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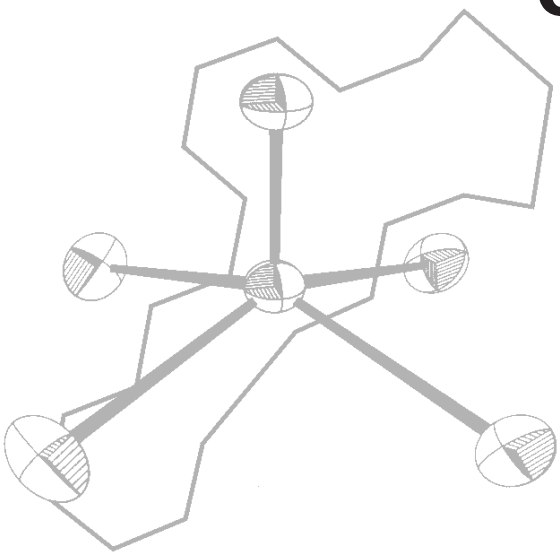

Volume 53, 2000

A journal for the publication of original research
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Aust. J. Chem., 2000, **53**, 545–549

Controlled Synthesis of Novel Dibenzene-1,2-diol Mannich Bases

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The synthesis of a number of novel dibenzene-1,2-diol Mannich bases can be achieved in good yields by the condensation of 2-methoxyphenol, formaldehyde and secondary diamines. The newly developed synthetic method utilizes 2-methoxyphenol instead of benzene-1,2-diol providing a useful tool for greater control over reaction products.

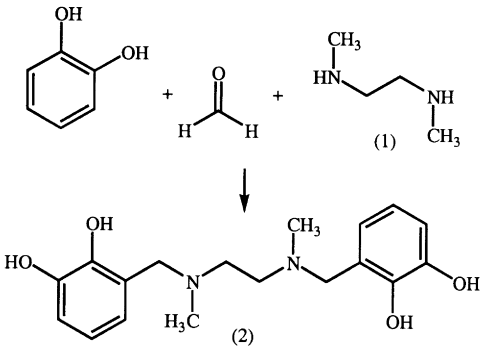
Keywords. Aminoalkylation; catechol; Mannich base; synthesis.

Introduction

The patent and scientific literature contains numerous reports on Mannich base derivatives of phenol regarding their chemistry and their applications.[1–6] Very few references, however, are made to Mannich base derivatives of benzene-1,2-diol, herein referred by its common name catechol, and, in particular, no reports pertaining to our target class of compounds, the dicatechol products. Our research program required multigram quantities of a range of dicatechol Mannich bases; therefore, an efficient synthetic method was required. We now report a convenient method for synthesizing these compounds in good yields and free from side products. This methodology is also generally applicable to the efficient synthesis mono *ortho* substituted catecholamines.

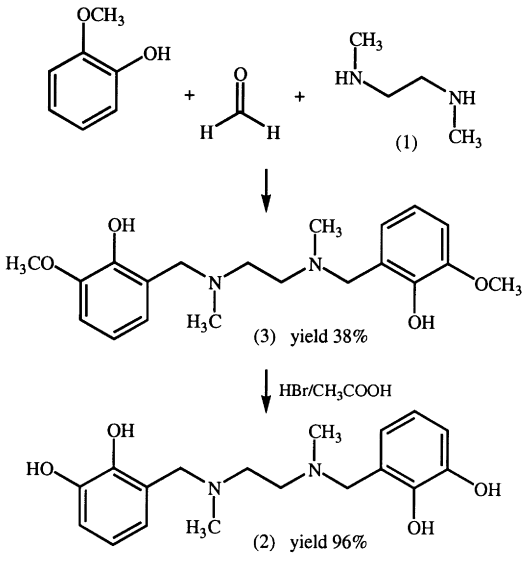
Results and Discussion

Our initial attempt to synthesize 3,3′-[ethylenebis(methyliminomethylene)]di(benzene-1,2-diol) (2) via the condensation of catechol, *N,N′*-dimethylethylenediamine (1) and formaldehyde (Scheme 1) resulted in a complex product mixture. Analysis of the crude reaction mixture by nuclear magnetic resonance (n.m.r.) indicated that the desired product was formed but in small amounts.



