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# DESIGNER LIGANDS. PART 5.[1] SYNTHESIS of POLYDENTATE BIPHENYL LIGANDS

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**Abstract.** Polydentate nitrogen donor ligands have been prepared for use in biomimetic dinuclear copper complexes designed to model the enzyme, tyrosinase.

The recent literature [2] reveals a continuing interest in the development of dinuclear copper(I) complexes which model the activity of tyrosinase, an enzyme exhibiting both phenolase (*ortho*-hydroxylating phenols) and catecholase (oxidising catechols to *ortho*-quinones) properties. Although the structure of tyrosinase has not been fully elucidated, it is believed that the active site resembles that of the oxygen carrier, haemocyanin,[3] in which histidyl ligands co-ordinate copper(I) ions.[4] In addition to binding molecular oxygen, however, tyrosinase is capable of binding and oxidatively transforming exogenous substrate molecules.

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Reglier *et al.*[5] have described the synthesis of the dinuclear copper(I) complex **4c** (Scheme 1), which incorporates imino-ethyl pyridyl ligands and a flexible biphenyl spacer, permitting bridging of the metal ions by a dioxygen bridge. For comparative purposes, we repeated the preparation of the complex **4c** and then attempted to extend Reglier's methodology to the synthesis of novel complexes, which contain imidazole- and benzimidazole-derived ligands as models for biogenetic histidyl donors. The histidyl imidazole ring is known to participate in intramolecular cyclisations,[6] which may be minimised by following a `template' approach.[7] Use of a benzimidazole system was expected to obviate this difficulty and, possibly, enhance binding of aromatic phenolic substrates *via* π-stacking interactions. In the event, we found evidence of cyclisation, even with the benzimidazole system, and both 'template' (Path I) and stepwise (*i.e. via* the free ligand; Path II) approaches to the complexes **4a** and **4b** presented difficulties.

Preliminary studies [8] revealed that some of the metal complexes, although clearly impure, were capable of catalysing coupling of 3,5-di-*tert*-butylphenol (DTBP), to give the dihydroxybiphenyl derivative[9] as the sole oxidation product,‡ [10] and effecting quantitative conversion of 3,5-di-*tert*-butylcatechol (DTBC) to 3,5-di-*tert*-butyl-*o*-quinone (DTBQ) within 24h. Encouraged by these results, we have explored approaches to analogous, but structurally well-defined, ligands and complexes.

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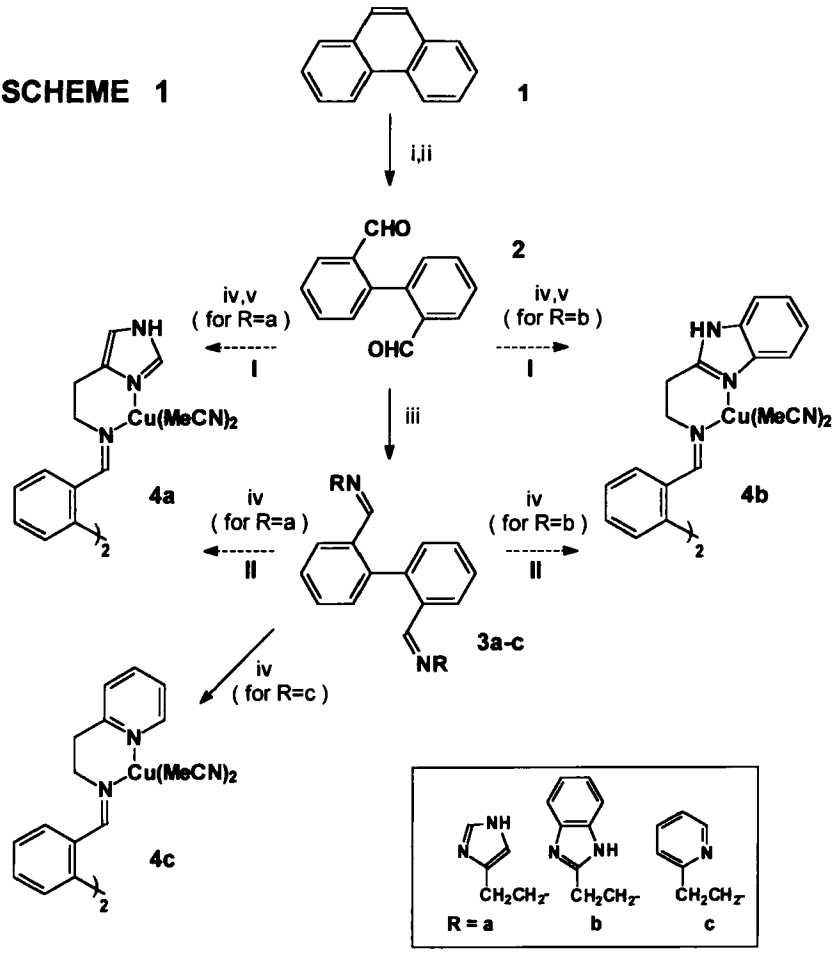
‡ Tyrosinase is also known to catalyse coupling of sterically hindered phenols, presumably *via* radical intermediates (see Ref. 11).

