# Metal Template Reactions. X\* Improved Syntheses of 2,2'-(Ethane-1,2-diyldiimino)bisbenzaldehyde and 2,2'-(Propane-1,3-diyldiimino)bisbenzaldehyde

# David St.C. Black, Corrie H. Bos Vanderzalm and Angus J. Hartshorn

Department of Chemistry, Monash University, Clayton, Vic. 3168.

### Abstract

2,2'-(Propane-1,3-diyldiimino)bisbenzaldehyde (2) has been synthesized by a high-yielding route involving the alkylation of the isatin anion with 1,3-dibromopropane. 2,2'-(Ethane-1,2-diyldiimino)-bisbenzaldehyde (1) can be synthesized most effectively by a route involving initial acylation of methyl anthranilate with oxalyl chloride. Subsequent reductive and oxidative transformations are then carried out in each case.

# Introduction

Diamino dialdehydes such as 2,2'-(ethane-1,2-diyldiimino)bisbenzaldehyde (1) have been shown to take part in metal template reactions with metal salts and diamines to afford macrocyclic metal complexes.<sup>1-3</sup> The synthesis of (1) involved<sup>1</sup> the alkylation of methyl anthranilate with 1,2-dibromoethane and subsequent transformation of methoxycarbonyl groups to hydroxymethylene and then formyl. The main disadvantage of this method is the low yield in the alkylation step.



- \* Part IX, Aust. J. Chem., 1976, 29, 2271.
- <sup>1</sup> Green, M., Smith, J., and Tasker, P. A., Inorg. Chim. Acta, 1971, 5, 17.
- <sup>2</sup> Black, D. St.C., and Lane, M. J., Aust. J. Chem., 1970, 23, 2039.
- <sup>3</sup> Black, D. St.C., and Kortt, P. W., Aust. J. Chem., 1972, 25, 281.

Alternatively, the compounds (3) and (4) have been synthesized<sup>2,3</sup> by a nucleophilic aromatic substitution process, which proceeds in good yield,\* but is restricted to nitro-substituted compounds. We now describe the synthesis of (2) by a route analogous to that described for (1) above, as well as improved methods for the preparation of both (1) and (2).

### **Results and Discussion**

The alkylation of methyl anthranilate with 1,3-dibromopropane afforded the diamino diester (5) in 22% yield. Reduction of (5) with lithium aluminium hydride gave the dialcohol (6), which was oxidized to the dialdehyde (2) by manganese dioxide (Scheme 1). The compounds (5), (6) and (2) were characterized by analytical and spectral data and showed properties similar to their ethylene analogues.<sup>1,2</sup>



The low yield in the alkylation step leading to the formation of the diester (5) can be improved by the use of the sodium salt of isatin. From reaction of the isatin salt with 1,3-dibromopropane, the bis-isatin compound (7) was obtained in 92% yield and underwent oxidative alkaline hydrolysis (cf.<sup>5</sup>) in 89% yield to the amino acid (8) (Scheme 2). Lithium aluminium hydride effected the direct reduction of (8) to the dialcohol (6) which was then oxidized to the dialdehyde (2) as before.

This overall synthetic sequence is not only higher yielding than the one involving alkylation of methyl anthranilate, but it is also potentially capable of greater generality, because of the availability of substituted isatins.<sup>6</sup> Our work is continuing in this area.

The dialdehyde (1) could also potentially be prepared by the isatin route. However, this example is a special case and an even simpler alternative synthesis is available.

Acylation of methyl anthranilate with oxalyl chloride afforded the oxanilide (9) in excellent yield. Reduction of this compound with lithium aluminium hydride gave the alcohol (10) which could be oxidized with manganese dioxide to the dialdehyde (1) (Scheme 3). A similar approach to the trimethylene dialdehyde (2) cannot be used because of the failure of the malonamide moiety of the diester (11) to undergo clean

<sup>\*</sup> Yields of 39% and 36% quoted in refs 2 and 3 have been improved to approximately 60%, by lowering the reaction temperature to  $80^{\circ}$ .<sup>4</sup>

<sup>&</sup>lt;sup>4</sup> Wong, L., unpublished data.

<sup>&</sup>lt;sup>5</sup> Sumpter, W. C., and Jones, W. F., J. Am. Chem. Soc., 1943, 65, 1082.

