

NEW SYNTHESIS OF BIFLAVONES OF CUPRESSUFLAVONE SERIES¹

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(Received in UK 22 September 1975; Accepted for publication 14 October 1975)

Abstract—7,7"-Dimethoxy cupressuflavone, 7,7"-dimethoxy 5,5",4',4"-tetraacetoxy cupressuflavone, cupressuflavone hexamethylether and 7,7",4',4"-tetramethoxy cupressuflavone have been synthesized by a new route via the corresponding bichalcones. It has the advantage over the synthesis via 8-iodo-apigenin trimethylether,² that in the last step of demethylation of cupressuflavone hexamethylether, the possibility of Wessley-Moser rearrangement can be avoided.³

The naturally occurring biflavones of cupressuflavone series have been previously synthesized by total or partial demethylation of cupressuflavone hexamethylether.^{2,4} In this reaction the possibility of Wessely-Moser rearrangement cannot be ruled out. We now describe the synthesis of some of the biflavones of cupressuflavone series via the symmetrical biphenyls. This method completely eliminates the possibility of any rearrangement.

Thus 2,4,6-trimethoxy-iodobenzene under Ullman conditions gave the symmetrical biphenyl **1** m.p. 158–59° in 60% yield. Friedel-Craft reaction on **1** with acetyl chloride and aluminium chloride in nitrobenzene gave a crystalline product. It gave +ve ferric test in alcohol and the IR spectrum showed a peak at 1620 cm⁻¹. This clearly indicated that acetylation was accompanied with demethylation. TLC showed that the product was indeed a mixture of at least three compounds. This product was thus methylated with dimethyl sulphate to give a single pure compound **2**. It gave –ve ferric test in alcohol. The structure of the compound was proved by its NMR spectrum (Table 1). The upfield shift at τ 6.6(6 H), of OMe groups at 2,2' is characteristic of such biphenyl.⁵ Similar shielding phenomenon have been described for methyl, methoxyl and carbomethoxy groups in hindered positions of various biphenyls.^{6–8} It is used as a diagnostic tool for the positioning of OMe groups in various natural products.⁹ The biphenyl **2** was also obtained by Ullman coupling of 5-iodo-2,4,6-trimethoxyacetophenone. The