Scheme 1

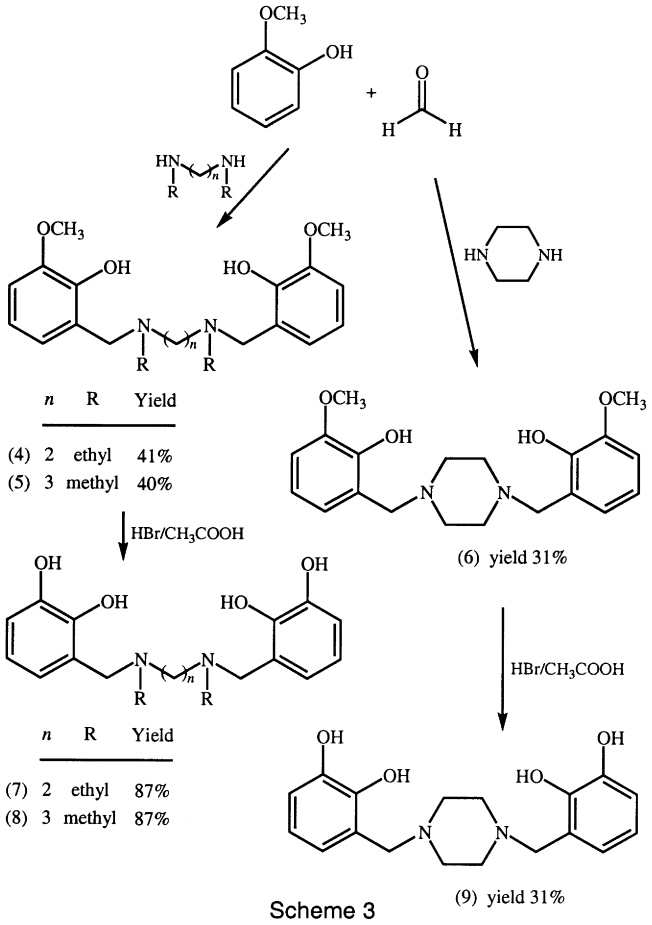
An alternative method of synthesizing (2) was developed using a two-step procedure (Scheme 2). 6,6′-Dimethoxy-2,2′-[ethylenebis(methyliminomethylene)]diphenol (3) was formed by the reaction between 2-methoxyphenol, formaldehyde and *N,N′*-dimethylethylenediamine (1) in a moderate yield of 38%. This methoxy intermediate was demethylated in an acetic acid solution of HBr to give the desired product with an excellent recovery of 96%. The blocking of the hydroxy group prevents further aminoalkylation of the aromatic ring giving rise to cleaner reaction products.



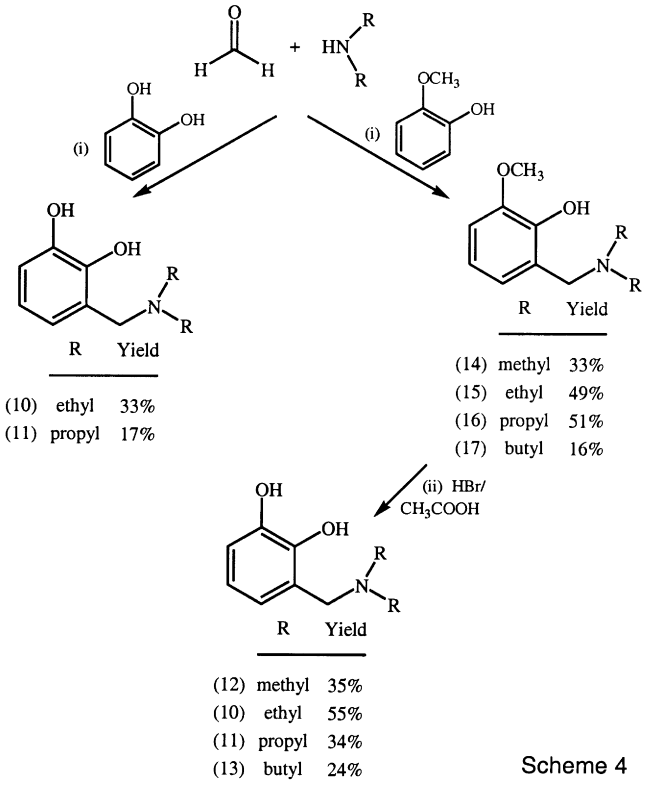
Scheme 2

This methodology was then applied to the synthesis of a range of previously unknown dicatechol Mannich base products (9)–(11) in good yields (Scheme 3). Although the methoxy intermediates (6)–(8) of these compounds were isolated and characterized, the crude product mixture from this initial step can be demethylated directly simplifying the reaction scheme.

Manuscript received 8 June 2000 10.1071/CH00079 0004-9425/00/070545



Scheme 3



Scheme 4

This methodology allows for easy isolation of the methoxy intermediates that are important in their own right. Similar compounds have been reported to exhibit interesting chemistry that has potential applications in various biological and pharmacological areas.[7–9] In a subsequent paper we will report results of biological screening data for a range of these Mannich bases.

Finally, the applicability of this method to the synthesis a number of mono *ortho* substituted catecholamines was tested. The preparation of 3-(diethylaminomethyl)benzene-1,2-diol (12) by our method gave the final product in a yield of 55%. The same product was prepared according to the literature method described by Jia Quiquan and coworkers,[10] in a comparatively low yield of 33%. The trend of increasing yields with our method is exemplified when larger amines are employed. For example, in the synthesis of 3-(dipropylaminomethyl)benzene-1,2-diol (13) a yield of 34% was achieved compared to a previously obtainable 17%. We noted, however, that the overall yield is lowered but the increase is just as significant (Scheme 4). As with the synthesis of the dicatechol Mannich bases, the methoxy intermediates (16)–(19) were isolated and characterized; however, the crude product mixture from the initial aminoalkylation step can be demethylated directly.

