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5,6,7-TRISUBSTITUTED FLAVONES FROM *GOMPHRENA MARTIANA*

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Key Word Index—*Gomphrena martiana*; Amaranthaceae; flavonoids; 5,6-dimethoxy-7-hydroxyflavone; 5,7-dihydroxy-6-methoxyflavone.

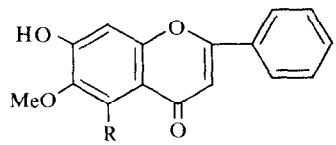
Abstract—Two 5,6,7-trisubstituted flavones have been isolated from *Gomphrena martiana* and identified as 5,6-dimethoxy-7-hydroxyflavone and 5,7-dihydroxy-6-methoxyflavone.

INTRODUCTION

We have previously characterized [1, 2] 3,5-dimethoxy-6,7-methylenedioxyflavone, 3,5,6,7-tetramethoxyflavone, 3,6-dimethoxy-5,7-dihydroxyflavone and 3,5,7-trimethoxyflavone from the whole plant petrol extract of *Gomphrena martiana* Moquin (Amaranthaceae). In continuation of our flavonoid studies on this species we now describe the isolation of two flavones with an unsubstituted B-ring: 5,6-dimethoxy-7-hydroxyflavone (**1**) and 5,7-dihydroxy-6-methoxyflavone (**2**). The former is described for the first time from a natural source, whilst the second has been previously isolated from *Oroxylum indicum* [3] and *Scutellaria* species [4–6].

RESULTS AND DISCUSSION

From a petrol extract of *G. martiana* two compounds were separated by chromatographic methods and identified as follows. Compound **1**, $C_{17}H_{14}O_5$, mp 207–209° (MeOH) was shown to be phenolic. Its UV spectrum indicated the absence of a free 5-hydroxyl since no shifts were observed with $AlCl_3$ and $AlCl_3$/HCl. A positive sodium acetate shift indicated that the 7-hydroxy was free. The ^{1}H NMR spectrum in $CDCl_3$ showed the presence of two methoxyl groups (δ 4 and 4.03, each a 3 H singlet), two aromatic protons (δ 6.67 and 6.93, each a 1 H singlet ascribed to H-3 and H-8, respectively) and an unsubstituted B-ring (δ 7.5 and 7.9, two complex multiplets integrating for 3 H and 2 H, respectively). On addition of Eu(fod)$_3$ the slopes ('S values') of the straight lines obtained by plotting δ values against the molar ratio of Eu(fod)$_3$ to the sample were in accordance with methoxyl groups at C-5 and C-6. The S values of two aromatic protons appearing between δ 6.6 and 7 in $CDCl_3$ confirm the above assignment of H-3 and H-8 [7, 8]. The signal of one methoxyl was partially shifted ($\Delta\delta$ 0.49 ppm) when the ^{1}H NMR spectrum was registered in benzene-d_6 indicating that this methoxyl (at C-6) is adjacent to two different functional groups. The other methoxyl showed a poor solvent shift ($\Delta\delta$ 0.04 ppm) as expected for one located at C-5 [9]. The presence of the methoxyl at C-5 was chemically confirmed by specific demethylation with $AlCl_3$ in acetonitrile [10] yielding a compound which gave bathocromic shifts with both $AlCl_3$ and $AlCl_3$/HCl in its UV spectrum.



1 R = OMe
2 R = OH

Fragments *m/z* 77 (Ph) and 105 (PhCO) in the mass spectrum of **1** confirmed the unsubstituted B-ring. Fragment A − Me accounted for a methoxyl at C-6. 5,6,7-Trisubstitution was confirmed by total methylation of **1**. The ^{1}H NMR spectrum of the methylated compound showed the presence of three methoxyl groups, one of which was strongly shifted (Δ 0.6 ppm) when running the spectrum in benzene-d_6. This behaviour is typical for a methoxyl at C-7 which is adjacent to a methoxyl at the 6- or 8-position. Another methoxyl was partially affected (Δ 0.19 ppm) indicating that it was at C-6 between two other methoxyls and the third showed a solvent shift of −0.12 ppm which is only possible for a methoxyl at C-5. Therefore, the three vicinal methoxyls are located at C-5, C-6 and C-7.