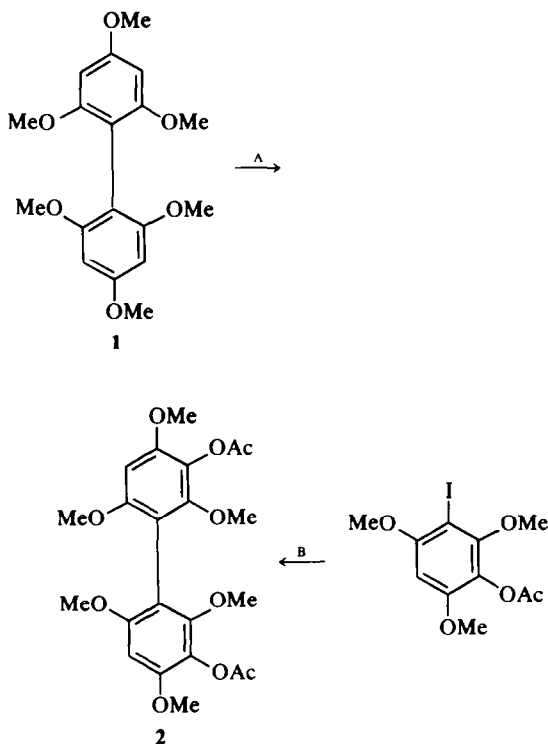


Table 1. NMR data of biphenyls obtained in CDCl₃ solutions in τ values

Compound	OMe at 2 and 2'	OMe at 4,4',6,6'	OMe at 4,6,6'	OMe at 2'	OAC	Aromatic protons	Phenolic protons
2	6.6(6 H),	6.28(6 H), 6.15(6 H),	—	—	7.50(6 H),	3.73(2 H),	—
4	—	6.07(6 H), 6.20(6 H),	—	—	7.38(6 H),	3.90(2 H),	— 4.0(2 H),
5	—	—	6.15(3 H), 6.07(3 H), 6.23(3 H),	6.53(3 H),	7.35(6 H),	3.70(1 H), 3.92(1 H),	— 3.53(1 H), — 3.98(1 H),
6	—	6.14(3 H), 6.20(3 H), 6.25(3 H), 6.32(3 H),	—	6.58(3 H),	7.40(3 H), 7.50(3 H),	3.72(1 H), 3.91(1 H),	— 3.93(1 H),

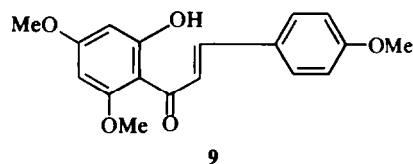
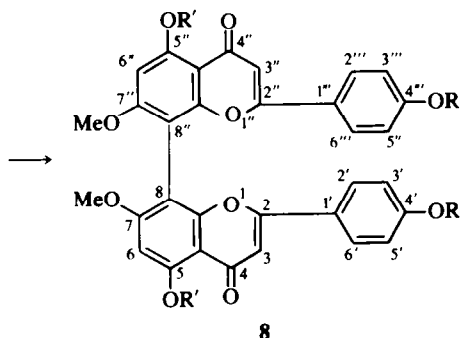
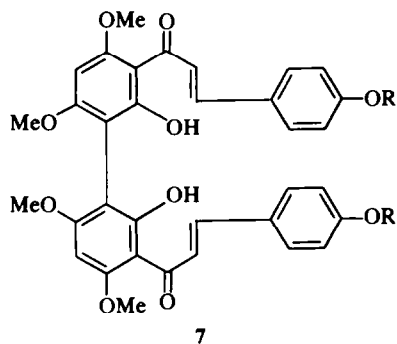
yield of the biphenyl was extremely poor in this reaction (about 3%) however, the biphenyl obtained was identical in all respects (TLC, IR, NMR) with **2** obtained through route A. Because of the poor yield through route B, we adopted route A in this synthesis.

Demethylation of **2** was carried out with boron trichloride at 0°. Boron trichloride is known to demethylate OMe groups *ortho* or *peri* to carbonyl functions.¹⁰ Since the boron atom cannot form dual complex with compounds of type **2** so these lose but one Me group per CO group. It was therefore hoped that the biphenyl **3**, **4** and **5** would be obtained. However contrary to expectations, **3** was distinctly missing and instead **6** was obtained alongwith **4** and **5**. These were separated on silica column followed by fractional crystallization. The structure of these biphenyls were established by IR, NMR spectra and elemental analysis and were distinguished from each other by NMR spectra only (Table 1). NMR spectrum of **4** showed signals at τ 6.07(6 H), and 6.20(6 H), which clearly indicated the presence of OMe groups at 4,4', 6 and 6'. Two phenolic protons were detected by the peak at τ 4.0(2 H), which readily exchanged with D₂O. This confirmed that demethylation had occurred at 2,2'.

The NMR spectrum of **5** gave only one signal at τ 6.53(3 H), high upfield which accounted for the three protons of the OMe group either at 2 or 2'. Two phenolic protons were detected by the peaks at τ 3.53(1 H), and τ 3.98(1 H), which readily exchanged with D₂O. The rest of the NMR spectrum (Table 1) is in accord with the proposed structure **5**.

The NMR spectrum of biphenyl **6** besides four OMe groups at 4,4', 6 and 6' (Table 1) showed a singlet at 6.58 (3 H), which distinctly indicated the presence of only one OMe either at 2 or 2'. The peak at τ 3.93(1 H), confirmed that partial demethylation had occurred. This was further confirmed by the IR of **6** which showed a peak at 1620 cm⁻¹ (O-hydroxyketone bonded CO) and a peak at 1690 cm⁻¹ (free CO).

