

## Evaluation of Through-Space Interaction in [2.2]Metacyclophanes by Diazo Coupling Reaction<sup>1</sup>

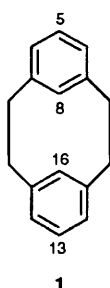
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An azobenzene moiety was introduced into various [2.2]metacyclophanes (MCPs) **1** via diazo coupling reactions. The functional groups on the inner (8,16-) or outer (13-) positions affect the reactivity of the outer (5-) position toward the diazonium salts to a large extent. It was also observed that one aromatic ring of [2.2]MCPs can be subject to attack of diazonium salts very easily; however, the other aromatic ring never undergoes attack. The electronic absorption wavelengths of the azo[2.2]MCPs are bathochromically shifted from those of model reference compounds. When the  $\lambda_{\max}$ -values of azo[2.2]MCPs which carry a functional group on the outer (13-) position are plotted against the substituent's Hammett constants ( $\sigma_p$ ), a straight line is obtained. These results established that the electronic effect of the functional group is transmittable between the two aromatic rings in [2.2]MCPs by a through-space interaction.

For some time, cyclophane compounds have been of interest to organic chemists for many reasons.<sup>2</sup> A topic of strong interest is the intramolecular interaction between the aromatic rings of small cyclophanes. Reports<sup>3</sup> dealing with this subject in [2.2]metacyclophane derivatives have been very limited, mainly



due to difficulties in preparing an adequate amount of appropriate metacyclophane compounds. Since we reported simple and efficient synthetic methods for the preparation of [2.2]MCPs and related compounds,<sup>4</sup> we have devoted our attention to their reactivity, especially toward electrophilic reagents. For instance, bromination<sup>5</sup> and nitration<sup>6</sup> of 8,16-dimethyl[2.2]MCPs yielded unexpected products depending on the reaction conditions. Although these results support the basic trends in reactivity of MCPs in electrophilic reactions, a systematic and detailed study of their electrophilic reactivity has not been carried out. In this study diazonium salts were selected as the electrophilic reagent because of their weak electrophilicity, and thus their reactivity would presumably be influenced by slight differences in the MCP's structure. Furthermore, UV spectra of azoMCP derivatives can give information about the electronic structure of MCPs, which should reflect upon their reactivity. This paper describes the comparison of reactivities among 8, 16- or 13-substituted [2.2]MCPs with nitro-substituted diazonium salts and an estimation of the through-space interactions in these compounds based on UV spectra.

### Results and Discussion

**Preparation of MCPs and Related Compounds.**—MCPs **2a–c** were prepared from anisole or *p*-tert-butyltoluene in 6–8 steps

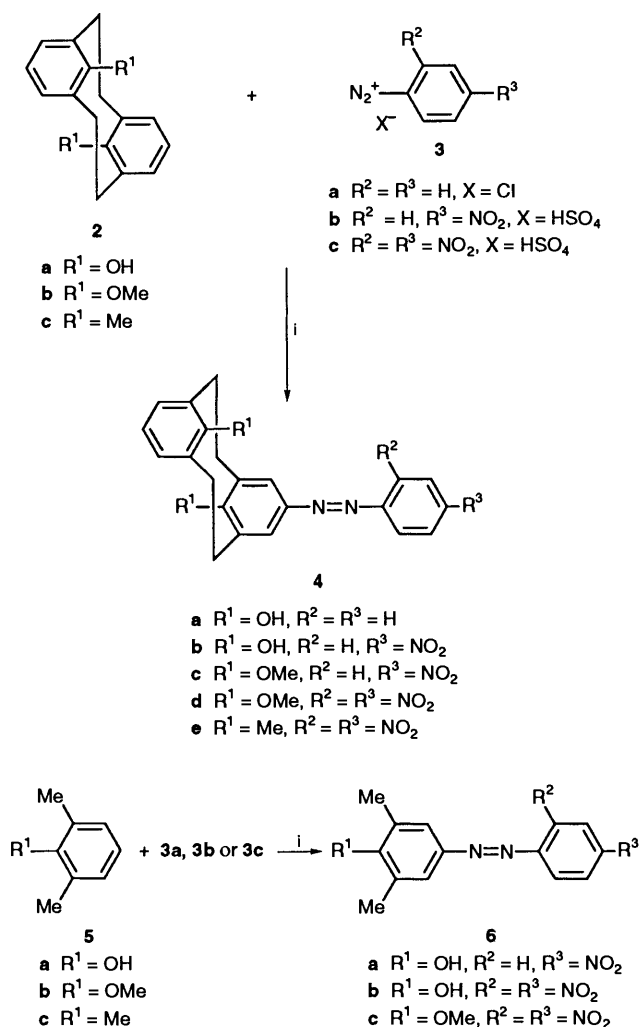
**Table 1** Yields (%) of diazo coupling reaction between MCPs **2**, **5**, **7** and **9a** with salts **3**

