SYNTHESIS OF 8-CHLORO-3′,4′,5,7-TETRAHYDROXYISOFLAVONE POSSESSING ANTIOXIDANT ACTIVITY

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Recently, three antioxidant isoflavonoids characterized as 4′,7,8-trihydroxyisoflavone, 3′,4′,7-trihydroxyisoflavone and 8-chloro-3′,4′,5,7-tetrahydroxyisoflavone (**1**) were isolated from the cultured broth of *Streptomyces* sp. OH-1049 by ŌMURA *et al.*[1,2]. Among them, **1** is a novel isoflavonoid possessing a chlorine atom in the molecule. This work is about the synthesis of **1**.

The starting material of the synthesis was 2-chloro-3,5-dimethoxyphenol (**2**) which was prepared from 3,5-dimethoxyphenol according to the method of GROVE *et al.*[3]. Acetylation of 2-chloro-3,5-dimethoxyphenol (**2**) afforded 2-chloro-3,5-dimethoxyphenyl acetate (**3**). Then the compound **3** was rearranged into 3-chloro-2-hydroxy-4,6-dimethoxyacetophenone (**4**) with $AlCl_3$ in nitrobenzene. 3′-Chloro-2′-hydroxy-3,4,4′,6′-tetramethoxychalcone (**5**) was prepared by the condensation of **4** and 3,4-dimethoxybenzaldehyde. Compound **5** was converted with thallium (III) nitrate into 8-chloro-3′,4′,5,7-tetramethoxyisoflavone (**6**) which was demethylated with pyridine hydrochloride to obtain 8-chloro-3′,4′,5,7-tetrahydroxyisoflavone (**1**). Structure of **1** synthesized was corroborated by spectroscopic measurements. Its UV spectra was characteristic for an isoflavone skeleton. In the ^1H NMR spectrum of **1** a singlet was found at δ 6.40 ppm which was assigned to the 6-H and typical lower field singlet at δ 8.00 (2-H) was observed. In its mass spectrum a molecular ion peak was observed at m/z 320 and two peaks at 188 and 134 belonging to fragment ions originating from the aromatic rings of **1**. The spectral properties of the natural and synthetic products are in good agreement.

Experimental

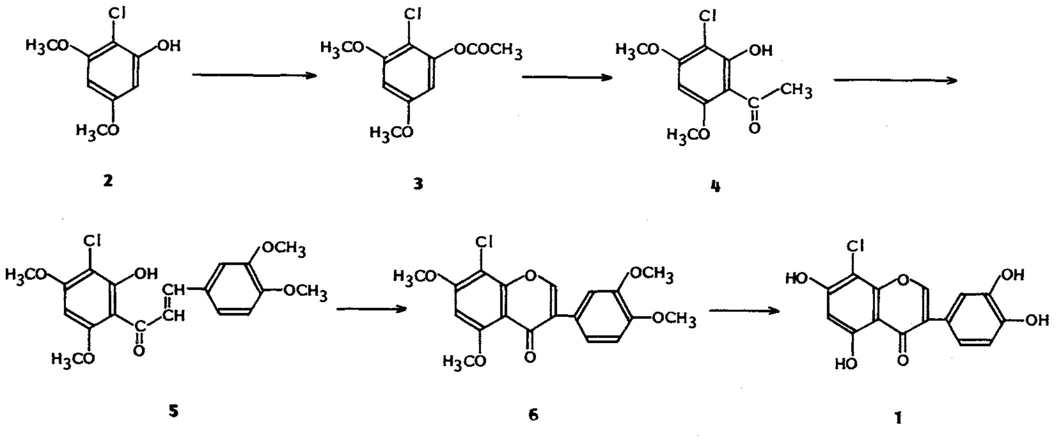
UV spectra were recorded in methanolic solutions with a UNICAM SP 800 apparatus. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometer WP 200 SY (200/50 MHz), internal standard TMS. MS were obtained with a VG-7035 type mass spectrometer. IR spectra were measured for KBr discs with a Perkin-Elmer 283 instrument.

2-Chloro-3,5-dimethoxyphenyl Acetate (3)

A mixture of 2-chloro-3,5-dimethoxyphenol (**2**, 2 g), sodium acetate (2 g) and acetic anhydride (4.5 ml) was heated on a steam-bath for 15 minutes, then cooled down and suspended in water. The precipitate was filtered off and crystallized from aqueous ethanol to afford 1.8 g (74%) of white crystalline product, mp 61°C. ^1H NMR δ 2.35 (3H, s, CH_3CO), 3.90 (3H, s, CH_3O), 3.78 (3H, s, CH_3O), 6.30 (1H, d, 4-H), 6.40 (1H, d, 6-H). *Anal* Calcd for $C_{10}H_{11}ClO_4$: C 52.07, H 4.80, Cl 15.37. Found: C 52.00, H 4.78, Cl 15.50.