From these results **1** is characterized as 5,6-dimethoxy-7-hydroxyflavone.

Compound **2**, $C_{16}H_{12}O_5$, mp 200–201° (MeOH) was shown also to be phenolic. Its UV spectrum indicated that one free hydroxyl is at C-5 (bathochromic shift with $AlCl_3$ and $AlCl_3$/HCl) and another at C-7 (bathochromic shift with NaOAc). Its ^{1}H NMR spectrum ($CDCl_3$) showed the presence of only one methoxyl group (δ 4.05, 3 H singlet), two aromatic protons (δ 6.62 and 6.67, each 1 H singlet) and an unsubstituted B-ring (δ 7.53 and 7.9, two multiplets, 3 H and 2 H, respectively). The signal at 12.97 was assigned to 5-OH. The ^{1}H NMR spectrum of **2** in acetone-d_6 showed, among other signals, singlets at δ 6.78 (1 H) and 6.90 (1 H) corresponding to H-3 and H-8, respectively ($\Delta\delta$ 0.12 ppm) [11]. Its mass spectrum confirmed the presence of an unsubstituted B-ring (*m/z* 105 and 77) as well as a methoxyl at position 6.

Acetylation of **2** gave spectral data identical with those of diacetyloroxylin [11]. Therefore, **2** is identified as 5,7-dihydroxy-6-methoxyflavone (oroxylin). This compound was also obtained by demethylation of **1** with $AlCl_3$ in acetonitrile.

Total methylation of **1** and **2** gave the same product, which was identified as 5,6,7-trimethoxyflavone (trimethylbaicalein) [12], indicating that both naturally occurring compounds have the same A-ring substitution.

EXPERIMENTAL

General details have been previously described [1,2].

Isolation and identification of the flavones. Upon concn of the whole plant petrol extract, a ppt. separated out and was filtered off. 3,5,6,7-Tetramethoxyflavone [2] as well as **1** was obtained from the filtrate by Si gel chromatography and purified by liquid chromatography. Repeated crystallizations of the previous ppt. yielded 3,5-dimethoxy-6,7-methylenedioxyflavone [1]; the residue obtained after evapn of the mother liquors was chromatographed on a Si gel column. Three main fractions were obtained. The first was a mixture of two phenolic compounds that were separated by liquid chromatography yielding 3,6-dimethoxy-5,7-dihydroxyflavone [2] and **2**. From the other fractions 3,5,7-trimethoxyflavone was isolated as previously reported [2].

5,6-Dimethoxy-7-hydroxyflavone (**1**). Mp 207–209° (MeOH); UV λ_{max}^{MeOH} nm: 242 (sh), 264 and 310; +NaOMe: 238, 268 and 356; +NaOAc: 269 and 356; +NaOAc/H_3BO_3: 269 and 356. No shifts were observed with $AlCl_3$ and $AlCl_3$/HCl. ^{1}H NMR ($CDCl_3$): δ 4 (3 H, *s*, 5-OMe), 4.03 (3 H, *s*, 6-OMe), 6.67 (1 H, *s*, H-3), 6.93 (1 H, *s*, H-8), 7.5 (3 H, *m*, H-3′, H-4′ and H-5′), 7.9 (2 H, *m*, H-2′ and H-6′); ($CDCl_3$ + Eu(fod)$_3$): Molar ratio Eu(fod)$_3$/sample: 0.136, 0.433, 0.722; S values: −1.1 (H-3); 1.2 (H-8); 8.8 (6-OMe); 14.0 (5-OMe); (C_6D_6): δ 3.54 (3 H, *s*, 6-OMe); 3.96 (3 H, *s*, 5-OMe); 6.6 (1 H, *s*); 6.78 (1 H, *s*). MS *m/z* (%): 298 (M, 92), 283 (M − Me, 100), 281 (M − OH, 7.8), 267 (M − OMe, 5.4), 255 (M − COMe, 15.5), 181 (A − Me, 4.1),153 (A − COMe, 8.4), 105 (PhCO, 8.8), 102 (PhC≡CH, 5.8), 77 (Ph, 8.1), 69 (38.6).

Demethylation of **1**. This was performed with $AlCl_3$ in acetonitrile [10] to give **2**.