Compound	Diazonium salt		
	3a	3b	3c
<b>2a</b>	<b>4a</b> (30)	<b>4b</b> (90)	<i>b</i>
<b>2b</b>	<i>a</i>	<b>4c</b> (95)	<b>4d</b> (89)
<b>2c</b>	<i>a</i>	<i>a</i>	<b>4e</b> (15)
<b>5a</b>	<i>a</i>	<b>6a</b> (85)	<b>6b</b> (92)
<b>5b</b>	<i>a</i>	<i>a</i>	<b>6c</b> (< 5)
<b>5c</b>	<i>a</i>	<i>a</i>	<i>a</i>
<b>7a</b>			<b>8a</b> (8)
<b>7b</b>			<b>8b</b> (96)
<b>7c</b>			<b>8c</b> (86)
<b>7d</b>			<b>8d</b> (95)
<b>9a</b>			<i>a</i>

<sup>a</sup> No reaction. <sup>b</sup> Complex mixture.

according to the reported method.<sup>4c,d,5a</sup> NitroMCPs **7a** and **9a**<sup>6</sup> were obtained by nitration of bis ether **2b** with Cu(NO<sub>3</sub>)<sub>2</sub> and of compound **2c** with fuming HNO<sub>3</sub> in 42 and 84% yield, respectively. Reduction of nitroMCP **9a** with Pd/C gave aminoMCP **9b** (85%),<sup>6</sup> which was treated with acetic anhydride to afford acetamidoMCP **9c**<sup>6</sup> in 95% yield. Formylation of compound **2b** with Cl<sub>2</sub>HCOMe with TiCl<sub>4</sub> as catalyst gave formylMCP **7c** in 44% yield. MethylMCP **7d** was obtained by reduction of formylMCP **7c** with AlCl<sub>3</sub>–LiAlH<sub>4</sub> in tetrahydrofuran (THF) (54%). Compound **2b** was treated with 1 mole equivalent of Br<sub>2</sub> in CCl<sub>4</sub> to give bromoMCP **7b** in 53% yield. The elemental analysis for brominated MCPs did not give satisfactory results. It seems that these MCPs might decompose slowly in air or on heating. In order to compare the spectral properties of azoMCPs, the reference compounds **4f** and **6d** were prepared. The former was obtained when aminoMCP **9b** was treated with nitrosobenzene, in 15% yield, while the latter was prepared by treatment of compound **6a** with NaH and methyl iodide, in 80% yield.

**Diazo Coupling.**—(i) 8,16-Disubstituted MCPs **2a–c**. The reactions of the MCPs **2a–c** and their corresponding reference compounds **5a–c** with diazonium salts **3a–c** were carried out in AcOH at room temperature (Scheme 1, Table 1). The reaction of



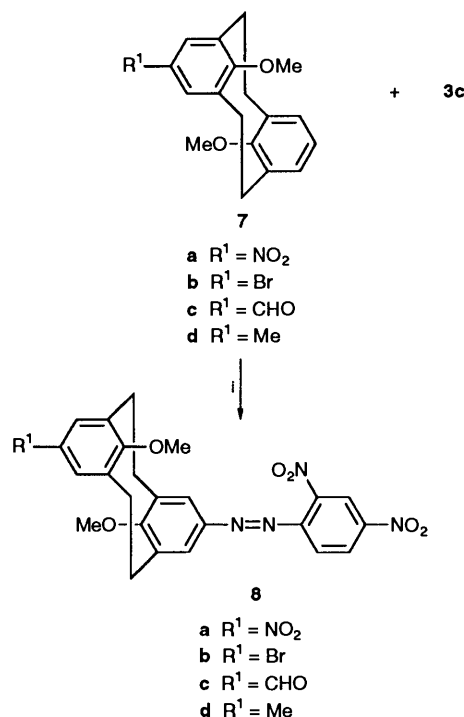
Scheme 1 Conditions: i, in AcOH, room temp.

hydroxyMCP **2a** with salts **3a** and **3b** proceeded very smoothly within a few minutes and gave azobenzenes **4a** and **4b** in 30 and 90% yield, respectively. It should be noted that the unsubstituted aromatic ring does not undergo attack by the diazonium salt. The reaction of hydroxyMCP **2a** with the most reactive diazonium salt **3c** gave an inseparable mixture. Although methoxyMCP **2b** reacted with nitro-substituted diazonium salts **3b** and **3c** to afford **4c** and **4d** in good yield (95 and 89%, respectively), no reaction with **3a** was observed. On the other hand, methylMCP **2c** reacted only with the salt **3c** to give compound **4e** in 15% yield. Under similar conditions, hydroxy derivative **5a** and methoxy derivative **5b** reacted with salts **3b**, **c** and **3c** to give compounds **6a**, **b** and **6c**,\* respectively, as shown in Table 1. However, methyl derivative **5c** was completely recovered from the reaction mixture with any diazonium salt used here even after an extended reaction time. From these results it seems apparent that MCPs **2a-c** exhibit a greater reactivity toward the diazonium salts than do the corresponding reference compounds **5a-c**. The enhancement for diazonium coupling is not so large, however, because MCPs **2b** and **2c** never undergo coupling with the weaker electrophiles **3a** and **3a, b**, respectively. Generally the stronger the electron-releasing character of the substituent group, the more easily the

