[Chem. Pharm. Bull.
32(6)2296—2300(1984)]

Synthetic Studies on the Flavone Derivatives. XII.[1,2] Synthesis of 2′,3′,5′- and 3′,4′,5′-Trioxygenated Flavones

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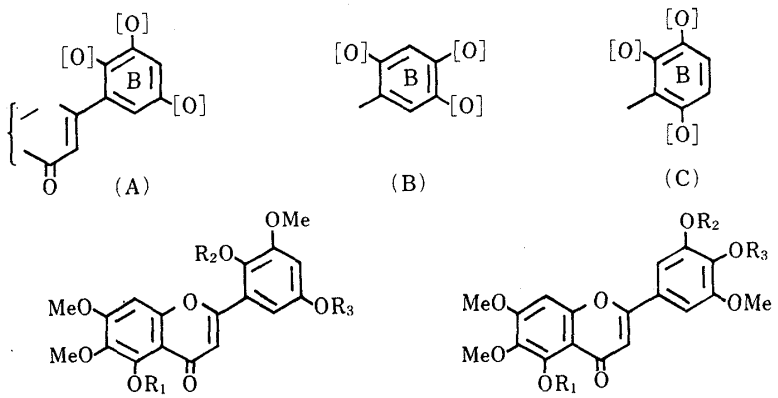
(Received October 12, 1983)

Two unusual flavones, 5,5′-dihydroxy-2′,3′,6,7-tetramethoxyflavone (**1**) from *Gardenia cramerii* and 4′,5-dihydroxy-3′,5′,6,7-tetramethoxyflavone (**6**) from *Artemisia mesatlantia*, and their position isomers were synthesized to investigate the structural correlation in terms of spectral data. The structure of the flavone from *G. cramerii* is discussed.

Keywords——5,5′-dihydroxy-2′,3′,6,7-tetramethoxyflavone; 2′,5-dihydroxy-3′,5′,6,7-tetramethoxyflavone; 5-hydroxy-2′,3′,5′,6,7-pentamethoxyflavone; 3′,5-dihydroxy-4′,5′,6,7-tetramethoxyflavone; 4′,5-dihydroxy-3′,5′,6,7-tetramethoxyflavone; 5-hydroxy-3′,4′,5′,6,7-pentamethoxyflavone

As a continuation of our studies on the synthesis of flavones, we report in this paper the synthesis of new flavones hexa-oxygenated at C-2′, -3′, -5, -5′, -6, -7 and C-3′, -4′, -5, -5′, -6, -7. Flavones oxygenated at C-3′, -4′ and -5′ are common among natural flavones tri-oxygenated in ring B, but flavones oxygenated at C-2′ and -5′ are not usual. The tri-oxygenated flavones with a hydroquinone moiety in ring B are classified into three types according to the position of the other O-functions, that is, 2′,3′,5′-[O]$_3$ (A), 2′,4′,5′-[O]$_3$ (B), and 2′,3′,6′-[O]$_3$ (C) (Chart 1). A few B type flavones have been found in nature.[3] On the other hand, A and C types are rare as naturally occurring flavones; the A type has been isolated from *Gardenia cramerii* and *G. fosbergii*,[4] and the C type from *Scutellaria baicalensis*.[5] A new flavone isolated from *G. cramerii* and deduced to be 5,5′-dihydroxy-2′,3′,6,7-tetramethoxyflavone (**1**), its isomer, 2′,5-dihydroxy-3′,5′,6,7-tetramethoxyflavone



1: $R_1=R_3=H$, $R_2=Me$
2: $R_1=R_2=H$, $R_3=Me$
3: $R_1=H$, $R_2=R_3=Me$
4: $R_1=R_2=R_3=Me$

5: $R_1=R_2=H$, $R_3=Me$
6: $R_1=R_3=H$, $R_2=Me$
7: $R_1=R_2=R_3=Me$

Chart 1

(**2**), and their monomethyl ether, 5-hydroxy-2′,3′,5′,6,7-pentamethoxyflavone (**3**), were synthesized to investigate the relation between structure and spectral properties. Further, 3′,5-dihydroxy-4′,5′,6,7-tetramethoxyflavone (**5**) and 4′,5-dihydroxy-3′,5′,6,7-tetramethoxyflavone (**6**), which has recently been isolated from *Artemisia mesatlantica* by Bouzid *et al.*,[6] were also prepared.

