Synthesis of Some Imidazole- and Pyrazole- Derived Chelating Agents

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Procedures involving condensation of *o*-phenylenediamines with carboxylic acids, and reaction of bifunctional alkyl halides with bifunctional nucleophiles are described. Syntheses are reported of 2,6-bis-(2-benzimidazyl)-pyridine, 1,3-bis(2-benzimidazyl)-2-thiapropane, 1,7-bis(2-benzimidazyl)-2,6-dithiaheptane, 2-hydroxymethyl-5,6-dimethylbenzimidazole, 2-chloromethyl-5,6-dimethylbenzimidazole hydrochloride, 1,7--bis(5,6-dimethyl-2-benzimidazyl)-2,6-dithiaheptane, 3,6-bis(1-pyrazolyl)pyridazine, 2-(2-hydroxy-3-methyl--phenyl)benzimidazole, 2-(2-hydroxyphenyl)benzimidazole, 5-(2-hydroxphenyl)-3-methyl-1-phenylpyrazole, 3(5)-(2-hydroxyphenyl)-5(3)-methylpyrazole, 3(5)-(2-hydroxyphenyl)-5(3)-phenylpyrazole, and 1,3-bis((5-methyl-pyridyl)imino)isoindoline.

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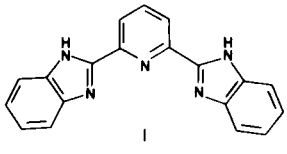
Our interest in metal complexes containing coordinated nitrogen heterocycles has led us to synthesize a number of substituted benzimidazole and pyrazole derivatives as potential complexing agents. Careful selection of substituents has allowed preparation of compounds with a range of complementary donor atoms and with stereochemistries favorable for metal ion coordination.

In most cases, benzimidazole derivatives were prepared by simple, one-step reactions involving condensation of a carboxylic acid with a diamine. These condensations were accomplished in a melt of the reactants or in polyphosphoric acid solution at 150-250°, according to the procedures developed by Thompson and others (1,2). The pyrazoles were obtained *via* condensation of hydrazine with the appropriate β-dicarbonyl, or by nucleophilic attack of pyrazolate on a halide. Compounds **1-6** are reported here for the first time; for those reported previously [**7** (3,4), **8** (5), **9** (5,6), **10** (7), **11**], we report a superior method of preparation and more complete characterization.

Benzimidazole formation from *o*-phenylenediamines and carboxylic acids or esters is often effected by heating the components in acidic media (1,4,9). Good yields are obtained from the polyphosphoric acid procedure, which is more convenient than the phosphorus(V) oxide reaction medium previouly used (3). The initially phosphorylated products are readily dephosphorylated by treatment with base. The pure reactant melt appears to be the best medium for the thiaether products **2-4** and, indeed, afforded the only successful route to **2**. It appears that acid-catalysed cleavage of the thiaethers renders polyphosphoric acid a less suitable medium for their reactions, as yields are often considerably reduced. Reaction in the melt also proved convenient for the preparation of



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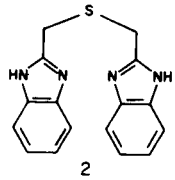

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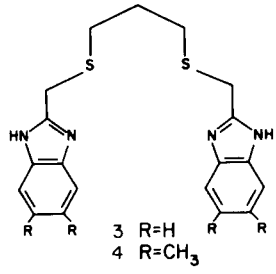
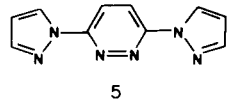


3 R=H
4 R=CH$_3$



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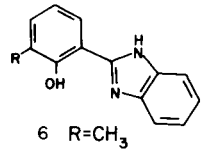
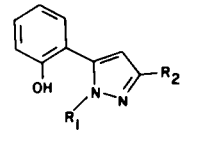
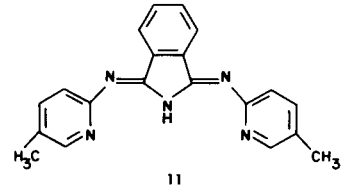


6 R=CH$_3$
7 R=H



8 R$_1$=Ph, R$_2$=CH$_3$
9 R$_1$=H, R$_2$=CH$_3$
10 R$_1$=H, R$_2$=Ph



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1,3-bis((5-methylpyridyl)imino)isoindoline, **12**, resulting in a considerable reduction in reaction time and work-up procedure compared to the previously reported method (8).