The biphenyl **4** on treatment with two moles of *p*-hydroxy benzaldehyde in presence of alkali gave a



yellow compound the bichalcone, m.p. 162–66° **7** (R=H). The IR of the bichalcone showed a broad peak at 1600–1618 (O-hydroxyketone) and 3500 cm⁻¹ (OH). The NMR of the compound indicated the presence of four olefinic protons at τ 2.24(4 H), and four OMe groups at 6.05(12 H). The structures of the bichalcones **7** (R=H and R=OMe) was further confirmed by comparison of their NMR spectra with that of the chalcone (monomer) **9**. The peak positions of **9** and **7** (R=OMe) were almost identical (Table 2) with the exception of two doublets showing meta split protons of Ring A of **9** which is replaced by a singlet in bichalcones as expected.

The bichalcone **7** (R=H) was oxidatively cyclized in presence of selenium dioxide to give a pale yellow product which on demethylation with boron trichloride at 0° gave yellow micro needles of **8** (R=R'=H) m.p. 314–320° which was found identical to 7,7'-dimethoxy cupressuflavone obtained by the known route² (IR, UV, m.p. and m.m.p.). The structure of this biflavone was further confirmed by acetylation of the biflavone and comparison of the spectral data of the tetraacetate with that of the 7,7'-dimethoxy-5,5'', 4',4'''-tetraacetoxy biflavone.¹¹ Both were found to be indistinguishable from each other (IR, m.p., m.m.p. and NMR data Table 2).

Similar treatment of **4** with anisaldehyde in presence of alkali gave the bichalcone **7** (R=OMe). It was cyclized in presence of selenium dioxide to give the biflavone **8** (R,R'=OMe). Demethylation of **8** (R,R'=OMe) with boron trichloride gave **8** (R=OMe, R'=H). It gave green ferric test in alcohol. Both **8** (R,R'=OMe and R=OMe, R'=H) were found to be identical (NMR, m.p., m.m.p.) with cupressuflavone hexamethylether and 7,7',4',4'''-

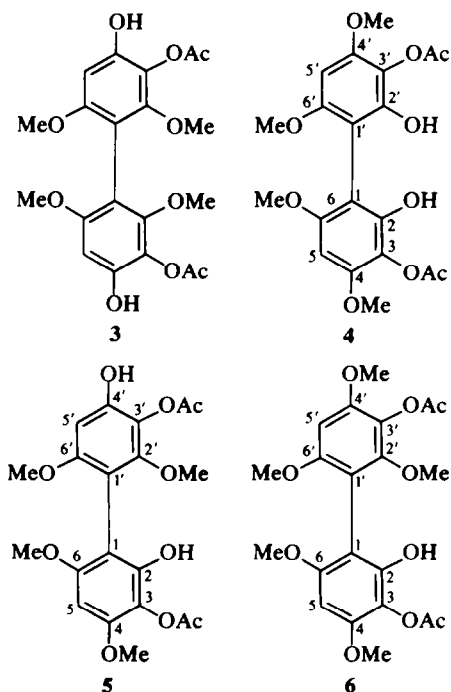


Table 2. NMR data of Biflavones and Chalcones in CDCl₃ solution in τ values

Compound	Methoxyl protons	Olefinic protons	Ring A aromatic protons	Ring B aromatic protons	Acetyl protons	Phenolic protons
8 R=R'=OMe	5.85(6 H), 6.13(6 H), 6.24(6 H),	3.37(2 H),	3.31(2 H),	2.70(4 H) _d , J = 9 c/s 3.25(4 H) _d , J = 9 c/s	—	—
8 R=OMe, R'=H	6.12(12 H),	Olefinic & aromatic protons together 3.45(4 H),	—	2.44(4 H) _d , J = 9 c/s 3.02(4 H) _d , J = 9 c/s	—	— 2.98(2 H),
8 R=R'=OAc	6.17(6 H),	3.41(2 H),	3.22(2 H),	2.65(4 H) _d , J = 9 c/s 2.92(4 H) _d , J = 9 c/s	7.76(6 H), 7.50(6 H),	—
7 R=OMe	5.98(6 H), 6.15(12 H),	2.20(4 H),	3.82(2 H),	3.05(4 H) _d , J = 8 c/s 2.40(4 H) _d , J = 8 c/s	—	— 4.15(2 H),
9	6.12(6 H), 6.17(12 H),	2.17(2 H),	3.83(1 H) _d , J = 2.5 c/s 4.0(1 H) _d , J = 2.5 c/s	3.03(2 H) _d , J = 8 c/s 2.40(2 H) _d , J = 8 c/s	—	— 4.33(1 H),