A convenient preparation of 2,3,5-trimethoxybenzaldehyde (**8**) and its carboxylic acid (**9**) had been previously reported by us.[7] Compound **9** was partially demethylated with BCl_3 in CH_2Cl_2[8] to 2-hydroxy-3,5-dimethoxybenzoic acid, which was benzylated then hydrolyzed to afford 2-benzyloxy-3,5-dimethoxybenzoic acid (**10**). The acid **10** was esterified with 2-hydroxy-4,5,6-trimethoxyacetophenone (**11**) to give 2-(2′-benzyloxy-3′,5′-dimethoxybenzoyloxy)-4,5,6-trimethoxyacetophenone (**12**). The ester **12** was subjected to the Baker–Venkataraman rearrangement to afford the β-diketone (**13**), which was converted to 2′-benzyloxy-3′,5,5′,6,7-pentamethoxyflavone (**14**) in acetic acid containing a small amount of sulfuric acid. Catalytic hydrogenation with 10% Pd–C of **14** gave 2′-hydroxy-3′,5,5′,6,7-pentamethoxyflavone (**15**), mp 232—234 °C, which was selectively demethylated at the methoxyl group at C-5 with BCl_3[9] to furnish **2** (mp > 260 °C). 5-Benzyloxy-2,3-dimethoxybenzaldehyde (**16**), as a starting material for the ring B moiety of **1**, was prepared as follows: 1-bromo-5-hydroxy-2,3-dimethoxybenzene (**17**), which was obtained from bromoveratraldehyde by means of the Baeyer–Villiger reaction, was transformed to 5-hydroxy-2,3-dimethoxybenzaldehyde (**18**) by conversion of the bromine at C-1 into a nitrile, then into an aldehyde moiety in a manner similar to that described previously.[7] Usual benzylation of **18** gave **16**. Compounds **8** and **16** were each condensed with the acetophenone **11** in the presence of KOH in ethanol to give 2′-hydroxy-2,3,4′,5,5′,6′-hexamethoxychalcone (**19**) and 5-benzyloxy-2′-hydroxy-2,3,4′,5′,6′-pentamethoxychalcone (**20**), respectively. The chalcones, **19** and **20**, were isomerized with H_3PO_4 to the corresponding flavanones (**21** and **22**), which were oxidized with DDQ in dry dioxane to the flavones **4** and 5′-benzyloxy-2′,3′,5,6,7-pentamethoxyflavone (**23**). Debenzylation of **23** by a method similar to that described above gave 5′-hydroxy-2′,3′,5,6,7-pentamethoxyflavone (**24**, mp 231—233 °C). Partial demethylation of **24** and **4** with BCl_3 gave the desired flavones, **1** (mp 261 °C, lit.[4] mp 218 °C) and **3** (mp 181—183 °C, lit.[4] mp 189—191 °C). 3′,5-Dihydroxy-4′,5′,6,7-tetramethoxyflavone (**5**, mp 216 °C (dec.)) was synthesized in the same way as **2** *via* 3-benzyloxy-2′-hydroxy-4,4′,5,5′,6′-pentamethoxychalcone after condensation of **11** with 3-benzyloxy-4,5-dimethoxybenzaldehyde prepared from *o*-vanillin by our new method.[1] The other flavone **4** was also prepared *via* 2-(4′-benzyloxy-3′,5′-dimethoxybenzoyloxy)-4,5,6-trimethoxyacetophenone (**25**) and 4′-benzyloxy-2-hydroxy-3′,4,5,5′,6-pentamethoxydibenzoylmethane (**26**) after esterification of **11** with 4-benzyloxy-3,5-dimethoxybenzoic acid (syringic acid benzyl ether, mp 153—154 °C) and application of the Baker–Venkataraman rearrangement. The β-diketone **26** gave 4′-hydroxy-3′,5,5′,6,7-pentamethoxyflavone (**27**) on treatment with sulfuric acid with simultaneous debenzylation. The flavone **27** was allowed to react with $AlCl_3$ in nitrobenzene to furnish **6** (mp 240—242 °C, lit.[6] mp 240—242 °C). In a direct comparison (mixed mp, co-thin-layer chromatography (TLC) and infrared (IR)) of **6** with the flavone isolated from *Artemisia mesaltantica*, the flavone was confirmed to be 4′,5-dihydroxy-3′,5′,6,7-tetramethoxyflavone. Both 3′-hydroxy-4′,5,5′,6,7-pentamethoxyflavone (an intermediate of **5**) and **27** were methylated to yield 3′,4′,5,5′,6,7-hexamethoxyflavone (**7**), which was identical with the authentic flavone isolated from *Bauhinia championii*.[10]