Conclusion

A straightforward synthetic route has been developed to access previously unknown mono *ortho* dicatechol Mannich bases in good yields. The use of the methyl-blocked catechol, 2-methoxyphenol, provides a means by which greater control can be exerted over the reaction and the resulting mixtures. Moreover, the methoxy intermediates are important in their own right as they may have potential application in other biological and pharmacological areas of study. Greatly increased yields are also observed with this method in the synthesis of the mono *ortho* catecholamines.

Experimental

Instrumentation

N.m.r. spectra were obtained in (D)chloroform (99.8%) (Cambridge Isotope Laboratories) by using a Varian Unity 400 MHz instrument unless otherwise specified. The abbreviation appr. (apparent) is used to denote second-order coupling. Infrared (i.r.) spectra were recorded on a Biorad FTS-60A Fourier-transform spectrometer. Microanalyses were performed by Chemical and Micro Analytical Services Pty Ltd, Victoria. Mass spectrometric data were obtained on an Analytical Concept Kratos ISQ instrument recorded at 70 eV from The University of Tasmania. Melting points were performed on an Electrothermal melting point apparatus and are uncorrected.

Liquid chromatography was performed by using Merk Kieselgel 60.

Reagents

Catechol (99%) was purchased from Aldrich and used without further purification. All amines were also purchased from Aldrich and distilled over KOH prior to use. 2-Methoxyphenol was obtained from ICN Biomedicals Inc. and distilled under vacuum prior to use. All solvents were of analytical grade. Dry ethanol was obtained by distillation over calcium hydride (CaH_2) under a nitrogen atmosphere and stored over 4 Å molecular sieves.

General Procedures

All reactions were performed under an argon atmosphere. Demethylation of the methoxy intermediate to give the free hydroxy

moiety was achieved by refluxing in a 20% solution of HBr in acetic acid (v/v) for 48 h.

The following standard workup procedure was used for each reaction unless stated otherwise. After the reaction was complete the solvent was removed under reduced pressure followed by acidification with concentrated HCl and ice. The aqueous mixture was washed with diethyl ether (3×20 ml) and neutralized with $NaHCO_3$. The reaction products were extracted into chloroform (4×20 ml). The organic extracts were collected, dried over Na_2SO_4 and concentrated under vacuum.

Synthesis of 6,6′-Dimethoxy-2,2′-[alkanediylbis(alkyliminomethylene)]diphenols (3) and (4)–(6)

The desired compounds (3) and (4)–(6) were prepared in good yields according to the following general method. A solution of finely ground paraformaldehyde (0.05 mol, 1 equiv.) and the appropriate amine (0.05 mol, 1 equiv.) in dry ethanol (10 ml) was added dropwise to a solution of 2-methoxyphenol (0.025 mol, 0.5 equiv.) in dry ethanol (10 ml) at room temperature. After the addition was complete, the reaction was heated to 40°C and stirred for a further 4 days. A standard workup followed and the product was isolated by using standard purification techniques.

6,6′-Dimethoxy-2,2′-[ethylenebis(methyliminomethylene)]diphenol (3)

Recrystallization of the crude material twice from hot ethanol afforded (3) as white *crystals* (3.40 g, 38%), m.p. 115–116°C (Found: C, 66.5; H, 7.9; N, 7.3. $C_{20}H_{28}N_2O_4$ requires C, 66.6; H, 7.8; N, 7.7%). I.r. ν_{max} (KBr) 2846, 2362, 1480, 1465, 1252, 1239 cm^{-1}. ^1H n.m.r. δ 2.30, s, NCH_3; 2.70, s, $NC\mathbf{H}_2C\mathbf{H}_2N$; 3.70, s, NCH_2; 3.86, s, OCH_3; 6.57, appr. d, *J* 7.3 Hz, ArH; 6.73, appr. t, *J* 7.7 Hz, ArH; 6.79, appr. d, *J* 7.2 Hz, ArH. ^{13}C n.m.r. δ 41.8; 54.4; 55.8; 61.3; 111.1; 118.8; 120.5; 121.8; 146.9; 147.9. Mass spectrum (e.i.) *m/z* 360 (3%), 180 (100), 137 (83), 107 (14) 44 (64) (Found: $M^{+\bullet}$, 360.20356. $C_{20}H_{28}N_2O_4$ requires $M^{+\bullet}$, 360.20491).

