

## Synthesis of Biflavonyl Ethers (I)

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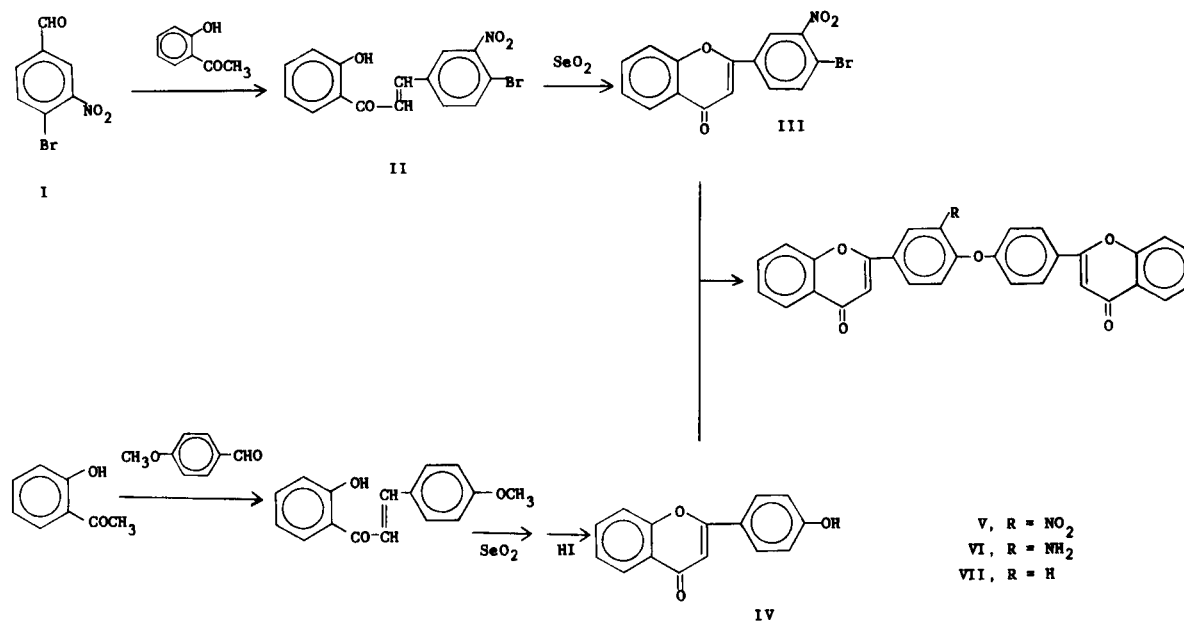
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In recent years a considerable interest has been focused on the systematic distribution of biflavonyl compounds throughout the plant kingdom (2). They are classified as biflavonyls (ginkgetin, isoginkgetin), bilobetin, sciadopitysin, amentoflavone, sotetsuflavone, and kayaflavone) and biflavonyl ethers (hinokiflavone, cryptomerin A and B, and isocryptomerin). Following the previous studies on the synthesis of biflavonyls (3), three new biflavonyl ethers containing the 4'-4'''-ether linkage have been synthesized.

The key step in the synthesis of these compounds was the Ullmann condensation in which an appropriate aromatic halide was condensed with a phenolate of a flavone to form a diaryl derivative having a linkage between 4'-hydroxyflavone and 4'-haloflavone. However, this reaction proceeded with difficulties. This problem was overcome by introducing a nitro group at the *ortho* position to activate the halogen function on the molecule (4). Synthesis of these compounds is shown in Scheme 1.

Scheme 1



## EXPERIMENTAL (5)

Melting points were determined on a Thomas-Hoover melting point apparatus and were corrected. Ultraviolet spectra were measured on a Bausch & Lomb spectrophotometer. Infrared spectra were run on a Perkin-Elmer 137 Infracord spectrophotometer using potassium bromide pellets. NMR spectra were recorded on a Varian A-60 using tetramethylsilane as the internal standard. Mass spectra were determined on an AEI MS-902 spectrometer. Elemental analyses were carried out by the Analytical Laboratory, National Taiwan University, Taipei, Formosa.

## 4-Bromo-3-nitrobenzaldehyde (I).

*p*-Bromobenzaldehyde (5 g.) was added gradually to a mixture of sodium nitrate (2.7 g.) and concentrated sulfuric acid (30 g.) maintained at 10-15°. The mixture was then heated to 50° for 10 minutes, allowed to cool and poured onto ice. The aldehyde which precipitated was collected, washed and crystallized from alcohol to pale yellow needles (7 g.), with m.p. 103-104° [reported m.p. 103° (6) and 106° (7)].

## 4-Bromo-3-nitro-2'-hydroxychalcone (II).

To a cooled mixture of *o*-hydroxyacetophenone (1.36 g.) and 4-bromo-3-nitrobenzaldehyde (2.3 g.) in alcohol (10 ml.) was added 5 ml. of cold 30% aqueous potassium hydroxide. The mixture was placed in a stoppered bottle and kept at 0° for 24 hours with occasional shaking. The mixture was diluted with water and acidified with dilute acetic acid. The chalcone thus precipitated was collected and crystallized from alcohol to yellow needles (1 g.) with m.p. 192-194°; UV  $\lambda$  max 265.5, 292.5 m $\mu$ ; IR 3075, 1700, 1645, 1580, 1537, 1430, 1138, 1030, 890, 848, 795, 690, 540, 490 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>15</sub>H<sub>10</sub>BrNO<sub>4</sub>: C, 51.76; H, 2.87; N, 4.03. Found: C, 51.35; H, 2.99; N, 4.25.