5,7-Dihydroxy-6-methoxyflavone (**2**). Mp 200–201° (MeOH); UV λ_{max}^{MeOH} nm: 247 (sh), 270 and 317; +NaOMe: 241, 270 and 365; +NaOAc: 271 and 365; +$AlCl_3$: 253, 281.5 and 339; +$AlCl_3$/HCl: 253, 281.5 and 339. ^{1}H NMR ($CDCl_3$): δ 4.05 (3 H, *s*, 6-OMe), 6.62 (1 H, *s*, H-3 or H-8), 6.67 (1 H, *s*, H-8 or H-3), 7.53 (3 H, *m*, H-3′, 4′ and H-5′), 7.9 (2 H, *m*, H-2′ and H-6′), 12.97 (1 H, *br. s*, 5-OH); (C_6D_6): δ 3.67 (3 H, *s*, 6-OMe); (Me_2CO-d_6): δ 3.97 (3 H, *s*, 6-OMe), 6.78 (1 H, *s*, H-3), 6.90 (1 H, *s*, H-8), 7.73 (3 H, *m*, H-3′, H-4′ and H-5′), 8.23 (2 H, *m*, H-2′ and H-6′), 9.48 (1 H, *br. s*, 7-OH), 13.45 (1 H, *br. s*, 5-OH). MS *m/z* (%): 284 (M, 100), 283 (M − 1, 7), 269 (M − Me, 68), 267 (M − OH, 9), 266 (M − H_2O, 47), 241 (M − COMe, 55), 167 (A − Me, 12), 139 (A − COMe, 27), 105 (PhCO, 4), 103 (15), 102 (PhC≡CH, 9), 77 (Ph, 15), 69 (C_3HO_2, 89).

Acetylation of **2**. This was performed by standard procedures yielding 5,7-diacetyl-6-methoxyflavone, mp 142–144° (MeOH). ^{1}H NMR ($CDCl_3$): δ 2.35 (3 H, *s*, MeCO), 2.46 (3 H, *s*, MeCO), 3.84 (3 H, *s*, 6-OMe), 6.55 (1 H, *s*, H-3), 7.20 (1 H, *s*, H-8), 7.44 (3 H, *m*, H-3′, H-4′ and H-5′), 7.75 (2 H, *m*, H-2′ and H-6′). MS *m/z* (%): 368 (M, 9.6), 326 (M − CH_2CO, 100), 285 (26.3), 284 (M − 2 CH_2CO, 97), 283 (15.8), 269 (M − 2 CH_2CO − Me, 92.9), 267 (26.3), 266 (98), 255 (29.8), 241 (51.9), 238 (17.3), 153 (34.6), 139 (A − COMe, 34.6), 105 (PhCO, 11.8), 102 (PhC≡CH, 11), 77 (Ph, 6.3), 69 (C_3HO_2, 67.7).

Methylation of **1** *and* **2**. This was achieved with Me_2SO_4–K_2CO_3 in Me_2CO in the usual manner. Both compounds gave the same total methylated product, 5,6,7-trimethoxyflavone. Its spectroscopical data were: UV λ_{max}^{MeOH} nm: 263 and 304. No shifts were observed with the usual UV reagents. ^{1}H NMR ($CDCl_3$): δ 3.91 (3 H, *s*, 7-OMe), 3.96 (3 H, *s*, 5-OMe), 3.99 (3 H, *s*, 6-OMe), 6.65 (1 H, *s*, H-3), 6.84 (1 H, *s*, H-8), 7.49 (3 H, *m*, H-3′, H-4′ and H-5′), 7.83 (3 H, *m*, H-2′ and H-6′); (C_6D_6): δ 4.08 (3 H, *s*, 5-OMe), 3.80 (3 H, *s*, 6-OMe), 3.31 (3 H, *s*, 7-OMe). MS *m/z* (%): 312 (M, 24.9); 311 (M − 1, 2.5); 297 (M − Me, 100); 281 (M − OMe, 5.4); 269 (M − COMe, 6.7); 254 (M − COMe − Me, 12); 195 (A − Me, 2.3); 167 (A − COMe, 11.9); 105 (PhCO, 23); 102 (PhC≡CH, 2.4); 77 (Ph, 3.4); 69 (9).

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