Synthesis of 5,7-Dihydroxy-2′,4′,5′-trimethoxyisoflavone and Its 7-Methyl Ether (Robustigenin)

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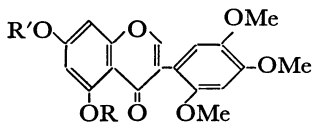
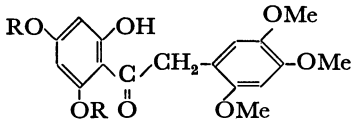
Synopsis. The treatment of 2,4,6-trihydroxy-2′,4′,5′-trimethoxydeoxybenzoin with benzyl chloride gave a dibenzyl ether. The condensation of the ether with ethyl formate, followed by the debenzylation of the resulting isoflavone, afforded 5,7-dihydroxy-2′,4′,5′-trimethoxyisoflavone, which was then converted into a pentamethoxyisoflavone. The partial demethylation of the pentamethoxyisoflavone gave 5-hydroxy-2′,4′,5′,7-tetramethoxyisoflavone, which was identical with natural robustigenin.

Recently, robustigenin, $C_{19}H_{18}O_7$, was isolated from seed shells of *Derris robusta*. Its structure was identified as 5-hydroxy-2′,4′,5′,7-tetramethoxyisoflavone (**1**) on the basis of spectral evidence.[1] We attempted the synthesis of **1** in order to confirm the proposed structure. This paper will describe the synthesis of 5,7-dihydroxy-2′,4′,5′-trimethoxyisoflavone (**2**), which may be expected to occur in nature, and 7-methyl ether of **2** (**1**, robustigenin).

The treatment of 2,4,6-trihydroxy-2′,4′,5′-trimethoxydeoxybenzoin (**3**)[2,3] with benzyl chloride and anhydrous potassium carbonate in acetone gave a dibenzyl ether (**4**). The condensation of **4** with ethyl formate in the presence of sodium gave 5,7-bis(benzyloxy)-2′,4′,5′-trimethoxyisoflavone (**5**). The debenzylation of **5** by hydrogenolysis with palladium on charcoal afforded a dihydroxyisoflavone (**2**), which was then easily converted into a dimethyl ether (**6**). The isoflavone (**6**) was also prepared by the following procedure. The Hoesch reaction of phloroglucinol dimethyl ether and 2,4,5-trimethoxyphenylacetonitrile,[4] or the treatment of phloroglucinol dimethyl ether and homoasaronic acid (2,4,5-trimethoxyphenylacetic acid)[5] in the presence of boron trifluoride etherate, yielded 2-hydroxy-2′,4,4′,5′,6-pentamethoxydeoxybenzoin (**7**). The reaction of **7** and ethyl formate yielded the isoflavone (**6**).



(**1**) R=H, R′=Me
(**2**) R=R′=H
(**5**) R=R′=$C_6H_5CH_2$
(**6**) R=R′=Me



(**3**) R=H
(**4**) R=$C_6H_5CH_2$
(**7**) R=Me

The partial demethylation of **6** with anhydrous aluminium chloride in acetonitrile[6] gave the desired isoflavone (**1**). The spectral properties of the two synthetic samples **2** and **6** were superimposable upon those recorded for natural robustigenin and its methyl ether.[1]

Experimental

The melting points are uncorrected. The IR spectra were measured in nujol, while the UV spectra were measured in an ethanol, unless otherwise stated. The NMR spectra were recorded on either a Hitachi R-20 (60 MHz) or JEOL JNM MH-100 (100 MHz) spectrometer, and the chemical shifts are reported in δ values, with TMS as the internal standard.

4,6-Bis(benzyloxy)-2-hydroxy-2′,4′,5′-trimethoxydeoxybenzoin (4). A mixture of 2,4,6-trihydroxy-2′,4′,5′-trimethoxydeoxybenzoin (**3**)[2,3] (1.0 g), anhydrous potassium carbonate (6.0 g), and benzyl chloride (0.9 ml) in dry acetone (60 ml) was refluxed for 6 h. The reaction mixture was then filtered, and the filtrate was evaporated *in vacuo*. The residue was recrystallized from acetone to give colorless needles of **4** (1.1 g) (mp 198—199 °C), which showed a pale brown color with ethanolic $FeCl_3$. IR: 1633 cm^{-1}. Found: C, 72.07; H, 6.18%. Calcd for $C_{31}H_{30}O_7$: C, 72.36; H, 5.88%.

5,7-Bis(benzyloxy)-2′,4′,5′-trimethoxyisoflavone (5). A solution of **4** (500 mg) in anhydrous ethyl formate (35 ml) was added to powdered sodium (600 mg) at 0 °C, and then the mixture was left at room temperature for 12 h. The mixture was treated with ice water and acidified with 6 M HCl. After almost all the ethyl formate had been evaporated *in vacuo*, the resulting semi-solid was dried and heated with acetic anhydride (10 ml) for 0.5 h. The reaction mixture was diluted with cold water to give pale yellow precipitates. The precipitates were collected and recrystallized from methanol to give colorless needles of **5** (200 mg); mp 163—164 °C; IR: 1650 cm^{-1}; UV λ_{max} nm (log ε): 255 (4.46), 291 (4.20). Found: C, 72.98; H, 5.66%. Calcd for $C_{32}H_{28}O_7$: C, 73.27; H, 5.38%.