Strong solvation of some of the benzimidazoles in the solid state is noted, presumably occurring because of their affinity for H-bonding.

The pyrazoles have been prepared previously by oxidation of the pyrazoline (6,7) or by utilizing the appropriately substituted chromone (5). The procedure we report here gives higher yields, with commercially available starting materials. Previous workers (5) have proposed that the phenyl substituent of **8** is located on the pyrazole nitrogen adjacent to the methyl group. However, our inability to isolate a copper(II) chelate of the compound leads us to assign our isolated compound **8** as the alternative isomer

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shown. The related compounds **9** and **10** do indeed coordinate to copper(II) in a presumably bidentate fashion, *via* the ring 1-nitrogen and the deprotonated phenolic oxygen (10).

EXPERIMENTAL

Proton nuclear magnetic resonance spectra were obtained at ambient temperature using a Varian Associates A-60 (60 MHz) instrument, chemical shifts being quoted with respect to TMS as internal standard. Uv spectra were measured at room temperture using a Perkin-Elmer 320 spectrophotometer, mass spectra on a Finnigan 4000 GC-MS. Melting points are uncorrected. Microanalyses were performed by Canadian Microanalytical Service Ltd. (Vancouver). Reagents for syntheses were used as received, from Frinton laboratories (*o*-hydroxydibenzoylmethane, salicoylacetone) and Aldrich/Sigma (Diamines, carboxylic acids, 1,2-dicyanobenzene, 2-chloromethylbenzimidazole).

2,6-Bis(2-benzimidazyl)pyridine (1).

Pyridine-2,6-dicarboxylic acid (3.35 g, 20 mmoles) was stirred with *o*-phenylenediamine (4.7 g. 44 mmoles) in syrupy phosphoric acid (40 ml) at *ca.* 230° for 4 hours. The colored melt was poured into 1 l of vigorously stirred cold water. When cool, the bulky blue-green precipitate was collected by filtration, then slurried in hot, 10% aqueous sodium carbonate solution (300 ml). The resulting solid was filtered off and recrystallized from methanol to give long, white prisms (3.3 g, 53%), mp > 250°; ms: (m/e) (11) 175 (29%), 174 (30%), 131 (52%), 63 (36%), 51 (59%), 50 (68%), 42 (93%), 41 (100%), 40 (72%); nmr (DMSO-d_6): 7.3-8.5 (m, aromatic), 13.2 (s, imino).

Anal. Calcd. for $C_{19}H_{13}N_5.2/3H_2O$: C, 70.6; H, 4.05; N, 21.7. Found: C, 71.0; H, 4.08; N, 21.8.

If the reaction is performed in a melt of the two reactants, without phosphoric acid, the yield is reduced.

1,3-Bis(2-benzimidazyl)-2-thiapropane (2).

Thiodiglycolic acid (3.45 g, 23 mmoles) and *o*-phenylenediamine (5.08 g, 47 mmoles) were fused for 2 hours at 180°. The resulting dark blue glass was dissolved in *N,N*-dimethylformamide and treated with decolorizing charcoal until the solution was pale yellow. Addition of water precipitated a cream solid, which was recrystallized from *N,N*-dimethylformamide/water to give white needles of the monohydrate (2.98 g, 44%), mp 212° dec.; ms: (m/e) (11) 143 (6%), 132 (10%), 131 (5%), 119 (7%), 107 (6%), 105 (8%), 97 (6%), 95 (10%), 93 (8%), 91 (13%), 83 (28%), 81 (24%), 79 (10%), 71 (15%), 69 (35%), 67 (17%), 57 (37%), 55 (86%), 45 (11%), 43 (100%), 41 (70%); nmr (DMSO-d_6): 4.1 (s, $-CH_2-$), 7.1-7.6 (m, aromatic). The imino proton resonance was not detected.