6,6′-Dimethoxy-2,2′-[ethylenebis(ethyliminomethylene)]diphenol (4)

Column chromatography (chloroform) afforded (4) as pale yellow *crystals* (2.96 g, 41%), m.p. 71–72°C (Found: C, 68.0; H, 8.3; N, 7.2. $C_{22}H_{32}N_2O_4$ requires C, 68.0; H, 8.3; N, 7.2%). I.r. ν_{max} (KBr) 2979, 2834, 1468, 1251, 1232, 1064 cm^{-1}. ^1H n.m.r. δ 1.07, t, *J* 7.1 Hz, $NCH_2C\mathbf{H}_3$; 2.59, q, *J* 7.2 Hz, $NC\mathbf{H}_2CH_3$; 2.79, s, $NC\mathbf{H}_2C\mathbf{H}_2N$; 3.74, s, NCH_2; 3.86, s, OCH_3; 6.56, appr. d, *J* 7.5 Hz, ArH; 6.71, appr. t, *J* 7.5 Hz, ArH; 6.79, dd, *J* 8.1, 1.4 Hz, ArH. ^{13}C n.m.r. δ 11.2; 47.9; 50.6; 55.9; 57.7; 111.0; 118.7; 120.5; 121.9; 147.2; 147.9. Mass spectrum (e.i.) *m/z* 388 (14%), 251 (2), 194 (96), 137 (100), 122 (4), 107 (12), 58 (84), 39 (11) (Found: $M^{+\bullet}$, 388.23551. $C_{22}H_{32}N_2O_4$ requires $M^{+\bullet}$, 388.23621).

6,6′-Dimethoxy-2,2′-[propane-1,3-diylbis(methyliminomethylene)]-diphenol (5)

Column chromatography (ethyl acetate) afforded (5) as orange *crystals* (2.48 g, 40%), m.p. 78–79°C (Found: C, 67.3; H, 8.1; N, 7.5. $C_{21}H_{30}N_2O_4$ requires C, 67.4; H, 8.1; N, 7.5%). I.r. ν_{max} (KBr) 2961, 2837, 1478, 1456, 1251, 1238 cm^{-1}. ^1H n.m.r. δ 1.87, quin, *J* 7.1 Hz, $NCH_2C\mathbf{H}_2CH_2N$; 2.27, s, NCH_3; 2.55, t, *J* 7.4 Hz, $NCH_2C\mathbf{H}_2CH_2N$; 3.70, s, NCH_2; 3.87, s, OCH_3; 6.58, dd, *J* 7.4, 1.0 Hz, ArH; 6.73, appr. t, *J* 7.8 Hz, ArH; 6.80, dd, *J* 8.1, 1.4 Hz, ArH. ^{13}C n.m.r. δ 24.7; 41.2; 54.9; 55.8; 61.2; 110.9; 118.7; 120.5; 121. 8; 147.1; 147.8. Mass spectrum (e.i.) *m/z* 374 (5%), 207 (11), 180 (36), 166 (30), 150 (5), 137 (100), 101 (26), 58 (30) (Found: $M^{+\bullet}$, 374.22059. $C_{21}H_{30}N_2O_4$ requires $M^{+\bullet}$, 374.22056).

6,6′-Dimethoxy-2,2′-(piperazine-1,4-diylbismethylene)diphenol (6)

Column chromatography (chloroform) followed by recrystallization from hot ethanol afforded (6) as white needlelike crystals (1.84 g, 31%), m.p. 197–198°C (Found: C, 67.1; H, 7.3; N, 7.9. Calc. for $C_{20}H_{26}N_2O_4$: C, 67.0; H, 7.3; N, 7.8%). I.r. ν_{max} (KBr) 2945, 2830, 1460, 1257, 1239 cm^{-1}. ^1H n.m.r. δ 2.37, br s, ring $C\mathbf{H}_aH_bC\mathbf{H}_aCH_b$; 2.93, br s, ring $CH_aH_bCH_aC\mathbf{H}_b$; 3.72, s, NCH_2; 3.87, s, OCH_3; 6.60, appr. d, *J* 7.4 Hz, ArH; 6.75, appr. t, *J* 7.8 Hz, ArH; 6.81, appr. d, *J* 7.6 Hz, ArH. ^{13}C n.m.r. δ 52.3; 55.8; 60.9; 111.1; 118.9; 120.7; 121.0; 146.8; 147.9. Mass spectrum (e.i.) *m/z* 358 (30%), 221 (61), 180 (29), 137 (100), 122 (9), 85 (36).

Synthesis of 3,3′-[Alkanediylbis(alkyliminomethylene)]di(benzene-1,2-diol) Mannich Bases (2) and (7)–(9)

The desired Mannich bases (2) and (7)–(9) were obtained in excellent yields by the demethylation of the corresponding 6,6′-dimethoxy-2,2′-[alkylenebis(alkyliminomethylene)]diphenol intermediate. After the demethylation was complete a standard workup followed and isolation of the product was achieved by standard purification techniques.