Chemical shift due to ring B in the proton nuclear magnetic resonance (^{1}H-NMR) spectra of the flavones thus obtained are shown in Table I. The equivalent protons (H-2′ and H-6′) in **6** and **7** were observed as a singlet at 7.39 and 7.02 ppm in $CDCl_3$,[10b] respectively, whereas in **5**, they appeared as separate singlets at lower field than the H-3′ and H-4′ signals.

Table I. ^{1}H-NMR Chemical Shifts of the Ring B Moieties of the Flavones (**1**—**6**)

	Chemical shifts (ppm)		
Reported flavone	6.9[a]	(1H, d, J=2 Hz, H-4′)	7.2[c] (2H, s, H-4′,6′)
(ref. 4)	7.2	(1H, d, J=2 Hz, H-6′)	
1	6.72[b]	(1H, d, J=3.0 Hz, H-4′)	
	6.80	(1H, d, J=3.0 Hz, H-6′)	
2	6.90[c]	(1H, d, J=2.3 Hz, H-4′)	
	7.09	(1H, d, J=2.3 Hz, H-6′)	
4	6.63[a]	(1H, d, J=3.0 Hz, H-4′)	
	6.76	(1H, d, J=3.0 Hz, H-6′)	
5	6.98[b]	(1H, d, J=2.2 Hz, H-2′)	
	7.16	(1H, d, J=2.2 Hz, H-6′)	
6	7.39[c]	(2H, s, H-2′ and H-6′)	

a) Measured in $CDCl_3$. *b*) In $CDCl_3$+DMSO-d_6. *c*) In DMSO-d_6.

Table II. UV Properties of **1**, **2**, **5** and **6** by the Use of Shift Reagents

	Position of hydroxy group		Bathochromic shifts (nm)		
			$AlCl_3$	NaOMe	NaOAc
1	5′	Band I	+30	(dec.)	+3
		Band II	+6		−7
2	2′	Band I	+30	+84	0
		Band II	0	0	0
5	3′	Band I	+23	+45	0
		Band II	+12	+10	0
6	4′	Band I	+19	+73	+1
		Band II	0	−1	0

On the other hand, the protons (H-4′ and H-6′) in 2′,3′,5′-type flavones (**1**, **2** and **3**) were observed as follows: one proton attributable to H-4′ appeared at high field (>6.90 ppm), and the other (H-6′) at slightly lower field, each as a doublet. Ultraviolet (UV) properties of the flavones (**1**, **2**, **5** and **6**) measured with the aid of shift reagents ($AlCl_3$, NaOMe and NaOAc) are summarized in Table II. It is generally known that flavones possessing a 4′-hydroxyl group show a large bathochromic shift of Band I[11] in the presence of NaOMe. A hydroxyl group at C-2′ as in **2**, however, caused a much larger bathochromic shift than one at C-4′. The λ_{max} positions of **5** (278 and 335 nm) are similar to those of the reported flavone (277 and 330 nm),[4] whereas the flavone **1** has λ_{max} at 282 and 322 nm. By comparison of the mp, ^{1}H-NMR and UV spectra of the reported flavone with those of **1** and **5**, the flavone isolated from *G. cramerii* was concluded 3′,5-dihydroxy-4′,5′,6,7-tetramethoxyflavone, not 5,5′-dihydroxy-2′,3′,6,7-tetramethoxyflavone. This conclusion is supported by the fact that the plant, *G. cramerii*, contained 5-hydroxy-3′,4′,5′,6,7-pentamethoxyflavone and 3′,5-dihydroxy-3,4′,5′,6,7-pentamethoxyflavone in addition to this new flavone.[4]