tetramethoxycupressuflavone respectively, obtained via the Ullman coupling of 5-iodo-apigenin trimethylether^{2,13} (Table 2).

EXPERIMENTAL

2,4,6-Trimethoxyiodobenzene. To the hot alcoholic soln of 2,4,6-trimethoxybenzene (3 g) was added aqueous soln of HIO₄ (0.63 g) and alcoholic soln of I₂ (1.815 g). The mixture was heated on waterbath until the colour of I₂ faded and a ppt appeared. The mixture was kept overnight at room temp. The ppt was washed with alcohol and crystallized from MeOH to give 4.84 g of large needles of 2,4,6-trimethoxyiodobenzene m.p. 122–24° (lit.¹² m.p. 119–21°).

2,2',4,4',6,6'-Hexamethoxybiphenyl 1. Trimethoxyiodobenzene (4 g) copper bronze (8 g) were thoroughly mixed in mortar and transferred to a test tube which was heated. The temp. was raised to 235° in 15 min and kept at 235–45° for 1 hr. The product was allowed to cool, powdered and extracted with MeOH for 3½ hr in soxhlet. MeOH soln concentrated to give colourless needles (1.41 g) m.p. 153–55° (lit.¹² m.p. 156°).

3,3' - Diacetyl - 2,2',4,4',6,6' - hexamethoxybiphenyl 2. The soln of hexamethoxybiphenyl (2 g) in nitrobenzene (20 ml) was added to the soln of anhydrous AlCl₃ (2.8 g) in warm nitrobenzene (25 ml). Acetyl chloride (6.5 g) was added to the above mixture (with stirring) at 40° over period of 20 min. The mixture was then stirred at room temp. for 22 hr. The AlCl₃ complex was broken with ice cold conc HCl. The nitrobenzene layer was separated and removed by steam distillation and the solid obtained was washed with water and crystallized from MeOH to give a colourless product which had a long range of m.p. starting from 145 to 212°. It gave positive ferric chloride test in alcohol; IR: 1600, 1620, 1692 cm⁻¹. This indicated that acetylation was accompanied with demethylation; TLC in EtOAc-benzene (2:8) on silica plate showed three spots.

The above mixture (1.2 g) was dissolved in acetone (115 ml) and anhyd K₂CO₃ (16 g) added and methylated by addition of excess Me₂SO₄. After usual workup it gave colourless needles of 3,3' - diacetyl - 2,2',4,4',6,6' - hexamethoxybiphenyl 2 from CHCl₃/MeOH (0.93 g) m.p. 161–63°. It gave - ve ferric chloride

test in alcohol; IR 1600, 1695 cm⁻¹; NMR τ 6.15(6 H)_s, 6.28(6 H)_s, 6.6(6 H)_s, 7.50(6 H)_s, 3.73(2 H)_s; (Found: C, 63.39; H, 6.01; OMe, 47.01. C₂₂H₂₀O₈ requires: C, 63.14; H, 6.26; OMe, 44.49%). 3 - Iodo - 2,4,6 - trimethoxyacetophenone (2 g) and copper bronze (13.34 g) were thoroughly mixed in mortar and heated in a test tube. The temp. was raised to 235° in 15 min and kept at 235–45° for 1 hr. The mixture was cooled, extracted with MeOH and the solvent evaporated to give a crude product (1 g). It was chromatographed on alumina (75 g) column. Elution with pet ether gave 2,4,6-trimethoxyacetophenone identified by m.p. and m.m.p. Further elution with ether gave 40 mg of the biphenyl m.p. 162–64° identical in all respects with 2 obtained by route A. (TLC, m.p. m.m.p., NMR).

