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Synthesis of Diphenyl-substituted Flavonoid Compounds on Both Benzene Rings

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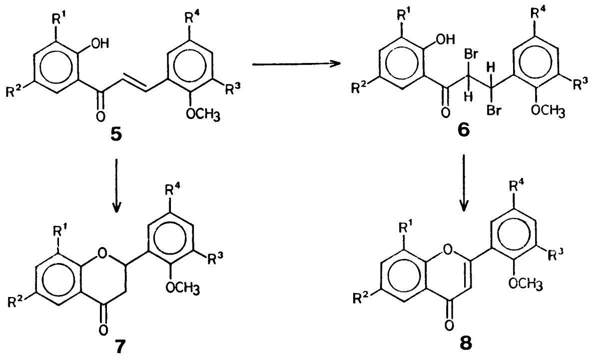
Synopsis. Condensation of *o*-hydroxyacetophenone and its 3- and 5-phenyl-substituted compounds with 2- or 4-methoxy-biphenyl-3-carbaldehyde gave six mono- and diphenyl-substituted 2′-hydroxychalcones (**5a**—**f**), which were cyclized with alkali to afford the flavanones. The chalcones **5a**—**f** were also converted to the corresponding flavones *via* chalcone bromides.

Little is known about phenyl-substituted flavonoid compounds, except for a few reports.[1] Previously, we reported the synthesis of 6- and 8-phenyl-substituted flavonoid compounds.[2] The present communication deals with the synthesis of flavonoid compounds having two phenyl groups in both benzene ring.



	R¹	R²	R³	R⁴
a	H	H	H	Ph
b	H	H	Ph	H
c	H	Ph	H	Ph
d	H	Ph	Ph	H
e	Ph	H	H	Ph
f	Ph	H	Ph	H

Scheme 1.

Results and Discussion

In starting materials, 3-acetylbiphenyl-4-ol and -2-ol (**4b** and **4c**) were prepared by the method described in the previous paper.[2] 4-Methoxybiphenyl-3-carbaldehyde (**3a**) was prepared by Duff's formylation[3] and methylation of biphenyl-4-ol (**1a**). Similarly, 2-methoxybiphenyl-3-carbaldehyde (**3b**) was newly obtained by formylation and methylation of biphenyl-2-ol (**1b**).

The *o*-hydroxyacetophenones (**4a**—**c**) were condensed with methoxy-substituted biphenyl-3-carbaldehydes (**3a** and **3b**) to afford mono- or diphenyl-substituted 2′-hydroxychalcones (**5a**—**f**) in good yields. The spectral data are summarized in Table 1. In the UV spectra, an introduction of the phenyl group at the 3-position exhibited no appreciable effect. On the other hand, the spectra of the 5-phenyl-substituted chalcones exhibited remarkable differences. In the NMR spectra, the signal (*δ ca.* 3.4) for the methoxyl protons of the 3-phenyl-substituted chalcones (**5b**, **d**, and **f**) shifted towards higher magnetic field than that (*δ ca.* 3.9) for the 5-phenyl-substituted chalcones (**5a**, **c**, and **e**). This might be caused by ring-current in the neighboring phenyl group.