<sup>&</sup>lt;sup>6</sup> Popp, F. D., Adv. Heterocycl. Chem., 1975, 18, 2.

reduction to a propylene chain. Complex mixtures were obtained from all attempts to reduce the malonamido diester (11).



### Experimental

Analyses were carried out by the Australian Microanalytical Service, Melbourne. Ultraviolet spectra were measured on a Unicam SP 800A spectrophotometer with solutions in 95% ethanol. Infrared spectra were measured with Perkin–Elmer 257 and 521 spectrometers and refer to mineral oil and hexachlorobutadiene mulls. P.m.r. spectra were measured on a Varian A56/60 or Varian HA 100 instrument. All chemical shifts are reported in ppm relative to tetramethylsilane ( $\delta 0.00$ ) as an internal reference standard. P.m.r. spectra are reported in this order: chemical shift ( $\delta$ ), multiplicity, coupling constant, proton count (assignment); multiplicities are reported as s (singlet), bs (broad singlet), d (doublet), t (triplet), p (pentuplet), m (multiplet). Low-resolution mass spectra were measured on a Hitachi Perkin–Elmer RMU-6E spectrometer. The principal ion peaks (m/e) are reported together with their intensities (usually  $\geq 10\%$ ) relative to the base peak.

# Dimethyl 2,2'-(Propane-1,3-diyldiimino)bisbenzoate (5)

A mixture of 1,3-dibromopropane (63  $\cdot$  7 g, 0  $\cdot$  32 mol), methyl anthranilate (87  $\cdot$  6 g, 0  $\cdot$  69 mol) and anhydrous sodium carbonate (150 g, 1  $\cdot$  42 mol) was heated under gentle reflux (oil bath temperature 160°) for 3 days, with constant stirring. On cooling, the mixture solidified and was extracted with boiling methylene chloride (3  $\times$  250 ml). The extract was concentrated to a brownish oil which afforded the crude product (21  $\cdot$  0 g, 22%) on addition of chloroform–light petroleum (2 : 1). Recrystallization from absolute ethanol gave large colourless *needles*, m.p. 95° (Found: C, 66  $\cdot$ 6; H, 6 $\cdot$ 5; N, 7 $\cdot$ 9.  $C_{19}H_{22}N_2O_4$  requires C, 66·7; H, 6·5; N, 8·2%).  $v_{max}$  3365, 3340, 1687, 1610, 1577, 1508 and 1500 cm<sup>-1</sup>. P.m.r. spectrum (CDCl<sub>3</sub>): 2·07, p, 7·0, 2H (H 2″); 3·40, d of t, 7·0, 4H (H 1″,3″); 3·86, s, 6H (CH<sub>3</sub>); 6·6, m, 4H (H 4,5); 7·4, m, 2H (H 3); 7·8, bs, 2H (NH) (exchangeable); 7·9, m, 2H (H 6). Mass spectrum: 342 (38%, M), 191 (77), 190 (35), 160 (28), 159 (74), 133 (29) and 132 (100).

#### 1,1'-(*Propane-1,3-diyl*)bis(2,3-dihydroindole-2,3-dione) (7)

Sodium hydride (10.0 g of a 74% dispersion in oil, 0.303 mol) was suspended in anhydrous dioxan (300 ml) under nitrogen and finely ground isatin (44.1 g, 0.3 mol) was added with stirring at such a rate that the temperature did not exceed 60°C. When all the isatin had been added the thick purple slurry of the sodium salt was heated at 60°C for 30 min. A solution of 1,3-dibromopropane (30.3 g, 0.15 mol) in anhydrous dimethyl sulphoxide (200 ml) was then added. The mixture was then heated at 100°C for 30 min and the resultant orange solution was poured, while hot, into 95% ethanol (300 ml) and allowed to cool to room temperature. The title compound was collected and recrystallized from dimethylformamide–ethanol as orange *crystals* (44.2 g, 92%), m.p. 244° (Found: C, 68.2; H, 4.5; N, 8.4. C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub> requires C, 68.3; H, 4.2; N, 8.4%).  $\lambda_{max}$  (e) 246 (34000), 251 (27000), 299 (4400), 409 nm (600).  $v_{max}$  1739, 1610, 1464, 1353, 1300, 1189, 1174, 768 and 752 cm<sup>-1</sup>. P.m.r. spectrum (CD<sub>3</sub>SOCD<sub>3</sub>): 2.13, p, 7.0, 2H (H2″); 3.87, t, 7.0, 4H (H1″, 3″); 7.0–7.8, 8H (H4–7). Mass spectrum: 334 (54%, M), 187 (100), 161 (60), 159 (33), 146 (36), 132 (87), 105 (34), 77 (88).