Anal. Calcd. for $C_{16}H_{14}N_4S{\cdot}H_2O$: C, 61.5; H, 5.16; N, 17.9. Found: C, 61.7; H, 5.13; N, 17.9.

1,7-Bis(2-benzimidazyl)-2,6-dithiaheptane (3).

(a) Synthesis of 2,6-dithiaheptane-1,7-dicarboxylic acid.

The compound was prepared by a procedure in which the functional groups (thiol and alkyl halide) of the reactant moieties were reversed in comparison with a previous procedure (12). Sodium borohydride (0.38 g, 0.01 mole) was added to 1,3-propanedithiol (21.6 g, 0.20 mole) stirred in 95% ethanol (50 ml), under dinitrogen. After 10 minutes water (50 ml) and 90% pellet potassium hydroxide (51.0 g, 0.80 mole) were added. A solution of iodoacetic acid (74.4 g, 0.40 mole) in 95% ethanol (100 ml) was then added over a period of 30 minutes and the reaction mixture was stirred at *ca.* 50° overnight. The solvent was removed (rotary evaporator), the solids were dissolved in water and impurities were extracted once with ether. The *p*H was adjusted to 0.5 with sulfuric acid and the product was ether extracted, dried over sodium sulfate and treated with sodium bisulfite (to remove iodine). The ether was removed and the product was dried *in vacuo* at 100°. The residue, on cooling, formed white, hygroscopic crystals (36.6 g, 82%); ms: (m/e) 224 (M^+, 6%), 165 (36%), 149 (12%), 132 (5%), 119 (15%), 106 (23%), 87 (20%), 77 (36%), 73 (90%), 61 (29%), 45 (100%); nmr (sodium carbonate, deuterium oxide): 1.98 (m, $-CH_2-$, J = 7), 2.83 (t, $-CH_2-$, J = 7), 3.43 (s, $-CH_2-$).

Anal. Calcd. for $C_7H_{12}O_4S_2{\cdot}1/2H_2O$: C, 36.0; H, 5.62. Found: C, 36.3; H, 5.33.

(b) Synthesis of 1,7-bis(2-benzimidazyl)-2,6-dithiaheptane.

The above diacid (6.4) g, 28 mmoles) was stirred in the molten state with *o*-phenylenediamine (6.5 g, 60 mmoles) at 165° for 3 hours. The frozen product was recrystallized from aqueous acetonitrile (charcoal) and dried at 120° to give the cream crystalline product (3.7 g, 35%), mp 225° dec.; ms: (m/e) 368 (2%, M^+), 237 (30%), 163 (21%), 132 (90%), 131 (100%), 77 (31%), 43 (32%), 41 (45%); nmr (pyridine-d_5): 1.87 (m, $-CH_2-$, J = 7), 2.64 (t, $-S-CH_2-$, J = 7), 4.1 (s, $-CH_2-S-$), 7.2-7.8 (m, aromatic), 10.7 (b, imino).

Anal. Calcd. for $C_{19}H_{20}N_4S_2$: C, 61.9; H, 5.47; N, 15.2. Found: C, 61.4; H, 5.32; N, 15.0.

The compound was also prepared by reaction of 2-chloromethybenzimidazole with 1,3-propanedithiol, in similar yield (see **4**, below).

1,7-Bis(5,6-dimethyl-2-benzimidazyl)-2,6-dithiaheptane (4).

(a) 2-Hydroxymethyl-5,6-dimethylbenzimidazole.