Experimental[12]

2-Benzyloxy-3,5-dimethoxybenzoic Acid (10)——2,3,5-Trimethoxybenzoic acid[7] (4.2 g, 20 mmol) in CH_2Cl_2 (30 ml) was cooled at −70 °C and treated with BCl_3 (2 ml) in CH_2Cl_2 (10 ml) at −70 °C.[9] The solution was allowed to warm to room temperature, and then poured into water (100 ml). The mixture was extracted with AcOEt. After evaporation of the AcOEt extract, the residue was recrystallized from C_6H_6 to give 2-hydroxy-3,5-dimethoxybenzoic

acid as pale yellow rectangles, in 75% yield, mp 174—176 °C. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 3.77, 3.87 (3H, each s, OCH_3), 6.72 (1H, d, J=3.0 Hz, H-4), 6.89 (1H, d, J=3.0 Hz, H-6), 10.12, 11.10 (2H, each br s, OH and COOH). The phenolic carboxylic acid (2.0 g, 0.10 mol) was benzylated with benzyl chloride (2.8 g, 0.022 mol) and K_2CO_3 (4 g, 0.03 mol) in MDF (30 ml). The benzoate obtained was hydrolyzed in 1 N KOH ethanol solution (50 ml) to give **10** as colorless needles, mp 47—50 °C. ^{1}H-NMR (CCl_4) δ: 3.72, 3.80 (3H, each s, OCH_3), 5.0 (2H, s, OCH_2Ph), 6.57 (1H, d, J=3.0 Hz, H-4), 6.95 (1H, d, J=3.0 Hz, H-6), 7.16—7.32 (5H, m, Ph), 10.29 (1H, s, COOH).

2′,5-Dihydroxy-3′,5′,6,7-tetramethoxyflavone (2)——The acid **10** (1.5 g, 5.2 mmol) and **11** (1.2 g, 5.2 mmol) were treated with trifluoroacetic anhydride (2 ml) in dry benzene (10 ml). The resulting solution was stirred at room temperature for 3 h. AcOEt (20 ml) was added and then the AcOEt layer was washed with water and evaporated under reduced pressure. The residue was chromatographed on silica gel (solvent: $CHCl_3$) to give **12** as a liquid in 77% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s, $COCH_3$), 3.79, 3.86, 3.89 (3H, each s, OCH_3), 3.98 (6H, s, 2 × OCH_3), 5.10 (2H, s, OCH_2Ph), 6.45 (1H, s, H-3), 6.75, 7.00 (1H, each d, J=2.3 Hz, H-4′,6′), 7.2—7.6 (5H, m, Ph). The ester **12** (1.0 g) was treated with powdered KOH (1.0 g) in pyridine (3 ml) at 100 °C for 20 min to give **13** in 85% yield. A solution of **13** (800 mg, 1.6 mmol) in acetic acid (5 ml) was added to acetic acid–sulfuric acid (10 : 1) solution (5 ml) and the mixture was stirred at room temperature for 1 h. The reactant was poured into water and the solution was extracted with AcOEt. The AcOEt extract was evaporated and the residue was recrystallized from EtOH to give **14**. Usual catalytic hydrogenation of **14** in AcOEt with 10% Pd–C gave **15** as pale yellow needles, mp 232—234 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 3.83 (3H, s, OCH_3), 3.86 (6H, s, 2 × OCH_3), 3.93, 4.00 (3H, each s, OCH_3), 6.88, 7.08 (1H, each d, J=2.3 Hz, H-4′,6′), 7.04, 7.25 (1H, each s, H-3, 8). The flavone **15** (300 mg, 1.3 mmol) was partially demethylated with BCl_3 in the same manner as described above to give **2** in 69% yield as a light yellow powder, mp >260 °C (dec.) (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 3.78, 3.83, 3.91, 3.99 (3H, each s, OCH_3), 6.90 (1H, d, J=2.3 Hz, H-4′), 7.09 (1H, d, J=2.3 Hz, H-6′), 7.00, 7.13 (1H, each s, H-3, 8), 12.80 (1H, s, OH). IR ν_{max}^{KBr} cm^{-1}: 3400, 1655, 1610, 1590. MS m/z (rel. int.): 374 (M^+) (100), 359 (71), 345 (17), 181 (17), 164 (11), 158 (12), 153 (26). UV λ_{max}^{MeOH} nm (log ε): 268 sh, (4.7), 277 sh (4.5), 310 (4.3), 360 sh (4.0). λ^{+AlCl_3}: 268 sh, 280, 294 sh, 335, 390. λ^{+AlCl_3+HCl}: 268 sh, 282, 295 sh, 334, 388. λ^{+MeONa}: 268 sh, 278 sh, 325 sh, 444. λ^{+AcONa}: 268 sh, 310, 360 sh.

