# $^{13}C$ Chemical Shifts of Symmetrically Substituted Biphenyls: Unambiguous Signal Assignment for the Carbons *ortho* and *para* to an Aryl Group

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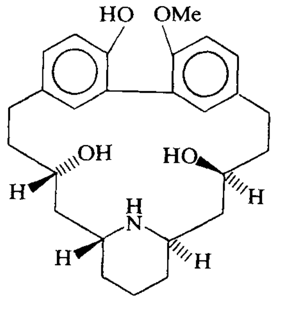
**The natural abundance $^{13}C$ NMR spectra of 2,2′-dimethyl-, 2,2′-dimethoxy- and 2,2′-dihydroxybiphenyls, and a series of 2,2′-dimethoxy-5,5′-disubstituted biphenyls were recorded. Unambiguous signal assignments of the carbons *ortho* and *para* to an aryl ring in biphenyls were made by selective deuteration and/or the graphical method for $^1H$ single frequency off-resonance decoupled spectra. Contrary to the reported assignments, it was shown that the signal for C-6 in 2,2′-dimethylbiphenyl clearly appears at lower field than that for C-4. The signals for the *ortho* carbons (C-6) of 2,2′-dimethoxy-5,5′-disubstituted biphenyls generally appeared at lower fields than those for the *para* carbons (C-4). The validity of applying deuterium isotope shifts to the assignments of $^{13}C$ chemical shifts of di- and tetra-substituted biphenyls is also discussed.**

## INTRODUCTION

Over 40 alkaloids have been isolated from the plants of Lythraceae.[1] Among them the type A alkaloids,[2] represented by lythranidine (**1**), have an unique skeleton which is regarded as a heterophane[3] of the *meta,meta*-biphenylene type. Since unambiguous $^{13}C$ NMR signal assignments of **1** and its derivatives have not yet been made, we intended to assign all the carbon signals in the type A alkaloids and their derivatives. The signals in the aromatic region were easily assigned by the standard substituent chemical shift values for substituted benzenes and $^1H$ single frequency off-resonance decoupling (SFORD), except for C-4, C-4′, C-6 and C-6′. The signal assignments for the latter carbons based on chemical shift data are unreliable, because they are located *ortho* to the alkyl side chain and *meta* to the oxygen function; moreover, the reported difference in the chemical shifts between C-2 and C-4 in biphenyl itself is extremely small (0–0.1 ppm in $CS_2$,[4,5] 0.3 ppm in tetrahydrofuran[6] and 0.4 ppm in acetone).[7]



Lythranidine (**1**)

As summarized in Table 1 (entries 1–21), detailed studies[7,8] on *para* substituted biphenyls **2** have shown that C-4′ resonates at lower field than C-2′ by 0.48–1.59 ppm when R is an electron withdrawing group and by 0.07–0.40 ppm when R is an electron donating group with one exception (entry 17). The signals due to the *para* carbons in the *meta* substituted biphenyls **3** (see entries 22–27, Table 1)[6,8,9] and *ortho* substituted biphenyls **4** (see entries 28–32)[6,10] have also been reported to appear at fields lower than those of *ortho* carbons, although two exceptions (entries 24 and 26) do exist. All the reported data suggested that in the biphenyls the *para* carbon signals tend to appear at lower fields than those of the *ortho* carbons. The difference in the chemical shifts between the *ortho* and the *para* carbons is, however, generally small, and there have been no reports on the $^{13}C$ chemical shifts of 2,2′,5,5′-tetra-substituted biphenyls.

Hence, more detailed studies on appropriate model compounds are necessary for the signal assignments of the *ortho* and the *para* carbons of the biphenyl moiety in the type A alkaloids of Lythraceae. In this paper, we describe the unambiguous signal assignment of the carbons *ortho* and *para* to the aryl group in 2,2′-disubstituted and 2,2′,5,5′-tetra-substituted biphenyls, which constitutes a preliminary fundamental $^{13}C$ NMR spectral investigation of the type A alkaloids.

## RESULTS AND DISCUSSION

### 2,2′-Disubstituted biphenyls

The reported $^{13}C$ signal assignments summarized in Table 1 (entries 28–32) indicate that the *para* carbons

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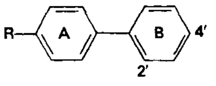
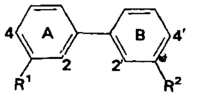
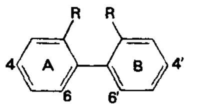
**Table 1. Comparison of the chemical shifts of *ortho* and *para* carbons in biphenyl derivatives**