3,3′-[Ethylenebis(methyliminomethylene)]di(benzene-1,2-diol) (2)

Column chromatography (ethyl acetate) afforded (2) as pale yellow *crystals* (1.16 g, 96%), m.p. 91–92°C (Found: C, 65.0; H, 7.3; N, 8.5. $C_{18}H_{24}N_2O_4$ requires C, 65.0; H, 7.3; N, 8.4%). I.r. ν_{max} (KBr) 3450, 3394, 1480, 1463, 1265, 1189 cm^{-1}. ^1H n.m.r. δ 2.27, s, NCH_3; 2.65, s, $NC\mathbf{H}_2C\mathbf{H}_2N$; 3.68, s, NCH_2; 6.51, appr. d, *J* 7.6 Hz, ArH; 6.69, appr. t, *J* 7.8 Hz, ArH; 6.85, appr. d, *J* 8.1 Hz, ArH. ^{13}C n.m.r. δ 41.5; 53.7; 61.3; 114.2; 119.5; 119.5; 121.5; 144.4; 144.8. Mass spectrum (e.i.) *m/z* 332 (4%), 166 (72), 122 (67), 94 (12), 66 (14), 44 (100) (Found: $M^{+\bullet}$, 332.17248. $C_{18}H_{24}N_2O_4$ requires $M^{+\bullet}$, 332.17361).

3,3′-[Ethylenebis(ethyliminomethylene)]di(benzene-1,2-diol (7)

The crude product was dissolved in acetone and passed through a plug of silica to afford (7) as pale yellow *crystals* (1.61 g, 87%), m.p. 143–144°C (Found: C, 66.7; H, 7.6; N, 8.0. $C_{20}H_{28}N_2O_4$ requires C, 66.6; H, 7.8; N; 7.8%). I.r. ν_{max} (KBr) 3451, 2979, 1482, 1468, 1373, 1289, 1258, 1189 cm^{-1}. ^1H n.m.r. δ 1.10, s, t, *J* 7.2 Hz, $NCH_2C\mathbf{H}_3$; 2.57, q, *J* 7.2 Hz $NC\mathbf{H}_2CH_3$; 2.70, s, $NC\mathbf{H}_2C\mathbf{H}_2N$; 3.73, s, NCH_2; 6.50, appr. d, *J* 7.5 Hz, ArH; 6.69, appr. t, *J* 7.7 Hz, ArH; 6.84, appr. d, *J* 7.9 Hz, ArH. ^{13}C n.m.r. δ 10.9; 47.5; 50.1; 57.3; 113.9; 119.5; 119.5; 121.4; 144.5; 144.7. Mass spectum (e.i.) *m/z* 360 (11%), 238 (12), 194 (4), 166 (9), 122 (83), 94 (55), 58 (100) (Found: $M^{+\bullet}$, 360.20518. $C_{20}H_{28}N_2O_4$ requires $M^{+\bullet}$, 360.20491).

3,3′-[Propane-1,3-diylbis(methyliminomethylene)]di(benzene-1,2-diol) (8)

The crude product was dissolved in a mixture of acetone and chloroform (1 : 1) and the solution was filtered to remove any insoluble residues. The organic filtrate was concentrated under reduced pressure. Column chromatography (acetone) afforded (8) as pale yellow *crystals* (1.73 g, 87%), m.p. 130°C (dec.) (Found: C, 66.0; H, 7.9; N, 7.6. $C_{19}H_{26}N_2O_4$ requires C, 65.9; H, 7.6; N, 8.0%). I.r. ν_{max} (KBr) 3412, 3051, 2962, 2846, 1475, 1354, 1196 cm^{-1}. ^1H n.m.r. δ 1.83, quin, $NCH_2C\mathbf{H}_2CH_2N$; 2.31, s, NCH_3; 2.52, t, *J* 7.5 Hz, $NC\mathbf{H}_2CH_2C\mathbf{H}_2N$; 3.70, s, NCH_2; 6.51, appr. d, *J* 7.6 Hz, ArH; 6.69, appr. t, *J* 7.7 Hz, ArH; 6.84, appr. d, *J* 7.9 Hz, ArH. ^{13}C n.m.r. δ 24.6; 41.4; 54.6; 61.1; 113.8; 119.3; 119.4; 121.3; 144.6; 144.6. Mass spectrum (e.i.) *m/z* 346 (12%), 224 (24), 193 (13), 166 (28), 152 (28), 122 (100), 94 (25), 71 (54), 58 (40) (Found: $M^{+\bullet}$, 346.18902. $C_{19}H_{26}N_2O_4$ requires $M^{+\bullet}$, 346.18926).