5,7-Dihydroxy-2′,4′,5′-trimethoxyisoflavone (2). A solution of **5** (180 mg) in ethyl acetate (30 ml) was submitted to catalytic hydrogenolysis in the presence of Pd–C (10%: 100 mg) at room temperature. After the catalyst had been filtered, the filtrate was evaporated *in vacuo*. The residue was recrystallized from methanol to give colorless needles of **2** (110 mg) (mp 243—244 °C), which showed a brown color with ethanolic $FeCl_3$. IR: 3350, 1655 cm^{-1}; UV λ_{max} nm (log ε): 260.5 (4.42), 296 (4.16). Found: C, 62.52; H, 4.77%. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68%.

Diacetate of 2: Hot acetic anhydride–pyridine method; mp 204—205 °C (colorless needles from methanol). IR: 1763, 1650 cm^{-1}; UV λ_{max} nm (log ε): 294.5 (4.11); NMR ($CDCl_3$): δ 2.38, 2.43 (each 3H, s, CH_3CO), 3.79, 3.88, 3.96 (each 3H, s, CH_3O), 6.67, 6.91 (each 1H, s, 3′-, 6′-H), 6.94, 7.29, (each 1H, d, J=2 Hz, 6-, 8-H), 7.93 (1H, s,

2-H). Found: C, 61.34; H, 4.90%. Calcd for $C_{22}H_{20}O_9$: C, 61.68; H, 4.71%.

2-Hydroxy-2',4,4',5',6-pentamethoxydeoxybenzoin (7). *Hoesch Reaction*: A mixture of phloroglucinol dimethyl ether (800 mg), 2,4,5-trimethoxyphenylacetonitrile[4] (1.0 g) and anhydrous zinc chloride (1.0 g) in dry ether (35 ml) was saturated with anhydrous hydrogen chloride at 0 °C for 3 h and then allowed to stand at room temperature for 12 h. The ethereal solution was decanted from the oily layer of ketimine hydrochloride which had separated. This oily layer was washed with dry ether and then heated with water on a steam bath for 1 h. After cooling and standing, the precipitates were collected and recrystallized from ethanol to give colorless needles of **7** (200 mg), mp 145—146.5 °C (lit, mp 143 °C,[2] mp 144—145 °C[3]), which showed a yellowish violet color with ethanolic $FeCl_3$. IR: 1645 cm^{-1}; UV λ_{max} nm (log ε); 289 (4.35). Found: C, 62.96; H, 6.09%. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12%.

BF_3 Method: A mixture of phloroglucinol dimethyl ether (1.0 g) and homoasaronic acid[5] (1.47 g) in dry ether (35 ml) was saturated with anhydrous boron trifluoride gas at 0 °C for 3 h and then heated on a steam bath for 0.5 h. After cooling and standing, the reaction mixture was diluted with water. The resulting precipitates were collected and recrystallized to give **7** (320 mg), mp 144—145 °C, whose IR spectrum was identical with those of the sample described above.

2',4',5,5',7-Pentamethoxyisoflavone (6). *From 2*: A mixture of **2** (100 mg), anhydrous potassium carbonate (500 mg), and methyl iodide (0.5 ml) in dry acetone (30 ml) was refluxed for 5 h. The reaction mixture was then filtered, and the filtrate was evaporated *in vacuo*. The residue was recrystallized from methanol to give colorless needles of **6** (90 mg), mp 190—191 °C (lit,[1] mp 192—193 °C); IR: 1658 cm^{-1}; UV λ_{max} nm (log ε): 255 (4.42), 291 (4.15); NMR ($CDCl_3$): δ 3.74, 3.83, 3.88, 3.92, 3.93 (each 3H, s, CH_3O), 6.39, 6.49 (each 1H, d, J=2 Hz, 6-, 8-H), 6.60, 6.98, 7.80 (each 1H, s, 3'- 6'-, 2-H), whose IR and NMR spectra were identical with those of the corresponding derivative from natural robustigenin.[1] Found: C, 64.21; H, 5.44%. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41%.

From 7: A solution of **7** (200 mg) in anhydrous ethyl formate (11 ml) was added to powdered sodium (300 mg) at 0 °C, and then the mixture was left at room temperature for 24 h. The reaction mixture was then worked up in the same manner as in the case of **5** to give **6** (180 mg), which was subsequently recrystallized from methanol as colorless needles; mp 189—191 °C. It was identical with the sample described above.

Robustigenin 5-Hydroxy-2',4',5',7-tetramethoxyisoflavone (1). A mixture of **6** (30 mg), anhydrous aluminium chloride (110 mg), and acetonitrile (7 ml) was stirred under gentle refluxing for 16 h. After the removal of the solvent, dilute hydrochloric acid was added to the residue. The resulting solid was collected, washed with water, dried, and then chromatographed on silica gel (10 g), using ether–benzene (5:95) as the eluent, to give colorless needles of **1** (10 mg), mp 177—178 °C (lit,[1] mp 174—175 °C), which showed a dark violet color with ethanolic $FeCl_3$. IR (KBr): 3090, 1660 cm^{-1}; UV λ_{max} nm (log ε): 260 (4.41); NMR ($CDCl_3$): δ 3.75 (3H, s, CH_3O), 3.83 (6H, s, CH_3O ×2), 3.89 (3H, s, CH_3O), 6.36 (2H, s, 6- and 8-H), 6.59, 6.86, 7.85 (each 1H, s, 3'-, 6'-, 2-H), 12.92 (1H, s, OH), whose IR, UV, and NMR spectra were identical with those of natural robustigenin.[1] Found: C, 63.82; H, 5.21%. Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06%.

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