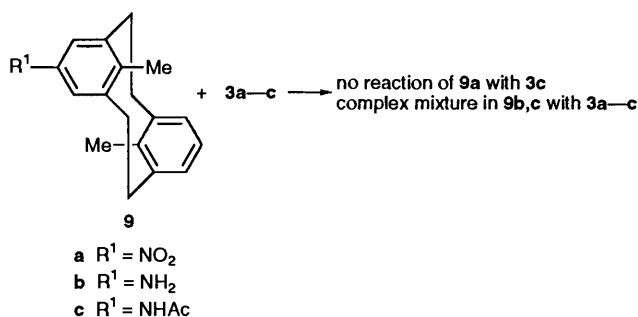
\* The structure of compound **6c** was based on only the mass spectrum [ $m/z$  330 ( $M^+$ )] and the UV spectrum ( $\lambda_{\max}$  367 nm), because of the small amount of material available.

ring undergoes attack by diazonium salts. From this point of view the enhancement can be explained in terms of the increased  $\pi$ -electron density of the aromatic ring undergoing attack, *i.e.* a  $\sigma$  complex intermediate can be stabilized by electron release from the opposite aromatic ring. The second attack does not occur because the introduced azo group functions as an electron-withdrawing group. In both cases these effects may derive from through-space interaction between the two aromatic rings. This finding is consistent with the result of nitration of **2c** in which only a mononitro compound was obtained.<sup>6</sup>

(ii) 13-Substituted MCPs **7a-d**, **9a-c**. Diazo coupling reactions of the 13-substituted MCPs **7a-d** and **9a-c** with diazonium salts **3a-c** were carried out in a similar manner as above (see Schemes 2 and 3). If through-space interactions of



Scheme 2 Conditions: i, in AcOH, room temp.



Scheme 3

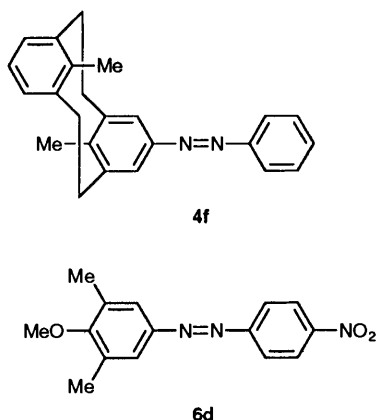
the two aromatic rings exist they should be affected by the functional groups at the outer (13-) position. Therefore, 13-substituted MCPs were also subjected to the diazo coupling reaction as shown in Scheme 2 and Table 1. NitroMCP **7a** reacts only with the most reactive diazonium salt **3c** to give compound **8a** in 8% yield, suggesting that the nitro group at the 13-position reduces the reactivity of the other aromatic rings. The nitro group at this position seems to be very effective in deactivating the opposite aromatic ring. In fact, no coupling occurred between nitroMCP **9a** and salt **3c** (Scheme 3).

**Table 2**  $\lambda_{\max}$ (nm) of azo compounds<sup>a</sup> **4**, **6** and **8**

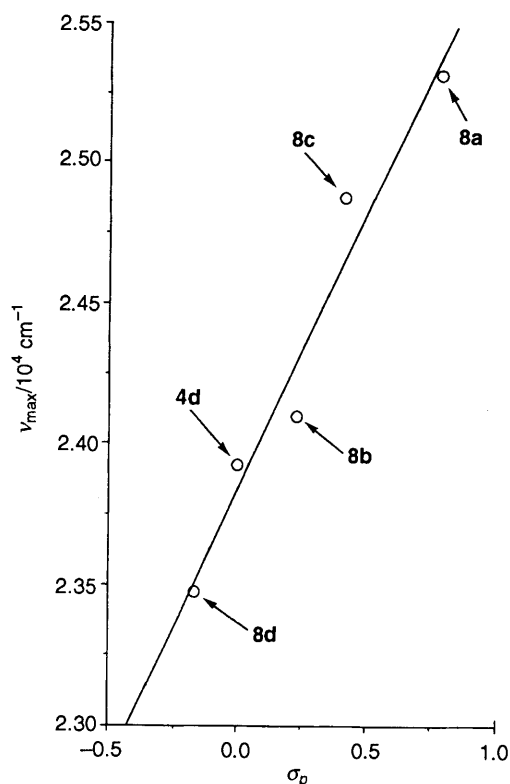
Azo compound <sup>b</sup>	$\lambda_{\max}$ /nm
<b>4a</b>	372
<b>4b</b>	440
<b>4c</b>	394
<b>4d</b>	418
<b>4e</b>	430
<b>4f</b>	368
<b>8a</b>	395
<b>8b</b>	415
<b>8c</b>	402
<b>8d</b>	426
<b>6a</b>	390
<b>6b</b>	445
<b>6c</b>	376
<b>6d</b>	361