3,3′-(Piperazine-1,4-diylbismethylene)di(benzene-1,2-diol) (9)

Column chromatography (chloroform) afforded (9) as pale yellow *crystals* (0.91 g, 90%), m.p. 210°C (dec.) (Found: C, 65.4; H, 6.8; N, 8.4. $C_{18}H_{22}N_2O_4$ requires C, 65.4; H, 6.7; N, 8.5%). I.r. ν_{max} (KBr) 3517, 2935, 2831, 1483, 1347, 1268, 1242, 1170 cm^{-1}. ^1H n.m.r. δ 2.35, br s, ring $C\mathbf{H}_aH_bC\mathbf{H}_aCH_b$; 2.95, br s, ring $CH_aH_bCH_aC\mathbf{H}_b$; 3.75, s, NCH_2; 6.53, appr. d, *J* 7.4 Hz, ArH; 6.71, appr. t, *J* 7.8 Hz, ArH; 6.85, dd, *J* 8.0, 1.3 Hz, ArH. ^{13}C n.m.r. δ 52.4; 60.8; 114.1; 119.7; 119.7; 120.5; 144.1; 144.5. Mass spectrum (e.i.) *m/z* 330 (20%), 166 (54), 122 (89), 85 (80), 56 (57), 44 (100) (Found: $M^{+\bullet}$, 330.15705. $C_{18}H_{22}N_2O_4$ requires $M^{+\bullet}$, 330.15796).

Synthesis of 3-(Dialkylaminomethyl)benzene-1,2-diol Mannich Bases (Two-Step Method)

The desired Mannich bases (10)–(13) were prepared in good yields by means of the following general method unless otherwise stated. A solution of finely ground paraformaldehyde (0.05 mol, 1 equiv.) and the

appropriate amine (0.10 mol, 2 equiv.) in dry ethanol (10 ml) was added dropwise to solution of 2-methoxyphenol (0.05 mol, 1 equiv.) in dry ethanol (10 ml) at room temperature. After the addition was complete the reaction mixture was stirred for 72 h. A standard workup followed and the crude mixture was demethylated. After demethylation a second workup followed and the product was isolated by standard purification techniques.

3-(Diethylaminomethyl)benzene-1,2-diol (10)

Two-step method. Column chromatography (acetone) afforded (10) as pale yellow grain-like crystals (5.33 g, 55%), m.p. 43–44°C (lit.[10] 44–45°C) (Found: C, 67.6; H, 8.6; N, 7.1. Calc. for $C_{11}H_{17}NO_2$: C, 67.7; H, 8.8; N, 7.2%). I.r. ν_{max} (KBr) 3436, 2975, 1475, 1261, 1181 cm^{-1}. ^1H n.m.r. 1.13, t, *J* 7.2 Hz, $NCH_2C\mathbf{H}_3$; 2.65, q, *J* 7.1 Hz, $NC\mathbf{H}_2CH_3$; 3.78, s, CH_2N; 6.52, appr. d, *J* 7.5 Hz, ArH; 6.67, appr. t, *J* 7.8 Hz, ArH; 6.84, dd, *J* 7.9, 1.3 Hz, ArH; 8.69 ArOH. ^{13}C n.m.r 11.0; 46.3; 56.2; 113.7; 119.0; 119.5; 121.3; 144.8; 145.1. Mass spectrum m/z (e.i.) 195 (53%), 166 (2), 137 (4), 123 (45), 72 (19), 58 (100).

Literature method.[10] A solution of crushed paraformaldehyde (1 equiv.) and diethylamine (2 equiv.) in dry ethanol (10 ml) was stirred for 1 h. Catechol (1 equiv.) was added and stirred for a further 72 h. Workup followed by column chromatography (acetone) afforded (10) as pale yellow grain-like crystals (3.29 g, 33%). The spectroscopic data were consistent with those obtained from the two-step method.

3-(Dipropylaminomethyl)benzene-1,2-diol (11)

Two-step method. Column chromatography (ethyl acetate) afforded (11) as pale yellow needlelike crystals (3.84 g, 34%), m.p. 34–35°C (Found: C, 69.7; H, 9.6; N, 6.4. Calc. for $C_{13}H_{21}NO_2$: C, 69.9; H, 9.5; N, 6.3%). I.r. ν_{max} (KBr) 3451, 2965, 2940, 1477, 1470, 1361, 1259, 1180 cm^{-1}. ^1H n.m.r. (CD_3OD) δ 0.80, *J* 7.4 Hz, $NCH_2CH_2C\mathbf{H}_3$; 1.92, m, $NCH_2C\mathbf{H}_2CH_3$; 2.38, m, $NC\mathbf{H}_2CH_2CH_3$; 3.64, s, CH_2N; 6.38, dd, *J* 7.5, 1.1 Hz, ArH; 6.48, appr. t, *J* 7.7 Hz, ArH; 6.60, dd, *J* 7.9, 1.5 Hz, ArH. ^{13}C n.m.r. (CD_3OD) δ 12.2; 20.7; 56.7; 59.0; 115.7; 120.1; 120.6; 124.2; 146.3; 147.0. Mass spectrum (e.i.) *m/z* 223 (9%), 194 (12), 122 (24), 72 (100), 43 (20).