**SCHEME 1**



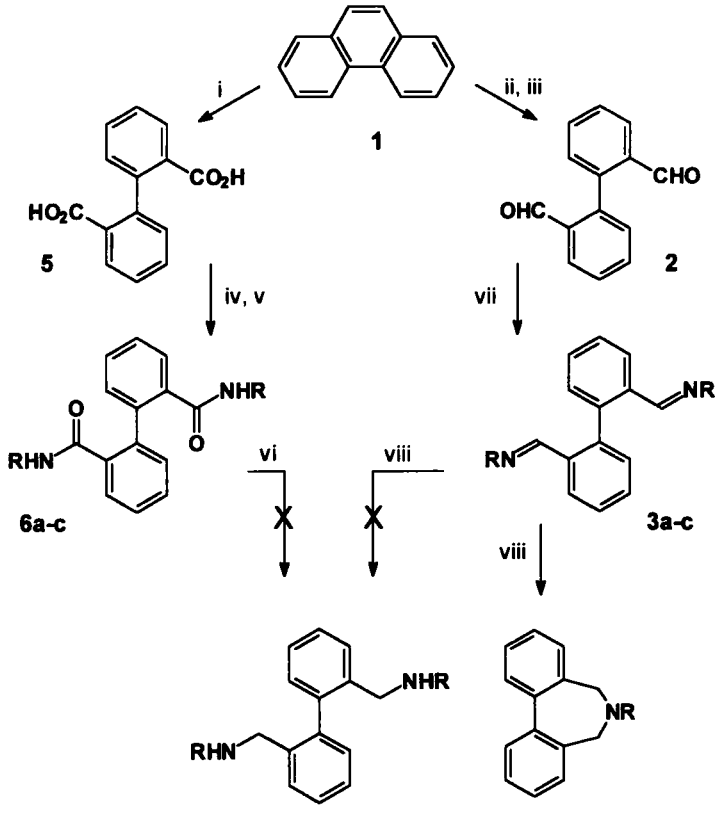

Reagents : i, $O_3$, MeOH, - 30°C ; ii, KI, AcOH ; iii, $RNH_2$, $CHCl_3$, reflux ; iv, $[Cu(MeCN)_4][PF_6]$, MeCN ; v, $RNH_2$ .

Since molecular cyclisation (involving attack by nitrogen nucleophiles on the imino moiety in compounds **3a** and **3b**) appeared to be a major complicating factor, saturation of the aliphatic side chains, to afford ligands of type **7**, was identified as the immediate synthetic objective (Scheme 2). Two strategies were followed, *viz.*, i) preparation and reduction of the corresponding dicarboxamides **6**, and ii) isolation and reduction of the imines **3**.