Glycolic acid (4.0 g, 50 mmoles) was fused with 4,5-dimethyl-*o*-phenylenediamine (6.8 g, 50 mmoles) at 250° until the water evolution ceased, and the reaction mixture crystallized. The crude product was recrystallized from methanol and dried *in vacuo* over phosphorus(V) oxide to give white prisms (6.4 g, 74%), mp 244° dec; ms: (m/e), 176 (M^+, 100%), 158 (45%), 147 (43%), 131 (37%), 118 (26%), 104 (14%), 91 (55%), 77 (28%), 65 (39%), 51 (34%), 43 (36%); nmr (pyridine-d_5): 2.33 (s, CH_3-), 5.10 (s, $-CH_2-$), 7.57 (s, aromatic).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.1; H, 6.87; N, 15.9. Found: C, 68.2; H, 7.04; N, 15.9.

(b) 2-Chloromethyl-5,6-dimethylbenzimidazole Hydrochloride.

To 6.0 g (34 mmoles) of the above alcohol, slurried in 30 ml of dichloromethane, was added 20 ml of thionyl chloride, followed after 15 minutes by slow addition of 20 ml methanol. The solution was (rotary) evaporated to dryness, the product was washed with dichloromethane and dried *in vacuo*, giving white crystals (7.4 g, 93%) of the hydrochloride; ms: (m/e) 194 (M^+, 25%), 179 (2%), 159 (100%), 144 (6%), 132 (5%), 116 (5%), 103 (5%), 91 (11%), 77 (11%), 65 (15%), 51 (14%); the m/e 159 peak lacks the ^{37}Cl accompaniment seen with the m/e 194 peak; nmr (methanol-d_4): 2.42 (s, CH_3), 5.27 (s, $-CH_2-$), 5.63 (s, iminium), 7.57 (s, aromatic).

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2$: C, 52.2; H, 4.82; N, 12.2. Found: C, 52.3; H, 5.32; N, 12.2.

(c) 1,7-Bis(5,6-dimethyl-2-benzimidazyl)-2,6-dithiaheptane (4).

To 0.86 g (8 mmoles) of 1,3-propanedithiol stirred in 40 ml of 70% ethanol under dinitrogen was added 40 mg (1 mmole) of sodium borohydride, followed 30 minutes later by 2.0 g of 90% pellet potassium hydroxide (32 mmoles). The hydrochloride (b) (37 g, 16 mmoles) dissolved in 50 ml of ethanol was added slowly, and the mixture was stirred 1 hour, refluxed briefly, and then concentrated (rotavapor). The feathery precipitate was recrystallized from 95% ethanol, and dried *in vacuo* at 55°, to give white prisms (2.0 g) of the monohydrate. Desolvation was effected by drying *in vacuo* at 120°, mp, 209°; ms: (m/e) 424 (M^+, 4%), 265 (18%), 235 (4%), 191 (18%), 17 (6%), 160 (100%), 145 (17%), 132 (1%), 106 (13%), 91 (30%), 77 (24%), 65 (26%), 55 (35%), 43 (85%); nmr (pyridine-d_5): 1.95 (m, $-CH_2-$, J = 7), 2.27 (s, $-CH_3$), 2.67 (t, $-CH_2$, J = 6.5), 4.13 (s, $-CH_2-S-$), 7.58 (s, aromatic).

Anal. Calcd. for $C_{23}H_{28}N_4S_2$: C, 65.0; H, 6.65; N, 13.2. Found: C, 65.2; H, 6.85; N, 13.3. Calcd. for monohydrate: C, 62.4; H, 6.84; N, 12.7. Found: C, 62.2; H, 7.05; N, 12.6.

The compound **4** was also prepared by the condensation of 4,5-dimethyl-*o*-phenylenediamine with 2,6-dithiaheptane-1,7-dicarboxylic acid (see **3** above), in similar yield.

3,6-Bis(1-pyrazolyl)pyridazine (5).