TABLE 1. CHARACTERISTICS FOR THE CHALCONES **5**

Compd	Reaction time / h	Yield / %	Characteristic data
5a	30	81	Mp 155—156 °C; IR (KBr) 1635 cm⁻¹ (C=O); UV (CH_3OH) 270 (log ε 4.40), 315 (4.24), 384 nm (4.21); NMR ($CDCl_3$) $\delta=3.90$ (s, 3H, OCH_3), 6.95 (dm, 1H, $J=8.5$ Hz, 3-H), 6.8—7.95 (m, 12H), 8.22 (d, 1H, $J=15.5$ Hz, β-H), 12.86 (s, 1H, OH). Found: C, 80.04; H, 5.61%. Calcd for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49%.
5b	15	94	Mp 135—136 °C; IR (KBr) 1640 cm⁻¹ (C=O); UV (CH_3OH) 328 nm (log ε 4.34); NMR ($CDCl_3$) $\delta=3.42$ (s, 3H, OCH_3), 6.7—8.0 (m, 13H), 8.22 (d, 1H, $J=15.5$ Hz, β-H), 12.78 (s, 1H, OH). Found: C, 79.76; H, 5.43%. Calcd for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49%.
5c	30	77	Mp 212—213 °C; IR (KBr) 1640 cm⁻¹ (C=O); UV (CH_3OH) 255 (log ε 4.72), 314 sh (4.08), 394 nm (3.98); NMR (DMSO-d_6) $\delta=3.94$ (s, 3H, OCH_3), 7.0—8.3 (m, 17H), 7.16 (d, 1H, $J=2.0$ Hz, 6′-H), 13.28 (s, 1H, OH). Found: C, 82.75; H, 5.36%. Calcd for $C_{28}H_{22}O_3$: C, 82.73; H, 5.45%.
5d	30	92	Mp 121—122 °C; IR (KBr) 1635 cm⁻¹ (C=O); UV (CH_3OH) 256 (log ε 4.58), 328 nm (4.35); NMR ($CDCl_3$) $\delta=3.41$ (s, 3H, OCH_3), 7.03 (d, 1H, $J=8.5$ Hz, 3′-H), 7.1—7.9 (m, 15H), 8.04 (d, 1H, $J=2.5$ Hz, 6′-H), 8.28 (d, 1H, $J=14.5$ Hz, β-H), 12.76 (s, 1H, OH). Found: C, 82.64; H, 5.73%. Calcd for $C_{28}H_{22}O_3$: C, 82.73; H, 5.45%.
5e	30	62	Mp 117—118 °C; IR (KBr) 1630 cm⁻¹ (C=O); UV (CH_3OH) 255 (log ε 4.48), 318 (4.33), 392 nm (4.26); NMR ($CDCl_3$) $\delta=3.90$ (s, 3H, OCH_3), 6.8—7.1 (m, 2H), 7.2—8.0 (m, 15H), 8.26 (d, 1H, $J=15.5$ Hz, β-H), 13.48 (s, 1H, OH). Found: C, 82.80; H, 5.57%. Calcd for $C_{28}H_{22}O_3$: C, 82.73; H, 5.45%.
5f	30	72	Mp 159—160 °C; IR (KBr) 1635 cm⁻¹ (C=O); UV (CH_3OH) 249 (log ε 4.48), 334 nm (4.43); NMR ($CDCl_3$) $\delta=3.34$ (s, 3H, OCH_3), 6.89 (d, 1H, $J=8.5$ Hz, 4′-H), 7.0—7.9 (m, 15H), 7.92 (dd, 1H, $J=8.0$, 2.0 Hz, 6′-H), 8.29 (d, 1H, $J=15.5$ Hz, β-H), 13.35 (s, 1H, OH). Found: C, 82.91; H, 5.67%. Calcd for $C_{28}H_{22}O_3$: C, 82.73; H, 5.45%.

TABLE 2. CHARACTERISTICS FOR THE CHALCONE DIBROMIDES **6**

Compd	Yield / %	Mp θ_m/°C	IR (KBr) $\nu_{C=O}$/cm⁻¹	Formula	Found(Calcd) (%) C	H
6a	75	160(decomp)	1640	$C_{22}H_{18}O_3Br_2$	54.05 (53.90	3.71 3.70)
6b	60	110(decomp)	1640	$C_{22}H_{18}O_3Br_2$	53.93 (53.90	3.42 3.70)
6c	78	274—175.5	1630	$C_{28}H_{22}O_3Br_2$	59.41 (59.38	3.85 3.92)
6d	83	160(decomp)	1645	$C_{28}H_{22}O_3Br_2$	59.08 (59.38	3.81 3.92)
6e	98	155(decomp)	1635	$C_{28}H_{22}O_3Br_2$	59.12 (59.38	4.16 3.92)
6f	100	175—178	1635	$C_{28}H_{22}O_3Br_2$	59.22 (59.38	4.01 3.92)

The bromination of the chalcones **5a**—**f** gave the corresponding dibromides **6a**—**f** in good yields. These characteristic data are listed in Table 2.