Literature method.[10] A solution of crushed paraformaldehyde (0.05 mo1, 1 equiv.) and dipropylamine (0.1 mol, 2 equiv.) was stirred for 1 h. Catechol (0.05 mol, 1 equiv.) was added and stirred for a further 72 h. Workup of the reaction followed by column chromatography (ethyl acetate) afforded (11) as pale yellow needlelike crystals (1.92 g, 17%). The spectroscopic data were consistent with those from the two-step method.

3-(Dimethylaminomethyl)benzene-1,2-diol (12)

Column chromatography (ethyl acetate) afforded (12) as pale orange needlelike crystals (2.98 g, 35%), m.p. 67–69°C (Found: C, 64.7; H, 7.9; N, 8.4. $C_9H_{13}NO_2$ requires C, 64.7; H, 7.8; N, 8.4%). I.r. ν_{max} (KBr) 3401, 1473, 1455, 1256, 1201, 1179 cm^{-1}. ^1H n.m.r. (CD_3OD) δ 2.31, s, NCH_3; 3.62, s, CH_2N; 6.52, dd, *J* 7.5, 1.4 Hz, ArH; 6.60, appr. t, *J* 7.7 Hz, ArH; 6.70; dd, *J* 7.9, 1.5 Hz, ArH. ^{13}C n.m.r. (CD_3OD) δ 44.8; 62.8; 115.8; 120.1; 121.0; 123.9; 146.4; 146.9. Mass spectrum (e.i.) *m/z* 167 (100%), 122 (41), 58 (4), 46 (4).

3-(Dibutylaminomethyl)benzene-1,2-diol (13)

The reaction mixture was heated to 70°C and stirred for 72 h. Column chromatography (acetone) afforded (13) as a yellow *oil* (3.05 g, 24%) (Found: C, 71.6; H, 10.1; N, 5.5. $C_{15}H_{25}NO_2$ requires C, 71.7; H, 10.0; N, 5.6%). I.r. ν_{max} (KBr) 2958, 2933, 2872, 1471, 1364, 1286, 1256, 1189 cm^{-1}. ^1H n.m.r. δ 0.91, *J* 7.4 Hz, $NCH_2CH_2CH_2C\mathbf{H}_3$; 1.30, m, $NCH_2CH_2C\mathbf{H}_2CH_3$; 1.52, m, $NCH_2C\mathbf{H}_2CH_2CH_3$; 2.52, m, $NC\mathbf{H}_2CH_2CH_2CH_3$; 3.76, s, CH_2N; 6.51, appr. d, *J* 7.5 Hz, ArH; 6.67, appr. t, *J* 7.7 Hz, ArH; 6.83, appr. d, *J* 8.1 Hz, ArH. ^{13}C n.m.r. δ 13.8; 20.4; 28.2; 53.0; 57.7; 113.4; 118.8; 119.1; 121.7; 144.5; 145.0. Mass spectrum (e.i) *m/z* 252 (100%), 208 (46), 123 (26) (Found: $M^{+\bullet}$, 251.18919. $C_{15}H_{25}NO_2$ requires $M^{+\bullet}$, 251.18853).

Synthesis of 2-(Diakylaminomethyl)-6-methoxyphenols (14)–(17)

The desired compounds (14)–(17) were obtained in good yields following a general method unless stated otherwise. A solution of finely ground paraformaldehyde (0.05 mol, 1 equiv.) and the appropriate amine (0.10 mol, 2 equiv.) in dry ethanol (10 ml) was added dropwise to a solution of 2-methoxyphenol (0.05 mol, 1 equiv.) at room temperature. After the addition was complete the reaction mixture was stirred for 72 h. A standard workup followed and the product was isolated by standard purification techniques.

2-(Dimethylaminomethyl)-6-methoxyphenol (14)

Column chromatography (acetone) followed by recrystallization from hot petroleum sprits (40–60°C) afforded (14) as white grain-like crystals (2.97 g, 33%), m.p. 47–49°C (Found: C, 66.1; H, 8.3; N, 7.6. Calc. for $C_{10}H_{15}NO_2$: C, 66.3; H, 8.3; N, 7.7%). I.r. ν_{max} (KBr) 2938, 2834, 1479, 1444, 1266, 1237, 1075 cm^{-1}. ^1H n.m.r. δ 2.35, s, NCH_3; 3.67, s, CH_2N; 3.87, s, OCH_3; 6.61, appr. d, *J* 7.4 Hz, ArH; 6.74, appr. t, *J* 7.8 Hz, ArH; 6.81, appr. t, *J* 8.1 Hz, ArH. ^{13}C n.m.r. δ 44.4; 55.8; 62.1; 110.9; 118.5; 120.5; 121.8; 147.3; 147.8. Mass spectrum (e.i.) *m/z* 181 (100%), 136 (41), 107 (18), 93 (4), 58 (15), 44 (17).