| Entry | | Lower field | Higher field | Δδ[a](ppm) | Solvent | Literature |
|---|---|---|---|---|---|---|
|  2 | | | | | | |
| 1 | R = $CH_3$ | C-4′ | C-2′ | +0.25 | Acetone | 7 |
| 2 | $CH_3$ | C-4′ | C-2′ | +0.22 | Acetone-$d_6$ | 8 |
| 3 | F | C-4′ | C-2′ | +0.48 | Acetone | 7 |
| 4 | Cl | C-4′ | C-2′ | +0.88 | Acetone | 7 |
| 5 | Br | C-4′ | C-2′ | +0.97 | Acetone | 7 |
| 6 | I | C-4′ | C-2′ | +1.09 | Acetone | 7 |
| 7 | OH | C-4′ | C-2′ | +0.07 | Acetone | 7 |
| 8 | $OCH_3$ | C-4′ | C-2′ | +0.17 | Acetone | 7 |
| 9 | CN | C-4′ | C-2′ | +1.51 | Acetone | 7 |
| 10 | $NO_2$ | C-4′ | C-2′ | +1.59 | Acetone | 7 |
| 11 | COOH | C-4′ | C-2′ | +1.27 | AcOH | 7 |
| 12 | $COOCH_3$ | C-4′ | C-2′ | +1.28 | Acetone | 7 |
| 13 | $COCH_3$ | C-4′ | C-2′ | +1.12 | Acetone | 7 |
| 14 | $NH_2$ | C-2′, C-4′[b] | | ±0 | Acetone | 7 |
| 15 | $NH_2$ | C-2′, C-4′[b] | | ±0[c] | $CH_3OH$ | 8 |
| 16 | $NH_2$ | C-4′ | C-2′ | ~+0.2[c] | $CH_3CN$ | 8 |
| 17 | $NH_2$ | C-2′ | C-4′ | ~−0.4[c] | $Cl_2C{=}CCl_2$ | 8 |
| 18 | $\overset{+}{N}H_3\cdot CF_3COO^-$ | C-4′ | C-2′ | ~+0.8[c] | DMF | 8 |
| 19 | $\overset{+}{N}H_3\cdot CF_3COO^-$ | C-4′ | C-2′ | ~+0.8[c] | $CH_3OH$ | 8 |
| 20 | $\overset{+}{N}H_3\cdot CF_3COO^-$ | C-4′ | C-2′ | ~+1.0[c] | $CF_3COOH$ | 8 |
| 21 | $\overset{+}{N}H_3\cdot CH_3COO^-$ | C-4′ | C-2′ | ~+0.8[c] | $CH_3COOH$ | 8 |
|  3 | | | | | | |
| 22 | $R^1 = R^2 = CH_3$ | C-2′, C-4′[b] | | ±0 | THF | 6 |
| 23 | $R^1 = Br, R^2 = H$ | C-4′ | C-2′ | ~+0.8[c] | Cyclohexane-$d_{12}$ | 9 |
| | | C-2, C-4[b] | | ±0[c] | Cyclohexane-$d_{12}$ | 9 |
| 24 | $R^1 = Br, R^2 = H$ | C-4′ | C-2′ | ~+1.2[c] | DMSO-$d_6$ | 9 |
| | | C-2 | C-4 | ~−0.6[c,d] | DMSO-$d_6$ | 9 |
| 25 | $R^1 = NO_2, R^2 = H$ | C-4′ | C-2′ | +1.5 | e | 9 |
| | | C-4 | C-2 | +0.8[d] | e | 9 |
| 26 | $R^1 = NH_2, R^2 = H$ | C-2′ | C-4′ | −0.07 | $Cl_2C{=}CCl_2$ | 8 |
| | | C-4 | C-2 | +0.28[d] | $Cl_2C{=}CCl_2$ | 8 |
| 27 | $R^1 = NH_2, R^2 = H$ | C-4′ | C-2′ | +0.16 | $CH_3OH$ | 8 |
| | | C-4 | C-2 | +0.49 | $CH_3OH$ | 8 |
|  4 | | | | | | |
| 28 | R = $CH_3$ | C-4(4′) | C-6(6′) | +2.1[f] | THF | 6 |
| 29 | $C_2H_5$ | C-4(4′) | C-6(6′) | +0.6[f] | THF | 6 |
| 30 | $i\text{-}C_3H_7$ | C-4(4′) | C-6(6′) | +2.1[f] | THF | 6 |
| 31 | $t\text{-}C_4H_9$ | C-4(4′) | C-6(6′) | +3.7[f] | THF | 6 |
| 32 | Cl | C-4(4′), C-6(6′)[b] | | ±0 | THF | 10 |

[a] δ *para*(C-4′) − δ *ortho*(C-2′).

[b] Overlapping signal.

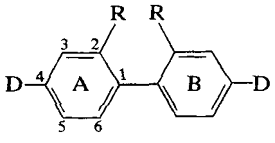
[c] Not precise, because the value was taken from the graphical display.

[d] δ *para*(C-4) − δ *ortho*(C-2).

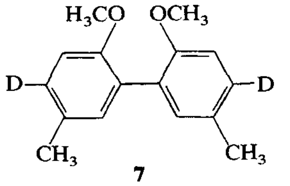
[e] Not specified.

[f] δ *para*(C-4′) − δ *ortho*(C-6′).