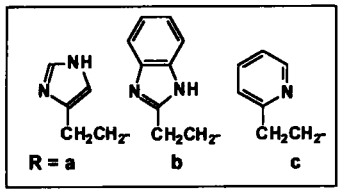
Oxidation of phenanthrene **1** with hydrogen peroxide in acetic acid[12] afforded diphenic acid **5** in 67% yield. Formation of the diamides **6a-c**, in yields ranging from 56% to 82%,was achieved by treating diphenic acid **5** with carbonyldiimidazole (CDI)[13] in dimethylformanide, followed by the respective primary amines:- 4-(2-aminoethyl)imidazole; 2-(2-aminoethyl)benzimidazole; and 2-(2-aminoethyl)pyridine (Scheme 2). Surprisingly, attempts to reduce the amides **6a-c** to the target compounds **7a-c**, using lithuim aluminium hydride or Raney nickel, proved unsuccessful.

Following the alternative approach, ozonolysis[14] of phenanthrene **1** gave, in 93% yield, the dicarbaldehyde **2**, which was reacted with the respective amines to afford the crude imines **3a-c**. Sodium borohydride reduction of these imines was expected to afford the target compounds **7a-c** but, in fact, gave the corresponding, cyclic tertiary amines **8a-c**. The structure of the pyridyl derivative **8c** was established by X-ray crystallographic analysis of the cobalt and nickel complexes.[15] The unexpected formation of the cyclic amines **8a-c** is attributed to a cyclisation-

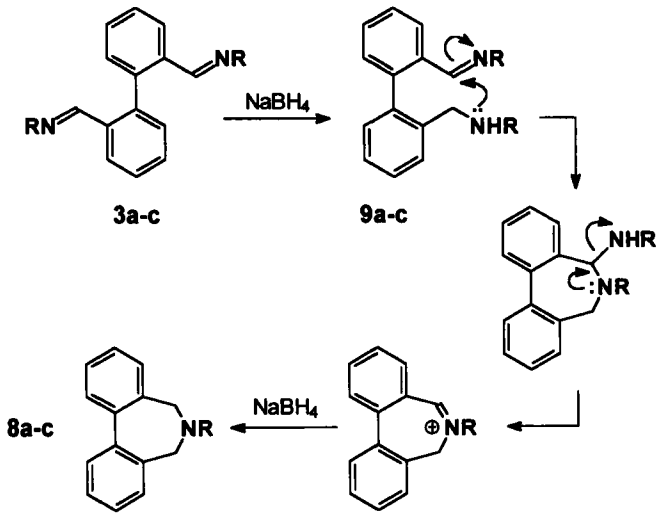



**SCHEME 2**

Reagents : i, $H_2O_2$, AcOH ;
ii, $O_3$, MeOH, - 30°C ;
iii, KI, AcOH ;
iv, CDI, DMF ;
v, $RNH_2$ ;
vi, $LiAlH_4$ or $H_2$-Raney Ni ;
vii, $RNH_2$, $CHCl_3$ ;
viii, $NaBH_4$, MeOH



elimination process involving the partially reduced intermediates **9a-c**, as illustrated in Scheme 3.




**SCHEME 3**

The ligands **6** and **8** have been reacted with various metal salts affording, in a number of cases, crystalline complexes; the structures, electrochemical properties and biomimetic potential of these complexes will be reported in due course.

## EXPERIMENTAL

Infrared spectra were recorded on Perkin Elmer 2000 and Perkin Elmer 180 spectrophotometers; NMR spectra were recorded on a Bruker AMX 400

spectrometer and chemical shifts are reported relative to the solvent peaks. Low resolution mass spectra were obtained on a Hewlett-Packard 5988A mass spectrometer and high resolution analyses on a Kratos MS80RF double-focussing magnetic sector instrument (Cape Technikon Mass Spectrometry Unit); FAB mass spectra were obtained on a VG Micromass 70-70E spectrometer (Iontech B11N FAB-gun), using Xe as bombarding gas (University of Potchefstroom).



