamine dihydrochloride). 2,6-Bis(chloromethyl)pyridine hydrochloride was prepared from 2,6-bis(hydroxymethyl)pyridine and thionyl chloride, according to the method of Baker [7].

2,6-Bis(*N*-methylimidazol-2'-ylthiomethyl)pyridine (1).

2-Mercapto-1-methylimidazole (1.14 g, 10 mmoles) and sodium hydroxide (0.40 g, 10 mmoles) were combined in 50 ml of ethanol under nitrogen. A solution of 2,6-bis(chloromethyl)pyridine hydrochloride (1.06 g, 5 mmoles) in 50 ml of ethanol was then added slowly with stirring. The resulting solution was stirred for three hours and then refluxed for two hours. The solvent volume was reduced fourfold by rotary evaporation and 1 *M* sodium hydroxide was added, to *p*H 12. Trituration in an ice-salt bath produced an off-white solid which was recrystallized from water (charcoal). (It was necessary to cool the solution to -7° to

precipitate the product.) The resulting white solid was dried *in vacuo* over phosphorus(V) oxide, whereupon it changed into a colorless liquid (0.30 g, 20%). It appears that the hydrated form of the product is a solid, while the anhydrous form is liquid; ms: (m/e) 219 (18%), 218 (76%), 217 (46%), 184 (9%), 175 (24%), 145 (11%), 136 (13%), 135 (8%), 131 (12%), 127 (11%), 115 (7%), 114 (70%), 113 (24%), 106 (15%), 104 (19%), 83 (43%), 82 (10%), 81 (16%), 79 (17%), 78 (62%), 77 (20%), 72 (100%), 69 (22%), 65 (22%); ^{1}H nmr (deuteriochloroform): 3.56 (s, 6, CH_3), 4.47 (s, 4, CH_2), 7.09-7.16 (m, 7, arom); uv (methanol): 272 (10,700), 216 (17,600).

Anal. Calcd. for $C_{15}H_{17}N_5S_2 \cdot \frac{1}{2}H_2O$: C, 52.9; H, 5.33; N, 20.6. Found: C, 52.7; H, 5.28; N, 20.5.

2,6-Bis(benzimidazol-2′-ylthiomethyl)pyridine (**2**).

To prepare this compound, 100 ml of an ethanol solution of 2-mercaptobenzimidazole (3.00 g, 20 mmoles) and sodium hydroxide (0.80 g, 20 mmoles) were combined and the mixture stirred for 30 minutes under nitrogen. An ethanol solution (50 ml) of 2,6-bis(chloromethyl)pyridine hydrochloride (2.12 g, 10 mmoles) was added slowly and the resulting mixture refluxed for one hour before adjusting the *p*H to 9 with 1 *M* sodium hydroxide. The ethanol was removed by rotary evaporation and 100 ml of water added. Filtration gave a cream-colored powder which was recrystallized from methanol (charcoal) to give 2.9 g of white, cubic crystals (72%) after drying *in vacuo* over phosphorous(V) oxide, mp 206°; ms: (m/e) 403 (M^+, 1%), 255 (7%), 254 (7%), 253 (20%), 222 (7%), 151 (12%), 150 (100%), 149 (12%), 137 (12%), 123 (9%), 122 (19%), 118 (19%), 106 (19%), 92 (13%), 91 (13%), 90 (10%), 78 (14%), 77 (11%), 75 (20%), 65 (32%), 64 (18%), 63 (22%); ^{1}H nmr (dimethyl sulfoxide-d6): 4.67 (s, 4, CH_2), 7.13 (m, 4, arom), 7.45 (m, 6, arom); uv (methanol): 292 (28,000), 284 (27,000), 277 (sh, 21,000), 257 (sh, 15,000), 250 (16,000), 213 (46,000).

Anal. Calcd. for $C_{21}H_{17}N_5S_2$: C, 62.5; H, 4.25; N, 17.4; S, 15.9. Found: C, 62.7; H, 4.32; N, 17.4; (remainder, 15.6).