5-Benzyloxy-2,3-dimethoxybenzaldehyde (16)——Treatment of **17** with CuCN in DMF gave 1-cyano-5-hydroxy-2,3-dimethoxybenzene as colorless needles, mp 155—158 °C (C_6H_6). IR ν_{max}^{KBr} cm^{-1}: 2240. A mixture of the nitrile and Raney Ni in 70% HCOOH was boiled for 4 h to yield **18** as colorless needles, mp 129—131 °C (C_6H_{14}–AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1668 (CHO). Benzylation of **18** (1.6 g, 8.8 mmol) with benzyl chloride (1.1 g, 9 mmol) and K_2CO_3 (2.5 g) in DMF (45 ml) gave **16** as a colorless oil. ^{1}H-NMR (CCl_4) δ: 6.67, 6.81 (1H, each d, J=2.5 Hz, H-4, 6), 10.22 (1H, s, CHO).

5-Hydroxy-2′,3′,5′,6,7-pentamethoxyflavone (3)——A solution of **11** (1.5 g, 6.6 mmol) and **8** (1.3 g, 6.6 mmol) in 50 ml of 80% EtOH containing KOH (8 g) was stirred at room temperature overnight. The mixture was acidified with 20% HCl and then extracted with AcOEt. The extract was concentrated under reduced pressure, and the residue was recrystallized from MeOH to give 2.1 g of **19** as reddish-orange needles, mp 122—124 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.25 (1H, s, H-3′), 6.52 (1H, d, J=3.0 Hz, H-4), 6.67 (1H, d, J=3.0 Hz, H-6), 7.82, 8.17 (1H, d, J=15.6 Hz, Hβ and α), 13.60 (1H, s, OH). A solution of **19** (2.1 g) in EtOH (100 ml) containing 16 g of 85% H_3PO_4 was boiled under reflux for 35 h, then extracted with water and AcOEt. The AcOEt extract was purified by column chromatography on silica gel, and 980 mg of **21** was obtained as colorless needles, mp 125—126 °C (C_6H_6–C_6H_{14}). ^{1}H-NMR ($CDCl_3$) δ: 2.81 (1H, d, J=5.7 Hz, H-3 *cis*), 2.88 (1H, d, J=10.5 Hz, H-3 *trans*), 5.73 (1H, dd, J=10.5, 5.7 Hz, H-2). A solution of **21** (600 mg, 1.5 mmol) and DDQ (410 mg, 1.8 mmol) in dry dioxane (30 ml) was boiled for 8 h, then cooled. The reducted hydroquinone was removed by filtration, and the residue was recrystallized from C_6H_6 to obtain 480 mg of **4** as colorless needles, mp 140—142 °C (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 3.80 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.89 (6H, s, 2 × OCH_3), 3.97 (6H, s, 2 × OCH_3), 6.63 (1H, d, J=3.0 Hz, H-4′), 6.76 (1H, d, J=3.0 Hz, H-6′), 6.77 (2H, s, H-3 and H-8). MS m/z (rel. int.): 402 (M^+) (35), 387 (100), 382 (11), 367 (29), 186 (17). UV λ_{max}^{MeOH} nm (log ε): 266 (4.2), 310 (4.3). BCl_3 (0.5 ml) was added to a solution of CH_2Cl_2 (30 ml) containing **4** (200 mg) at −70 °C, and the mixture was left at room temperature for 1 h. The mixture was poured into water and extracted with AcOEt. The AcOEt extract was evaporated and the residue was purified by column chromatography to give **3** as yellow rectangles, mp 181—183 °C (AcOEt–C_6H_{14}). MS m/z (rel. int.): 388 (M^+) (22), 374 (100), 356 (23), 328 (16). UV λ_{max}^{MeOH} nm (log ε): 278 (4.4), 322 (4.1). λ^{+AlCl_3}: 288, 345. λ^{+AlCl_3+HCl}: 288, 340.