A mixture of 3,6-dichloropyridazine (3.0 g, 20 mmoles) and pyrazole

(5.0 g, 70 mmoles) was refluxed in ethanol (50 ml) for 2 hours. After removal of solvent, excess pyrazole was extracted with water and the insoluble residue was dissoved in 20 ml of warm hydrochloric acid (12 *M*). The solution was diluted with a large volume of cold water and the precipitated product was collected by filtration, washed with aqueous ammonia (5 *M*) and recrystallized from acetonitrile, to give white flakes (2.8 g, 65%), mp 238-240°; ms: (m/e) 212 (M^+, 21%), 156 (9%), 131 (8%), 105 (15%), 80 (40%), 79 (23%), 78 (26%), 77 (16%), 65 (11%), 64 (13%), 53 (39%), 52 (100%), 51 (42%), 41 (16%), 40 (28%). The compound was insufficiently soluble for nmr measurements.

Anal. Calcd. for $C_{10}H_8N_6$: C, 56.6; H,3.80; N, 39.6. Found: C, 56.9; H, 3.78; N, 39.8.

2-(2-Hydroxy-3-methylphenyl)benzimidazole (**6**).

3-Methylsalicylic acid (5.02 g, 33 mmoles) and *o*-phenylenediamine (3.68 g, 34 mmoles) were stirred in syrupy phosphoric acid (60 ml) at *ca.* 200° for 2 hours. The hot mixture was poured into vigorously stirred cold water (500 ml). The bulky pale blue precipitate obtained was slurried in cold water (200 mL), and sodium hydroxide solution (5 *M*) was added until the *p*H of the mixture was brought to 7. The resulting tan solid was recrystallized from methanol to give cream needles (4.98 g, 67%; ms: (m/e) 224 (M^+, 100%), 195 (80%), 169 (12%), 92 (39%), 77 (24%), 65 (53%), 64 (21%), 63 (30%), 52 (26%), 51 (27%), 41 (17%), 39 (13%); nmr (DMSO-d_6): 2.3 (s, -CH_3), 7.1-8.3 (m, aromatic), 3.4 (b, -OH), 13.7 (b, imino).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.9; H, 5.39; N, 12.5. Found: C, 74.8; H, 5.42; N, 12.2.

2-(2-Hydroxyphenyl)benzimidazole (**7**).

The compound was prepared in a manner similar to that described above, using salicylic acid. Recrystallization of the crude product from ethanol (charcoal) gave white crystal (58%), mp 238° [lit. (3) mp 238-239°]; ms: (m/e) 210 (M^+, 100%), 182 (51%), 181 (43%), 92 (25%), 91 (52%), 90 (22%), 78 (47%), 77 (35%), 65 (67%), 64 (48%), 63 (61%), 52 (39%), 51 (41%), 50 (23%), 40 (20%); nmr (DMSO-d_6): 6.9-8.2 (m, aromatic), 3.43 (b, -OH), 13.1 (b, imino).

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.3; H, 4.79; N, 13.3. Found: C, 74.1; H, 4.78; N, 13.3.

5-(2-Hydroxyphenyl)-3-methyl-1-phenylpyrazole (**8**).

A mixture of phenylhydrazine (3.2 g, 30 mmoles) and salicoylacetone (5.0 g. 28 mmoles) was refluxed in methanol (100 ml) for 12 hours. After removal of solvent, the crude product was recrystallized from acetonitrile, in the presence of magnesium sulfate and charcoal, and dried *in vacuo* over phosphorus(V) oxide to give tan crystals (1.7 g, 24%), mp 190° [lit. (5) mp 192°: *vide supra*]; ms: (m/e) 250 (M^+, 14%) 249 (74%), 248 (29%), 179 (10%), 118 (24%), 115 (19%), 91 (44%), 90 (15%), 89 (22%), 78 (20%), 77 (100%), 76 (14%), 65 (21%), 64 (28%), 63 (32%), 52 (16%), 51 (96%), 50 (19%), 42 (28%), 41 (13%), 40 (12%); nmr (DMSO-d_6): 2.3 (s, CH_3), 3.3 (s, -OH), 6.3 (s, pyrazolyl-H_4), 5.7-7.3 (m, aromatic).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.8; H, 5.64; N, 11.2. Found: C, 76.5; H, 5.60; N, 11.2.