The chalcones **5a**—**f** were heated in the presence of alkali to cyclize to flavanones **7a**—**f**. These spectral data are summarized in Table 3. The UV spectra of **7a** and **7b** exhibited no appreciable effect of the phenyl group at the 3′- and 5′-positions. In the UV spectra of **7c**—**f**, the phenyl group at the 6- and 8-positions caused bathochromic shift of the maximum at longer wavelength band. The NMR spectra showed

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TABLE 3. CHARACTERISTICS FOR THE FLAVANONES **7**

Compd	Reaction time h	Yield %	Characteristic data
7a	1.5	61	Mp 106.5—107.5 °C; IR (KBr) 1670 cm^{-1} (C=O); UV (CH_3OH) 257 (log ε 4.42), 319 nm (3.52); NMR($CDCl_3$) δ=2.87 (dd, 1H, J=18.0, 9.5 Hz, 3a-H), 2.99 (dd, 1H, J=18.0, 7.0 Hz, 3e-H), 3.80 (s, 3H, OCH_3), 5.83 (dd, 1H, J=9.5, 7.0 Hz, 2-H), 6.89 (d, 1H, J=9.5 Hz, 3'-H), 7.03 (d, 1H, J=7.0 Hz, 8-H), 7.2—7.7 (m, 8H), 7.85 (s, 1H, 6'-H), 7.91 (dd, 1H, J=7.0, 2.5 Hz, 5-H). Found: C, 79.77; H, 5.44%. Calcd for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49%.
7b	2	40	Mp 113.5—114.5 °C; IR (KBr) 1685 cm^{-1} (C=O); UV (CH_3OH) 250 (log ε 4.35), 326 nm (3.54); NMR ($CDCl_3$) δ=2.89 (dd, 1H, J=16.0, 6.0 Hz, 3e-H), 3.05 (dd, 1H, J=16.0, 11.0 Hz, 3a-H), 3.29 (s, 3H, OCH_3), 5.84 (dd, 1H, J=11.0, 6.0 Hz, 2-H), 6.8—7.8 (m, 11H), 7.91 (dd, 1H, J=8.5, 2.5 Hz, 5-H). Found: C, 80.02; H, 5.51%. Calcd for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49%.
7c	5	23	Mp 132—132.5 °C; IR (KBr) 1690 cm^{-1} (C=O); UV (CH_3OH) 251 (log ε 4.69), 343 nm (3.36); NMR ($CDCl_3$) δ=2.94 (dd, 1H, J=18.5, 9.5 Hz, 3a-H), 3.06 (dd, 1H, J=18.5, 7.0 Hz, 3e-H), 3.83 (s, 3H, OCH_3), 6.02 (dd, 1H, J=9.5, 7.0 Hz, 2-H), 6.90 (d, 1H, J=9.5 Hz, 3'-H), 7.09 (d, 1H, J=9.5 Hz, 8-H), 7.2—8.0 (m, 13H), 8.16 (d, 1H, J=2.5 Hz, 5-H). Found: C, 82.86; H, 5.73%. Calcd for $C_{28}H_{22}O_3$: C, 82.73; H, 5.45%.
7d	4	40	Mp 144—145 °C; IR (KBr) 1680 cm^{-1} (C=O); UV (CH_3OH) 248 (log ε 4.69), 346 nm (3.35); NMR ($CDCl_3$) δ=2.97 (dd, 1H, J=15.5, 5.5 Hz, 3e-H), 3.11 (dd, 1H, J=15.5, 10.0 Hz, 3a-H), 3.32 (s, 3H, OCH_3), 5.88 (dd, 1H, J=10.0, 5.5 Hz, 2-H), 7.07 (d, 1H, J=9.0 Hz, 8-H), 7.1—7.6 (m, 13H), 7.68 (dd, 1H, J=9.0, 3.0 Hz, 7-H), 8.16 (d, 1H, J=3.0 Hz, 5-H). Found: C, 82.47; H, 5.55%. Calcd for $C_{28}H_{22}O_3$: C, 82.73; H, 5.45%.
7e	1	30	Mp 174—175 °C; IR (KBr) 1700 cm^{-1} (C=O); UV (CH_3OH) 242 (log ε 4.50), 336 nm (3.63); NMR ($CDCl_3$) δ=2.7—3.4 (m, 2H, 3e, 3a-H), 3.81 (s, 3H, OCH_3), 5.96 (dd, 1H, J=9.5, 7.0 Hz, 2-H), 6.8—7.9 (m, 15H), 8.01 (dd, 1H, J=8.0, 2.0 Hz, 5-H). Found: C, 82.48; H, 5.45%. Calcd for $C_{28}H_{22}O_3$: C, 82.73; H, 5.45%.
7f	3	53	Mp 143.5—144.5 °C; IR (KBr) 1670 cm^{-1} (C=O); UV (CH_3OH) 241 (log ε 4.57), 336 nm (3.65); NMR ($CDCl_3$) δ=2.8—3.2 (m, 2H, 3e, 3a-H), 3.18 (s, 3H, OCH_3), 5.79 (dd, 1H, J=8.5, 8.5 Hz, 2-H), 6.9—7.7 (m, 15H), 7.93 (dd, 1H, J=8.0, 2.5 Hz, 5-H). Found: C, 82.58; H, 5.66%. Calcd for $C_{28}H_{22}O_3$: C, 82.73; H, 5.45%.