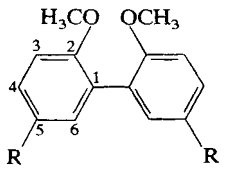
(C-4 and C-4′) resonate at lower magnetic fields than the *ortho* carbons (C-6 and C-6′). In our experiment (see Table 2), four peaks at $\delta$129.8, 127.0, 125.5 and 129.2 in **4**, $R = CH_3$, gave doublets in the SFORD spectrum. The signal at $\delta$125.5 was easily assigned to C-5 and C-5′ from the chemical shift. The assignments of the carbons of the second ring in symmetric biphenyls will be omitted in the following discussion. The assignment of the other three signals from the standard shielding values for substituted benzenes could lead to erroneous conclusions because they are very closely spaced. We investigated the $^{13}C$ spectrum of the *para* deuterio derivative **5**, $R = CH_3$, in order to assign these peaks unambiguously. Contrary to our expectation, the peak at $\delta$127.0 in **4**, $R = CH_3$, disappeared in **5**, $R = CH_3$; this fact clearly indicated that C-4 resonates at higher field than C-6 in **4**, $R = CH_3$.



**5**



**7**



**6** $R = CH_3$
**8** $R = CH_2OH$
**9** $R = C_2H_5$
**10** $R = CH(OH)—CH_3$
**11** $R = CH_2COOCH_3$
**12** $R = CH_2CH_2CH_2OH$

**13** $R = CH_2CH_2COOCH_3$
**14** $R = NH_2$
**15** $R = CHO$
**16** $R = COOCH_3$
**17** $R = COCH_3$
**18** $R = COC_2H_5$
**19** $R = NO_2$

The peak at 129.8 was assigned to C-3 by the deuterium-induced isotope shifts which will be discussed later. In conclusion, the reported assignment[6] that C-4 resonates at lower field than C-6 in **4**, $R = CH_3$, should be reversed. Inspection of the $^{13}C$ NMR spectrum of the *p*-deuteriobiphenyl **5**, $R = OCH_3$, revealed that in the case of the 2,2′-dimethoxybiphenyl **4**, $R = OCH_3$, the *ortho* carbon (C-6) signal again appeared at lower field ($\delta$131.4) than that of the *para* carbon C-4 ($\delta$128.5). Based upon these results, the downfield peak ($\delta$131.5) and the upfield peak ($\delta$129.6) in 2,2′-dihydroxybiphenyl (**4**, $R = OH$) were assigned to C-6 and C-4, respectively. We also suggest that the reported assignments[6] for the C-4 and C-6 signals in *ortho* substituted biphenyls **4** (entries 29–31 in Table 1), are, presumably, reversed.

It has been reported that the signals of carbons *ortho* to the carbon bearing the deuterium in monosubstituted benzenes are always shifted upfield though the extent is very small (~0.1 ppm).[11] Close inspection of the $^{13}C$ spectrum of **5**, $R = CH_3$, revealed that the C-3 ($\delta$ 129.6) and C-5 ($\delta$ 125.3) signals were obviously shifted upfield compared to the corresponding signals in the protio derivative **4**, $R = CH_3$. Similarly, the C-3 and C-5 signals in **5**, $R = OCH_3$, and **7** appeared at 0.1 ppm to higher field (0.1 ppm) than do those of the corresponding parent compounds **4**, $R = OCH_3$, and **6** (entries 3 and 4 in Table 2, and entries 1 and 2 in Table 3). Assignments of $^{13}C$ chemical shifts by deuterium isotope shifts should, therefore, be applicable to di- and tetrasubstituted biphenyls, as well as mono-substituted benzenes.

## 2,2′-Dimethoxy-5,5′-disubstituted biphenyls

The $^{13}C$ NMR spectra of the symmetrical biphenyls **6–19** were studied to see if any general trends could be discerned.

In the simplest model compound, **6**, all the peaks except those at $\delta$ 128.6 and 131.7 were easily assigned by the standard shielding values and the SFORD technique. The $^{13}C$ spectrum of the *para* deuterio derivative, **7**, was investigated to distinguish between these two peaks. The disappearance of the upfield signal at $\delta$128.6 in the spectrum of **7** suggested that the downfield signal at $\delta$131.7 should be assigned to C-6. This conclusion evidently contradicted the assumptions based on the reported data (Table 1) and, hence, the $^{13}C$ spectra of the analogues were studied further.