2-(Diethylaminomethyl)-6-methoxyphenol (15)

Column chromatography (chloroform) afforded (15) as an orange *oil* (5.79 g, 49%) (Found: C, 68.7; H, 9.2; N, 6.6. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.2; N, 6.7%). I.r. ν_{max} (KBr) 2971, 2935, 2831, 1471, 1415, 1250, 1239, 1081 cm^{-1}. ^1H n.m.r. δ 1.09, t, *J* 7.2 Hz, $NCH_2C\mathbf{H}_3$; 2.60, q, *J* 7.2 Hz, $NC\mathbf{H}_2CH_3$; 3.75, s, CH_2N; 3.84, s, OCH_3; 6.56, appr. d, *J* 7.4 Hz, ArH; 6.69, appr. t, *J* 7.8 Hz, ArH; 6.77, appr. d, *J* 8.2 Hz, ArH. ^{13}C n.m.r. δ 11.1; 46.2; 55.7; 56.7; 110.5; 118.2; 120.2; 122.1; 147.1; 147.8. Mass spectrum (e.i.) *m/z* 209 (23%), 195 (36), 137 (87), 107 (16), 72 (21), 58 (100) (Found: $M^{+\bullet}$, 209.14173. $C_{12}H_{19}NO_2$: requires $M^{+\bullet}$, 209.14158).

3-(Dipropylaminomethyl)-6-methoxyphenol (16)

Column chromatography (ethyl acetate) afforded (16) as a dark orange *oil* (5.65 g, 51%) (Found: C, 70.8; H, 9.9; N, 6.0. $C_{14}H_{23}NO_2$ requires C, 70.9; H, 9.8; N, 5.9%). I.r. ν_{max} (KBr) 2962; 2935, 2874, 2830 1468, 1415, 1249, 1082 cm^{-1}. ^1H n.m.r. δ 0.88, t, *J* 7.4 Hz, $NCH_2CH_2C\mathbf{H}_3$; 1.56, m, $NCH_2C\mathbf{H}_2CH_3$; 2.47, m, $NC\mathbf{H}_2CH_2CH_3$; 3.75, s, CH_2N; 3.86, s, OCH_3; 6.57, dd, *J* 7.5, 1.1 Hz, ArH; 6.71, appr. t, *J* 7.7 Hz, ArH; 6.79, dd, *J* 8.0, 1.3 Hz, ArH. ^{13}C n.m.r. δ 11.8; 19.4; 55.4; 55.8; 55.1; 110.6; 118.3; 120.3; 122.3; 147.5; 147.9. Mass spectrum (e.i.) *m/z* 237 (11%), 208 (45), 137 (100), 122 (7), 107 (7), 72 (75) (Found: $M^{+\bullet}$, 237.17343. $C_{14}H_{23}NO_2$ requires $M^{+\bullet}$, 237.17288).

2-(Dibutylaminomethyl)-6-methoxyphenol (17)

The reaction mixture was heated at 70°C for 72 h. Workup gave the crude product as a sticky pale orange residue. The residue was dissolved in a mixture of chloroform and ethyl acetate (1 : 1) and the solution was filtered to remove any insoluble residues. The organic filtrate was concentrated under reduced pressure. Column chromatography (chloroform) afforded (17) as a dark orange *oil* (2.10 g, 16%) (Found: C, 72.4; H, 10.2; N, 5.3. $C_{16}H_{27}NO_2$ requires C, 72.4; H, 10.3; N, 5.3%). I.r. ν_{max} (KBr) 2957, 2932, 1588, 1465, 1249, 1081 cm^{-1}. ^1H n.m.r. δ 0.88, t, *J* 7.2 Hz, $NCH_2CH_2CH_2C\mathbf{H}_3$; 1.30, m, $NCH_2CH_2C\mathbf{H}_2CH_3$; 1.52, m, $NCH_2C\mathbf{H}_2CH_2CH_3$; 2.50, m, $NC\mathbf{H}_2CH_2CH_2CH_3$; 3.75, s, CH_2N; 3.86, s, OCH_3; 6.57, appr. d, *J* 7.5 Hz, ArH; 6.71, appr. t, *J* 7.8 Hz, ArH; 6.79, appr. d, *J* 8.1 Hz, ArH. ^{13}C n.m.r. δ 13.9; 20.5; 28.3; 53.12; 6.76; 58.0; 110.6; 118.3; 120.3; 122.2; 147.5; 147.8. Mass spectrum (e.i.) *m/z* 265 (6%), 222 (38), 137 (80), 122 (4), 107 (10), 86 (100), 65 (33) (Found: $M^{+\bullet}$, 265.20350. $C_{16}H_{27}NO_2$ requires $M^{+\bullet}$, 265.20418).

Acknowledgments

The authors would like to thank Comalco Aluminium Limited and the Australian Research Council for financial assistance.

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