5,5′-Dihydroxy-2′,3′,6,7-tetramethoxyflavone (1)——The flavone **1** was prepared through the intermediates **20**, **22** and **24** in a manner similar to that described for **3**. 5-Benzyloxy-2′-hydroxy-2,3,4′,5′,6′-pentamethoxychalcone (**20**): an orange-yellow oil. ^{1}H-NMR (CCl_4) δ: 6.15 (1H, s, H-3′), 6.63 (1H, d, J=3.0 Hz, H-4), 6.70 (1H, d, J=3.0 Hz, H-2), 7.81 (2H, br s, H-β and α), 12.27 (1H, s, OH). 5′-Benzyloxy-2′,3′,5,6,7-pentamethoxyflavonone (**22**): mp 105—106 °C (C_6H_6–C_6H_{14}), colorless needles. ^{1}H-NMR ($CDCl_3$) δ: 2.85 (1H, d, J=6.0 Hz, H-3 *cis*), 2.89 (1H, d, J=10.8 Hz, H-3 *trans*), 5.67 (1H, dd, J=10.8, 6.0 Hz, H-2), 6.37 (1H, s, H-8), 6.61 (1H, d, J=3.0 Hz, H-4′), 6.78 (1H, d, J=3.0 Hz, H-6′). 5′-Hydroxy-2′,3′,5,6,7-pentamethoxyflavone (**24**): mp 231—233 °C (EtOH), a colorless powder. MS m/z (rel. int.): 388 (M^+) (31), 373 (100), 357 (27), 167 (2). 5,5′-Dihydroxy-2′,3′,6,7-tetramethoxyflavone (**1**): mp 261 °C (AcOEt–C_6H_{14}), a yellow powder. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 3.79 (6H, s, 2 × OCH_3), 3.89 (6H, s, 2 × OCH_3), 6.58, 6.71 (1H, each s, H-3, 8), 6.72 (1H, d, J=3.0 Hz, H-4′), 6.80 (1H, d, J=3.0 Hz, H-6′), 12.58, 12.70

(1H, each s, OH). MS *m/z* (rel. int.): 374 (M^+) (18), 360 (100), 346 (53), 342 (29), 331 (11), 314 (22). IR ν_{max}^{KBr} cm^{-1}: 3400, 2950, 2840, 1660, 1580, 1470. UV λ_{max}^{MeOH} nm (log ε): 282 (4.2), 322 (4.1). λ^{+AlCl_3}: 288, 352. λ^{+AlCl_3+HCl}: 290, 344. λ^{+NaOAc}: 275, 325.

