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Studies of the Selective *O*-Alkylation and Dealkylation of Flavonoids. XIX.[1] A Convenient Method for Synthesizing 3,5,6,7,8-Pentaoxygenated Flavones

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The methoxymethyl ethers of 6-hydroxy-5,7,8-trimethoxyflavones, which were derived from 2′,5′-dihydroxy-3′,4′,6′-trimethoxyacetophenone, were oxidized with dimethyldioxirane to give the corresponding 3-hydroxyflavones. Selective *O*-alkylation and dealkylation of the 3-hydroxyflavones were examined and a convenient method for synthesizing the following ten kinds of 3,5,6,7,8-pentaoxygenated flavones was established: 3-hydroxy-5,6,7,8-tetramethoxyflavones, 3,5-dihydroxy-6,7,8-trimethoxyflavones, 3,6-dihydroxy-5,7,8-trimethoxyflavones, 3,5,6-trihydroxy-7,8-dimethoxyflavones, 3,5,6,7-tetrahydroxy-8-methoxyflavones, and their 3-methyl ethers. Furthermore, 3,5,8-trihydroxy-4′,6,7-trimethoxyflavone, 3,8-dihydroxy-4′,5,6,7-tetramethoxyflavone, and 5,8-dihydroxy-3,6,7-trimethoxyflavones were similarly synthesized and their spectral properties were examined. Additionally, the proposed structures of three natural flavones were revised.

Key words 3,5,6,7,8-pentaoxygenated flavone; ^{13}C-NMR; selective demethylation; oxidation with dimethyldioxirane; synthesis; revised structure

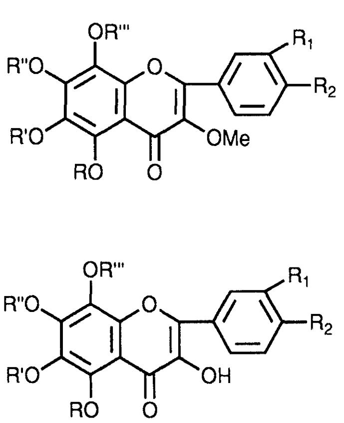
In a previous paper,[2] we have reported an unambiguous method for synthesizing 5,8-dihydroxy-6,7-dimethoxyflavones and we revised the structures of four natural flavones which had been proposed to have the above structures to the isomeric 5,7-dihydroxy-6,8-dimethoxyflavones. The structural elucidation of flavones such as 3,5,6,7,8-pentaoxygenated flavones by ^{1}H-NMR is generally difficult due to lack of aromatic protons in the A-ring[2,3] and ^{13}C-NMR may be the preferred approach. Convenient methods for synthesizing these flavones, however, have not been established so far and their general properties are not always clear, although some have been synthesized by using the Allan–Robinson reaction[4,5] or oxidative cyclization of chalcones with hydrogen peroxide[6] (AFO reaction).

We have been trying to develop convenient methods for synthesizing polyhydroxyflavones by the application of selective *O*-alkylation and dealkylation in order to clarify their general properties and to survey their biological activities,[7] and we reported in the previous paper that 3,5,6,7-tetrahydroxyflavones are easily synthesized from 6-hydroxy-5,7-dimethoxyflavones.[1] The method may also be applicable for the synthesis of various 3,5,6,7,8-pentaoxygenated flavones from flavones such as 6-hydroxy-5,7,8-trimethoxyflavones (**17**).[2,8] Here we describe a convenient method for synthesizing several kinds of 3,5,6,7,8-pentaoxygenated flavones (**1**—**13**) and isomeric flavone derivatives,[2] and we discuss their spectral properties. Additionally, we have revised the structures of two natural flavones,[9,10] proposed to be 8-hydroxyflavone derivatives, and a flavone,[11] isolated from *Anisomeles* ovata and proposed to have the structure **2b**.

Results and Discussion

Synthesis of 3,5,6,7,8-Pentaoxygenated Flavones In our synthetic study of polyhydroxyflavones, the following results have been obtained: (1) 3-hydroxy-5,7-dimethoxy-6-methoxymethoxyflavones[1] can be conveniently synthesized from 5,7-dimethoxy-6-(methoxymethoxy)flavones by oxidation with dimethyldioxirane; (2) the 5- or 3-methoxy group in 3-hydroxy-5-methoxy- or 5-hydroxy-3-methoxyflavones is quantitatively cleaved with anhydrous aluminum bromide in acetonitrile *via* the corresponding tosylate[12,13]; (3) the 5- and 7-methoxy groups in 6-hydroxy-5,7-dimethoxyflavones[14,15] and 6-hydroxy-5,7,8-trimethoxyflavones[8] can be selectively cleaved. The results suggest that the several 3,5,6,7,8-pentaoxygenated flavones may be conveniently synthesized from 6-hydroxy-5,7,8-trimethoxyflavone (**17**). Therefore, a method for synthesizing the flavones (**1**—**5**) with the 3-methoxy group was examined first according to the process shown in Chart 1.

The mono(methoxymethyl) ether (**15**) of 2′,5′-dihydroxy-3′,4′,6′-trimethoxyacetophenone (**14**)[16] was benzoylated with substituted benzoyl chloride and then transformed with potassium hydroxide in pyridine to give a diketone



1a,b R=R'=R''=R'''=Me
2a,b,f R=H, R'=R''=R'''=Me
3a,b R=R''=R'''=Me, R'=H
4a,b R=R'=H, R''=R'''=Me
5a,b R=R'=R''=H, R'''=Me
11a,e R=R'''=H, R'=R''=Me

6a,b R=R'=R''=R'''=Me
7a,b R=H, R'=R''=R'''=Me
8a,b R=R''=R'''=Me, R'=H
9a,b R=R'=H, R''=R'''=Me
10a,b R=R'=R''=H, R'''=Me
12a R=R'''=H, R'=R''=Me
13a R=R'=R''=Me, R'''=H

a; R_1=H, R_2=OMe **b**; R_1=OMe, R_2=OH

e; R_1=R_2=H **f**; R_1=OH, R_2=OMe

Fig. 1

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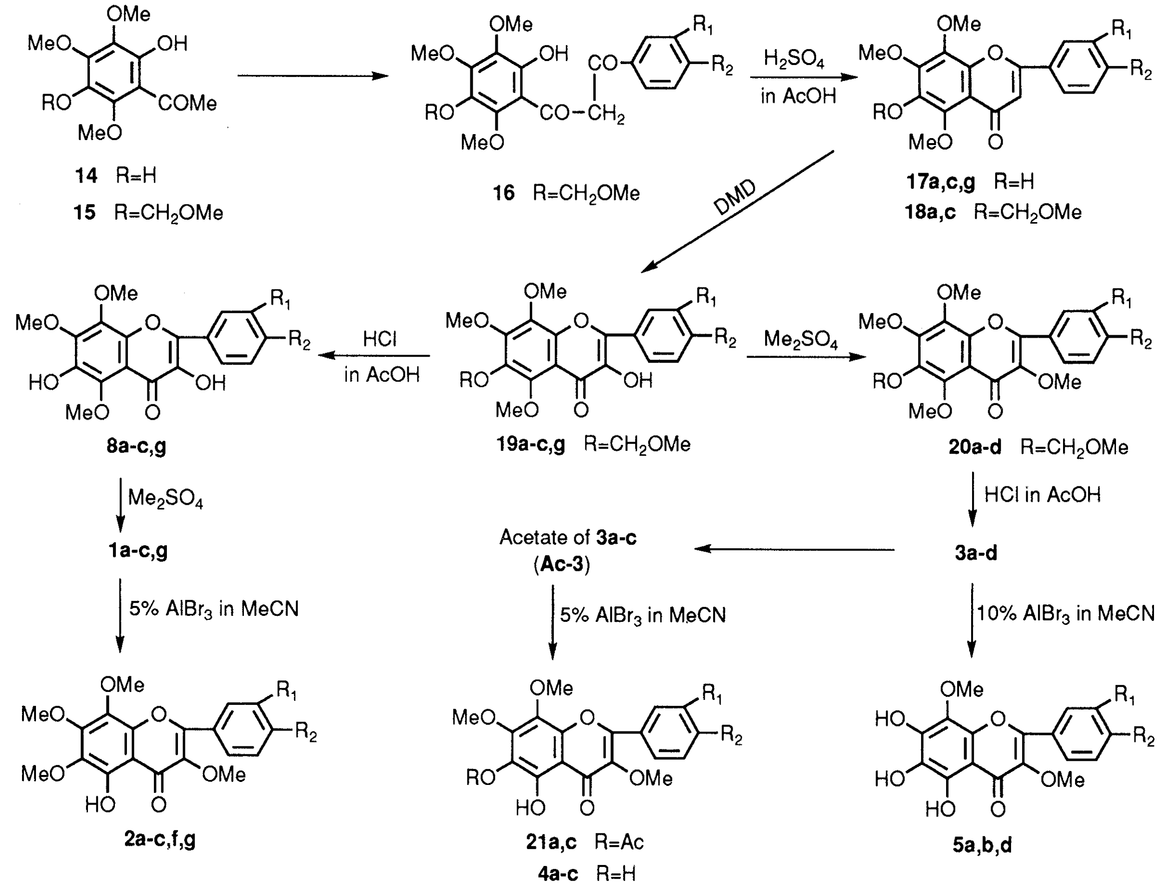

a; R_1=H, R_2=OMe **b**; R_1=OMe, R_2=OH **c**; R_1=OMe, R_2=OCH$_2$Ph **d**; R_1=OMe, R_2=OTs
f; R_1=OH, R_2=OMe **g**; R_1=OCH$_2$Ph, R_2=OMe

Chart 1

derivative (**16a, c**). Cyclization of the diketone **16** with a small amount of sulfuric acid in acetic acid afforded 6-hydroxy-5,7,8-trimethoxyflavone (**17a, c**) accompanied with demethoxymethylation. The methoxymethyl ether (**18a, c**) of **17** was converted into 3-hydroxy-5,7,8-trimethoxy-6-(methoxymethoxy)flavone (**19a, c**) in high yield by oxidation with dimethyldioxirane (DMD) followed by treatment with a small amount of *p*-toluenesulfonic acid.17) The flavone **19b** was obtained from **19c** by hydrogenolysis with palladium on charcoal.