<sup>a</sup> In benzene at 27 °C. <sup>b</sup>  $\sim 3 \times 10^{-5}$  mol dm<sup>-3</sup>.

Although bromine and formyl groups are destabilizing, the effect is not so strong as that of a nitro group. This fact is reflected in the coupling reaction between bromoMCP **7b** and formylMCP **7c** with salt **3c**, in which the coupled products **8b** and **8c** were obtained in high yield (96 and 86%, respectively). As expected, the reaction of methylMCP **7d** having an electron-releasing group proceeded very smoothly to afford compound **8d** in 95% yield. This result encouraged us to introduce a strong electron-releasing group into position 13 of the MCP **2c** in order to enhance its reactivity. Thus, the diazo couplings of aminoMCP **9b** and acetamidoMCP **9c** with salts **3a-c** were carried out (Scheme 3). However, a complex mixture was obtained in every case, even with the weakest salt **3a**. Although attack of diazonium salts on both aromatic rings in compound **9b** is possible, it is not clear at present why the complex mixture is formed. Therefore, the effect of an electron-releasing group on the reactivity of MCPs toward diazonium salts could not be determined. Nevertheless, the results obtained here strongly suggest the existence of through-space interaction in the [2.2]MCP skeleton with transfer of  $\pi$ -electron density between the two aromatic rings.



**Spectra.**—Although we have reported a number of unique reactions of MCPs,<sup>5b-d,6,7</sup> it is very hard to estimate them systematically or quantitatively. It is expected, however, that a change of  $\pi$ -electron density in the aromatic ring would affect the absorption spectra of the azobenzene component. Thus, UV spectra of the coupled products were measured in benzene (Table 2). Although the azochromophore **6a** shows an absorption peak at 390 nm, it is shifted to 440 nm in the corresponding MCP **4b**. This red shift ( $\Delta\lambda$  50 nm) was also observed in the spectra of analogues **4c** and **6d** (33 nm).



**Fig. 1** Plots of  $\lambda_{\max}$  of azoMCPs against Hammett  $\sigma_p$ : **4d**; **8a** ( $R^1 = \text{NO}_2$ ); **8b** ( $R^1 = \text{Br}$ ); **8c** ( $R^1 = \text{CHO}$ ); **8d** ( $R^1 = \text{Me}$ ).

Similarly, a bathochromic shift (42 nm) was observed between azochromophores in compounds **4d** and **6c**. These shifts can probably be ascribed to the effect of the cyclophane skeleton working as an electron-releasing group upon the azochromophore. Focusing on the outer (C-13) substituent  $R^1$ , methylMCP **8d** shows an absorption peak at 426 nm which is 8 nm red shifted from that of compound **4d**. On the other hand blue shifts were observed in the spectra of nitroMCP **8a**, bromoMCP **8b**, and formylMCP **8c**, when compared with **4d**. The  $\lambda_{\max}$ -values of MCPs **4d**, **8a**, **8b**, **8c** and **8d**, including the compounds with the most electron-withdrawing groups, are bathochromically shifted from that of compound **6c**. Considering the nature of these substituents, it is obvious that the methyl group assists in the electron-releasing effect of the MCP skeleton. The electron-withdrawing substituents (nitro, bromo, and formyl groups) compensate for this effect. In other words this should be viewed as an enhancement, *via* through-space interaction, of the second MCP aromatic ring rather than as a reduction. The Hammett constants of substituents<sup>8</sup> are widely used to express the electronic effects of the substituent. Thus, when  $v_{\max}$ (cm<sup>-1</sup>)-values for the azoMCPs are plotted against  $\sigma_p$ , a straight line results as shown in Fig. 1. Unfortunately, preparation of azo[2.2]MCPs bearing substituents with large negative  $\sigma_p$ -values has not yet been successful. This result strongly suggests that electronic effects of the substituents on the aromatic ring are probably transferred to the other ring *via* through-space interactions.