Literature methods were used to prepare compounds **2**;[14] **3a-c** and **4c**;[5] and **5**.[12] The crude imino compounds **3a,b** are prone to cyclisation and were used without further purification. The synthesis of the new compounds **6a-c** and **8a-c** is illustrated by the following examples.

*2,2'-Bis{[2-(2-pyridyl)ethylamino]carbonyl}biphenyl* **6c**.

Diphenic acid **5** (1.00 g, 4.1 mmol) was dissolved in dry DMF (10 mL) in a round-bottomed flask fitted with a reflux condenser and drying tube. The solution was warmed to 40°C, and CDI (2.13 g, 13.1 mmol) was added with stirring. The mixture was stirred at 40°C for 5 min.(after which time gas evolution had ceased), and then allowed to cool to room temperature. 2-(2-Aminoethyl)pyridine (1.1 mL, 9.0 mmol) was added and, after stirring the resulting solution for 1 h, $H_2O$ (7 mL) was added. Volatiles were removed under reduced pressure, and 1M aq. $Na_2CO_3$ (50 mL) was added to the residual oil. The mixture was extracted with EtOAc (2 x 80 mL), and the combined extracts were washed with $H_2O$ (80 mL) and brine (80 mL), and then dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [flash

chromatography on silica gel; elution with $CHCl_3$-hexane-MeOH (3:3:1)] to afford, as a brown oil, *2,2'-bis{[2-(2-pyridyl)ethylamino]carbonyl}biphenyl* **6c** (1.00 g, 54%) (Found: $M^+$, 450.2044. $C_{28}H_{26}O_2N_4$ requires *M*, 450.2056); $\nu_{max}$(thin film/$cm^{-1}$) 3321 (NH) and 1634 (CO); $\delta_H$(400 MHz; $CDCl_3$) 2.68 (4H, quintet, $NHCH_2CH_2$), 3.42-3.67 (4H, m, $NHCH_2CH_2$), 7.02-7.12 (6H, m, ArH), 7.25-7.35 (4H, m, ArH), 7.48 (2H, m, ArH), 7.52-7.58 (2H, m, ArH), 7.74 (2H, t, NH) and 8.45 (2H, d, ArH); $\delta_C$(100 MHz; $CDCl_3$) 37.1 ($NHCH_2CH_2$), 39.1 ($NHCH_2CH_2$), 121.7, 123.6, 127.4, 128.0, 129.6, 129.7, 136.6, 136.8, 139.4, 149.4 and 159.6 (ArC) and 170.1 (CO).

*1-[2-(2-Benzimidazolyl)ethyl]dibenzo[c,e]perhydroazepine* **8b**.

A solution of biphenyl-2,2'-dicarbaldehyde **2** (0.49 g, 2.3 mmol) and 2-(2-amino-ethyl)benzimidazole (0.74 g, 4.6 mmol) in $CHCl_3$ (100 mL) was boiled under reflux for 59 h. The solvent was removed under reduced pressure, and the residue recrystallised from MeCN to afford, as a yellow powder, the crude diimine **3b** (0.9 g, 80%). $NaBH_4$ (0.27 g, 7.1 mmol) was then added to a solution of the diimine **3b** in MeOH (10 mL), and the resulting mixture was boiled under reflux for *ca.* 35 min. Ice was added to quench the reaction, precipitating, as a pale yellow powder, *1-[2-(2-benzimidazolyl)ethyl]dibenzo[c,e]perhydroazepine* **8b** (0.49 g, 65%) (Found: $MH^+$, 340.1814. $C_{23}H_{21}N_3$ requires $MH^+$, 340.1814), mp 184-186 °C; $\nu_{max}$(KBr/$cm^{-1}$) 3174 (NH); $\delta_H$(400 MHz; MeOH-$d_4$) 3.10 (2H, m, $NCH_2CH_2$), 3.23 (2H, t, $NCH_2CH_2$), 3.50 (4H, s, $ArCH_2$), 7.17-7.21 (2H, m, ArH), 7.34-7.41 (4H, m, ArH), 7.44-7.48 (2H, m, ArH) and 7.49-7.52 (4H, m, ArH); $\delta_C$(100 MHz;

MeOH-$d_4$)[¶] 28.2 ($NCH_2CH_2$), 54.4 ($NCH_2CH_2$), 56.0 ($ArCH_2$), 115.5, 123.4, 128.8, 129.1, 129.8, 131.2, 134.7, 139.4, 142.5 and 154.7 (ArC).