Hydrolysis of **19a** with hydrochloric acid in acetic acid afforded quantitatively 3,6-dihydroxy-4′,5,7,8-tetramethoxyflavone (**8a**), which was converted into 3,4′,5,6,7,8-hexamethoxyflavone (**1a**) by methylation. The demethylation of **1a** with 5% (w/v) anhydrous aluminum bromide in acetonitrile afforded 5-hydroxy-3,4′,6,7,8-pentamethoxyflavone (**2a**). The flavone **19a** was also converted into 6-hydroxy-3,4′,5,7,8-pentamethoxyflavone (**3a**) *via* its methyl ether (**20a**). Although the direct demethylation of **3a** to **4a** was accompanied with the formation of 5,6,7-trihydroxy-3,4′,8-trimethoxyflavone (**5a**), the 5-methoxy group in the acetate (Ac-**3a**) of **3a** was selectively cleaved to give quantitatively 6-acetoxy-5-hydroxy-3,4′,7,8-tetramethoxyflavone (**21a**), which was easily hydrolyzed to **4a**, as in the case of the demethylation of 6-hydroxy-5,7,8-trimethoxyflavones.8) On the other hand, the 5- and 7-methoxy groups in **3a** were simultaneously cleaved with 10% (w/v) anhydrous aluminum bromide in acetonitrile at 50 °C to give **5a** in high yield.

In all the synthetic reactions except for the demethylation of **3a** to **5a**, the benzyloxy group at the B-ring in the flavone skeleton was stable. Therefore, the flavones (**1c**—**4c**) with a benzyloxy group in the B-ring could be synthesized from **19c** by the same method, and the desired flavones (**1b**—**4b**) were easily obtained from these by hydrogenolysis with palladium on charcoal. In the demethylation of **3c** with 10% (w/v) aluminum bromide in acetonitrile, however, the cleavage of the 3′-methoxy group proceeded with participation of the neighboring 4′-hydroxy group formed by the debenzylation to afford a large amount of a further demethylated product of **5b** with increasing reaction time. Therefore, 4′,5,6,7-tetrahydroxy-3,3′,8-trimethoxyflavone (**5b**) was synthesized as follows. That is, 4′-hydroxy-3,3′,5,7,8-pentamethoxy-6-(methoxymethoxy)flavone (**20b**), which was obtained from **20c** by hydrogenolysis, was converted into 6-hydroxy-3,3′,5,7,8-pentamethoxy-4′-tosyloxyflavone (**3d**) by tosylation, followed by demethoxymethylation. The demethylation of **3d** proceeded smoothly to give the 5,6,7-trihydroxyflavone (**5d**) in high yield. Although the direct hydrolysis of **5d** to **5b** was not achieved,1,13) the 4′-tosyloxy group in the crude methoxymethyl ether obtained from **5d** by methoxymethylation [main product; 6,7-bis(methoxymethyl) ether] was smoothly hydrolyzed

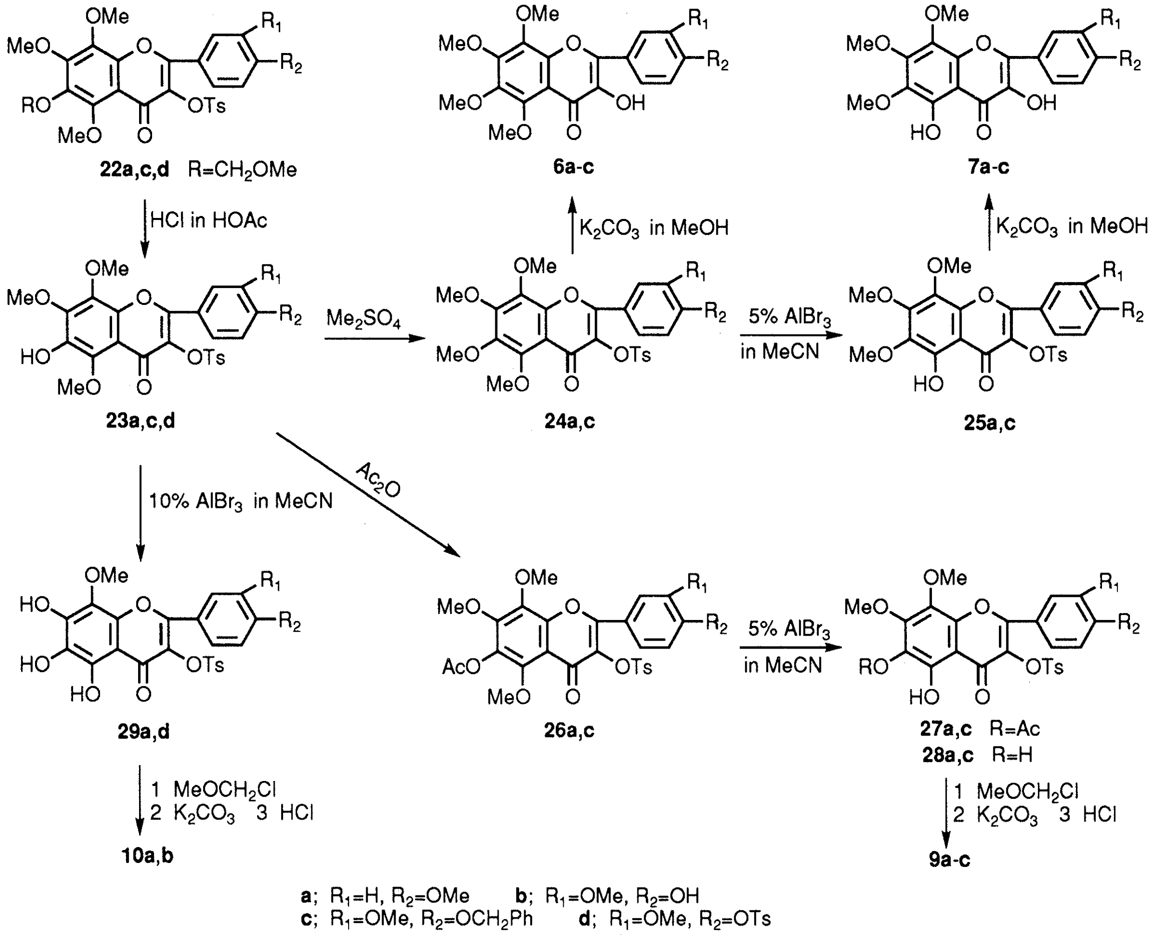

Chart 2

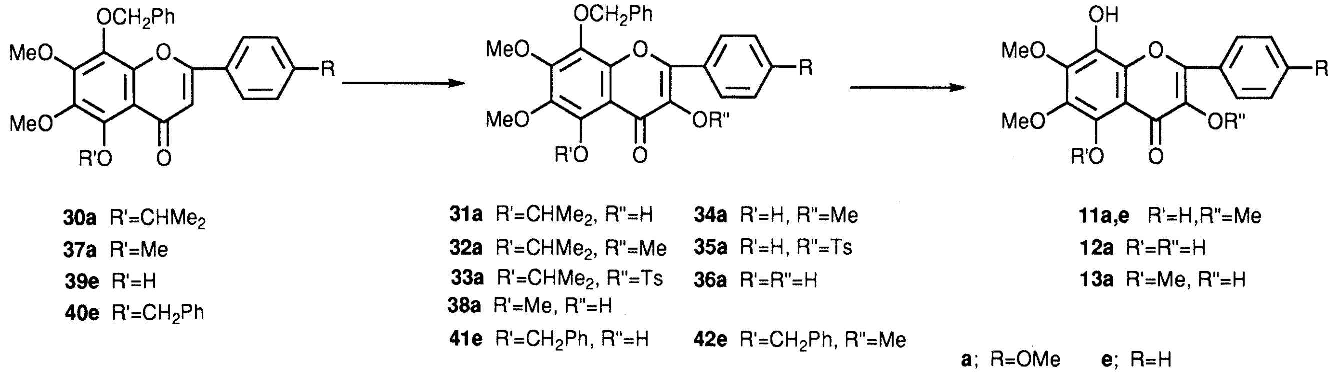

Chart 3

with potassium carbonate in methanol and the resultant compound was demethoxymethylated with hydrochloric acid in acetic acid to give the desired **5b** without the formation of by-product, in contrast to the deprotection of 3,5-dihydroxy-4′-methoxy-6,7-bis(methoxymethoxy)-flavone.[1)]

The flavones (**6**—**10**) with the 3-hydroxy group were also synthesized by a similar method (Chart 2). That is, the 3-tosyloxyflavones (**22a, c, d**) which were obtained from **19a, c, b** by tosylation were demethoxymethylated to give **23a, c, d**. The flavones **23a, c** were converted into 5-hydroxyflavones **25a, c** and **28a, c** *via* their methyl ethers (**24a, c**) or acetates (**26a, c**). The direct demethylation of **23a, d** with 10% (w/v) anhydrous aluminum bromide in acetonitrile afforded the 5,6,7-trihydroxyflavones **29a, d** in high yield. The 3-tosyloxy group in **24a, c** and **25a, c** was directly hydrolyzed with potassium carbonate in methanol to give **6a, c** and **7a, c**. The tosyloxy groups in **28a, c** and **29a, d** were hydrolyzed *via* their methoxymethyl ethers as in the case of the hydrolysis of **5d** to **5b**, to give **9a, c** and **10a, b**, respectively. The benzyloxyflavones (**6c, 7c, 8c**, and **9c**) were quantitatively converted into the corresponding hydroxyflavones (**6b, 7b, 8b**, and **9b**).