**Conclusions.**—The results obtained in this study reveal that in [2.2]MCPs the reactivity of one aromatic ring is enhanced and the other is reduced toward coupling with diazonium salts, which results from through-space interaction between the two aromatic rings. We also conclude that a substituent on one aromatic ring in [2.2]MCPs can regulate the reactivity of the other aromatic ring. Such a through-space interaction was evaluated by comparison of the absorption spectra of azobenzene derivatives. A straight line is obtained for a plot of

the Hammett constant ( $\sigma_p$ ) of the substituent on one aromatic ring and  $\lambda_{\max}$  of the azobenzene moiety of the other side. This result indicates that electronic effects of the outer (C-13) substituents are transmitted to the 5-position *via* a through-space interaction. Furthermore, it should be noted that the electronic excitation involved may well be of the charge-transfer type, placing a + charge in the MCP ring bearing the substituent. This would explain the Hammett correlation (Fig. 1) and also agree with the reactivity data from the azo coupling reactions where a + charge is transferred in part to the second MCP aromatic ring during the course of this electrophilic substitution reaction.

## Experimental

**General.**—All m.p.s were measured on a Yanagimoto micro melting apparatus and are uncorrected.  $^1\text{H}$  NMR spectra were recorded on a Nippon Denshi GSX-270 spectrometer for solutions in  $\text{CDCl}_3$  unless otherwise stated, with  $\text{Me}_4\text{Si}$  as internal reference.  $J$ -Values are given in Hz. IR spectra were measured on a Nippon Bunko JASCO IR-700 spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-01-SG2 spectrometer at 75 eV using a direct-inlet system. Column chromatography was carried out on silica gel (Wako gel, C-300). The amounts of silica gel used were 5–100 g.

**Nitration of Compound 2b with  $\text{Cu}(\text{NO}_3)_2$ .**—To a solution of compound **2b** (100 mg, 0.37 mmol) in acetic anhydride ( $25\text{ cm}^3$ ) was added  $\text{Cu}(\text{NO}_3)_2$  (100 mg, 0.48 mmol). After the reaction mixture had been stirred at room temperature for 30 min, it was poured into water and extracted with methylene dichloride. The extract was washed with water, dried ( $\text{MgSO}_4$ ), and evaporated to leave a residue, which was chromatographed with hexane–benzene (1 : 1) as eluent and recrystallized to afford *nitro compound 7a* (49 mg, 42%) as yellow prisms, m.p. 196–199 °C (from benzene) (Found: C, 68.7; H, 6.3; N, 4.3;  $\text{M}^+$ , 313.  $\text{C}_{18}\text{H}_{19}\text{NO}_4$  requires C, 68.98; H, 6.12; N, 4.47%;  $\text{M}$ , 313);  $\nu_{\max}/\text{cm}^{-1}$  2930, 1582, 1505, 1463, 1421, 1341, 1263, 1206, 1089, 1014, 907 and 778;  $\delta_{\text{H}}$  2.55–2.90 (8 H, m), 2.93 (3 H, s), 3.04 (3 H, s), 6.85–7.15 (3 H, m) and 7.99 (2 H, m).

**Formylation of Compound 2b with  $\text{Cl}_2\text{HCOMe}$ .**—To a solution of compound **2b** (50 mg, 0.19 mmol) and dichloromethyl methyl ether (50 mg, 0.38 mmol) in methylene dichloride ( $30\text{ cm}^3$ ) at 0 °C was added dropwise  $\text{TiCl}_4$  (80 mg, 0.38 mmol). The reaction mixture was stirred at 0 °C for 15 min and poured into water, then extracted with methylene dichloride. After the extract had been washed with water, dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure, the resultant residue was chromatographed with benzene as eluent. Recrystallization gave *compound 7c* (25 mg, 44%) as prisms, m.p. 164–166 °C (from hexane) (Found: C, 76.8; H, 6.85;  $\text{M}^+$ , 296.  $\text{C}_{19}\text{H}_{20}\text{O}_3$  requires C, 76.99; H, 6.81%;  $\text{M}$ , 296);  $\nu_{\max}/\text{cm}^{-1}$  2930, 1681, 1589, 1421, 1118, 1011, 780 and 680;  $\delta_{\text{H}}$  2.50–2.90 (8 H, m), 2.89 (3 H, s), 3.30 (3 H, s), 6.85–7.10 (3 H, m), 7.62 (2 H, s) and 9.88 (1 H, s).