The $^{13}C$,$^{1}H$ coupling constant, $^{1}J(CH)$ and the residual coupling, ($J_R$) are approximately related according to the following relationship,[12]

$$\gamma B_2/2\pi = {}^{1}J(\mathrm{CH}) \cdot \Delta f/J_R$$

where $\gamma$ is the gyromagnetic ratio, $B_2$ is the strength of the applied field, and $\Delta f$ is the difference between the resonance frequency of the corresponding decoupled nuclei and the decoupling frequency. At constant power, $J_R$ should vary linearly with $\Delta f$. Thus, it is possible to assign closely spaced peaks by graphically plotting peak frequencies in the selectively $^{1}H$ decoupled $^{13}C$ spectra as a function of the position of

**Table 2. Carbon-13 chemical shifts of 2,2′-disubstituted biphenyls**[a]

| Entry | Compound | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | Others |
|---|---|---|---|---|---|---|---|---|
| | | | | Chemical shift[b] | | | | |
| 1 | **4**, $R = CH_3$ | 141.5 | 135.6 | 129.8 | 127.0 | 125.5 | 129.2 | 19.8 ($-CH_3$) |
| 2 | **5**, $R = CH_3$ | 141.5 | 135.7 | 129.6 | — | 125.3 | 129.2 | 19.8 ($-CH_3$) |
| 3 | **4**, $R = OCH_3$ | 127.9 | 157.0 | 111.1 | 128.5 | 120.3 | 131.4 | 55.7 ($-OCH_3$) |
| 4 | **5**, $R = OCH_3$ | 127.9 | 157.0 | 111.0 | — | 120.2 | 131.4 | 55.7 ($-OCH_3$) |
| 5 | **4**, $R = OH$ | 124.5 | 152.5 | 116.7 | 129.6 | 121.6 | 131.5 | |

[a] 20% in $CDCl_3$ at 25 °C.
[b] $\delta_c$ (ppm downfield from internal TMS).

**Table 3. Carbon-13 chemical shifts of 2,2′-dimethoxy-5,5′-substituted biphenyls[a]**

| Entry | Compound | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | $-OCH_3$ | Others | Δδ[b](ppm) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **6** | 127.6 | 154.7 | 110.9 | 128.6[c] | 129.2 | 131.7[c] | 55.8 | $CH_3$<br>20.5 | 3.1 |
| 2 | **7** | 127.6 | 154.7 | 110.8 | — | 129.1 | 131.7 | 55.8 | $CH_3$<br>20.4 | |
| 3 | **8** | 127.5 | 156.4 | 110.9 | 127.5 | 132.6 | 130.2 | 55.7 | $-CH_2-OH$<br>65.0 | 2.7 |
| 4 | **9** | 127.9 | 155.2 | 111.1 | 127.5[c] | 135.9 | 130.9[c] | 55.8 | $-CH_2-CH_3$<br>27.9 15.7 | 3.4 |
| 5 | **10** | 127.6 | 156.2 | 111.0 | 125.6 | 137.7 | 128.8 | 55.7 | $-CHOH\cdot CH_3$<br>69.6 24.8 | 3.4 |
| 6 | **11** | 125.6 | 156.2 | 111.2 | 129.3[c] | 127.6 | 132.3[c] | 55.7 | $-CH_2-COOCH_3$<br>40.2 172.1 51.8 | 3.0 |
| 7 | **12** | 127.6 | 155.1 | 111.1 | 128.2[c] | 133.5 | 131.4[c] | 55.8 | $-CH_2-CH_2\cdot CH_2OH$<br>31.1 34.2 61.9 | 3.2 |
| 8 | **13** | 127.9 | 155.6 | 111.3 | 128.2[c] | 132.2 | 131.3[c] | 55.7 | $-CH_2\cdot CH_2\cdot COOCH_3$<br>30.2 35.9 173.2 51.4 | 3.1 |
| 9 | **14**[d] | 128.5 | 147.9 | 112.5 | 113.0[c] | 141.3 | 117.0[c] | 55.8 | | 4.0 |
| 10 | **15** | 127.2 | 162.0 | 111.0 | 131.9[c] | 129.6 | 132.8[c] | 56.0 | $-CHO$<br>190.6 | 0.9 |
| 11 | **16** | 126.5 | 160.4 | 110.1 | 130.9[c] | 122.0 | 132.6[c] | 55.6 | $-CO_2-CH_3$<br>166.3 51.6 | 1.7 |
| 12 | **17** | 126.9 | 161.0 | 110.4 | 130.3 | 130.0 | 131.9 | 55.9 | $-CO-CH_3$<br>196.6 26.3 | 1.6 |
| 13 | **18** | 126.8 | 160.7 | 110.4 | 129.8 | 129.8 | 131.6 | 55.8 | $-CO\cdot CH_2-CH_3$<br>199.3 31.5 8.5 | 1.8 |
| 14 | **19**[d] | 125.2 | 161.5 | 111.6 | 125.6[c] | 140.0 | 126.1[c] | 56.5 | | 0.5 |

[a] 20% in $CDCl_3$ at 25 °C unless otherwise stated.
[b] $\delta$(C-6) − $\delta$(C-4).
[c] Assigned by the graphical method.
[d] 20% in DMSO-$d_6$ at 25 °C.

irradiation in the $^1$H spectrum.[13] To evaluate the utility of this graphical method, it was applied to the biphenyl **6**, the assignment of which had been confirmed by selective deuteration.