The method is useful as a general one for synthesizing 3,5,6,7,8-pentaoxygenated flavones and the 8-hydroxyflavones (**11**—**13**) can be synthesized by a similar process (Chart 3). The oxidation of 8-benzyloxy-5-isopropoxy-4′,6,7-trimethoxyflavone (**30a**)[2)] with dimethyldioxirane

Table 1. UV Spectral Data for 3,5,6,7,8-Pentaoxygenated Flavones[a)]

Compd.	λ_{max} nm (log ε)											
	EtOH				EtOH–$AlCl_3$				EtOH–NaOAc			
1a		268 (4.31)	330 (4.37)									
2a		279 (4.31)	334 (4.32)		290 (4.26)	311 (4.26)	355 (4.37)	420 (3.86)		279 (4.33)	334 (4.32)	
3a		276 (4.30)	330 (4.38)							282 (4.28)	332 (4.35)	
4a		292 (4.33)	334 (4.27)			311 (4.36)	364 (4.39)	430sh (3.61)		297 (4.32)		
11a		290—302 (4.35)	333 (4.26)		300sh (4.25)	322 (4.37)	357 (4.33)	445 (3.70)		300 (4.36)		
5a		281 (4.29)	375i (3.96)			307 (4.32)	379 (4.30)			272 (4.31)	376 (4.02)	
6a	260 (4.30)		362 (4.31)		271 (4.38)			429 (4.43)	261 (4.31)		366 (4.25)	415i (3.71)
7a	258 (4.17)	278 (4.26)	339 (4.23)	380 (4.20)	265 (4.22)	286 (4.21)	368 (4.26)	438 (4.21)	262 (4.34)		342 (4.00)	427 (4.16)
8a	262 (4.30)	270sh (4.28)	347 (4.35)			272 (4.44)		428 (4.42)	261 (4.26)	296 (4.16)	355 (4.32)	420i (3.62)
13a	273 (4.29)	339 (4.21)	365 (4.21)		269 (4.41)	375sh (4.05)		431 (4.39)	277 (4.22)	291 (4.22)	320 (4.20)	342 (4.21)
9a	258 (4.12)	283 (4.24)	345 (4.30)	383i (4.05)		295 (4.20)	379 (4.39)	432sh (3.89)		274 (4.23)	385 (4.20)	
12a	258 (4.14)	283 (4.32)	340 (4.27)	388 (4.06)	268 (4.27)	288 (4.27)	373 (4.28)	445 (4.13)		280 (4.34)	387 (4.18)	
10a		279 (4.25)	305 (4.11)	380 (4.13)		280 (4.21)	307sh (4.09)	397 (4.35)		278 (4.17)	387 (4.00)	
1b	254 (4.34)	267i (4.26)	347 (4.37)						254 (4.31)		350 (4.21)	414 (4.10)
2b	261 (4.26)	279 (4.25)	356 (4.29)		270 (4.20)	289 (4.24)	372 (4.33)	415i (4.04)		270 (4.27)		430 (4.26)
3b	258 (4.27)	274 (4.25)	346 (4.39)						258 (4.26)		350 (4.29)	407 (4.04)
4b	261 (4.15)	288 (4.25)	351 (4.32)		265 (4.11)	302 (4.25)	378 (4.38)			288 (4.17)	352 (4.18)	406sh (4.09)
5b		278 (4.27)	325 (4.18)	370 (4.14)	266 (4.17)	296 (4.21)	390 (4.38)			271 (4.23)	328 (4.15)	388 (4.19)
6b	257 (4.38)		371 (4.36)		267 (4.43)			436 (4.47)	257 (4.35)		377 (4.27)	420sh (3.92)
7b	261 (4.35)	277i (4.21)	384 (4.29)		271 (4.31)		381 (4.26)	442 (4.25)	262 (4.39)			432 (4.21)
8b	261 (4.32)		366 (4.35)		272 (4.43)			435 (4.45)	260 (4.40)		367 (4.39)	415i (4.21)
9b	263 (4.14)	286 (4.18)	357 (4.14)		268 (4.18)	294 (4.18)	391 (4.39)	440i (4.05)		293 (4.22)	386 (4.01)	
10b	260 (4.15)		320 (4.09)	365i (3.98)	274 (4.21)			406 (4.35)		272 (4.09)	327 (4.02)	

a) sh, Shoulder; i, inflection point.

afforded the 3-hydroxyflavone **31a**, which was converted into the methyl ether (**32a**) and tosylate (**33a**). The 5-isopropoxy group in **32a** and **33a** was selectively cleaved with anhydrous aluminum chloride in acetonitrile at room temperature without the cleavage of the 8-benzyloxy group to give the 5-hydroxyflavones (**34a** and **35a**). The flavone **34a** was debenzylated to the 5,8-dihydroxyflavone (**11a**), which had been synthesized by the oxidative demethylation of **1a** with nitric acid by Herz *et al.*,[6)] and the flavone **35a** was also converted into **12a** *via* **36a**. The 3,8-dihydroxyflavone **13a** was synthesized from 8-benzyloxy-4′,5,6,7-tetramethoxyflavone (**37a**)[2)] *via* **38a**. 5,8-Dihydroxy-3,6,7-trimethoxyflavone (**11e**) was also synthesized from 8-benzyloxy-5-hydroxy-6,7-dimethoxyflavone (**39e**)[2)] *via* **40e**, **41e**, and **42e**.

Characterization of the 3,5,6,7,8-Pentaoxygenated Flavones and Identification of Some Natural Flavones The UV spectra of the synthesized flavones (**1**—**13**) exhibit a characteristic absorption pattern corresponding to the respective structures and the absorption bands of the hydroxyflavones are characteristically shifted upon the addition of aluminum chloride or sodium acetate, as shown in Table 1. In the spectra, the bathochromic shift of band I for the 3-hydroxyflavones is greater than that for the 3-methoxyflavones upon addition of aluminum chloride and a clear absorption band appears at 400—440 nm. Upon the addition of sodium acetate, the UV spectra of 3-methoxyflavones (**3a**, **4a**, and **11a**) with a hydroxy group at the 6- or 8-position change to a characteristic absorption pattern without the bathochromic

Table 2. ^{1}H-NMR Spectral Data for 3,5,6,7,8-Pentaoxygenated Flavones[a)]

