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Flavonoids Syntheses. IV.[1] Syntheses of 2′,3,4′,5,5′,6,7,8-Octaoxygenated Flavones

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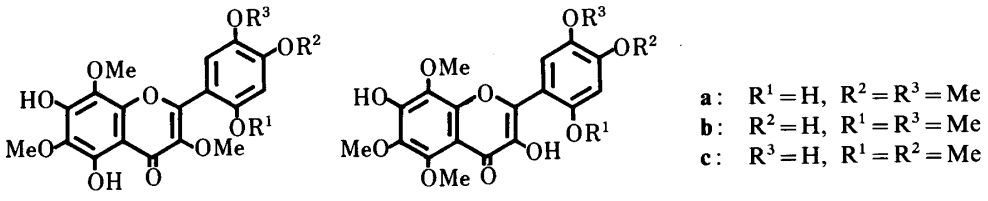
Six trihydroxy-pentamethoxyflavones were synthesized to confirm the structure of 2′,5,7-trihydroxy-3,4′,5′,6,8-pentamethoxyflavone, isolated from *Gutierreizia microcephala*.

Keywords——flavone synthesis; trihydroxy-pentamethoxyflavone; 2′,5,7-trihydroxy-3,4′,5′,6,8-pentamethoxyflavone; *Gutierreizia microcephala*

Several new polyoxygenated flavonols were isolated from *Gutierreizia microcephala* (Compositae) by Fang *et al.*[2]Among them, one flavonol (M^+: *m/z* 420) was concluded to be either 2′, 5,7-trihydroxy-3,4′,5′,6,8-pentamethoxyflavone (**1a**) or 5,5′,7-trihydroxy-2′,3,4′,6,8-pentamethoxyflavone (**1c**), but the position of a hydroyl group in ring B[3,4] could not be settled. A spectral comparison of synthetic **1a** and **1c**, especially in terms of mass spectra (MS), finally demonstrated that the natural flavonol is **1a**.[2] In this paper, syntheses of **1a**, **1c** and related flavones (**1b**, **2a**, **2b** and **2c**) are described.

4-Benzyloxy-2-hydroxy-3,5,6-trimethoxyacetophenone (**3**)[5] obtained from pyrogallol in nine steps was condensed with 2-benzyloxy-4,5-dimethoxybenzaldehyde (**4**)[4] in the presence of potassium hydroxide in methyl cellosolve (10%w/v) to give 2,4′-dibenzyloxy-2′-hydroxy-3′,4,5,5′,6′-pentamethoxychalcone (**5**), which was subjected to the Algar–Flynn–Oyamada method (AFO method)[6] to furnish 2′,7-dibenzyloxy-3-hydroxy-4′,5,5′,6,8-pentamethoxyflavone (**6**). Debenzylation of **6** with 10% Pd–C in ethyl acetate gave 2′,3,7-trihydroxy-4′,5,5′,6,8-pentamethoxyflavone (**2a**). Methylation of **6** with dimethylsulfate in acetone under reflux gave 2′,7-dibenzyloxy-3,4′,5,5′,6,8-hexamethoxyflavone (mp 135—137 °C) (**7**). The flavone **7** was debenzylated to give 2′,7-dihydroxy-3,4′,5,5′,6,8-hexamethoxyflavone, which was partially demethylated with boron trichloride in dichloromethane at −50 °C. The resulting demethylated product (mp 184—185 °C) was different from **2a** on the basis of chromatographical and spectral data (see Experimental). Consequently, this partial demethylation occurred only at the C-5 position, not at C-3, and gave the desired flavone **1a**. In a similar manner, condensation of **3** with 4-benzyloxy-2,5-dimethoxybenzaldehyde and of **3** with 5-benzyloxy-2,4-dimethoxybenzaldehyde gave 4,4′-dibenzyl-