2-(4′-Piperidyl)benzimidazole (**3**).

This compound was prepared by combining isonipecotic acid (4-piperidinecarboxylic acid) (6.45 g, 50 mmoles) and *o*-phenylenediamine (5.4 g, 50 mmoles) in 100 ml of 4 *M* hydrochloric acid and refluxing the mixture for 48 hours, after which the *p*H was adjusted to 12 with 5 *M* sodium hydroxide. The white precipitate which formed was filtered off and recrystallized from water (charcoal) to give slightly hygroscopic pale yellow platelets which were dried *in vacuo* over phosphorus(V) oxide (4.7 g, 47%), mp 230° dec; ms: (m/e) 201 (M^+, 4%), 173 (2%), 159 (6%), 158 (6%), 157 (3%), 156 (3%), 146 (14%), 145 (100%), 143 (5%), 132 (12%), 119 (11%), 118 (6%), 92 (14%), 65 (11%); ^{1}H nmr (pyridine-d_6): 2.20 (d, 4, J = 3.5 Hz, Pip-3,5), 2.67 (t, 2, Pip-2), 3.12 (m, 2, Pip-6), 7.32 (q, 4, Bzim), 7.7 (s, 1, Bzim-NH); uv (methanol): 279 (4200), 273 (5100), 269 (sh, 4900), 249 (sh, 5100), 243 (5500), 213 (5300).

Anal. Calcd. for $C_{12}H_{15}N_3 \cdot \frac{1}{4}H_2O$: C, 70.0; H, 7.59; N, 20.4. Found: C, 69.9; H, 7.55; N, 20.4.

2-(3′-Piperidyl)benzimidazole (**4**).

This compound was prepared by combining ethyl nipecotate (7.85 g, 50 mmoles) and *o*-phenylenediamine (5.4 g, 50 mmoles) in 50 ml of 4 *M* hydrochloric acid and refluxing the solution for 72 hours. Addition of 5 *M* sodium hydroxide to *p*H 12 gave a yellow solid which was filtered off and then recrystallized from water (charcoal) to give 4.7 g of yellow product (47%) after drying *in vacuo* over phosphorus(V) oxide, mp 228°; ms: (m/e) 202 (5%), 201 (M^+, 40%), 172 (8%), 171 (19%), 159 (10%), 158 (16%), 146 (15%), 145 (100%), 132 (27%), 119 (42%), 92 (11%), 83 (19%); ^{1}H nmr (deuteriochloroform): 1.25 (t, 2, J = 7.5, Pip), 1.75 (m, 2, Pip), 2.05 (m, 2, Pip), 3.07 (t, 2, Pip), 3.37 (m, 2, Pip), 3.48 (m, 2, Pip), 7.22 (q, 2, Bzim), 7.54 (q, 2, Bzim); uv (methanol): 281 (6600), 273 (6500), 270 (sh, 5100), 248 (sh, 5200), 243 (5500), 208 (16,000).

Anal. Calcd. for $C_{12}H_{15}N_3 \cdot H_2O$: C, 65.7; H, 7.81; N, 19.2. Found: C, 65.9; H, 7.87; N, 19.1.

2-(3′-*N*′-Methylpiperidyl)benzimidazole (**5**).

