

Synthesis of 6-Chlorogenistein

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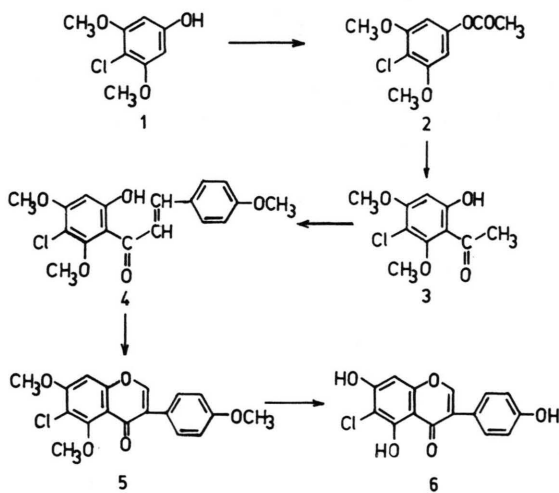
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Chloroachalcone, Chloroisoflavone, Oxidation with Thallium(III) Nitrate

An unambiguous synthesis of 6-chlorogenistein (5,7,4'-trihydroxy-6-chloroisoflavone) has been worked out *via* the oxidation of 2'-hydroxy-4,4',6'-trimethoxy-5'-chloroachalcone with thallium(III) nitrate followed by the demethylation of the 5,7,4'-trimethoxy-6-chloroisoflavone.

Genistein (5,7,4'-trihydroxyisoflavone) and its two chlorinated derivatives, 6-chlorogenistein and 6,3'-dichlorogenistein, were isolated from the soybean meal-containing culture medium of the *Streptomyces griseus* by König *et al.* in 1977 [1]. The structure of the compounds isolated was elucidated by means of spectroscopic (UV, IR, $^1\text{H-NMR}$ and MS) methods. In the present paper we report on the synthesis of 6-chlorogenistein.



The starting material of the synthesis was 4-chloro-3,5-dimethoxyphenol (**1**) which was prepared from 3,5-dimethoxyphenol according to the method of Grove *et al.* [2]. 4-Chloro-3,5-dimethoxyphenol (**1**) was acetylated with the mixture of acetic anhydride and sodium acetate to afford 4-chloro-3,5-

dimethoxyphenyl acetate (**2**). Substance **2** was rearranged into 2-hydroxy-4,6-dimethoxy-5-chloroacetophenone (**3**) with AlCl_3 in nitrobenzene. 2'-Hydroxy-4,4',6'-trimethoxy-5'-chloroachalcone (**4**) was prepared by the condensation of compound **3** and 4-methoxybenzaldehyde. Compound **4** was oxidized with thallium(III) nitrate to yield the corresponding 1,2-diaryl-3,3-dimethoxypropan-1-one which was converted into 5,7,4'-trimethoxy-6-chloroisoflavone (**5**) without isolation. The 5,7,4'-trimethoxy-6-chloroisoflavone (**5**) was demethylated with pyridine hydrochloride to obtain 5,7,4'-trihydroxy-6-chloroisoflavone (**6**, 6-chlorogenistein).

Structure of the 6-chlorogenistein (**6**) synthesized was corroborated by spectroscopic measurements. Its UV and IR spectra were characteristic for an isoflavone skeleton. In the $^1\text{H-NMR}$ spectrum of compound **6** a singlet was found at 6.52 ppm which could be assigned to the H-C(8) and the signal belonging to the H-C(6) was absent. This unequivocally proved that the chlorine was built into the position 6 of the isoflavone molecule. In its mass spectrum a molecular ion peak was observed at m/e 304 and two characteristic peaks at m/e 186 and 118 belonging to fragment ions originating from the aromatic rings of compound **6**.

The spectral properties of the natural and synthetic products are in good agreement [3]. Furthermore, UV, IR and $^1\text{H-NMR}$ spectra of compounds **5** and **6** were compared to those of the 5,7,4'-trimethoxyisoflavone and 5,7,4'-trihydroxyisoflavone which also proved the correctness of their structure.

Experimental

$^1\text{H-NMR}$ spectra were recorded on a Jeol MH 100 spectrometer at 100 MHz in CDCl_3 unless otherwise stated (internal standard TMS, $\delta = 0.0$ ppm) at room temperature. The IR spectra were measured for KBr discs with a Perkin-Elmer 283 instrument. UV spectra were recorded in ethanolic solutions with a UNICAM SP 800 apparatus. The mass spectrum was measured with a V. G. Micromass 7035 instrument using direct inlet; source temperature 180 $^\circ\text{C}$, electron energy 70 eV.

4-Chloro-3,5-dimethoxyphenyl acetate (**2**)

A mixture of 4-chloro-3,5-dimethoxyphenol (**1**, 7.5 g), sodium acetate (3.3 g) and acetic anhydride

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(20.4 ml) was heated on a steam-bath for 15 min, then cooled down and suspended in water. The precipitate was filtered off and crystallized from aqueous ethanol to afford 8.5 g (92%) of white crystalline substance, m. p. 74 °C. $^1\text{H-NMR}$ 2.22 (s, CH_3CO), 3.8 (s, 2 CH_3O), 6.26 (s, H-C(2) and H-C(6)).