The results in Fig. 1 clearly show that the biphenyl **6** exhibits its *ortho* carbon (C-6) signal at a field lower than that of the *para* carbon (C-4), and this should be applicable in assigning the $^{13}$C chemical shifts of the model biphenyls. Thus, the $^{13}$C chemical shifts of biphenyls **8–19** have been mainly determined by the graphical method. As shown in Table 3, C-6 is more deshielded than C-4 by 2.7–4.0 ppm when R is an electron donating group (entries 1–9) and by 0.5–1.8 ppm when R is an electron withdrawing group (entries 10–14).

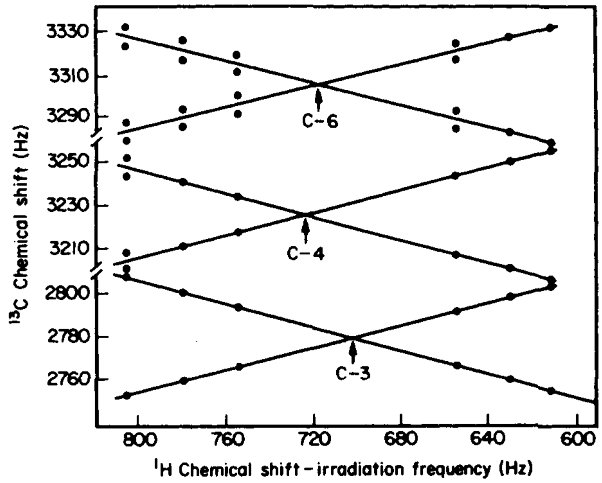


**Figure 1.** Plot of peak frequencies in the $^1$H off-resonance selectively decoupled $^{13}$C spectra of biphenyl **6** as a function of the position of irradiation in the $^1$H spectrum, expressed in Hz downfield from internal TMS. The arrows indicate the point of collapse of the $^{13}$C doublet or quartet and the connection between a given $^{13}$C peak and the assigned proton peak [H-4: $\delta$ 7.05 (dd, $J \triangleq 8$ Hz, 3 Hz), H-6: $\delta$ 7.03 (d, $J = 3$ Hz), H-3: $\delta$ 6.84 (d, $J = 8$ Hz)]. Small doublet splittings are observed for some of the signals from long-range CH spin-coupling interaction.

## CONCLUSION

It has been shown that the signals due to *ortho* carbons (C-6) of 2,2′-dimethoxy-5,5′-di-substituted biphenyls generally appear at lower fields than those due to the *para* carbons (C-4). Much caution should be exercised in the assignment of the $^{13}$C chemical shifts of *ortho* and *para* carbons in the substituted biphenyl series, because the chemical shift differences of the aromatic ring carbons which are *ortho* and *para* to another ring are inherently small and may have a reversed sign depending on the substitution pattern of the aromatic rings.

## EXPERIMENTAL

Melting points were determined on a micro hot-stage and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a JEOL JNM-FX 100 spectrometer operating at 99.55 MHz and 25.05 MHz, respectively. General $^{13}$C NMR spectral and instrumental parameters used were: internal deuterium lock to solvent, spectral width 5000 or 6024 Hz, data points 8192, a flip angle of 45° and a pulse repetition time of 2.5 s. Chemical shifts are reported as $\delta$ (ppm downfield from internal tetramethylsilane). Mass spectra were determined on a JEOL JMS-01SG double focusing mass spectrometer.

### Compounds

Biphenyls **4**, R = $CH_3$,[14] **4**, R = $OCH_3$,[15] **6**,[16] **8**,[17] **11**,[18] **12**,[19] **13**,[19] **15**,[19] **16**,[20] **17**,[20] and **19**[21] are known compounds. Biphenyl **4**, R = OH, is commercially available.

### Synthesis of deuterated biphenyls

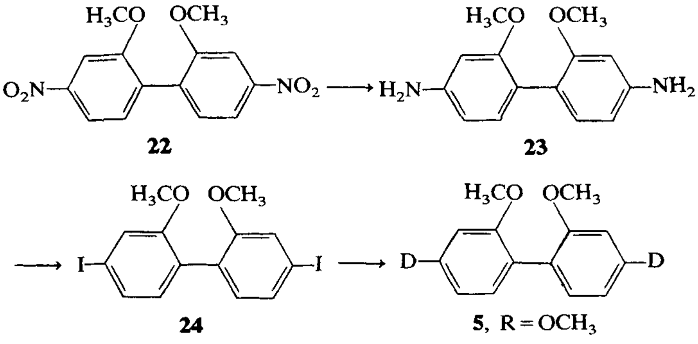
The deuterated biphenyls **5** and **7** were prepared by the regioselective exchange reaction of the corresponding iodide with $NaBD_4$ in the presence of 10% palladium on carbon.[22] The synthetic routes from known compounds are shown in Schemes 1, 2 and 3. The $^1H$ NMR data for the biphenyl intermediates are collected in Table 4.