**Reduction of Aldehyde 7c with  $\text{AlCl}_3$ – $\text{LiAlH}_4$ .**—To a solution of aldehyde **7c** (100 mg, 0.34 mmol) in THF ( $15\text{ cm}^3$ ) was added a suspension of  $\text{LiAlH}_4$  (190 mg, 5 mmol) and  $\text{AlCl}_3$  (670 mg, 5 mmol) in THF ( $5\text{ cm}^3$ ). After the reaction mixture had been refluxed for 1 h, it was poured into water and extracted with methylene dichloride. The extract was washed with water, dried ( $\text{MgSO}_4$ ) and evaporated to leave a residue, which was chromatographed with benzene as eluent and recrystallized to give *compound 7d* (52 mg, 54%) as prisms, m.p. 146–149 °C (from MeOH) (Found: C, 80.5; H, 7.8;  $\text{M}^+$  282.  $\text{C}_{19}\text{H}_{22}\text{O}_2$  requires C, 80.80; H, 7.86%;  $\text{M}$ , 282);  $\nu_{\max}/\text{cm}^{-1}$  2926, 1472,

1247, 1208, 1125, 1073, 1020 and 755;  $\delta_{\text{H}}$  2.27 (3 H, s), 2.50–2.80 (8 H, m), 2.91 (3 H, s), 2.94 (3 H, s), 6.80–7.05 (3 H, m) and 7.36 (2 H, s).

**Bromination of Compound 2b with  $\text{Br}_2$ .**—To a solution of compound **2b** (30 mg, 0.11 mmol) in  $\text{CCl}_4$  ( $25\text{ cm}^3$ ) was added a solution of  $\text{Br}_2$  (9 mg, 0.06 mmol) in  $\text{CCl}_4$  ( $9\text{ cm}^3$ ). After the reaction mixture had been stirred at room temperature for 15 min, it was concentrated under reduced pressure to leave the residue, which was chromatographed with hexane as eluent. Recrystallization afforded bromide **7b** (20 mg, 53%) as prisms, m.p. 145–150 °C (from hexane) (Found:  $\text{M}^+$ , 347.  $\text{C}_{18}\text{H}_{19}\text{BrO}_2$  requires  $\text{M}$ , 347);  $\nu_{\max}/\text{cm}^{-1}$  2930, 1460, 1419, 1203, 1019, 880 and 765;  $\delta_{\text{H}}$  2.50–2.80 (8 H, m), 2.91 (3 H, s), 2.99 (3 H, s), 6.80–7.10 (3 H, m) and 7.17 (2 H, s). Elemental analysis gave unsatisfactory results.

**Diazo Coupling.**—*Typical procedure: Preparation of compound 4a.* To a solution of compound **2a** (100 mg, 0.34 mmol) in acetic acid ( $50\text{ cm}^3$ ) was added the diazonium salt **6a** (260 mg, 1.7 mmol) prepared from aniline and isopentyl nitrite with conc. HCl in EtOH. After the reaction mixture had been stirred at room temperature for 2 h it was poured into water and extracted with methylene dichloride. The extract was washed with water, dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. After purification by chromatography with benzene–hexane (1 : 1) as eluent, the resultant residue was recrystallized to yield *compound 4a* (35 mg, 30%) as orange prisms, m.p. 104–106 °C (from hexane) (Found: C, 77.05; H, 5.9; N, 8.2;  $\text{M}^+$ , 344.  $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2$  requires C, 76.71; H, 5.86; N, 8.14%;  $\text{M}$ , 344);  $\nu_{\max}/\text{cm}^{-1}$  2930, 1600, 1534, 1478, 1256, 886, 745 and 692;  $\delta_{\text{H}}$  1.40–1.70 (1 H, br s, exchanged by  $\text{D}_2\text{O}$ ), 2.70–3.10 (8 H, m), 3.30 (1 H, s, exchanged by  $\text{D}_2\text{O}$ ), 6.90–7.00 (1 H, m), 7.12–7.15 (2 H, m), 7.40–7.55 (3 H, m), 7.71 (2 H, s) and 7.84–7.90 (2 H, m).

Similarly prepared were the following azobenzenes.

**Compound 4b** (90%); red prisms, m.p. > 300 °C (from THF) (Found: C, 65.7; H, 4.95; N, 10.6;  $\text{M}^+$ , 389.  $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_4 \cdot 0.6\text{H}_2\text{O}$  requires C, 66.01; H, 4.95; N, 10.59%;  $\text{M}$ , 389);  $\nu_{\max}/\text{cm}^{-1}$  2926, 1588, 1545, 1495, 1477, 1330, 1270, 1107, 999 and 648;  $\delta_{\text{H}}$  ( $[\text{}^2\text{H}_5\text{]pyridine}$ ) 3.00–3.60 (8 H, m), 7.00–7.20 (3 H, m), 7.15 (2 H, s), 7.60 (2 H, d,  $J$  9.53), 8.30 (2 H, d,  $J$  9.53), 8.60 (1 H, s) and 9.60 (1 H, s).