Ligand **8c**, isolated as a brown oil, was characterised by single crystal X-ray analysis of its cobalt(II) and nickel(II) complexes.[15] Analytical data for other new compounds prepared in this study are as follows.

*2,2'-Bis{[2-(4-imidazolyl)ethylamino]carbonyl}biphenyl* **6a** (1.44 g, 82%), mp 232-234°C (from DMF-$H_2O$)(Found: $M^+$, 428.1955. $C_{24}H_{24}O_2N_6$ requires *M*, 428.1961); $\nu_{max}$(KBr/cm$^{-1}$) 3187 (NH) and 1640 (CO); $\delta_H$(400 MHz; DMSO-$d_6$) 2.51 (4H, s, $NHCH_2CH_2$), 3.34 (4H, s, $NHCH_2CH_2$) , 6.73 (2H, s, ArH), 7.08 (2H, m, ArH), 7.40 (4H, m, ArH), 7.48 (2H, m, ArH) and 7.53 (2H, s, ArH); $\delta_C$(100 MHz; DMSO-$d_6$) 27.53 ($NHCH_2CH_2$), 40.52 ($NHCH_2CH_2$), 117.9, 128.4, 128.9, 130.6, 130.7, 135.7, 136.1, 137.4 and 140.4 (ArC) and 172.5 (CO).

*2,2'-Bis{[2-(2-benzimidazolyl)ethylamino]carbonyl}biphenyl* **6b** (1.21 g, 56%), mp > 250°C (Found: $M^+$, 528.2261. $C_{32}H_{28}O_2N_6$ requires *M*, 528.2274) $\nu_{max}$(KBr/cm$^{-1}$) 3172 (NH) and 1656 (CO); $\delta_H$(400 MHz; DMSO-$d_6$) 2.62 (4H, s, $NHCH_2CH_2$), 3.43 (4H, s, $NHCH_2CH_2$), 6.99 (2H, d, ArH), 7.05-7.16 (4H, m, ArH), 7.28-7.37 (4H, m, ArH), 7.38-7.42 (4H, m, ArH), 7.49 (2H, d, ArH), 8.64 (2H, m, amide NH) and

[¶] The coincidence of some $^{13}C$ signals is presumed.

12.14 (2H, s, ArNH); $\delta_C$ (100 MHz; DMSO-$d_6$ )[1] 28.2 ($NHCH_2CH_2$), 37.2, ($NHCH_2CH_2$), 110.7 118.0, 120.7, 121.4, 126.9, 127.2, 128.9, 134.2, 136.2, 138.5, 143.2 and 152.1 (ArC) and 169.0 (CO).

*1-[2-(4-imidazolyl)ethyl]dibenzo[c,e]perhydroazepine* **8a** (0.32 g, 33%), mp 149-151°C(Found: $MH^+$, 290.1657. $C_{19}H_{19}N_3$ requires $MH^+$, 290.1657; $\nu_{max}$(KBr/cm$^{-1}$) 3413 (NH); $\delta_H$(400 MHz; MeOH-$d_4$) 2.89 (2H, m, $NCH_2CH_2$), 2.95 (2H, m, $NCH_2CH_2$), 3.46 (4H, s, $ArCH_2$), 6.83-6.87 (1H, m, ArH), 7.37-7.44 (4H, m, ArH), 7.45-7.58 (4H, m, ArH) and 7.59-7.63 (1H, m, ArH).



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