### 4,4′-Diiodo-2,2′-dimethylbiphenyl (21)

To a solution of 2,2′-dimethyl-4,4′-diaminobiphenyl (**20**)[23] (150 mg) in 5% $H_2SO_4$ (20 ml) was added dropwise 3% $NaNO_2$ at 0° followed by addition of a 10% aqueous solution of urea to decompose the excess $NaNO_2$. After addition of a 20% aqueous solution of KI (5 ml) the mixture was heated at 70 °C for 15 min and extracted with methylene chloride. The organic layer was washed with aqueous sodium thiosulphate, dried, and evaporated to afford the crude material. Recrystallization from $CH_3OH$ gave **21** (192 mg), m.p. 62–63 °C. Anal: calc. for $C_{14}H_{12}I_2$: C% 38.71, H% 2.76. Found: C% 39.01; H% 2.92.

### 4,4′-Dideuterio-2,2′-dimethylbiphenyl (5, R = $CH_3$).

To a mixture of **21** (131 mg) and 10% palladium on carbon in $D_2O$ (2 ml), $CH_3OD$ (3 ml), 40% aqueous NaOD (0.5 ml) and a few drops of tetrahydrofuran was added $NaBD_4$ (100 mg) and the mixture stirred vigorously at 40 °C for 30 min. Excess $NaBD_4$ was decomposed with 10% HCl and palladium on carbon was removed by filtration. Extractive work-up with ether gave **5**, R = $CH_3$ (50 mg). Incorporation of deuterium was determined to be 93.5% by mass spectrometry.[24]



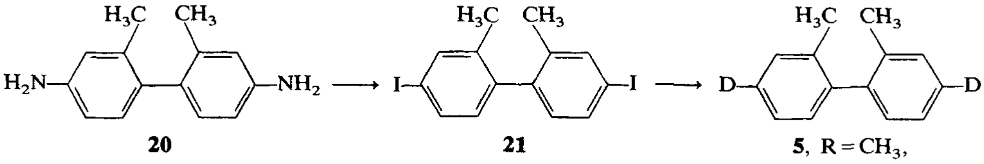
**Scheme 2**

### 4,4′-Diamino-2,2′-dimethoxybiphenyl (23)

To a solution of **22**[25] (207 mg) in $CH_3OH$ (50 ml) and hydrazine hydrate (2 ml) was added Raney-nickel and

**Table 4. $^1H$ chemical shifts for biphenyls in $CDCl_3$**

| Compound | Chemical shift: δ (multiplicity, *J*) | | | |
|---|---|---|---|---|
| | H-3,3′ | H-5,5′ | H-6,6′ | Others |
| **5**, R = $CH_3$, | 7.22 (d, 2.5) | 7.20 (dd, 8, 2.5) | 7.07 (d,8) | 2.25 (s, $CH_3$) |
| **5**, R = $OCH_3$ | 6.97 ~ 7.00 (m) | | 7.24 (d, 8) | 3.77 (s, $OCH_3$) |
| **7** | 6.84 (s) | —— | 7.02 (s) | 2.31 (s, $CH_3$)<br>3.73 (s, $OCH_3$) |
| **21** | 7.56 (d, 3) | 7.48 (dd, 12, 3) | 6.72 (d, 12) | 1.98 (s, $CH_3$) |
| **23** | 6.28 ~ 6.38 (m) | | 6.98 (d, 8) | 3.66 (br. s, $NH_2$)<br>3.70 (s, $OCH_3$) |
| **24** | 7.27 (d, 2) | 7.30 (dd, 8, 2) | 6.86 (d, 8) | 3.73 (s, $OCH_3$) |
| **30** | 7.56 (s) | —— | 7.13 (s) | 2.56 (s, $CH_3$)<br>3.83 (s, $OCH_3$) |
| **31** | 6.20 (s) | —— | 6.87 (s) | 2.10 (s, $CH_3$)<br>3.60 (br. s, $NH_2$)<br>3.69 (s, $OCH_3$) |
| **32** | 7.02 (s) | —— | 7.35 (s) | 2.38 (s, $CH_3$)<br>3.75 (s, $OCH_3$) |