Compd.	Solv.	OMe						Arom. H				OH or OAc					
		C_3	C_5	C_6	C_7	C_8	B ring	$C_{3'}$	$C_{5'}$	$C_{2'}$	$C_{6'}$	C_3	C_5	C_6	C_7	C_8	$C_{4'}$
1a	DMSO	3.75	3.71	3.79	3.95	3.87	3.79	7.02 d (2H)		7.89 d (2H)		—	—	—	—	—	—
2a	DMSO	3.77	—	3.77	3.97	3.83	3.82	7.10 d (2H)		7.98 d (2H)		—	12.31	—	—	—	—
3a	DMSO	3.74	3.74	—	3.93	3.89	3.83	7.07 d (2H)		7.95 d (2H)		—	—	9.20	—	—	—
4a	DMSO	3.79	—	—	3.94	3.87	3.85	7.11 d (2H)		8.00 d (2H)		—	12.08	9.01 br s	—	—	—
11a	DMSO	3.81	—	3.87	3.94	—	3.84	7.16 d (2H)		8.13 d (2H)		—	12.13	—	—	9.30	—
5a	DMSO	3.80	—	—	—	3.86	3.83	7.17 d (2H)		8.03 d (2H)		—	12.21	9.05 br	10.26 br	—	—
6a	DMSO	—	3.78	3.78	3.96	3.89	3.78	7.01 d (2H)		8.01 d (2H)		9.00 br s	—	—	—	—	—
7a	DMSO	—	—	3.77	3.96	3.84	3.79	7.05 d (2H)		8.07 d (2H)		9.60 br s	12.09	—	—	—	—
8a	DMSO	—	3.73	—	3.92	3.89	3.78	7.05 d (2H)		8.04 d (2H)		9.08	—	8.90	—	—	—
13a	DMSO	—	3.86	3.88	3.94	—	3.81	7.14 d (2H)		8.24 d (2H)		9.65	—	—	—	9.17	—
9a	DMSO	—	—	—	3.92	3.85	3.80	7.06 d (2H)		8.14 d (2H)		9.47	11.91	8.95 br s	—	—	—
12a	DMSO	—	—	3.86	3.95	—	3.85	7.15 d (2H)		8.26 d (2H)		9.66	11.95	—	—	9.26	—
10a	DMSO	—	—	—	—	3.85	3.85	7.16 d (2H)		8.15 d (2H)		9.45	11.97	8.94	10.22	—	—
1b	DMSO	3.82	3.80	3.85	4.03	3.96	3.88	—	7.00 d	7.67 d′	7.62 dd	—	—	—	—	—	9.89
2b	DMSO	3.83	—	3.83	4.03	3.91	3.88	—	7.01 d	7.69 d′	7.65 dd	—	12.46	—	—	—	10.03
2f	DMSO	3.83	—	3.82	4.03	3.91	3.88	—	7.15 d	7.61 br s	7.62 dd	—	12.45	—	—	—	9.55[b)]
3b	DMSO	3.79	3.77	—	3.97	3.95	3.88	—	6.99 d	7.67 d′	7.61 dd	—	—	9.29	—	—	9.85
4b	DMSO	3.83	—	—	3.96	3.92	3.88	—	7.01 d	7.69 d′	7.65 dd	—	12.21	9.12	—	—	10.00
5b	DMSO	3.83	—	—	—	3.88	3.87	—	7.00 d	7.68 d′	7.63 dd	—	12.25	9.01 br s	10.23 br s	—	9.95
6b	DMSO	—	3.84	3.86	4.04	3.99	3.87	—	6.98 d	7.78 d′	7.75 dd	9.15	—	—	—	—	9.72
7b	DMSO	—	—	3.84	4.03	3.94	3.87	—	6.99 d	7.79 br s	7.78 dd	9.66	12.27	—	—	—	9:85
8b	DMSO	—	3.80	—	3.984	3.98	3.87	—	6.98 d	7.77 d′	7.74 dd	9.24 br s	—	9.02	—	—	9.70 br s
9b	DMSO	—	—	—	3.97	3.94	3.87	—	6.99 d	7.79 br s	7.78 dd	9.51	11.99	9.02 br s	—	—	9.83
10b	DMSO	—	—	—	—	3.89	3.87	—	6.99 d	7.79 d′	7.75 dd	9.36	11.99	8.90 br s	10.18	—	9.77
Ac-**2a**	$CDCl_3$	3.75	—	3.84	4.04	3.97	3.84	6.95 d (2H)		8.04 d (2H)		—	2.45	—	—	—	—
Ac-**3a**	$CDCl_3$	3.85	3.90	—	4.01	3.98	3.86	6.98 d (2H)		8.07 d (2H)		—	—	2.38	—	—	—
Ac-**4a**	$CDCl_3$	3.77	—	—	4.01	3.99	3.85	6.95 d (2H)		8.02 d (2H)		—	2.41	2.30	—	—	—
Ac-**11a**	$CDCl_3$	3.77	—	3.89	4.03	—	3.89	7.01 d (2H)		7.95 d (2H)		—	2.51	—	—	2.46	—
Ac-**5a**	$CDCl_3$	3.72	—	—	—	3.93	3.80	6.88 d (2H)		7.92 d (2H)		—	2.40	2.33	2.29	—	—
Ac-**6a**	$CDCl_3$	—	3.88	3.88	4.03	3.92	3.81	6.93 d (2H)		7.82 d (2H)		2.33	—	—	—	—	—
Ac-**7a**	$CDCl_3$	—	—	3.83	4.04	3.96	3.83	6.91 d (2H)		7.73 d (2H)		2.30	2.43	—	—	—	—
Ac-**8a**	$CDCl_3$	—	3.84	—	3.97	3.93	3.84	6.93 d (2H)		7.79 d (2H)		2.34	—	2.34	—	—	—
Ac-**13a**	$CDCl_3$	—	3.96	3.98	4.04	—	3.88	7.00 d (2H)		7.74 d (2H)		2.35	—	—	—	2.42	—
Ac-**9a**	$CDCl_3$	—	—	—	3.98	3.94	3.81	6.92 d (2H)		7.74 d (2H)		2.29	2.37	2.29	—	—	—
Ac-**12a**	$CDCl_3$	—	—	3.89	4.04	—	3.88	7.00 d (2H)		7.72 d (2H)		2.32	2.47	—	—	2.42	—
Ac-**10a**	$CDCl_3$	—	—	—	—	3.96	3.82	6.93 d (2H)		7.77 d (2H)		2.29	2.37	2.32	2.29	—	—
Ac-**1b**	$CDCl_3$	3.90	3.95	3.98	4.10	3.99	3.92	—	7.19 d	7.88 d′	7.80 dd	—	—	—	—	—	2.36
Ac-**2b**	$CDCl_3$	3.83	—	3.89	4.10	4.02	3.92	—	7.19 d	7.83 d′	7.77 dd	—	2.51	—	—	—	2.36
Ac-**3b**	$CDCl_3$	3.89	3.93	—	4.05	3.99	3.92	—	7.19 d	7.87 d′	7.79 dd	—	—	2.40	—	—	2.37
Ac-**4b**	$CDCl_3$	3.82	—	—	4.07	4.02	3.92	—	7.19 d	7.82 d′	7.76 dd	—	2.46	2.36	—	—	2.36
Ac-**5b**	$CDCl_3$	3.82	—	—	—	4.02	3.91	—	7.19 d	7.78 d′	7.73 dd	—	2.45	2.37	2.34	—	2.36
Ac-**6b**	$CDCl_3$	—	3.95	3.94	4.10	3.98	3.90	—	7.18 d	7.53 br s	7.52 dd	2.37	—	—	—	—	2.36
Ac-**7b**	$CDCl_3$	—	—	3.88	4.10	4.01	3.89	—	7.18 d	7.48 br s	7.49 dd	2.34	2.47	—	—	—	2.36
Ac-**8b**	$CDCl_3$	—	3.90	—	4.06	3.98	3.89	—	7.19 d	7.52 d′	7.52 dd	2.37	—	2.40	—	—	2.36
Ac-**9b**	$CDCl_3$	—	—	—	4.07	4.01	3.89	—	7.19 d	7.47 br s	7.48 dd	2.33	2.42	2.35	—	—	2.36
Ac-**10b**	$CDCl_3$	—	—	—	—	4.01	3.88	—	7.19 d	7.45 br s	7.46 dd	2.33	2.41	2.37	2.33	—	2.36

a) br s, broad singlet; br, broad; d, doublet (J=8.5 Hz); d′, doublet (J=2.5 Hz); dd, double doublet (J=8.5, 2.5 Hz). *b*) 3′-Hydroxyl proton.

shift of band I and a bathochromic shift attributed to the 4′-hydroxy group is observed as in the spectra of **1b**—**4b**, but this characteristic shift is not clearly observed in the spectra for all 3-hydroxyflavones because the shift is also caused by the 3-hydroxy group. These features are usable for the structural elucidation of natural flavones, but care is needed in interpretation.

The ^{1}H-NMR spectra of the flavones and their acetates supported the structures assigned, as shown in Table 2. The oxyganation pattern of the B-ring in the flavones can be evaluated from the spectral data, but the assignment of the substitution pattern in the A-ring, except for the 5-hydroxy group, is difficult, since the methoxyl or acetoxyl signals appear in a narrow range and the aromatic protons in the A-ring are also substituted. On the other hand, the ^{13}C-NMR spectra show a characteristic pattern reflecting the respective substitution pattern and the signals are assigned as shown in Table 3. The carbon signals at the 2- to 10-positions are less affected by the substituents in the B-ring and reflect well the substitution pattern in the A- and C-rings. In a comparison between the 3-methoxyflavones (**1a**, **b**—**5a**, **b** and **11a**) and 3-hydroxyflavones (**6a**, **b**—**10a**, **b** and **12a**) bearing the same oxygenation pattern on the A-ring, the carbon signals at the 2- to 10-positions in the 3-methoxyflavones are diamagnetically shifted by removal of the 3-methyl group (conversion to the 3-hydroxyflavones) and the shift ranges of the respective carbon signals are similar to those of the corresponding 3-hydroxyflavones (Table 3). That is, the shift ranges of the carbon signals at the 2-position are the