This compound was prepared by combining ethyl *N*-methylnipecotate (9.16 g, 50 mmoles) and *o*-phenylenediamine (5.4 g, 50 mmoles) in 50 ml of 4 *M* hydrochloric acid and refluxing the mixture for 72 hours. Addition of 5 *M* sodium hydroxide to *p*H 12 gave a red-brown solid which was filtered off and then recrystallized from water (charcoal) to give 1.8 g of slightly hygroscopic white flakes (17%) after drying *in vacuo* over phosphorus(V) oxide, mp 200°; ms: (m/e) 216 (24%), 215 (M^+, 42%), 186 (6%), 171 (12%), 159 (11%), 158 (17%), 145 (64%), 144 (11%), 142 (12%), 132 (16%), 119 (58%), 97 (100), 96 (19%), 84 (13%), 82 (11%), 71 (11%), 58 (16%); ^{1}H nmr (pyridine-d_6): 1.64 (m, 2, Pip-4,5-eq), 1.95 (m, 2, Pip-4,5 ax), 2.16 (m, 4, Pip-6 ax, NCH_3), 2.56 (q, 2, J = 10.5, Pip-6 eq, 2-ax), 3.17 (d, 1, J = 10.7, Pip-2 eq), 3.45 (m, 2, Pip-3), 7.32 (m, 4, Bzim), 7.82 (s, 1, Bzim-NH); uv (methanol): 280 (7000), 273 (6900), 269 (sh, 5200), 248 (sh, 5300), 243 (5800), 208 (16,000).

Anal. Calcd. for $C_{12}H_{15}N_3 \cdot \frac{1}{4}H_2O$: C, 71.3; H, 8.01; N, 19.2. Found: C, 71.3; H, 7.97; N, 19.2.

2-(3′-*N*′-Methylpiperidyl)-*N*-methylbenzimidazole (**6**).

This compound was prepared by combining ethyl *N*-methylnipecotate (7.33 g, 40 mmoles) and *N*-methyl-*o*-phenylenediamine (4.3 g, 40 mmoles) in 40 ml of 4 *M* hydrochloric acid and refluxing the mixture for 72 hours. Addition of 5 *M* sodium hydroxide to *p*H 12 gave a red-brown oil. The tetrafluroborate salt of the ligand was prepared by combining iron(II) tetrafluroborate hexahydrate (0.68 g, 2 mmoles) and the above oil (1.38 g, 6 mmoles) in deoxygenated methanol. The white solid that formed was filtered off and the filtrate was reduced in volume on the rotary evaporator to give a white solid. This latter solid was filtered off and gave 0.52 g of light tan-colored crystals (81%) after drying *in vacuo* over phosphorus(V) oxide, mp 216°; ms: (m/e) 216 (24%), 215 (M^+, 42%), 186 (6%), 171 (12%), 159 (11%), 158 (17%), 145 (64%), 144 (11%), 142 (12%), 132 (16%), 119 (58%), 97 (100), 96 (19%), 84 (13%), 82 (11%), 71 (11%), 58 (16%); ^{1}H nmr (deuteriochloroform): 1.25 (t, 2, J = 6.9, Pip), 1.57 (s, broad, NCH_3), 2.15 (m, 1, Pip), 2.92 (s, 1, Pip), 3.49 (m, 1, Pip), 3.72 (q, 2, J = 7.1, Pip), 4.17 (s, 1, Pip), 3.38 (m, 1, Pip), 7.62 (m, 2, Bzim), 7.26 (s, Bzim, chloroform); uv (methanol): 282 (6600), 275 (6700), 268 (sh, 5200), 252 (6500), 248 (sh, 6300), 200 (15,000).

Anal. Calcd. for $C_{14}H_{20}N_3BF_4$: C, 53.0; H, 6.36; N, 13.3. Found: C, 52.6; H, 6.28; N, 13.1.

2-(2′-Hydroxybenzyl)benzimidazole (**7**).

This benzimidazylphenol was also prepared by the Phillips' condensation, [5] of *o*-hydroxyphenylacetic acid (6.1 g, 40 mmoles) with *o*-phenylenediamine (4.4 g, 42 mmoles), which were refluxed together in 4 *M* hydrochloric acid (40 ml, 60 hours). The resulting two-phase system was allowed to cool, the pale green crystals produced were filtered off, washed with water, recrystallized from 4 *M* hydrochloric acid (charcoal) and dried over

potassium hydroxide to give white prisms of the salt.