$\text{C}_{10}\text{H}_{11}\text{ClO}_4$ (230.64)

Found: Cl 15.58, Calcd: Cl 15.37.

2-Hydroxy-4,6-dimethoxy-5-chloroacetophenone (3)

4-Chloro-3,5-dimethoxyphenyl acetate (**2**, 4.6 g) and anhydrous AlCl_3 (3.1 g) were heated in nitrobenzene (4.5 ml) for 5 min at 90 °C then for another 5 min at 130 °C. The mixture was poured onto crushed ice, treated with cc HCl (10 ml) and extracted with ether (150 ml).

The extract was dried over MgSO_4 and the solvent evaporated. The residue was purified on Kieselgel 40 column using benzene:methanol = 89:11 (v/v) eluant and crystallized from ethanol to give 0.5 g (11%) of **3**, m. p. 193–194 °C. $^1\text{H-NMR}$ 2.58 (s, CH_3CO), 3.85 (s, 2 CH_3O), 5.87 (s, H-C(3)).

$\text{C}_{10}\text{H}_{11}\text{ClO}_4$ (230.64)

Found: Cl 15.36, Calcd: Cl 15.37.

2'-Hydroxy-4,4',6'-trimethoxy-5'-chlorochalcone (4)

2-Hydroxy-4,6-dimethoxy-5-chloroacetophenone (**3**, 0.35 g) and 4-methoxybenzaldehyde (0.27 g) were dissolved in ethanol (15 ml) and 60% KOH (4.2 ml) was added. The mixture was stirred for 12 h at room temperature, then acidified with 1 N HCl, the precipitate filtered off, washed with water and crystallized from ethanol to yield 0.37 g (71%) of **4**, m. p. 164–165 °C. $^1\text{H-NMR}$ 3.80 (s, CH_3O), 3.90 (s, 2 CH_3O), 5.95 (s, H-C(3')), 6.8 and 6.9 (2s,

H-C(3) and H-C(5)), 7.45 and 7.55 (2s, H-C(2) and H-C(6)), 7.72 (2s, H-C(α) and H-C(β)).

$\text{C}_{18}\text{H}_{17}\text{ClO}_5$ (348.77)

Found: Cl 10.23, Calcd: Cl 10.16.

5,7,4'-Trimethoxy-6-chloroisoflavone (5)

A methanolic solution (20 ml) of 2'-hydroxy-4,4',6'-trimethoxy-5'-chlorochalcone (**4**, 0.2 g) and thallium(III) nitrate trihydrate (0.4 g) was stirred for 4.5 h at room temperature. The inorganic salt was filtered off, 2 N HCl (2 ml) was added to the solution and refluxed for 2 h, then the methanol evaporated. The precipitate was filtered off, washed free of acid and crystallized from methanol to obtain 0.034 g (17%) of **5**, m. p. 199–200 °C. UV λ_{max} [nm] (log ϵ) 257 (4.69), 285 sh (4.17), 320 sh (3.95). IR $\nu_{\text{C}=\text{C}}$ 1610 and $\nu_{\text{C}=\text{O}}$ 1650 cm^{-1} . $^1\text{H-NMR}$ 3.78 (s, CH_3O), 3.90 (s, 2 CH_3O), 6.34 (s, H-C(8)), 6.86 and 6.94 (2s, H-C(3') and H-C(5')), 7.40 and 7.48 (2s, H-C(2') and H-C(6')), 7.78 (s, H-C(2)).

$\text{C}_{18}\text{H}_{15}\text{ClO}_5$ (346.75)

Found: Cl 10.40, Calcd: Cl 10.21.

5,7,4'-Trihydroxy-6-chloroisoflavone (6)

A mixture of 5,7,4'-trimethoxy-6-chloroisoflavone (**5**, 0.1 g) and pyridine hydrochloride (2 g) was heated for 9 h at 210 °C, then cooled down and triturated with water. The precipitate was filtered off, washed free of acid and crystallized from aqueous methanol to afford 0.027 g (31%) of **6**, m. p. 237–239 °C. UV λ_{max} [nm] (log ϵ) 266 (4.45), 335 (3.98). IR $\nu_{\text{C}=\text{C}}$ 1615 and $\nu_{\text{C}=\text{O}}$ 1650 cm^{-1} . $^1\text{H-NMR}$ (acetone- d_6) 6.52 (s, H-C(8)), 6.80 and 6.88 (2s, H-C(3') and H-C(5')), 7.36 and 7.42 (2s, H-C(2') and H-C(6')), 8.10 (s, H-C(2)).

[1] W. A. König, C. Krauss, and H. Zähler, *Helv. Chim. Acta* **60**, 2071 (1977).

[2] J. F. Grove, J. McMillan, T. P. C. Mulholland, and J. Zealley, *J. Chem. Soc.* **1952**, 3967.

[3] No direct comparison was possible, since the authors [1] who described the isolation of the 6-chlorogenistein could not send us an authentic sample.