Table 3. ^{13}C-NMR Data for 3,5,6,7,8-Pentaoxygenated Flavones in DMSO-d_6

Compd.	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	$C_{1'}$	$C_{2'}$	$C_{6'}$	$C_{3'}$	$C_{5'}$	$C_{4'}$	OMe					
																C_3	C_5	C_6	C_7	C_8	B ring
1a	152.5	137.4	172.2	147.2	146.2	150.8	139.8	143.2	114.4	122.5	129.5		114.3		161.0	59.2	61.7	61.3	61.8	61.5	55.3
$\Delta\delta$	−9.7	0	−1.0	−0.3	−0.1	−0.1	−2.1	−0.2	−2.2	+1.0	−0.8		−0.2		−0.8						
6a	142.8	137.4	171.2	146.9	146.1	150.7	137.7	143.0	112.2	123.5	128.7		114.1		160.2	—	61.7	61.3	61.9	61.5	55.3
2a	155.7	137.8	178.6	148.1	135.4	152.3	132.5	144.4	106.7	122.1	129.9		114.4		161.5	59.7	—	60.5	61.8	61.4	55.4
$\Delta\delta$	−8.6	−1.6	−2.0	−0.7	−0.5	−0.2	−0.1	−0.2	−1.1	+1.1	−0.6		−0.3		−0.8						
7a	147.1	136.2	176.6	147.4	134.9	152.1	132.4	144.2	105.6	123.2	129.3		114.1		160.7	—	—	60.5	61.7	61.4	55.3
3a	152.5	137.6	172.3	141.0	139.7	146.4	140.4	142.8	114.4	122.7	129.5		114.2		160.9	59.2	61.4	—	61.7	60.8	55.3
$\Delta\delta$	−9.6	−0.1	−1.1	−0.4	−2.2	+0.1	−0.5	0	−2.3	+1.0	−0.8		−0.1		−0.8						
8a	142.9	137.5	171.2	140.6	137.5	146.5	139.9	142.8	112.1	123.7	128.7		114.1		160.1	—	61.4	—	61.6	60.8	55.2
4a	155.6	137.7	178.5	141.0	133.8	148.0	132.7	142.4	106.7	122.3	129.8		114.3		161.4	59.7	—	—	61.7	60.9	55.4
$\Delta\delta$	−8.7	−1.8	−2.0	0	−0.6	0	0	−0.6	−1.2	+1.1	−0.5		−0.2		−0.8						
9a	146.9	135.9	176.5	141.0	133.2	148.0	132.7	141.8	105.5	123.4	129.3		114.1		160.6	—	—	—	61.7	60.9	55.3
5a	154.8	137.5	178.2	142.2	129.3	147.2	127.7	141.7	103.4	122.5	129.7		114.3		161.2	59.7	—	—	—	61.1	55.4
$\Delta\delta$	−8.9	−1.9	−2.1	−0.7	−0.6	−0.1	−0.1	0	−1.2	+1.0	−0.7		−0.2		−0.9						
10a	145.9	135.6	176.1	141.5	128.7	147.1	127.6	141.7	102.2	123.5	129.0		114.1		160.3	—	—	—	—	61.0	55.3
11a	155.7	137.7	178.8	140.7	135.8	147.8	130.5	144.2	106.9	122.2	130.2		114.2		161.4	59.7	—	60.4	61.1	—	55.4
$\Delta\delta$	−8.7	−1.7	−2.1	0	−0.5	−0.3	−0.1	−0.7	−1.2	+1.1	−0.6		−0.2		−0.8						
12a	147.0	136.0	176.7	140.7	135.3	147.5	130.4	143.5	105.7	123.3	129.6		114.0		160.6	—	—	60.4	61.1	—	55.3
13a	143.1	137.6	171.4	142.7	142.4	145.3	135.7	143.0	112.3	123.6	129.0		113.9		160.1	—	61.4	61.0	61.9	—	55.2
1b	152.6	137.4	172.2	147.2	146.1	150.7	139.7	143.2	114.4	121.1	111.4	121.7	149.3	115.7	147.4	59.2	61.7	61.3	61.8	61.4	55.4
6b	143.3	137.3	171.1	146.9	146.0	150.6	137.5	142.8	112.1	122.2	110.8	121.2	148.4	115.6	147.4	—	61.6	61.3	61.9	61.5	55.5
2b[a]	155.8	137.7	178.5	148.0	135.4	152.3	132.4	144.3	106.7	120.7	111.6	122.3	150.0	115.7	147.5	59.6	—	60.5	61.7	61.4	55.4
7b	147.4	136.0	176.4	147.4	134.9	152.0	132.4	144.1	105.5	121.9	111.2	121.9	149.0	115.6	147.4	—	—	60.5	61.6	61.4	55.5
3b	152.6	137.5	172.3	140.9	139.6	146.4	140.4	142.7	114.3	121.3	111.4	121.6	149.2	115.6	147.4	59.2	61.4	—	61.6	60.8	55.4
8b	143.1	137.3	171.1	140.5	137.4	146.5	139.9	142.8	112.1	122.4	110.8	121.1	148.3	115.6	147.4	—	61.4	—	61.6	60.9	55.4
4b	155.7	137.5	178.5	140.9	133.7	148.0	132.7	142.5	106.6	120.9	111.6	122.2	149.9	115.7	147.4	59.6	—	—	61.7	60.9	55.4
9b	147.2	135.7	176.3	140.9	133.1	148.0	132.6	141.8	105.4	122.1	111.2	121.8	148.9	115.6	147.3	—	—	—	61.6	60.9	55.5
5b	154.9	137.3	178.1	142.2	129.2	147.2	127.7	141.6	103.3	121.1	111.5	121.9	149.6	115.7	147.4	59.6	—	—	—	61.0	55.4
10b	146.2	135.4	176.0	141.5	128.8	147.1	127.6	141.6	102.2	122.3	111.1	121.5	148.6	115.6	147.3	—	—	—	—	61.0	55.5
2f	155.8	137.9	178.6	148.0	135.4	152.3	132.4	144.3	106.7	120.4	112.0	122.2	146.4	114.8	150.5	59.6	—	60.5	61.8	61.4	55.6

a) The data were consistent with those for the natural flavone isolated by Roitmann and James.[21)]

largest (*ca.* $\Delta\delta$ −8.7) and those at the other positions decrease in the order of the 4-, 3-, and 10-positions. In the flavones with the 5-methoxy group (**1a** *vs.* **6a** and **3a** *vs.* **8a**), however, the tendency changes slightly because of the effect of the newly formed hydrogen bond between the 3-hydroxy group and 4-carbonyl group. These features may be useful for the assignment of 3,5,6,7,8-pentaoxygenated flavones.

The three flavones synthesized are corresponding to the natural ones, **2a**,[18,19)] **2b**,[20,21)] and **7b**,[22)] and their properties are consistent with those of the synthetic ones, respectively, showing that the assigned structures of the natural products are correct. However, a flavone, isolated from *Gutierrezia resinosa* and proposed to be **2b** by Bittner *et al.*,[11)] and two natural ones,[9,10)] proposed to be 8-hydroxyflavone derivatives, were not consistent with the synthetic products, as shown in Table 4.

The UV spectral data for the former natural flavone are similar to those for the synthetic compound, but no bathochromic shift attributed to the 4′-hydroxy group is observed upon the addition of sodium acetate. Although the ^{1}H-NMR signals of the natural flavone diacetate are also similar to those of the synthetic one, the 6′-proton signal at δ 8.07 is at lower field than that at δ 7.77 in Ac-**2b** and the spectral pattern of the protons of the B-ring is similar to that in 5,6,7,3′-tetraacetoxy-3,4′-dimethoxyflavones.[15)] The result suggests that the structure of the natural flavone is an isomeric 5,3′-dihydroxy-3,4′,6,7,8-pentamethoxyflavone (**2f**) which has been isolated from *Polanisia trachysperma* by Wollenweber *et al.*[19)] Therefore, the flavone **2f** was also synthesized by the method shown in Chart 1 and the properties of the natural flavone were compared with those of the synthesized **2f** and **2b**. As shown in Table 4, the spectral data for the natural flavone and its acetate are not consistent with those of **2b** and Ac-**2b**, but coincide well with those of **2f** and Ac-**2f**. Consequently, the structure of the natural flavone was revealed to be **2f**.

A flavone, eriostemin, isolated from *Eriostemon* species, has been proposed to be **13a** on the basis of the spectral data reported by Lassak and Southwell.[9)] Although the properties of the natural flavone and its acetate are not consistent with those of the synthetic compounds, the ^{1}H-NMR spectral data are similar to each other (Table 4), suggesting that the natural product is an isomeric flavone. In the ^{1}H-NMR data for the natural flavone in $CDCl_3$, the signal at δ 11.51 is attributed to the 5-hydroxyl proton and the signal at δ 4.12 shows the existence of the 7-methoxy group.[2)] Furthermore, the UV spectrum of the natural flavone exhibited a large bathochromic shift upon the addition of sodium acetate, as seen with the flavone **7a**. The result suggests that the structure of the natural flavone **7a**, an isomer of **13a**, and the properties coincide well with those of the synthesized **7a**, as shown in Table 4. Consequently, the structure of the natural flavone, is concluded to be 3,5-dihydroxy-4′,6,7,8-tetramethoxyfla-

Table 4. Comparisons of the Natural Flavones with the Synthetic and Isomeric Flavones[a)]