## 3'-Nitro-4'-bromoflavone (III).

A mixture of the chalcone (II, 1 g.), selenium dioxide (1 g.) and isoamyl alcohol (20 ml.) was refluxed for 48 hours. After the isoamyl alcohol was removed by steam distillation, the solid flavone remained in the container was collected and crystallized from acetone to give pale yellow needles (0.8 g.) with m.p. 245-246°; UV  $\lambda$  max 250, 312.5 m $\mu$ ; IR 3200, 2650, 1633, 1604, 1582, 1569, 1518, 1485, 1393, 1300, 1265, 1183, 1125, 1059, 915, 840, 780, 760, 645, 535, 520 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>15</sub>H<sub>8</sub>BrNO<sub>4</sub>: C, 52.06; H, 2.31; N, 4.05. Found: C, 51.98; H, 2.58; N, 4.26.

## 4'-Hydroxyflavone (IV).

This material was prepared by condensing *o*-hydroxyacetophenone and *p*-anisaldehyde according to the previously described method (8). The m.p. of the material was 269-271° [reported 268° (9)].

## 3'-Nitro-4',4'''-biflavonyl Ether (V).

A mixture of bromo-nitroflavone (III, 0.3 g.), 4'-hydroxyflavone (IV, 0.2 g.), potassium carbonate (3 g.), and dimethyl sulfoxide (10 ml.) was heated to 125° for 1 hour with occasional stirring. The mixture was allowed to cool and poured into water (100 ml.), and the dark yellow precipitate was collected by filtration, washed with water and dried. Upon recrystallization from dioxane, it yielded yellow prisms (0.27 g.) with m.p. 257-258°; UV  $\lambda$  max 252.5, 305 m $\mu$ ; IR 3075, 1650, 1540, 1475, 1360, 1270, 1195, 1097, 1030, 955, 920, 860, 840, 685, 618, 580 cm<sup>-1</sup>.

Because of the insolubility of this compound, NMR spectrum could not be obtained.

*Anal.* Calcd. for C<sub>30</sub>H<sub>17</sub>NO<sub>7</sub>: C, 71.60; H, 3.38; N, 2.78. Found: C, 71.25; H, 3.76; N, 2.55.

## 3'-Amino-4'''-biflavonyl Ether (VI).

To a stirring solution of 3'-nitro-4'-4'''-biflavonyl ether (V, 0.27 g.) in dimethylformamide (15 ml.) was added sodium persulfate (5 g.) at 80-90° over a period of 30 minutes. The mixture was allowed to cool and water was added to precipitate the reaction product. The yellow precipitate was collected by filtration, washed with water, and recrystallized from alcohol to yield pale yellow needles (0.19 g.) with m.p. 228-230°; UV  $\lambda$  max 252, 307.5 m $\mu$ ; IR 3450, 3360, 1640, 1605, 1505, 1470, 1448, 1430, 1380, 1315, 1245, 1180, 1140, 1055, 970, 918, 840, 780, 765, 613 cm<sup>-1</sup>; NMR (in DMSO-d<sub>6</sub>)  $\tau$  1.35-2.84 (m, 15H, aromatic), 2.94 (s, 1H), 3.08 (s, 1H), 4.42-4.60 (m, 2H).

*Anal.* Calcd. for C<sub>30</sub>H<sub>19</sub>NO<sub>5</sub>: C, 76.13; H, 4.01; N, 2.96. Found: C, 75.88; H, 4.25; N, 2.80.

## 4',4'''-Biflavonyl Ether (VII).

A solution of 3'-amino-4',4'''-biflavonyl ether (VI, 0.27 g.) in alcohol (5 ml.) and concentrated sulfuric acid (1 ml.) was diazotized with 10% sodium nitrite. After the addition of 50% hypophosphorus acid (2 ml.) the mixture was left standing overnight in a refrigerator. The product was precipitated by the addition of water. The precipitate was collected by filtration, washed with water, and recrystallized from alcohol to give yellow needles with m.p. 236-238°; UV  $\lambda$  max 252.5, 315 m $\mu$ ; IR 3075, 1635, 1480, 1434, 1385, 1236, 1143, 1060, 1032, 925, 866, 850, 780, 755, 690, 620, 540, 520 cm<sup>-1</sup>; NMR (in DMSO-d<sub>6</sub>)  $\tau$  1.46-2.80 (m, 16H, aromatic), 3.12 (s, 2H). Mass 458.

*Anal.* Calcd. for C<sub>30</sub>H<sub>18</sub>O<sub>5</sub>: C, 78.60; H, 3.93. Found: C, 78.35; H, 4.05.

The mass spectrum of this compound indicated a value of 458 with 30 carbon atoms in the molecule, which corresponded to the calculated values for this compound. Since VII is the final product of the synthetic route as outlined in the scheme, these data implicated the validity of this series of synthesis and the accuracy of the chemical nature of the compounds presented in this paper.

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