3-Chloro-2-hydroxy-4,6-dimethoxyacetophenone (4)

2-Chloro-3,5-dimethoxyphenyl acetate (**3**, 2 g) and anhydrous $AlCl_3$ (1.5 g) were heated in



nitrobenzene (2.25 ml) for 5 minutes at 90°C then for another 5 minutes at 130°C. The mixture was poured onto crushed ice, treated with conc HCl and extracted with ether. The organic phase was extracted with 1.8 M NaOH (50 ml) and acidified with 2.8 M HCl. The product precipitated was crystallized from ethanol to yield 0.49 g (24%) of **4**, mp 188°C. ^{1}H NMR δ 2.60 (3H, s, CH_3CO), 3.92 (3H, s, CH_3O), 3.95 (3H, s, CH_3O), 6.0 (1H, s, 5-H). *Anal* Calcd for $C_{10}H_{11}ClO_4$: C 52.07, H 4.80, Cl 15.37. Found: C 52.01, H 4.85, Cl 15.30.

3′-Chloro-2′-hydroxy-3,4,4′,6′-tetramethoxychalcone (5)

3-Chloro-2-hydroxy-4,6-dimethoxyacetophenone (**4**, 0.23 g) and 3,4-dimethoxybenzaldehyde (0.19 g) were suspended in ethanol (20 ml) and 14 M KOH (2.8 ml) was added. The clear solution was stirred for 24 hours at room temperature, then acidified with 2.8 M HCl. The precipitate was filtered off, washed with water and crystallized from ethanol to yield 0.15 g (39%) of **5**, mp 175°C. ^{1}H NMR δ 3.90 (6H, s, $2\times CH_3O$), 4.0 (6H, s, $2\times CH_3O$), 6.50 (1H, s, 5′-H), 6.90 (1H, d, 2-H), 7.10 (1H, d, α-H), 7.20 (1H, dd, 6-H), 7.25 (1H, d, β-H, $J_{\alpha,\beta}=12$ Hz), 7.80 (1H, d, 5-H), 13.8 (1H, s, OH). *Anal* Calcd for $C_{19}H_{19}ClO_6$: C 60.24, H 5.05, Cl 9.35. Found: C 60.30, H 5.01, Cl 9.30.

8-Chloro-3′,4′,5,7-tetramethoxyisoflavone (6)

A methanolic solution (160 ml) of **5** (0.21 g) and thallium (III) nitrate trihydrate (0.4 g) was stirred for 4 hours at room temperature. 2.8 M HCl (2 ml) was added to the solution and refluxed for 1 hour, then the methanol evaporated. The residue was suspended in water filtered off and crystallized from methanol to obtain 0.1 g (55%) of **6**, mp 158°C. UV λ_{max}^{MeOH} nm 261, 288 (sh). IR $\nu_{C=C}$ cm^{-1} 1610 and $\nu_{C=C}$ cm^{-1} 1650. ^{1}H NMR δ 3.90 (6H, s, $2\times CH_3O$), 4.0 (6H, s, $2\times CH_3O$), 6.45 (1H, s, 6-H), 6.90 (2H, m, 2′-H, 6′-H), 7.20 (1H, d, 5′-H), 7.90 (1H, s, 2-H). MS: *m/z* 376 (M$^+$). *Anal* Calcd for $C_{19}H_{17}ClO_6$: C 60.56, H 4.54, Cl 9.40. Found: C 60.51, H 4.50, Cl 9.42.

8-Chloro-3′,4′,5,7-tetrahydroxyisoflavone (1)

A mixture of **6** (0.1 g) and pyridine hydrochloride (2 g) was heated for 8 hours at 210°C, then cooled down and triturated with water and crystallized from aqueous methanol to afford 0.04 g (47%) of **1**, mp 220°C. UV λ_{max}^{MeOH} nm 264, 293 (sh). IR $\nu_{C=C}$ cm^{-1} 1612 and $\nu_{C=O}$ cm^{-1} 1650. ^{1}H NMR δ 6.37 (1H, s, 6-H), 7.0 (2H, m, 2′-H, 6′-H), 7.2 (1H, d, 5-H), 8.0 (1H, s, 2-H). MS: *m/z* 320 (M$^+$), 188, 134. *Anal* Calcd for $C_{15}H_9ClO_6$: C 56.17, H 2.82, Cl 11.05. Found: C 56.20, H 2.85, Cl 11.12.

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