	Synthetic	Natural	Isomeric
	5,4′-Dihydroxy-3,3′,6,7,8-pentamethoxyflavone (**2b**) (Isolated from *Gutierrezia resinosa*[11)])		5,3′-Dihydroxy-3,4′,6,7,8-pentamethoxyflavone (**2f**)
mp (°C)	170—171	174—176	169—170
UV λ_{max} nm MeOH	(EtOH) 261 279 356	260 278 350	(EtOH) 261 (4.30) 278 (4.28) 351 (4.28)
+$AlCl_3$	270 289 372 415i	273 286 305sh 374	272i (4.22) 286 (4.24) 367 (4.27)
+NaOAc	270 430	260 278 348	262 (4.30) 278 (4.28) 351 (4.26)
MS m/z (rel. int. %)	404 (M$^+$, 57) 389 (100) 374 (5) 373 (5) 359 (5) 331 (6) 211 (9) 202 (5)	404 (M$^+$) 389 (100) 374 359 202 84	404 (M$^+$, 67) 389 (100) 374 (5) 373 (6) 371 (4) 359 (3) 211 (7) 202 (5)
^{1}H-NMR for the diacetate in $CDCl_3$	2.36 s 2.51 s 3.83 s 3.89 s 3.92 s 4.02 s 4.10 s 7.19 d 7.83 d′ 7.77 dd	2.37 s 2.51 s 3.82 s 3.89 s 3.93 s 4.02 s 4.10 s 7.10 d 7.89 d′ 8.07 dd	2.37 s 2.50 s 3.81 s 3.89 s 3.92 s 4.01 s 4.09 s 7.10 d 7.89 d′ 8.07 dd
	3,8-Dihydroxy-4′,5,6,7-tetramethoxyflavone (**13a**)[9)]		**7a**
mp (°C)	142—143	167—168	161—163
^{1}H-NMR in $CDCl_3$	3.89 s 3.96 s 3.99 s 4.12 s 5.71 s (OH) 7.05 d 8.24 d	3.88 s 3.96 s 3.98 s 4.12 s 6.76 s (OH) 7.01 d 8.21 d 11.51 s (OH)	3.90 s 3.96 s 3.98 s 4.13 s 6.20 s (OH) 7.06 d 8.25 d 11.53 s (OH)
UV λ_{max} nm MeOH	(EtOH) 273 (4.27) 339 (4.21) 365 (4.21)	258 (4.22) 278 (4.28) 337 (4.23) 376 (4.28)	258 (4.17) 278 (4.26) 339 (4.23) 380 (4.20)
+$AlCl_3$	269 (4.41) 375sh (4.05) 431 (4.39)	270 (4.35) 283 (4.29) 312 (3.72) 374 (4.17) 436 (4.28)	265 (4.22) 286 (4.21) 310i (3.88) 368 (4.26) 438 (4.21)
+NaOAc	277 291 320 342	262 (4.37) 275 (4.26) 340 (3.82) 420 (4.16)	262 (4.34) 275i (4.24) 342 (4.00) 427 (4.16)
MS m/z (rel. int. %)	374 (M$^+$, 100) 359 (87) 356 (50) 345 (7) 331 (10)	374 (M$^+$, 100) 359 (90) 345 (5) 331 (26)	374 (M$^+$, 83) 359 (100) 345 (4) 331 (23)
Diacetate: mp (°C)	140—141	123—124	148—149
^{1}H-NMR for the diacetate in $CDCl_3$	2.35 s 2.42 s 3.88 s 3.94 s 3.98 s 4.04 s 7.00 d 7.74 d	2.33 s 2.46 s 3.89 s 4.02 s 4.10 s (4 × OMe) 7.04 d 7.87 d	2.34 s 2.47 s 3.88 s 3.89 s 4.02 s 4.10 s 7.02 d 7.85 d
	5,8-Dihydroxy-3,6,7-trimethoxyflavone (**11e**)[10)]		5,7-Dihydroxy-3,6,8-trimethoxyflavone (**43**)[23)]
mp (°C)	206—207	177—178	172—174
^{1}H-NMR in $CDCl_3$	3.87 s 3.98 s 4.14 s 5.40 br s (OH) 7.53 m (3H) 8.14 m (2H) 12.10 s (OH)	3.88 s 3.98 s 4.03 s 6.58 br s (OH) 7.46 m (2H) 8.08 m (3H) 11.30 br s (OH)	3.88 s 3.99 s 4.05 s 6.43 s (OH) 7.53—7.56 m (3H) 8.12—8.15 m (2H) 12.54 (OH)
UV λ_{max} nm MeOH	(EtOH) 287 (4.46) 372 (3.55)	277 324sh 375sh	278 (4.43) 322 (4.00)
+$AlCl_3$	305 (4.45) 345i (3.89) 450 (3.53)	252sh 291 341 420sh	293 (4.42) 347 (4.13) 422 (3.65)
+NaOAc	289 (4.41)	280 375	283 (4.44) 380 (4.03)
MS m/z (rel. int. %)	344 (M$^+$, 100) 329 (80) 325 (11) 311 (18) 301 (4)	344 (M$^+$, 81) 329 (100) 301 (12.5)	344 (M$^+$, 72) 329 (100) 325 (5) 311 (7) 301 (9)

a) s, singlet; sh, shoulder; i, inflection point.

vone (**7a**).

A flavone, isolated from *Gnaphalium gaudichaudianum*, has been proposed to be **11e** on the basis of the spectral data reported by Guerreiro *et al.*[10)] Although the ^{1}H-NMR spectral data are similar to those for the synthetic flavone **11e**, the signal at δ 4.10—4.15 attributed to the 4′-methoxy group[2)] is not observed. Furthermore, the UV spectral data are greatly different from those for **11e** and band I is bathochromically shifted upon the addition of sodium acetate. The behavior suggests that the structure of the natural flavone is 5,7-dihydroxy-3,6,8-trimethoxyflavone (**43**), an isomer of **11e**. The physical data for the flavone coincide well with those for our synthetic flavone **43**,[23)] as shown in Table 4. Thus, the structure of the natural flavone must be revised to **43**, which has been isolated as araneol from *Anaphalis araneosa* by Ali *et al.*[24)]

Experimental

All melting points were determined in glass capillaries and are uncorrected. ^{1}H-NMR (at 400 MHz or 60 MHz) and ^{13}C-NMR (at 100.4 MHz) spectra were recorded on a JEOL EX400 or Hitachi R-24B spectrometer, using tetramethylsilane as an internal standard, and chemical shifts are given in δ values. UV spectra and MS were recorded on a Hitachi 124 spectrophotometer and on a Shimadzu QP 1000 spectrometer, respectively. Column chromatography was carried out on Kiesel-gel 60 (70—230 mesh; Merck). Elemental analyses were performed with a Yanaco CHN corder Model MT-5.

6-Hydroxy-5,7,8-trimethoxyflavones (17a, c, g) A mixture of 2′,5′-dihydroxy-3′,4′,6′-trimethoxyacetophenone (**14**) (5.0 g; 20.6 mmol), $MeOCH_2Cl$ (2.2 ml; 30 mmol), and *N*,*N*-diisopropylethylamine (10 ml) in CH_2Cl_2 (80 ml) was stirred at room temperature till the starting material disappeared (3—4 h). The mixture was washed with cooled 2—3% HCl, aqueous $NaHCO_3$, and water, dried over Na_2SO_4, and evaporated to give a crude methoxymethyl ether (**15**).

To a solution of the crude ether **15** in pyridine (15 ml), a substituted benzoyl chloride (25—30 mmol) was added. The mixture was heated at 60—80 °C for 2 h and poured into a mixture of ice and HCl. The separated oily materials were extracted with EtOAc and the extract was washed with cooled 2—3% HCl, aqueous K_2CO_3 and water, dried over Na_2SO_4 and evaporated to give a crude benzoate. A mixture of the crude benzoate and freshly powdered KOH (12 g) in pyridine (25 ml) was heated with stirring at 60—70 °C for 2 h and poured into a mixture of ice and HCl. The separated oily materials were extracted with EtOAc and the extract was washed with aqueous K_2CO_3, dried over Na_2SO_4, and evaporated to give a crude oily diketone (**16**). The diketone **16** was warmed in AcOH (25 ml) containing a small amount of H_2SO_4 at 50 °C for 1 h, diluted with a saturated aqueous solution of $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was chromatographed over a silica gel column with $CHCl_3$–EtOAc (5 : 1) and the product was recrystallized from $CHCl_3$–MeOH to give **17**. Flavone **17a**: mp 180—182 °C; yield, 5.2 g (70%). *Anal.* Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06%. Found: C, 63.50; H, 5.13%. Flavone **17c**: mp 172—173 °C; yield, 6.4 g (67%). *Anal.* Calcd for $C_{26}H_{24}O_8$: C, 67.23; H, 5.21. Found: C, 67.20; H, 5.26. Flavone **17g**: mp 187—189 °C; yield, 4.6 g (48%). *Anal.* Calcd for $C_{26}H_{24}O_8$: C, 67.23; H, 5.21. Found: C, 67.09; H, 5.23.

3-Hydroxy-5,7,8-trimethoxy-6-methoxymethoxyflavones. (19a—c, f)