3′,5-Dihydroxy-4′,5′,6,7-tetramethoxyflavone (5)——The flavone **5** was synthesized through the intermediates **28** and **29** in a manner similar to that described for **1**. 3′-Benzyloxy-4′,5,5′,6,7-pentamethoxyflavone (**28**): mp 179 °C (EtOH), colorless needles. ^{1}H-NMR ($CDCl_3$) δ: 6.60, 6.78 (1H, each s, H-3,8), 7.09, 7.16 (1H, each d, J=2.3 Hz, H-2′,6′). 3′-Hydroxy-4′,5,5′,6,7-pentamethoxyflavone (**29**): mp 224—225 °C (EtOH), yellow prisms. ^{1}H-NMR ($CDCl_3$) δ: 3.96 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.03 (9H, s, 3 × OCH_3), 6.63, 6.82 (1H, each s, H-3,8), 6.96, 7.23 (1H, each d, J=2.3 Hz, H-2′,6′). UV λ_{max}^{MeOH} nm: 269, 320. 3′,5-Dihydroxy-4′,5′,6,7-tetramethoxyflavone (**5**): mp 216 °C (dec.) (C_6H_6), pale yellow needles. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 3.93, 3.95, 3.99, 4.00 (3H, each s, OCH_3), 6.60 (2H, s, H-3 and H-8), 6.98, 7.16 (1H, each d, J=2.2 Hz, H-2′,6′). UV λ_{max}^{MeOH} nm (log ε): 278 (4.1), 335 (4.3). λ^{+AlCl_3}: 290, 300 sh, 358. λ^{+AlCl_3+HCl}: 290, 300 sh, 355. λ^{+MeONa}: 288, 297 sh, 380 sh. λ^{+AcONa}: 278, 355. MS *m/z* (rel. int.): 374 (M^+) (35), 360 (100), 346 (43). IR ν_{max}^{KBr} cm^{-1}: 3400, 1650, 1590.

4′,5-Dihydroxy-3′,5′,6,7-tetramethoxyflavone (6)——The flavone **6** was synthesized through **25**, **26** and **27** in manner similar to that described for **2**. 2-(4′-Benzyloxy-3′,5′-dimethoxybenzoyloxy)-4,5,6-trimethoxyacetophenone (**25**): mp 98—99 °C (MeOH), colorless needles. ^{1}H-NMR ($CDCl_3$) δ: 3.91 (3H, s, OCH_3), 3.96 (9H, s, 3 × OCH_3), 3.99 (3H, s, OCH_3), 5.15 (2H, s, OCH_2Ph), 6.60 (1H, s, H-3), 7.41 (2H, s, H-2′ and H-6′), 7.38—7.52 (5H, m, Ph). 4′-Benzyloxy-2-hydroxy-3′,4,5,5′,6-pentamethoxydibenzoylmethane (**26**): mp 125—126 °C (MeOH), yellow prisms. ^{1}H-NMR ($CDCl_3$) δ: 3.85 (3H, s, OCH_3), 3.92 (9H, s, 3 × OCH_3), 5.14 (2H, s, OCH_2Ph), 6.32 (1H, s, H-3), 7.20 (2H, s, H-2′ and H-6′), 7.38 (2H, s, $COCH_2CO$), 7.14—7.57 (5H, m, Ph), 12.82 (1H, s, OH). 4′-Hydroxy-3′,5,5′,6,7-pentamethoxyflavone (**27**): mp 210—211 °C (MeOH), pale yellow needles. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s, OCH_3), 4.01 (12H, s, 4 × OCH_3), 6.61, 6.84 (1H, each s, H-3,8), 7.12 (2H, s, H-2′ and H-6′). MS *m/z* (rel. int.): 388 (M^+) (29), 373 (20), 342 (9). *Anal.* Calcd for $C_{20}H_{20}O_8$: C, 61.85; H, 5.19. Found: C, 61.61; H, 5.18; 4′,5-Dihydroxy-3′,5′,6,7-tetramethoxyflavone (**6**): mp 240—242 °C (AcOEt), a yellow powder. ^{1}H-NMR (DMSO-d_6) δ: 3.79 (3H, s, OCH_3), 3.94 (6H, s, 2 × OCH_3), 3.99 (3H, s, OCH_3), 6.97, 7.03 (1H, each s, H-3,8), 7.39 (2H, s, H-2′ and H-6′). IR ν_{max}^{KBr} cm^{-1}: 3150, 2970, 2930, 2840, 1650, 1605. MS *m/z* (rel. int.): 374 (M^+) (100), 359 (89), 345 (23), 331 (25), 328 (27). *Anal.* Calcd for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 61.20; H, 4.87. UV λ_{max}^{MeOH} nm (log ε): 269 sh (4.6), 278 sh (4.3), 349 (4.5). λ^{+AlCl_3}: 269 sh, 280 sh, 368. λ^{+AlCl_3+HCl}: 269 sh, 282, 372. λ^{+NaOMe}: 268 sh, 280 sh, 422. λ^{+AcONa}: 269 sh, 277 sh, 350.