**Compound 4c** (95%); orange prisms, m.p. 222.5–225.5 °C (from hexane) (Found: C, 69.3; H, 5.6; N, 10.1;  $\text{M}^+$ , 417.  $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_4$  requires C, 69.04; H, 5.56; N, 10.06%;  $\text{M}$ , 417);  $\nu_{\max}/\text{cm}^{-1}$  2934, 1588, 1520, 1465, 1418, 1347, 1272, 1105, 1017 and 754;  $\delta_{\text{H}}$  2.60–2.90 (8 H, m), 2.96 (3 H, s), 3.05 (3 H, s), 6.85–7.10 (3 H, m), 7.74 (2 H, s), 8.00 (2 H, d,  $J$  9) and 8.38 (2 H, d,  $J$  9).

**Compound 4d** (89%); orange prisms, m.p. 198.5–202 °C (from hexane) (Found: C, 62.6; H, 5.0; N, 12.25;  $\text{M}^+$ , 462.  $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_6$  requires C, 62.32; H, 4.80; N, 12.12%;  $\text{M}$ , 462);  $\nu_{\max}/\text{cm}^{-1}$  2930, 1534, 1400, 1348, 1275, 1108 and 710;  $\delta_{\text{H}}$  2.60–2.90 (8 H, m), 2.97 (3 H, s), 3.08 (3 H, s), 6.85–7.15 (3 H, m), 7.72 (2 H, s), 7.90 (1 H, d,  $J$  8.8), 8.52 (1 H, dd,  $J$  2.2 and 8.8) and 8.77 (1 H, d,  $J$  2.2).

**Compound 4e** (15%); orange prisms, m.p. 281–284 °C (from MeOH) (Found: C, 66.8; H, 5.15; N, 12.7;  $\text{M}^+$ , 430.  $\text{C}_{24}\text{H}_{22}\text{N}_4\text{O}_4$  requires C, 66.95; H, 5.15; N, 13.02%;  $\text{M}$ , 430);  $\nu_{\max}/\text{cm}^{-1}$  2930, 1532, 1398, 1351, 1270, 1107 and 718;  $\delta_{\text{H}}$  0.70 (3 H, s), 0.72 (3 H, s), 2.80–3.20 (8 H, m), 6.80–7.20 (3 H, m), 7.75 (2 H, s), 7.90 (1 H, d,  $J$  8.8), 8.53 (1 H, dd,  $J$  2.2 and 8.8) and 8.77 (1 H, d,  $J$  2.2).

**Compound 8a** (8%); red prisms, m.p. 150–155 °C (from benzene) (Found: C, 56.7; H, 4.2; N, 13.8;  $\text{M}^+$ , 507.  $\text{C}_{24}\text{H}_{21}\text{N}_5\text{O}_8$  requires C, 56.79; H, 4.17; N, 13.81%;  $\text{M}$ , 507);  $\nu_{\max}/\text{cm}^{-1}$  2934, 1535, 1468, 1419, 1343, 1264, 1108 and 1012;  $\delta_{\text{H}}$  2.60–3.10 (8 H, m), 3.07 (3 H, s), 3.09 (3 H, s), 7.75 (2 H, s),

8.03 (2 H, s), 7.89 (1 H, d,  $J$  8.8), 8.55 (1 H, dd,  $J$  2.5 and 8.8) and 8.80 (1 H, d,  $J$  2.5).

**Compound 8b** (96%); red prisms, m.p. 174–179 °C [from benzene–hexane (1:1)] (Found: C, 53.1; H, 3.9; N, 10.3;  $M^+$ , 539.  $C_{24}H_{21}BrN_4O_6$  requires C, 53.33; H, 3.92; N, 10.37%;  $M$ , 539);  $\nu_{max}/cm^{-1}$  2930, 1530, 1346, 1277, 1109, 1009 and 665;  $\delta_H$  2.60–3.00 (8 H, m), 3.00 (3 H, s), 3.15 (3 H, s), 7.21 (2 H, s), 7.71 (2 H, s), 7.89 (1 H, d,  $J$  9.2), 8.50 (1 H, dd,  $J$  1.8 and 9.2) and 8.77 (1 H, d,  $J$  1.8).

**Compound 8c** (86%); red prisms, m.p. 232–235 °C [from benzene–hexane (1:1)] (Found: C, 61.3; H, 4.55; N, 11.3;  $M^+$ , 490.  $C_{25}H_{22}N_4O_7$  requires C, 61.21; H, 4.52; N, 11.43%;  $M$ , 490);  $\nu_{max}/cm^{-1}$  2930, 1690, 1528, 1347, 1273 and 1124;  $\delta_H$  2.60–3.00 (8 H, m), 3.03 (3 H, s), 3.07 (3 H, s), 7.66 (2 H, s), 7.74 (2 H, s), 7.87 (1 H, d,  $J$  8.8), 8.51 (1 H, dd,  $J$  2.6 and 8.8), 8.79 (1 H, d,  $J$  2.6) and 9.92 (1 H, s).