Table 5. 3,6-Dihydroxy-5,7,8-trimethoxyflavone Derivatives

Compd.	Starting material	mp (°C)	Recystn. solvent	Formula	Found (%)		Calcd (%)	
					C	H	C	H
8c	**19c**	161—162	$CHCl_3$–MeOH	$C_{26}H_{24}O_9$	64.76	4.86	65.00	5.03
8g	**19g**	138—139	MeOH	$C_{26}H_{24}O_9$	64.87	5.08	65.00	5.03
1c	**8c**	126—127	$CHCl_3$–MeOH	$C_{28}H_{28}O_9$	65.96	5.59	66.13	5.55
1g	**8g**	124—125	$CHCl_3$–MeOH	$C_{28}H_{28}O_9$	66.05	5.52	66.13	5.55
2c	**1c**	93—95	MeOH	$C_{27}H_{26}O_9 \cdot 1/2H_2O$	64.39	5.23	64.41	5.40
2g	**1g**	102—103	MeOH	$C_{27}H_{26}O_9$	65.61	5.27	65.58	5.30
20a	**19a**	107—108	aq. MeOH	$C_{22}H_{24}O_9$	61.06	5.56	61.11	5.59
20b	**20c**	148—149	MeOH	$C_{22}H_{24}O_{10}$	59.07	5.48	58.93	5.39
20c	**19c**	102—103	MeOH	$C_{29}H_{30}O_{10}$	64.88	5.55	64.68	5.61
20d	**20b**	103—105	MeOH	$C_{29}H_{30}O_{12}S$	57.75	5.02	57.80	5.02
3c	**20c**	138—139	$CHCl_3$–MeOH	$C_{27}H_{26}O_9$	65.36	5.27	65.58	5.30
3d	**20d**	170—171	MeOH	$C_{27}H_{26}O_{11}S$	58.14	4.75	58.06	4.69
Ac-**3c**	**3c**	144—145	$CHCl_3$–MeOH	$C_{29}H_{28}O_{10}$	64.88	5.40	64.92	5.26
21a	Ac-**3a**	170—172	$CHCl_3$–MeOH	$C_{21}H_{20}O_9$	60.76	4.85	60.58	4.84
21c	Ac-**3c**	142—143	$CHCl_3$–MeOH	$C_{28}H_{26}O_{10}$	64.09	4.92	64.36	5.02
4c	**21c**	135—136	$CHCl_3$–MeOH	$C_{26}H_{24}O_9$	64.80	5.03	65.00	5.03
5d	**3d**	178—180	Me_2CO–hexane	$C_{25}H_{22}O_{11}S$	56.40	4.07	56.60	4.18
22a	**19a**	118—120	$CHCl_3$–MeOH	$C_{28}H_{28}O_{11}S$	58.46	4.86	58.73	4.93
22c	**19c**	139—140	$CHCl_3$–MeOH	$C_{35}H_{34}O_{12}S$	61.71	4.97	61.94	5.05
22d	**19b**	136—137	$CHCl_3$–MeOH	$C_{35}H_{34}O_{14}S_2$	58.15	4.38	58.37	4.31
23a	**22a**	169—170	$CHCl_3$–MeOH	$C_{26}H_{24}O_{10}S \cdot 1/2H_2O$	58.25	4.87	58.09	4.69
23c[a]	**22c**	156—157	$CHCl_3$–MeOH	$C_{33}H_{30}O_{11}S$	62.35	4.77	62.45	4.76
23d	**22d**	193—194	$CHCl_3$–MeOH	$C_{33}H_{30}O_{13}S_2$	52.75	3.77	52.47	3.85
24a	**23a**	137—138	$CHCl_3$–MeOH	$C_{27}H_{26}O_{10}S$	59.64	4.78	59.77	4.83
24c	**23c**	180—182	$CHCl_3$–MeOH	$C_{34}H_{32}O_{11}S$	62.87	4.88	62.95	4.97
6c	**24c**	158—159	$CHCl_3$–MeOH	$C_{27}H_{26}O_9$	65.37	5.23	65.58	5.30
25a	**24a**	157—159	$CHCl_3$–MeOH	$C_{26}H_{24}O_{10}S$	58.88	4.36	59.09	4.58
25c	**24c**	176—178	$CHCl_3$–MeOH	$C_{33}H_{30}O_{11}S$	62.28	4.68	62.45	4.76
7c	**25c**	152—153	$CHCl_3$–MeOH	$C_{26}H_{24}O_9$	64.71	5.04	65.00	5.03
26a	**23a**	133—134	MeOH	$C_{28}H_{26}O_{11}S$	58.81	4.54	58.94	4.59
26c	**23c**	181—182	$CHCl_3$–MeOH	$C_{35}H_{32}O_{12}S$	61.95	4.69	62.12	4.77
27a	**26a**	188—190	$CHCl_3$–MeOH	$C_{27}H_{24}O_{11}S$	58.01	4.16	58.27	4.35
27c	**26c**	170—171	$CHCl_3$–MeOH	$C_{34}H_{30}O_{12}S$	61.39	4.58	61.63	4.56
28a	**27a**	112—114	$CHCl_3$–MeOH	$C_{25}H_{22}O_{10}S \cdot 1/2H_2O$	57.19	4.47	57.36	4.43
28c	**27c**	170—171	$CHCl_3$–MeOH	$C_{32}H_{28}O_{11}S \cdot 3/2H_2O$	59.20	4.86	59.35	4.82
29a	**23a**	113—115	$CHCl_3$–MeOH	$C_{24}H_{20}O_{10}S \cdot H_2O$	55.43	3.99	55.60	4.28
29d	**23d**	227—228	Me_2CO–MeOH	$C_{31}H_{26}O_{13}S_2$	55.43	3.99	55.60	4.28

a) The compound was sintered at 95—97 °C then resolidified.

A flavone **17** was methoxymethylated with $MeOCH_2Cl$ and *N*,*N*-diisopropylethylamine in CH_2Cl_2 to give quantitatively a methoxymethyl ether (**18a, c, g**). Flavone **18a**: mp 104—105 °C (from MeOH). *Anal.* Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51. Found: C, 62.55; H, 5.54. Flavone **18c**: mp 136—137 °C (from $CHCl_3$–MeOH). *Anal.* Calcd for $C_{28}H_{28}O_9$: C, 66.13; H, 5.55. Found: C, 65.86; H, 5.59.

An acetone solution of dimethyldioxirane (*ca.* 0.1 mol/l; 40 ml) was added to a cooled solution of a flavone **18** (2.0 mmol) in CH_2Cl_2 (30 ml). The mixture was stirred at 0 °C for 10—12 h and the solvent was evaporated off under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 ml), and the solution was stirred with a small amount of TsOH (5—10 mg) at 0 °C for 10—20 min, then diluted with CH_2Cl_2. The mixture was washed with aqueous $NaHCO_3$ and H_2O, dried over Na_2SO_4, and evaporated to give a 3-hydroxyflavone (**19a, c, g**). Flavone **19a**: mp 137—139 °C (from $CHCl_3$–MeOH); yield, 80%. *Anal.* Calcd for $C_{21}H_{22}O_9$: C, 60.28; H, 5.30. Found: C, 60.25; H, 5.22. Flavone **19c**: mp 161—162 °C (from $CHCl_3$–MeOH); yield, 83%. *Anal.* Calcd for $C_{28}H_{28}O_{10}$: C, 64.12; H, 5.38. Found: C, 63.87; H, 5.33. Flavone **19g**: mp 110—111 °C (from $CHCl_3$–MeOH); yield, 80% (from **17g**). *Anal.* Calcd for $C_{28}H_{28}O_{10}$: C, 64.12; H, 5.38. Found: C, 64.04; H, 5.35. Flavone **19b** was synthesized from **19c** by hydrogenolysis with 10% Pd–C in MeOH–EtOAc: mp 161—162 °C (from $CHCl_3$–MeOH); yield, 96%. *Anal.* Calcd for $C_{21}H_{22}O_{10}$: C, 57.47; H, 4.26. Found: C, 57.65; H, 4.13.

Synthesis of 3,5,6,7,8-Pentaoxygenated Flavones (1—10) The flavones **1**—**10** were synthesized from the flavones **19** by using the following procedures and the results are shown in Table 5. All reactions in this process proceeded quantitatively and the products were obtained in more than 80% yield as a pure form.

Methylation: A mixture of hydroxyflavone (1 mmol), Me_2SO_4 (2—3 eq), and anhydrous K_2CO_3 (10—20 eq) in acetone (30—35 ml) was refluxed with stirring till the starting material disappeared. The mixture was diluted with H_2O, refluxed for 10—15 min to decompose the excess Me_2SO_4, and then treated in a usual way to give a methyl ether.

Tosylation: A mixture of hydroxyflavone (1 mmol), TsCl (1.3—1.5 eq), and anhydrous K_2CO_3 (10—20 eq) in Me_2CO (30—35 ml) was refluxed with stirring till the starting material disappeared. The mixture was diluted with cooled water and concentrated under reduced pressure. The precipitates were collected by filtration, washed with water, and recrystallized to give a tosylate.

Selective Demethylation of the 5-Methoxy Group A cooled solution of 5-methoxyflavone (1 mmol) in MeCN (8 ml) was treated with 10% (w/v) anhydrous $AlBr_3$–MeCN (8 ml; 3 mmol), and the mixture was allowed to stand at 0 °C for 30—40 min. It was then diluted with 2—3% HCl, warmed at 50—60 °C for 30 min and concentrated. The separated crystals were collected and recrystallized to give a 5-hydroxyflavone.

Selective Demethylation of the 5- and 7-Methoxy Groups A solution of 6-hydroxyflavone (**3a, d** or **23a, d**) (0.4 mmol) in MeCN (4 ml) was treated with 20% (w/v) anhydrous $AlBr_3$–MeCN (4 ml; 3.0 mmol). The mixture was heated at 50 °C for 5 h and treated as described above to give a 5,6,7-trihydroxyflavone.

Demethoxymethylation: Concentrated HCl (0.5—1.0 ml) was added to a solution of methoxymethoxyflavone (1—2 mmol) in HOAc (5—10 ml). The mixture was stirred at room temperature for 1—2 h. The separated precipitates were collected and recrystallized to give a hydroxyflavone.