**Scheme 1**

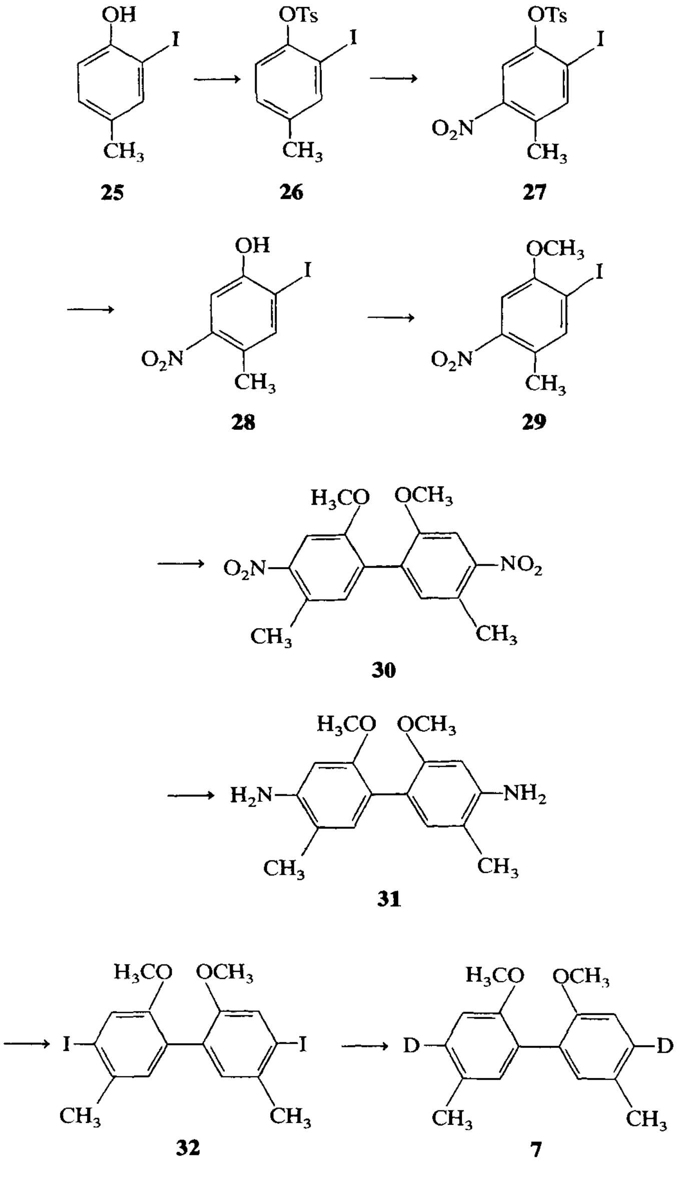
the mixture was refluxed for 15 min. Filtration and removal of the solvent afforded a white crystalline residue which was recrystallized from $CH_3OH$ to give **23** (157 mg), m.p. 159–160 °C. Anal.: calc. for $C_{14}H_{16}O_2N_2$: C% 68.85; H% 6.56; N% 11.47. Found: C% 68.61; H% 6.65; N% 11.26.

### 4,4′-Diiodo-2,2′-dimethoxybiphenyl (24)

Dimethoxydiaminobiphenyl **23** afforded **24**, (m.p. 85–86 °C from $CH_3OH$-methylene chloride) in 83.5% yield through the same procedure used in the conversion of **20** into **21**. Anal.: calc. for $C_{14}H_{12}O_2I_2$: C% 36.05; H% 2.57. Found: C% 36.35%; H% 2.63.

### 4,4′-Dideuterio-2,2′-dimethoxybiphenyl (5, R = $OCH_3$)

Diiodide **24** was treated in the same manner described for **21** to give **5**, R = $OCH_3$, in 88.4% yield. Deuterium incorporation[25] was 94.9%.



Scheme 3

### 2-Iodo-4-methylphenyl-*p*-toluenesulphonate (26)

A solution of **25**[26] (17 g) and *p*-toluenesulphonyl chloride (15 g) in pyridine (50 ml) was heated at 80 °C for 30 min. After cooling, the reaction mixture gave white crystals on addition of water, m.p. 105–106 °C (from ethanol). Anal.: calc. for $C_{14}H_{13}IO_3S$: C% 43.30; H% 3.35. Found: C% 43.15; H% 3.28. $^1H$ NMR ($CDCl_3$): δ2.29 (3H, s), 2.47 (3H, s), 7.13–7.87 (6H, m).

### 2-Iodo-4-methyl-5-nitrophenyl-*p*-toluenesulphonate (27)

To a solution of **26** (20 g) in acetic anhydride was added fuming nitric acid (10 ml) dropwise under ice-cooling. After stirring for 2 h at room temperature, the reaction mixture was worked up as usual to afford **27** (9.6 g), m.p. 97–98 °C (from $CH_3OH$). Anal.: calc. for $C_{14}H_{12}NO_5IS$: C% 38.80; H% 2.77; N% 3.23. Found: C% 38.76; H% 2.67; N% 3.28. $^1H$ NMR ($CDCl_3$): δ 2.49 (3H, s), 2.55 (3H, s), 7.27–7.87 (6H, m).

### 2-Iodo-4-methyl-5-nitrophenol (28)

A mixture of **27** (9.6 g) and KOH (5 g) in $H_2O$ (60 ml) and ethanol (40 ml) was refluxed for 30 min under nitrogen. Extractive work-up with ethyl acetate in acidic media gave **28** (4.3 g), m.p. 175–176 °C (from methylene chloride). Anal.: calc. for $C_7H_6INO_3$: C% 30.11%; H% 2.15; N% 5.02. Found: C% 30.12; H% 2.12; N% 5.00. $^1H$ NMR ($CDCl_3$): δ 2.48 (3H, s), 7.52 (1H, s), 7.63 (1H, s).