Demethylation of 3,3' - diacetyl - 2,2',4,4',6,6' - hexamethoxybiphenyl with boron trichloride. To a soln of the above biphenyl (500 mg) in CH₂Cl₂ (30 ml) was added excess of BCl₃ soln in CH₂Cl₂ (10 ml) at 0°. The soln which immediately turned yellow was kept at 0° for 45 min after which it was poured into cold NaOAc aq. The mixture was extracted with CH₂Cl₂ and the organic layer washed, dried evaporated to give a crystalline product which was chromatographed on a silica column (40 g). Elution with pet ether-benzene (1:1) gave pale needles of 3,3' - diacetyl - 2,2' - dihydroxy - 4,4',6,6' - tetramethoxybiphenyl 4 (118 mg) m.p. 260–62°; IR 1580, 1600–1620 cm⁻¹ (broad peak); NMR τ 6.07(6 H)_s, 6.20(6 H)_s, 7.38(6 H)_s, 3.90(2 H)_s, and - 4.0(2 H)_s. (Found: C, 60.87; H, 5.45; OMe, 29.38. C₂₀H₂₂O₈ requires: C, 61.53; H, 5.65; OMe, 32.78%). Elution with pet ether-benzene (1:2) gave colourless needles from CHCl₃/MeOH of 3,3' - diacetyl - 2,4' - dihydroxy - 2',4,6,6' - tetramethoxybiphenyl 5 (74 mg) m.p. 186–88°; IR 1580, 1600–1616 cm⁻¹ (broad peak); NMR τ 6.53(3 H)_s, 6.15(3 H)_s, 6.07(3 H)_s, 6.23(3 H)_s, 7.35(6 H)_s, 3.70(1 H)_s, 3.92(1 H)_s, - 3.53(1 H)_s, - 3.98(1 H)_s. (Found: C, 61.29; H, 5.50; OMe, 31.10. C₂₀H₂₂O₈ requires: C, 61.53; H, 5.65; OMe, 32.78%). Further elution with benzene gave 3,3' - diacetyl - 2 - hydroxy - 2',4,4',6,6' - pentamethoxybiphenyl 6 (32 mg) m.p. 211–13°; IR 1575, 1620, 1690 cm⁻¹; NMR τ 6.14(3 H)_s, 6.20(3 H)_s, 6.25(3 H)_s, 6.32(3 H)_s, 6.58(3 H)_s, 7.40(3 H)_s, 7.50(3 H)_s, 3.72(1 H)_s, 3.91(1 H)_s, and - 3.93(1 H)_s. (Found: C, 62.22; H, 5.81. C₂₁H₂₄O₈ Requires: C, 62.37; H, 5.98%).

Synthesis of bichalcones 7 (R=H and 7 R=OMe). The biphenyl 4 (195 mg) and *p*-hydroxybenzaldehyde (122 mg) were dissolved in EtOH (20 ml). This soln was mixed with 10% KOH aq (20 ml) and heated on water bath for 3 hr after which it was left overnight. It was poured into excess ice cold 10% HCl and the yellow ppt extracted with EtOAc and washed with water. Evaporation of the solvent and crystallization from MeOH gave microneedles of 7 (R=H, 140 mg) m.p. 162–66°; IR 1565, 1600–1615 cm⁻¹ (broad peak); NMR τ 2.24(4 H)_s, 3.84(2 H)_s, 6.05(12 H)_s, 2.97(4 H)_d J = 9 c/s, 2.35 (4 H)_d J = 9 c/s, -3.98(2 H)_s, 0.65(2 H)_s. (Found: C, 68.02; H, 4.89. C₃₄H₃₀O₁₀ requires: C, 68.22; H, 5.05%).