TABLE 4. CHARACTERISTICS FOR THE FLAVONES **8**

Compd	Yield %	Characteristic data
8a	85	Mp 147—148 °C; IR (KBr) 1640 cm^{-1} (C=O); UV (CH_3OH) 255 (log ε 4.50), 344 nm (3.92); NMR ($CDCl_3$) δ=3.87 (s, 3H, OCH_3), 7.01 (d, 1H, J=8.5 Hz, 3'-H), 7.09 (s, 1H, 3-H), 7.1—7.8 (m, 9H), 7.96 (d, 1H, J=2.5 Hz, 6'-H), 8.15 (dm, 1H, J=8.0 Hz, 5-H). Found: C, 80.21; H, 4.93%. Calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91%.
8b	78	139—140 °C; IR (KBr) 1645 cm^{-1} (C=O); UV (CH_3OH) 248 (log ε 4.48), 304 nm (3.92); NMR ($CDCl_3$) δ=3.37 (s, 3H, OCH_3), 6.89 (s, 1H, 3-H), 7.0—7.8 (m, 11H), 8.19 (dm, 1H, J=8.0 Hz, 5-H). Found: C, 80.17; H, 5.12%. Calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91%.
8c	84	Mp 92—93 °C; IR (KBr) 1640 cm^{-1} (C=O); UV (CH_3OH) 267 (log ε 4.51), 338 nm (4.03); NMR ($CDCl_3$) δ=3.92 (s, 3H, OCH_3), 7.00 (d, 1H, J=8.5 Hz, 3'-H), 7.10 (s, 1H, 3-H), 7.1—7.9 (m, 13H), 8.03 (d, 1H, J=2.0 Hz, 6'-H), 8.40 (d, 1H, J=2.0 Hz, 5-H). Found: C, 83.21; H, 4.91%. Calcd for $C_{28}H_{20}O_3$: C, 83.15; H, 4.98%.
8d	73	Mp 127—128 °C; IR (KBr) 1640 cm^{-1} (C=O); UV (CH_3OH) 266 (log ε 4.64), 308 nm sh (4.23); NMR ($CDCl_3$) δ=3.36 (s, 3H, OCH_3), 6.96 (s, 1H, 3-H), 7.0—8.0 (m, 15H), 8.35 (d, 1H, J=2.5 Hz, 5-H). Found: C, 82.93; H, 5.04%. Calcd for $C_{28}H_{20}O_3$: C, 83.15; H, 4.98%.
8e	71	Mp 210—211 °C; IR (KBr) 1650 cm^{-1} (C=O); UV (CH_3OH) 254 (log ε 4.52), 295 nm (4.21); NMR ($CDCl_3$) δ=3.91 (s, 3H, OCH_3), 7.01 (d, 1H, J=8.0 Hz, 3'-H), 7.16 (s, 1H, 3-H), 7.2—7.8 (m, 13H), 7.85 (d, 1H, J=2.5 Hz, 6'-H), 8.22 (dd, 1H, J=8.0, 2.5 Hz, 5-H). Found: C, 82.89; H, 5.14%. Calcd for $C_{28}H_{20}O_3$: C, 83.15; H, 4.98%.
8f	67	Mp 172—173 °C; IR (KBr) 1640 cm^{-1} (C=O); UV (CH_3OH) 248 (log ε 4.54), 316 nm (4.23); NMR ($CDCl_3$) δ=3.22 (s, 3H, OCH_3), 7.11 (s, 1H, 3-H), 7.2—7.9 (m, 15H), 8.20 (dd, 1H; J=8.0, 2.5 Hz, 5-H). Found: C, 83.18; H, 5.01%. Calcd for $C_{28}H_{20}O_3$: C, 83.15; H, 4.98%.