a: $R^1=H$, $R^2=R^3=Me$
b: $R^2=H$, $R^1=R^3=Me$
c: $R^3=H$, $R^1=R^2=Me$

Chart 1

TABLE I. Physical and Spectral Properties of the Synthetic Flavones

Compound	mp (°C)	^{1}H-NMR (DMSO-d_6)	MS m/z (rel. int.)	UV$_{max}^{MeOH}$ nm (log ε)
1a	184—185 (C_6H_6)	3.71 (1), 3.72 (1), 3.78 (3), 6.60 (3′), 6.96 (6′)	420 (100), 405 (34), 389 (17), 375 (10), 359 (10), 207 (34), 197 (32), 194 (24), 193 (41), 181 (10), 169 (11)	266 (4.3), 305 sh (3.9), 355 (4.0) a) 275, 329, 390 b) 277, 329, 371 c) 277, 340 sh, 392 d) 271, 364 e) 276, 357
1b	182—183 (AcOEt–C_6H_{14})	3.71 (1), 3.75 (2), 3.78 (2), 6.64 (3′), 7.00 (6′)	420 (95), 405 (100), 389 (12), 387 (8), 377 (5), 359 (9), 347 (5), 331 (9), 289 (5), 210 (9), 203 (8), 197 (8), 194 (10), 181 (11)	257 (4.8), 312 sh (4.4), 350 (4.5) a) 278, 328, 400 b) 276, 325 sh, 364, 410 sh c) 275, 335 sh, 398 d) 270, 360 e) 256, 352
1c	145—150 (AcOEt–C_6H_{14})	3.81 (2), 3.84 (1), 3.95 (2), 6.70 (3′), 6.93 (6′)	420 (100), 405 (95), 389 (34), 387 (8), 359 (10), 331 (8), 210 (8), 202 (9), 197 (10), 194 (10), 181 (7), 179 (10)	266 (4.4), 306 (3.9), 354 (4.1) a) 270, 335 sh, 370 b) 277, 330 sh, 366 c) 278, 374 d) 277, 366 e) 267, 315 sh, 358
2a	174—175 (AcOEt–C_6H_{14})	3.71 (1), 3.80 (1), 3.82 (2), 3.84 (1), 6.57 (3′) 7.02 (6′)	420 (100), 405 (95), 387 (34), 385 (12), 359 (6), 348 (10), 241 (6), 227 (16), 210 (7), 200 (8), 198 (10), 194 (8), 193 (10), 185 (6), 181 (10)	255 (4.5), 358 (4.3) a) 271, 332 sh, 430 b) 270, 332 sh, 427 c) 274, 335, 400 d) 272, 335, 404 e) 262, 378
2b	201—202 (C_6H_6)	3.74 (1), 3.77 (1), 3.85 (3), 6.64 (3′), 7.05 (6′)	420 (87), 405 (100), 388 (27), 241 (47), 227 (67), 214 (30), 211 (31), 198 (33), 192 (67), 183 (47), 181 (45), 167 (40)	254 (4.5), 305 sh (4.2), 350 (4.4) a) 267, 293, 325, 416 b) 266, 323, 412 c) 270, 330, 390 d) 270, 330 sh, 368 e) 260, 280 sh, 345
2c	205 (C_6H_6)	3.86 (1), 3.97 (4), 6.67 (3′), 7.15 (6′)	420 (81), 405 (100), 389 (40), 371 (20), 359 (16), 227 (22), 192 (69)	256 (4.6), 308 (4.2), 352 (4.4) a) 269, 293 sh, 328, 419 b) 276, 290 sh, 325, 415 c) 272, 335 sh, 378 d) 270, 335 sh, 370 e) 256, 276 sh, 352

The numbers in parentheses after methoxy signals in the ^{1}H-NMR indicate the numbers of methoxy groups. Numbers in parentheses after other ^{1}H-NMR signals indicate the locations of hydrogens. *a*) $AlCl_3$. *b*) $AlCl_3$+HCl. *c*) NaOMe. *d*) NaOAc. *e*) NaOAc+H_3BO_3.

oxy-2′-hydroxy-2,3′,5,5′,6′-pentamethoxy- (**8**) and 4′,5-dibenzyloxy-2′-hydroxy-2,3′,4,5′,6′-pentamethoxychalcone (**9**), respectively. These chalcones were derived into **1b**, **2b** and **1c**, **2c** by a method similar to that used for **1a** and **2a**. Physical and spectral properties of the six flavones thus obtained are given in Table I. By comparison of the natural flavone with the six synthetic flavones, especially in terms of the MS, the structure of the natural product was concluded to be 2′,5,7-trihydroxy-3,4′,5′,6,8-pentamethoxyflavone.

Experimental

Details of the flavonol synthesis and the apparatus used were described in our previous paper.[1]

2′,5,7-Trihydroxy-3,4′,5′,6,8-pentamethoxyflavone (1a) and 2′,3,7-Trihydroxy-4′,5,5′,6,8-pentamethoxyflavone (2a)——Compound **3** (2.1 g, 6.3 mmol) and **4** (1.7 g, 6.3 mmol) were added to a solution of methyl cellosolve containing KOH (10 g) (100 ml). The solution was stirred overnight at room temperature. A usual work-up of the