3(5)-(2-Hydroxyphenyl)-5(3)-methylpyrazole (**9**).

Hydrazine hydrate (1.48 g, 30 mmoles) was added dropwise to salicoylacetone (5.0 g, 28 mmoles) in refluxing methanol (100 ml). After 5 hours the solvent was removed (rotary evaporator) and the crude product was recrystallized from toluene/cyclohexane (charcoal) to give white laths (3.34 g, 69%), mp 132° [lit. (6) mp 130°]; ms: (m/e) 174 (100%, M^+), 173 (51%), 146 (17%), 145 (30%), 131 (62%), 115 (15%), 104 (23%), 91 (13%), 77 (16%), 73 (17%), 65 (15%), 63 (20%), 51 (22%), 42 (34%), 41 (12%), 40 (13%); nmr (acetone-d_6): 2.4 (s, -CH_3), 3.1 (b, -OH), 6.5 (s, pyrazolyl-H_4), 6.7-7.7 (m, aromatic), 11.2 (b, imino), 12.1 [b, -OH (hydrogen bonded)].

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 69.0; H, 5.75; N, 16.1. Found: C, 69.1; H, 5.78; N, 15.9.

3(5)-(2-Hydroxyphenyl)-5(3)-phenylpyrazole (**10**).

Hyrazine hydrate (1.65 g, 33 mmoles) in ethanol (25 ml) was added to *o*-hydroxydibenzoylmethane (7.2 g, 30 mmoles) in refluxing ethanol (100 ml) over a period of 15 minutes. The yellow reaction mixture was refluxed (20 hours) and the resulting pink solution was evaporated to dryness. The crude product was recrystallized from toluene/cyclohexane and dried *in vacuo* over phosphorus(V) oxide to give colorless prisms (5.0 g, 71%), m.p. 144°; ms: (m/e) 236 (M^+, 100%), 207 (30%), 104 (49%), 89 (22%), 77 (48%), 76 (67%), 75 (22%), 64 (35%), 63 (29%), 62 (38%), 51 (50%), 50 (73%), 40 (31%); nmr (acetone-d_6): 2.6 (b, -OH), 6.3-7.3 (m, aromatic and pyrazolyl H_4), 10.7 (b, imino), 12.6 (b, -OH(hydrogen bonded)).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.3; H, 5.12; N, 11.9. Found: C, 76.4; H, 5.00; N, 12.0.

1.3-Bis((5-methylpyridyl)imino)isoindoline (**11**).

1,2-dicyanobenzene (1.5 g, 9 mmoles) and 2-amino-5-methylpyridine (2.05 g, 19 mmoles) were heated together at *ca.* 175° for 3 hours. After cooling, the product was recrystallized from methanol to give yellow needles (1.67 g, 57%), mp 216° [lit. (8) mp 215-216°]; ms (m/e) 326 (M^+, 4%), 234 (8%), 219 (3%), 102 (8%), 93 (11%), 92 (8%), 91 (8%), 66 (21%), 65 (100%), 64 (9%), 53 (25%), 52 (15%), 51 (11%), 43 (18%), 42 (5%), 41 (25%), 40 (8%); nmr (deuteriochloroform): 2.38 (s, 6H, methyl), 7.24-8.14 (m, 8H, aromatic), 8.44 (s, 2H, pyridyl α-H) [lit. (8)], 14.1 (s, 1H, pyrrole H).

Anal. Calcd. for $C_{20}H_{17}N_5$: C, 73.4; H, 5.23; N, 21.4. Found: C, 73.4; H, 5.15; N, 21.4.

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