#### 2,2'-(Propane-1,3-diyldiimino)bis(benzoic acid) (8)

1,1'-(Propane-1,3-diyl)bis(2,3-dihydroindole-2,3-dione) (7) (16.7 g, 0.05 mol) was added to a stirred solution of sodium hydroxide (750 ml, 2.5 N). The mixture quickly became yellow and a yellow precipitate formed. Hydrogen peroxide (750 ml, 3%) was added and the mixture was stirred for 30 min, then acidified with 5 N hydrochloric acid and the resulting precipitate was collected. The title compound was obtained as a cream *powder* (14.0 g, 89%), which was recrystallized from ethanol-water, m.p. > 250° (Found: C, 64.8; H,  $5.8 \text{ C}_{1.7}\text{H}_{18}\text{N}_2\text{O}_4$  requires C, 65.0; H, 5.8%).  $\lambda_{max}$  ( $\varepsilon$ ) 223 (48000), 258 (18400), 352 nm (10500).  $\nu_{max}$  3372, 1657, 1577, 1514, 1438, 1406, 1245, 1162, 753 and 740 cm<sup>-1</sup>. P.m.r. spectrum (CD<sub>3</sub>SOCD<sub>3</sub>): 1.92, p, 6.5, 2H (H2"); 3.29, t, 6.5, 4H (H1", 3"); 6.4-7.9, 8H (H3-6); 9.70, bs, 4H (NH, CO\_2H). Mass spectrum: 314 (28%, M), 177 (44), 159 (38), 132 (100), 77 (29).

#### 2,2'-(Propane-1,3-diyldiimino)bis(benzyl alcohol) (6)

(i) The diester (5) (6.0 g, 0.018 mol) was extracted during 4 h from a Soxhlet thimble into a refluxing suspension of lithium aluminium hydride (2.0 g) in dry ether (500 ml). After cooling, the reaction mixture was treated sequentially with water (2 ml), sodium hydroxide (2 ml of 15%), water (6 ml), then filtered. The precipitate was extracted with chloroform (4 × 200 ml) and the extracts and filtrate were combined, dried (MgSO<sub>4</sub>) and concentrated to a white solid, which was recrystallized from chloroform–light petroleum (1 : 1) to afford the *dialcohol* (6) (5.8 g, 75%) as colourless needles, m.p. 85° (Found: C, 71.4; H, 7.5; N, 9.7. C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> requires C, 71.3; H, 7.7; N, 9.8%).  $\nu_{max}$  3308, 3285, 1604, 1583, 1500, 1286, 1197, 1119, 1016, 940, 864, 828, 756 and 697 cm<sup>-1</sup>. P.m.r. spectrum (CD<sub>3</sub>SOCD<sub>3</sub>): 1.92, p, 6.8, 2H (H2"); 3.24, m, 4H (H1",3") (after D<sub>2</sub>O exchange, t, 6.8); 4.45, d, 5.0, 4H (HOCH<sub>2</sub>) (after D<sub>2</sub>O exchange, s); 5.9, m, 4H (NH and OH) (exchangeable); 6.4–7.3; 8H (H3–6). Mass spectrum: 286 (26%, M), 268 (20), 163 (25), 149 (86), 145 (39), 144 (49), 134 (57), 132 (73), 120 (43), 119 (100).

(ii) The dicarboxylic acid (8)  $(15 \cdot 7 \text{ g}, 0.05 \text{ mol})$  was added as a solid to a well stirred, boiling mixture of lithium aluminium hydride  $(5 \cdot 0 \text{ g}, 0.13 \text{ mol})$  and ether (300 ml). On completion of the addition, the mixture was heated under reflux for a further 2 h, then cooled. The reaction mixture was then treated with water (5 ml), sodium hydroxide (5 ml of 15%), water (15 ml) and filtered. The product (6) was isolated as above (12.9 g, 90%).