Similar treatment of 4 (668 mg) with anisaldehyde (468 mg) gave yellow needles of 7 (R=OMe, 685 mg) from MeOH m.p. 282–85°; IR 1560, 1600–1615 cm⁻¹ (broad peak); NMR τ 2.20 (4 H)_s, 3.82(2 H)_s, 5.98(6 H)_s, 6.15(12 H)_s, 3.05(4 H)_d J = 8 c/s, 2.40(4 H)_d J = 8 c/s, -4.15(2 H)_s. (Found: C, 68.94, H, 5.40. C₃₆H₃₄O₁₀ requires: C, 69.00; H, 5.47%).

Cyclization of bichalcones into biflavones. The bichalcone 7 (R=H; 108 mg) and SeO₂ (210 mg) were taken up in amyl alcohol (40 ml) and soln refluxed for 14 hr. Amyl alcohol removed by steam distillation and the aqueous layer extracted with EtOAc. The organic layer was washed dried and evaporated to yield a semi crystalline product which was dissolved in CH₂Cl₂ and treated with BCl₃ at 0° for 30 min. After the usual work up it gave yellow micro needles from MeOH of 7,7'-dimethoxycupressuflavone 8 (R'=R=H; 29 mg) m.p. 316–23° (Lit.^{2,11} 310° and 316–18°); IR 1670, 1600 cm⁻¹ UV MeOH nm (log E) 220 (4.68), 268 (4.49), 320 (4.50). (Found: C, 67.71; H, 3.87. C₃₂H₂₂O₁₀ requires: C, 67.84; H, 3.91%).

The above biflavone 8 (R=R'=H; 15 mg) was acetylated with pyridine and Ac₂O to give colourless needles (12 mg) from MeOH of 5,5',4',4'' - tetraacetoxy - 7,7'' - dimethoxycupressuflavone 8 (R=R'=OAc) m.p. 275–82° (lit.^{2,11} 275–80° and 279–80°); IR 1775, 1640, 1600 cm⁻¹; NMR τ 6.17(6 H)_s, 3.41(2 H)_s, 3.22(2 H)_s, 2.92(4 H)_d J = 9 c/s, 2.65(4 H)_d J = 9 c/s, 7.76(6 H)_s, 7.50(6 H)_s.

The bichalcone 7 (R=OMe; 75 mg) was similarly cyclized as 7 (R=H) with exception that dioxane was used instead of amyl alcohol as the solvent. After the usual work up pale yellow needles of 7,7'',5,5'',4',4'' - hexamethoxycupressuflavone 8 (R=R'=OMe) were obtained (27 mg) m.p. 294–95° (lit.² 295–97°); IR 1648, 1602,

1512 cm⁻¹; NMR τ 5.85(6 H)_s, 6.13(6 H)_s, 6.24(6 H)_s, 3.37(2 H)_s, 3.31(2 H)_s, 2.70(4 H)_d J = 9 c/s, 3.25(4 H)_d, J = 9 c/s. (Found: C, 69.58; H, 4.72. C₃₆H₃₀O₁₀ requires: C, 69.44; H, 4.86%).

The above biflavone 8 (R=R'=OMe; 15 mg) was similarly treated with BCl₃ as for 8 (R=H, R'=OMe). The product crystallized from MeOH as pale yellow needles m.p. 260–62° (lit.² 259–61°) of 7,7',4',4'' - tetramethoxycupressuflavone 8 (R=OMe, R'=H) IR 1670, 1602 cm⁻¹; NMR τ 6.12(12 H)_s, 3.45(4 H)_s, 2.44(4 H)_d, J = 9 c/s, 3.02(4 H)_d, J = 9 c/s, -2.98(2 H)_s. (Found: C, 68.61; H, 4.8. C₃₄H₂₆O₁₀ requires: C, 68.68; H, 4.41%).

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