**Compound 8d** (95%); red prisms, m.p. 197–199 °C [from benzene–hexane (1:1)] (Found: C, 63.3; H, 5.1; N, 11.5;  $M^+$ , 476.  $C_{25}H_{24}N_4O_6$  requires C, 63.00; H, 5.08; N, 11.76%;  $M$ , 476);  $\nu_{max}/cm^{-1}$  2928, 1531, 1399, 1347, 1276 and 1111;  $\delta_H$  2.30 (3 H, s), 2.65–2.95 (8 H, m), 2.95 (3 H, s), 3.10 (3 H, s), 6.89 (2 H, s), 7.71 (2 H, s), 7.88 (1 H, d,  $J$  8.8), 8.50 (1 H, dd,  $J$  2.2 and 8.8) and 8.76 (1 H, d,  $J$  2.2).

**Compound 6a** (85%); orange prisms, m.p. 176–181 °C (from EtOH) (Found: C, 61.8; H, 5.0; N, 15.5;  $M^+$ , 271.  $C_{14}H_{13}N_3O_3$  requires C, 61.97; H, 4.83; N, 15.50%;  $M$ , 271);  $\nu_{max}/cm^{-1}$  1591, 1512, 1340, 1245, 1184, 1119 and 1103;  $\delta_H$  2.34 (6 H, s), 5.15 (1 H, s, exchanged by  $D_2O$ ), 7.62 (2 H, s), 7.90 (2 H, d,  $J$  6.0) and 8.28 (2 H, d,  $J$  6.0).

**Compound 6b** (92%); orange prisms, m.p. 213–217 °C (from  $CHCl_3$ ) (Found: C, 53.3; H, 3.9; N, 17.45;  $M^+$ , 316.  $C_{14}H_{12}N_4O_5$  requires C, 53.15; H, 3.83; N, 17.72%;  $M$ , 316);  $\nu_{max}/cm^{-1}$  1618, 1428, 1348, 1151, 1103, 1023, 921, 835 and 741;  $\delta_H$  2.09–2.19 (6 H, m), 7.10–7.30 (2 H, m), 8.18 (1 H, d,  $J$  9.5), 8.43 (1 H, dd,  $J$  2.6 and 9.5), 9.18 (1 H, d,  $J$  2.6) and 12.04 (1 H, s, exchanged by  $D_2O$ ).

**Preparation of Compound 6d.**—To a suspension of NaH (24 mg, 1 mmol) in THF (20  $cm^3$ ) was added a solution of compound 6a (200 mg, 0.73 mmol) in THF (15  $cm^3$ ) under  $N_2$  at room temperature. After the suspension had been stirred for 1.5 h, methyl iodide (0.12 g, 0.85 mmol) was added. The reaction mixture was then stirred for an additional 2 h before being poured into water and extracted with chloroform. The extract was washed with water, dried ( $MgSO_4$ ), and evaporated to leave a residue, which on chromatography with benzene–hexane (1:1) as eluent gave compound 6d (0.17 g, 80%) as orange needles, m.p. 117.5–119.5 °C (from hexane) (Found: C, 63.2; H, 5.45; N, 14.6;  $M^+$ , 285.  $C_{15}H_{15}N_3O_3$  requires C, 63.13; H, 5.30; N, 14.73%;  $M$ , 285);  $\nu_{max}/cm^{-1}$  2975, 1620, 1590,

1530, 1345, 1230, 1120, 1000, 860 and 680;  $\delta_H$  2.40 (6 H, s), 3.80 (3 H, s), 7.68 (2 H, s), 7.99 (2 H, d,  $J$  4.8) and 8.37 (2 H, d,  $J$  4.8).

**Preparation of Compound 4f.**—After a solution of 9b (100 mg, 0.4 mmol) and nitrosobenzene (43 mg, 0.4 mmol) in acetic acid (25  $cm^3$ ) had been stirred under  $N_2$  for 48 h, it was poured into water and extracted with benzene. The extract was washed with water, dried ( $MgSO_4$ ), and evaporated to leave a residue, which was chromatographed with benzene as eluent, followed by recrystallization to afford compound 4f (20 mg, 15%) as orange prisms, m.p. 169–171 °C (from MeOH) (Found: C, 84.9; H, 7.1; N, 8.4;  $M^+$ , 340.  $C_{24}H_{24}N_2$  requires C, 84.66; H, 7.11; N, 8.23%;  $M$ , 340);  $\nu_{max}/cm^{-1}$  2930, 1583, 1468, 1451, 1263, 1182, 1103, 766, 720 and 688;  $\delta_H$  0.67 (3 H, s), 0.74 (3 H, s), 2.70–3.20 (8 H, m), 6.80–7.20 (3 H, m), 7.75 (2 H, s) and 7.40–7.90 (5 H, m).

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