the typical ABX pattern of 2-, 3e-, and 3a-protons.

The chalcone dibromides **6a**—**f** were treated with alkali to afford the corresponding flavones **8a**—**f** in good yields. The characteristic data are summarized in Table 4. In the UV spectra of **8a** and **8b**, the phenyl group at the 3'-position exhibited no effect but the phenyl group at the 5'-position exhibited bathochromic shift of the maximum at longer wavelength band. The NMR spectra showed a sharp singlet peak for the 3-H proton at δ 6.9—7.1. The methoxyl protons of the 3'-phenylflavones (**8b**, **d**, and **f**) were also observed in higher magnetic field than those of 5'-phenylflavones (**8a**, **c**, and **e**).

Experimental

The IR, UV, and NMR spectra were taken on a JASCO 403G, a Hitachi EPS-3T, and a Hitachi R-24 (60 MHz) spectrometer, respectively.

2-Methoxybiphenyl-3-carbaldehyde (3b). Methylation of 2-hydroxybiphenyl-3-carbaldehyde (**2b**)[4] (2.4 g, 12 mmol) with dimethyl sulfate (1.5 g, 12 mmol) in acetone (100 ml) in the presence of potassium carbonate (1.7 g, 12 mmol) gave 2-methoxybiphenyl-3-carbaldehyde (**3b**) as colorless crystals (from methanol). Yield, 2.0 g (73%). Mp 53—54 °C, IR (KBr) 1680 cm^{-1}. Found: C, 79.36; H, 5.43%. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70%.

4-Methoxybiphenyl-3-carbaldehyde (3a). This compound also prepared in a similar manner to the preparative method of **3b**. Yield, 86%. Mp 77—78 °C (lit,[5] 76.5—77 °C).

The Chalcones 5a—f. A solution of 2-hydroxyacetophenone (**4a**—**c**) (2.4 mmol) and 2- or 4-methoxybiphenyl-3-carbaldehyde (**3a**, **b**) (500 mg, 2.4 mmol) in ethanol (3 ml) was stirred at 50 °C in the presence of 60% potassium hydroxide solution (2.5 ml). The mixture was slightly acidified with 3 M hydrochloric acid (1 M=1 mol dm^{-3}) extracted with ether, and worked up to give the chalcone **5a**—**f**.

The Chalcone Dibromides 6a—f. A bromine (320 mg, 2 mmol) solution in carbon tetrachloride (2 ml) was added dropwise to a solution of the chalcone **5a**—**f** (500 mg) in carbon tetrachloride (5 ml) at room temperature to afford the chalcone dibromide **6a**—**f** (from acetone).

The Flavanones 7a—f. A solution of the chalcone **5a**—**f** (330—400 mg, 1 mmol) in acetone (8 ml) was refluxed for 90 min in the presence of 1% potassium hydroxide solution (0.5 ml). The mixture was concentrated and allowed to stand overnight to give a precipitate, which was chromatographed on an alumina column to afford the flavanone **7a**—**f** (from acetone).

The Flavones 8a—f. To a suspended solution of the chalcone dibromide **6a**—**f** (450 mg) in acetone (2 ml) was added 20% potassium hydroxide solution (1 ml) at room temperature. The mixture was diluted with water and slightly acidified with 3 M hydrochloric acid to give a precipitate, which was chromatographed on a silica-gel column to afford the flavone **8a**—**f** (from acetone).

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