### 2,2'-(Propane-1,3-diyldiimino)bisbenzaldehyde (2)

The dialcohol (6) (5.5 g, 0.019 mol) in dry ether (250 ml) and active manganese dioxide<sup>7</sup> (50 g) were stirred and refluxed together for 5 h. The manganese dioxide was filtered off and extracted with

<sup>7</sup> Harfenist, M., Bavley, A., and Lazier, W. A., J. Org. Chem., 1954, 19, 1608.

boiling chloroform. The combined extracts and filtrate were concentrated to a yellow oil which crystallized and was recrystallized from chloroform-light petroleum to afford the *dialdehyde* (2) (3.9, 73%), m.p. 82° (Found: C, 72.0; H, 6.5; N, 10.0.  $C_{17}H_{18}N_2O_2$  requires C, 72.3; H, 6.4; N, 9.9%).  $v_{max}$  3281, 2821, 2743, 1644, 1572, 1508, 1430, 1333, 1314, 1201, 1185, 1182, 1039 and 755 cm<sup>-1</sup>. P.m.r. spectrum (CDCl<sub>3</sub>): 2.04, p, 6.8, 2H (H 2"); 3.38, m, 4H (H 1", 3") (after D<sub>2</sub>O exchange, t, 6.8); 6.6-7.5, 8H (H 3-6); 8.40, bs, 2H (NH) (exchangeable); 9.85, s, 2H (CHO). Mass spectrum: 282 (72%, M), 135 (75), 134 (100), 132 (59), 131 (45), 130 (41), 118 (41), 77 (59).

## Dimethyl 2,2'-(Oxalyldiimino)bisbenzoate (9)

A solution of oxalyl chloride  $(13 \cdot 8 \text{ ml}, 0.15 \text{ mol})$  in dry ether (150 ml) was added cautiously to an ice-cooled, stirred solution of methyl anthranilate  $(97 \cdot 5 \text{ g}, 0.6 \text{ mol})$  in dry ether (600 ml). A white precipitate formed during addition, which was collected, triturated in methanol and crystallized from dimethylformamide to yield colourless *needles* (34.6 g, 65%), m.p. 251–252° (Found: C, 60.6; H, 4.6; N, 7.9. C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub> requires C, 60.7; H, 4.5; N, 7.9%).  $\nu_{max}$  3200, 1720, 1670, 1584 and 1270 cm<sup>-1</sup>. Mass spectrum: 356 (13%, M), 178 (43), 151 (35), 146 (100), 119 (24). A clear p.m.r. spectrum could not be obtained because of insolubility of the compound.

### 2,2'-(Ethane-1,3-diyldiimino)bis(benzyl alcohol) (10)

The pure diester (9)  $(18 \cdot 0 \text{ g}, 0 \cdot 06 \text{ mol})$  was added during 1 h to a suspension of lithium aluminium hydride (100 g) in dry ether (600 ml) and the resulting mixture was heated under reflux for 12 h. After cooling, the reaction mixture was treated sequentially with water (10 ml), sodium hydroxide (10 ml of 30%), water (30 ml) then filtered. The precipitate was extracted with chloroform (4 × 400 ml) and the combined extracts and filtrate afforded the dialcohol (10), which was crystallized from chloroform-light petroleum (1 : 1) (12 \cdot 5 g, 90%), m.p. 118° (lit.<sup>1</sup> 124–126°). The compound was identical with an authentic sample.<sup>1</sup>

### Dimethyl 2,2'-(Malonyldiimino)bisbenzoate (11)

A solution of malonyl chloride (0.7 ml, 0.1 mol) in dry ether (100 ml) was added cautiously to a cooled and stirred solution of methyl anthranilate  $(65 \cdot 0 \text{ g}, 0.4 \text{ mol})$  in dry ether (400 ml) and the resulting white precipitate was collected, triturated with cold, 50% aqueous methanol (500 ml) and crystallized from ethanol to yield the *ester* (11) (25.8 g, 81%), m.p. 148–149° (Found: C, 61.7; H, 4.7; N, 7.5. C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub> requires C, 61.6; H, 4.7; N, 7.6%).  $v_{max}$  3270, 3215, 1692, 1605, 1590, 1322, 1299, 1269, 1092 and 756 cm<sup>-1</sup>. P.m.r. spectrum (CDCl<sub>3</sub>): 3.60, s, 2H (COCH<sub>2</sub>CO); 3.9, s, 6H (CH<sub>3</sub>); 6.9–8.1, 8H (H3–6); 10.8, s, 2H (NH) (exchangeable with D<sub>2</sub>O). Mass spectrum: 370 (25%, M), 193 (25), 161 (20), 151 (100).

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