reaction mixture gave **5** (3.1 g) as an orange-yellow powder, mp 161—163 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 3.83 (9H, s, 3 × OCH_3), 3.89 (6H, s, 2 × OCH_3), 5.15, 5.18 (2H each, s, OCH_2Ar), 6.53 (1H, s, H-3), 7.15 (1H, s, H-6), 7.40 (10H, br s, 2 × Ar), 7.85 (1H, d, J = 15.8 Hz, H-α), 8.33 (1H, d, J = 15.8 Hz, H-β), 13.75 (1H, s, OH). MS m/z: 586 (M^+). A solution containing the chalcone **5** (900 mg) in methyl cellosolve (100 ml) was mixed with 30% H_2O_2 (16 ml), then a solution of 20% NaOH (30 ml) was added dropwise. The whole was stirred for 20 min at room temperature. Extraction of the reaction mixture with AcOEt after acidification gave **6** (640 mg) as yellow rectangles, mp 140—142 °C (MeOH–H_2O). ^{1}H-NMR ($CDCl_3$) δ: 3.82 (3H, s, OCH_3), 3.87 (6H, s, 2 × OCH_3), 3.91, 3.99 (3H each, s, OCH_3), 5.13, 5.26 (2H each, s, OCH_2Ar), 6.66 (1H, s, H-3′), 7.13 (1H, s, H-6′), 7.25—7.60 (10H, m, 2 × Ar). The flavone **6** (150 mg) was debenzylated in AcOEt (120 ml) with 10% Pd–C (35 mg) under an H_2 atmosphere to give **2a** (70 mg). Compound **6** (300 mg, 0.5 mmol) was methylated with $(CH_3)_2SO_4$ (63 mg, 0.5 mmol) and K_2CO_3 (1 g) in dry acetone to give **7** (240 mg) as a colorless powder, mp 135—137 °C (MeOH). ^{1}H-NMR (CCl_4) δ: 3.78 (3H, s, OCH_3), 3.88 (15H, s, 5 × OCH_3), 5.09, 5.14 (2H each, s, OCH_2Ar), 6.50 (1H, s, H-3′), 6.90 (1H, s, H-6′), 7.20—7.38 (10H, m, 2 × Ar). Debenzylation of **7** (240 mg), followed by partial demethylation with BCl_3 (0.5 ml) gave **1a** as yellow prisms (90 mg).

4′,5,7-Trihydroxy-2′,3,5′,6,8-pentamethoxyflavone (1b) and 3,4′,7-Trihydroxy-2′,5,5′,6,8-pentamethoxyflavone (2b)——The same procedure as described above was used. 4,4′-Dibenzyloxy-2′-hydroxy-2,3′,5,5′,6′-pentamethoxychalcone (**8**); mp 103—104 °C (MeOH), reddish needles. ^{1}H-NMR ($CDCl_3$) δ: 7.78 (1H, d, J = 16 Hz, H-α), 8.18 (1H, d, J = 16 Hz, H-β), 13.31 (1H, s, OH). 4′,7-Dibenzyloxy-3-hydroxy-2′,5,5′,6,8-pentamethoxyflavone (**10**); mp 124—126 °C (EtOH), colorless needles. ^{1}H-NMR ($CDCl_3$) δ: 6.63 (1H, s, H-3′), 7.15 (1H, s, H-6′). Debenzylation of a portion of **10** (150 mg) gave **2b** (60 mg) as colorless needles. The remainder of **10** (340 mg) was methylated to give 4′,7-dibenzyloxy-2′,3,5,5′,6,8-hexamethoxyflavone (**11**) (330 mg), mp 149 °C (EtOH), colorless needles. MS m/z (rel. int.): 614 (M^+) (100), 599 (42), 584 (39), 523 (94), 495 (24), 491 (14), 417 (26), 389 (25), 361 (14). ^{1}H-NMR ($CDCl_3$) δ: 6.55 (1H, s, H-3′), 6.93 (1H, s, H-6′). Debenzylation of **11** (200 mg), followed by partial demethylation, gave **1b** as yellow needles.

5,5′,7-Trihydroxy-2′,3,4′,6,8-pentamethoxyflavone (1c) and 3,5′,7-Trihydroxy-2′,4′,5,6,8-pentamethoxyflavone (2c)——The same procedure as described above was used. 4′,5-Dibenzyloxy-2′-hydroxy-2,3′,4,5′,6′-pentamethoxychalcone (**9**); an orange-yellow oil. ^{1}H-NMR (CCl_4) δ: 7.58 (1H, d, J = 16 Hz, H-α), 8.03 (1H, d, J = 16 Hz, H-β), 13.95 (1H, s, OH). 5′,7-Dibenzyloxy-3-hydroxy-2′,4′,5,6,8-pentamethoxyflavone (**12**); mp 215 °C (MeOH), a pale yellow powder. ^{1}H-NMR ($CDCl_3$) δ: 6.65, 6.91 (1H each, s, H-3′ and 6′). MS m/z (rel. int.): 600 (M^+) (100), 425 (10), 418 (14), 403 (12), 385 (14). Debenzylation of **12** (120 mg) gave **2c** as yellow rectangles. 4′,7-Dibenzyloxy-2′,3,4′,5,6,8-hexamethoxyflavone (**13**); ^{1}H-NMR (CCl_4) δ: 3.90 (18H, s, 6 × OCH_3), 5.05, 5.19 (2H each, s, OCH_2Ar), 6.63, 6.98 (1H each, s, H-3′ and 6′), 7.31 (10H, br s, 2 × Ar). Debenzylation of **13** (220 mg), followed by partial demethylation, gave **1c** (85 mg) as yellow prisms.

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