Methylation of 27——The flavone **27** (190 mg, 0.49 mmol) was methylated with dimethyl sulfate (65 mg, 0.5 mmol) and K_2CO_3 (140 mg) in acetone to afford **7**, mp 113—114 °C (lit.[10b] mp 114 °C). ^{1}H-NMR ($CDCl_3$) δ: 6.60, 6.81 (1H, each s, H-3,8), 7.03 (2H, s, H-2′ and H-6′).

Acknowledgement The authors are most grateful to Dr. B. Voirin, Université de Lyon, for providing the authentic sample of 4′,5-dihydroxy-3′,5′,6,7-tetramethoxyflavone.

References and Notes

1) Part XI: M. Iinuma, T. Tanaka, and S. Matsuura, *J. Chem. Soc.*, submitted.
2) A part of this work was presented at the 103rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, 1983.
3) For instance; oxyayanin-A: F. E. King, T. J. King, and P. J. Stokes, *J. Chem. Soc.*, **1954**, 4587. Apulein: R. B. Filho and O. R. Gottlieb, *Phytochemistry*, **40**, 2433 (1971). Tabularin: K. K. Puroshothaman, A. Sarada, G. Saraswathi, and J. D. Connolly, *Phytochemistry*, **16**, 398 (1977), S. Ahmad, H. Wagner, and S. Razao, *Tetrahedron*, **34**, 1593 (1978).
4) A. A. L. Gunatilaka, S. R. Sirimanne, S. Sotheeswaran, and H. T. B. Sriyan, *Phytochemistry*, **21**, 805 (1982).
5) T. Tomimori, Y. Miyaichi, N. Kizu, Y. Imoto, and Y. Tanabe, the 29th Annual Meeting of the Japanese Society of Pharmacognosy, Sapporo, 1982, p. 42.
6) N. Bouzid, I. Fouraste, B. Voirin, J. Favre-Bonvin, and Ph. Lebreton, *Phytochemistry*, **21**, 803 (1982).
7) M. Iinuma and S. Matsuura, *Yakugaku Zasshi*, **100**, 657 (1980).
8) F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price and N. Somvichien, *Tetrahedron Lett.*, **1966**, 4153.
9) M. Iinuma and S. Matsuura, *Yakugaku Zasshi*, **99**, 657 (1979).
10) *a*) C. Chen, Y. Chen, H. Hsu, and Y. Chen, *Chem. Pharm. Bull.*, **32**, 166 (1984); *b*) M. Iinuma, T. Tanaka, and S. Matsuura, *Yakugaku Zasshi*, **103**, 994 (1983).
11) J. B. Harborne, T. J. Mabry, and H. Mabry, "The Flavonoids," Chapman and Hall Ltd., 1975, pp. 45—61.
12) Melting point were determined on a Büchi melting point apparatus, and are uncorrected. UV spectra were taken on a Hitachi 323 spectrometer and mass spectra (MS) were obtained on a JEOL JMS-300 mass spectrometer at 70 eV. ^{1}H-NMR spectra were taken on a Hitachi R-20B at 60 MHz and chemical shifts are given in δ values (ppm) with tetramethylsilane as an internal standard.