### 2-Iodo-4-methyl-5-nitroanisole (29)

A mixture of **28** (4.3 g), dimethyl sulphate (5 ml), and anhydrous $K_2CO_3$ (5 g) in benzene (50 ml) was refluxed for 1 h. The usual work-up afforded **29** (3.9 g), m.p. 117–118 °C (from $CH_3OH$). Anal.: calc. for $C_8H_8O_3NI$: C% 32.77; H% 2.73; N% 4.78. Found: C% 32.78; H% 2.64; N% 4.73. $^1H$ NMR ($CDCl_3$): δ 2.50 (3H, s), 3.93 (3H, s), 7.40 (1H, s), 7.76 (1H, s).

### 2,2′-Dimethoxy-5,5′-dimethyl-4,4′-dinitrobiphenyl (30)

A mixture of **29** (575 mg) and copper powder (575 mg) was heated at 220 °C in a sealed tube for 6 h. The usual work-up followed by chromatography on a silica gel column ($CH_2Cl_2$) afforded **30** (191 mg) m.p. 212–213 °C (from $CH_3OH$). Anal.: calc. for $C_{16}H_{16}N_2O_6$: C% 57.83; H% 4.85; N% 8.43. Found: C% 58.03; H% 4.85; N% 8.12.

### 4,4′-Diamino-2,2′-dimethoxy-5,5′-dimethylbiphenyl (31)

By the same procedure as described above the dinitrobiphenyl **30** (700 mg) was reduced into the diamine

**31** (580 mg), m.p. 159–160 °C (from $CH_3OH$). Anal.: calc. for $C_{16}H_{20}N_2O_2$: C% 70.56; H% 7.40; N% 10.29. Found: C% 70.41; H% 7.38; N% 10.07.

### 4,4′-Diiodo-2,2′-dimethoxy-5,5′-dimethylbiphenyl (32)

In the same manner as described for **21**, **31** (377 mg) afforded **32** (520 mg), m.p. 145–146 °C (from $CH_3OH$–methylene chloride). Anal.: calc. for $C_{16}H_{16}I_2O_2$: C% 38.88; H% 3.24. Found: C% 39.14; H% 3.28.

### 4,4′-Dideuterio-2,2′-dimethoxy-5,5′-dimethylbiphenyl (7)

Diiodide **32** (54 mg) was treated in the same manner as described in the preparation of **5**, R = $CH_3$, to give **7** (23 mg). Deuterium incorporation[24] was 97.2%.

### 5,5′-Diethyl-2,2′-dimethoxybiphenyl (9)

To a solution of **17** (190 mg) in ethanol (25 ml) was added $NaBH_4$ (300 mg) and the mixture was stirred at room temperature for 8 h. The usual work-up gave oily **10** (190 mg), which was hydrogenated over Raney-nickel in $CH_3OH$. Purification on a silica gel column (*n*-hexane–methylene dichloride) afforded **9** (155 mg), m.p. 70.5–71 °C (from ethyl acetate). Anal.: calc. for $C_{18}H_{22}O_2$: C% 79.96; H% 8.20. Found: C% 79.81; H% 8.09. $^1H$ NMR ($CDCl_3$): $\delta$1.22 (6H, t, $J = 8$), 2.61 (4H, q, $J = 8$), 3.71 (6H, s), 6.84 (2H, d, $J = 8$), 7.04 (2H, br. s), 7.10 (2H, dd, $J = 8, 2$). The signal at $\delta$7.04 was unresolvable due to the partial overlapping with the signal at $\delta$7.10, although it should be a doublet ($J = 2$ Hz).

### 5,5′-Diamino-2,2′-dimethoxybiphenyl (14)

2,2′-Dimethoxy-5,5′-dinitrobiphenyl (**19**) was reduced in the same manner as described for **23** to give diamine **14** in 92.3% yield, m.p. 165–166 °C (from $CH_3OH$). Anal.: calc. for $C_{14}H_{16}N_2O_2$: C% 68.83; H% 6.60; N% 11.47. Found: C% 68.63; H% 6.62; N% 11.38. $^1H$ NMR ($CDCl_3$): $\delta$3.51 (6H, s), 4.50 (4H, br. s), 6.38 (2H, d, $J = 3$), 6.46 (2H, dd, $J = 9, 3$), 6.68 (2H, d, $J = 9$).

### 2,2′-Dimethoxy-5,5′-dipropionylbiphenyl (18)

To a stirred solution of **4** (400 mg) in anhydrous methylene chloride was added $AlCl_3$ (800 mg) at 0 °C followed by addition of propionyl chloride (530 mg). After standing for 12 h at room temperature the usual work-up afforded **18** (580 mg), m.p. 150–151.5 °C (from acetone). Anal.: calc. for $C_{20}H_{22}O_4$; C% 73.60; H% 6.79. Found: C% 73.58; H% 6.80. $^1H$ NMR ($CDCl_3$): $\delta$1.21 (6H, t, $J = 7$), 2.95 (4H, q, $J = 7$), 3.80 (6H, s), 6.90 (2H, d, $J = 8$), 7.66 (2H, d, $J = 3$), 7.93 (2H, dd, $J = 8.3$).

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