Synthesis of 6-Chlorogenistein

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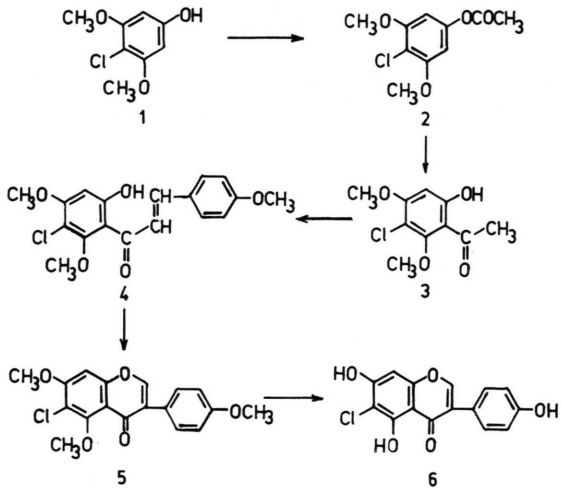
An unambiguous synthesis of 6-chlorogenistein (5,7,4′-trihydroxy-6-chloroisoflavone) has been worked out *via* the oxidation of 2′-hydroxy-4,4′,6′-trimethoxy-5′-chlorochalcone with thallium(III) nitrate followed by the demethylation of the 5,7,4′-trimethoxy-6-chloroisoflavone.

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}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′-chlorochalcone (**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}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}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}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 °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}H-NMR 2.22 (s, CH_3CO), 3.8 (s, $2CH_3O$), 6.26 (s, H–C(2) and H–C(6)).

$C_{10}H_{11}ClO_4$ (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}H-NMR 2.58 (s, CH_3CO), 3.85 (s, $2CH_3O$), 5.87 (s, H–C(3)).

$C_{10}H_{11}ClO_4$ (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}H-NMR 3.80 (s, CH_3O), 3.90 (s, $2CH_3O$), 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)).

$C_{18}H_{17}ClO_5$ (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 νC=C 1610 and νC=O 1650 cm^{-1}. ^{1}H-NMR 3.78 (s, CH_3O), 3.90 (s, $2CH_3O$), 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)).

$C_{18}H_{15}ClO_5$ (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 νC=C 1615 and νC=O 1650 cm^{-1}. ^{1}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. Zähner, 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.