Anal. Calcd. for $C_{14}H_{12}N_2O$·HCl: C, 64.5; H, 5.03; N, 10.7. Found: C, 64.4; H, 5.03; N, 10.8.

The free base was isolated by dissolving the hydrochloride-salt in hot water and adjusting the *p*H to 7 (sodium hydroxide). The precipitate from the cooled solution was recrystallized from aqueous methanol and dried over phosphorus(V) oxide, to give an overall yield of 6.6 g (73%) of white rhombs, mp 226-229°; ms: 224 (M^+, 100%), 207 (56%), 195 (29%), 149 (17%), 118 (38%), 77 (46%), 65 (26%), 51 (14%); ^{1}H nmr (hexadeuterioacetone): 4.29 (s, CH_2), aromatic resonances at 6.82 (t), 6.96 (d), 7.18 (d), 7.25 (m), 7.57 (m).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 75.0; H, 5.39; N, 12.5; O, 7.13. Found: C, 74.9; H, 5.10; N, 12.7 (remainder, 7.30).

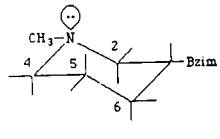
2-(2'-Hydroxybenzyl)-*N*-methylbenzimidazole (**8**).

o-Hydroxyphenylacetic acid (6.08 g, 40 mmoles) and *N*-methyl-*o*-phenylenediamine dihydrochloride (7.80 g, 40 mmoles) were refluxed in 4 *M* hydrochloric acid (50 ml) for 75 hours. Cooling gave a light blue crystalline solid which was dissolved in ethanol and the *p*H adjusted to 7 with 5 *M* sodium hydroxide. The volume of solvent was reduced (rotary evaporation) to a few ml and 100 ml of water added. The resulting grey solid was filtered off and recrystallized from ethanol (charcoal) to give 6.6 g (70% yield) of pink solid, mp 123-126°; ms: (m/e) 239 (9%), 238 (M^+, 46%), 237 (8%), 222 (8%), 241 (25%), 221 (41%), 133 (12%), 132 (100%), 136 (17%), 131 (38%), 119 (12%), 107 (20%), 105 (11%), 104 (20%), 103 (11%), 92 (14%), 91 (16%), 78 (19%), 77 (55%), 65 (15%), 63 (15%); ^{1}H nmr (deuteriochloroform): 3.80 (s, 3, NCH_3), 4.47 (s, 2, CH_2), 4.91 (s, 1, OH), 6.70 (t, 1, arom), 7.01 (t, 1, arom), 7.15 (m, 1, arom), 7.39 (m, 4, arom), 7.74 (m, 1, arom); uv (ethanol): 283 (8200), 276 (9000), 269 (sh, 7200), 254 (7200), 248 (sh, 6800), 228 (sh, 2100).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.6; H, 5.92; N, 11.8; O, 6.7. Found: C, 75.5; H, 5.86; N, 11.7; (remainder, 6.9).

Conclusion.

The ultraviolet spectra of the heterocycles are mostly dominated by the $\pi \rightarrow \pi^*$ transitions of the benzimidazole which occur in the 230-290 nm region [8]. The ^{1}H-nmr spectrum suggests that the solution conformation of **5** is principally that shown below:



The slightly larger splitting of the δ = 1.95 resonance favors its assignment as being due to the axial piperidine-4 and -5 protons rather than the alternative of the piperidine-4 protons. The smaller splitting of the δ = 1.64 resonance would then be due to the equatorial protons of piperidine-4 and -5 and not the piperidine-5 protons. Data from the decoupling experiment do not clearly favour one assignment.

The metal-chelating properties of certain of these molecules will be reported elsewhere [9]. However, **6** is clearly a poor ligand for iron(II), as evidenced by our failure to isolate the iron(II) complex, as outlined in the experimental section. The benzimidazole **7** is unusual in its properties, in that the hydrochloride salt of this compound is a potent gelling agent for aqueous solutions.

Acknowledgements.

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