Table 6. 3,5,6,7,8-Pentaoxygenated Flavones (**1**—**10**) and Their Acetate (Ac-**1**—Ac-**10**)

Compd.	Starting material	mp (°C)	Recystn. solvent	Formula	Found (%)		Calcd (%)	
					C	H	C	H
1a	**8a**	123—125	MeOH	$C_{21}H_{22}O_8$	62.47	5.42	62.68	5.51
1b	**1c**	187—188	$CHCl_3$–MeOH	$C_{21}H_{22}O_9$	60.36	5.28	60.28	5.30
2a	**1a**	118—120	aq. MeOH	$C_{20}H_{20}O_8$	61.71	5.21	61.85	5.19
2b	**2c**	170—171	$CHCl_3$–MeOH	$C_{20}H_{20}O_9$	59.31	4.99	59.41	4.99
2f	**2g**	169—170	EtOAc	$C_{20}H_{20}O_9$	59.39	5.02	59.41	4.99
3a	**20a**	160—162	MeOH	$C_{20}H_{20}O_8$	61.90	5.21	61.85	5.19
3b	**3c**	166—167	aq. MeOH	$C_{20}H_{20}O_9$	59.20	4.99	59.41	4.99
4a	**21a**	156—158	$CHCl_3$–MeOH	$C_{19}H_{18}O_8$	60.76	4.84	60.96	4.85
4b	**4c**	174—175	aq. MeOH	$C_{19}H_{18}O_9$	58.42	4.66	58.46	4.65
5a	**3a**	158—160	aq. EtOH	$C_{18}H_{16}O_8 \cdot H_2O$	56.87	4.90	57.14	4.80
5b	**5d**	243—244	MeOH	$C_{18}H_{16}O_9$	57.18	4.30	57.45	4.29
6a	**24a**	147—149	$CHCl_3$–MeOH	$C_{20}H_{20}O_8$	61.74	5.12	61.85	5.19
6b	**6c**	171—172	$CHCl_3$–MeOH	$C_{20}H_{20}O_9$	59.15	4.94	59.41	4.99
7a	**25a**	161—163	$CHCl_3$–MeOH	$C_{19}H_{18}O_8$	60.75	4.79	60.96	4.85
7b	**7c**	165—166	$CHCl_3$–MeOH	$C_{19}H_{18}O_9$	58.51	4.63	58.46	4.65
8a	**19a**	180—182	MeOH	$C_{19}H_{18}O_8$	61.02	4.84	60.96	4.85
8b	**8c**	206—207	aq. Me_2CO	$C_{19}H_{18}O_9$	58.18	4.54	58.46	4.65
9a	**28a**	172—174	aq. DMF	$C_{18}H_{16}O_8$	59.81	4.53	60.00	4.48
9b	**28c**	183—185	aq. Me_2CO	$C_{18}H_{16}O_9$	57.26	4.30	57.45	4.29
10a	**29a**	226—227	aq. Me_2CO	$C_{17}H_{14}O_8 \cdot 1/2H_2O$	57.65	4.13	57.47	4.26
10b	**29d**	257 dec.	aq. MeOH	$C_{17}H_{14}O_9$	56.23	4.14	56.36	3.89
Ac-**1b**		113—114	aq. MeOH	$C_{23}H_{24}O_{10}$	59.74	5.15	60.00	5.25
Ac-**2a**		140—141	$CHCl_3$–MeOH	$C_{22}H_{22}O_9$	61.17	5.07	61.39	5.15
Ac-**2b**		133—134	$CHCl_3$–MeOH	$C_{24}H_{24}O_{11}$	59.08	5.01	59.02	4.95
Ac-**2f**		130—131	aq. MeOH	$C_{24}H_{24}O_{11}$	58.81	4.86	59.02	4.95
Ac-**3a**		127—128	$CHCl_3$–MeOH	$C_{22}H_{22}O_9$	61.45	5.09	61.39	5.15
Ac-**3b**		149—150	$CHCl_3$–MeOH	$C_{24}H_{24}O_{11}$	58.86	4.90	59.02	4.95
Ac-**4b**		166—167	$CHCl_3$–MeOH	$C_{23}H_{22}O_{10}$	59.99	4.76	60.26	4.84
Ac-**4c**		166—168	$CHCl_3$–MeOH	$C_{25}H_{24}O_{12}$	58.03	4.60	58.14	4.68
Ac-**5a**		177—179	$CHCl_3$–MeOH	$C_{24}H_{22}O_{11}$	59.07	4.52	59.26	4.56
Ac-**5b**		175—176	$CHCl_3$–MeOH	$C_{26}H_{24}O_{13}$	57.12	4.42	57.36	4.44
Ac-**6a**		130—131	$CHCl_3$–MeOH	$C_{22}H_{22}O_9$	61.42	5.25	61.39	5.15
Ac-**6b**		117—118	MeOH	$C_{24}H_{24}O_{11}$	58.76	5.06	59.02	4.95
Ac-**7a**		148—149	$CHCl_3$–MeOH	$C_{23}H_{22}O_{10}$	59.99	4.95	60.26	4.84
Ac-**7b**		157—158	$CHCl_3$–MeOH	$C_{25}H_{24}O_{12}$	57.97	4.58	58.14	4.68
Ac-**8a**		162—164	$CHCl_3$–MeOH	$C_{23}H_{22}O_{10}$	60.28	4.89	60.26	4.84
Ac-**8b**		153—154	$CHCl_3$–MeOH	$C_{25}H_{24}O_{12}$	58.00	4.59	58.14	4.68
Ac-**9a**		164—166	$CHCl_3$–MeOH	$C_{24}H_{22}O_{11}$	59.28	4.62	59.26	4.56
Ac-**9b**		218—219	$CHCl_3$–MeOH	$C_{26}H_{24}O_{13}$	57.10	4.35	57.36	4.44
Ac-**10a**		203—205	$CHCl_3$–MeOH	$C_{25}H_{22}O_{12}$	58.15	4.38	58.37	4.31
Ac-**10b**		235—236	$CHCl_3$–MeOH	$C_{27}H_{24}O_{14}$	56.45	4.16	56.65	4.23

Hydrolysis of the Tosyloxy Group A) Detosylation of the Flavones **24** and **25**: A mixture of a flavone (0.5 mmol) and anhydrous K_2CO_3 (0.8—1.0 g) in MeOH (30—35 ml) was refluxed with stirring for 1—2 h and then acidified with diluted HCl. The solvent was evaporated off and the separated crystals were collected and recrystallized to give a hydroxyflavone.

B) Detosylation of the Flavones (**5d**, **28**, **29**): A flavone (**5d**, **28**; 0.8 mmol: **29**; 0.6 mmol) was methoxymethylated with $MeOCH_2Cl$ (0.20 ml) and *N*,*N*-diisopropylethylamine (1.0 ml) in CH_2Cl_2 (20—30 ml) at room temperature for 30—40 min to give a crude methoxymethyl ether. The crude ether was hydrolyzed according to method A and then demethoxymethylated with HCl in HOAc to give the desired flavone (**5b**, **9a**, **c**, or **10a**, **b**). The flavone **9c** was converted into **9b** by hydrogenolysis with Pd–C without purification.

Other Procedures Debenzylation: benzyloxyflavones were hydrogenolyzed with 10% Pd–C in MeOH–EtOAc. Acetylation: hot acetic anhydride–pyridine method. Hydrolysis of acetoxy group: acetates were hydrolyzed with 15% aqueous HCl–MeOH (1 : 10).

Synthesis of 3,5,8-Trihydroxy-4′,6,7-trimethoxyflavone (12a) and Its 3- (11a) or 5-Methyl Ether (13a) 8-Benzyloxy-4′,6,7-trimethoxy-5-isopropoxyflavone (**30a**) (715 mg; 1.5 mmol) was oxidized with dimethyldioxirane to give the 3-hydroxyflavone (**31a**): mp 113—114 °C (from Et_2O–hexane); yield, 595 mg (81%). *Anal.* Calcd for $C_{28}H_{28}O_8$: C, 68.28; H, 5.73. Found: C, 68.13; H, 5.74. Its methyl ether (**32a**): mp 107—108 °C (from MeOH). *Anal.* Calcd for $C_{29}H_{30}O_8$: C, 68.76; H, 5.97. Found: C, 68.82; H, 5.98. The methyl ether **32a** was dealkylated with 5% (w/v) anhydrous $AlCl_3$–MeCN at room temperature for 40 min to give quantitatively the 5-hydroxyflavone **34a**: mp 131—132 °C (from $CHCl_3$–MeOH). *Anal.* Calcd for $C_{26}H_{24}O_8$: C, 67.23; H, 5.21. Found: C, 67.11; H, 5.26. 5,8-Dihydroxy-3,4′,6,7-tetramethoxyflavone (**11a**): mp 207—209 °C (from aq. MeOH containing SO_2) (lit.[6]) mp 203—205 °C). *Anal.* Calcd for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 60.72; H, 4.76. Its acetate (Ac-**11a**): mp 158—159 °C (MeOH). *Anal.* Calcd for $C_{23}H_{22}O_{10}$: C, 60.26; H, 4.84. Found: C, 60.22; H, 4.81.

The crude tosylate **33a** obtained from **31a** was dealkylated with 5% (w/v) anhydrous $AlCl_3$–MeCN to give quantitatively the 5-hydroxyflavone **35a**: mp 145—146 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{32}H_{28}O_{10}S$: C, 63.57; H, 4.67. Found: C, 63.46; H, 4.70. 8-Benzyloxy-3,5-dihydroxy-4′,6,7-trimethoxyflavone (**36a**): mp 145—146 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{25}H_{22}O_8$: C, 66.66; H, 4.92. Found: C, 66.66; H, 4.94. 3,5,8-Trihydroxy-4′,6,7-trimethoxyflavone (**12a**): mp 181—182 °C (from aqueous MeOH). *Anal.* Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48. Found: C, 59.95; H, 4.40. Its acetate (Ac-**12a**): mp 202—203 °C (from MeOH). *Anal.* Calcd for $C_{24}H_{22}O_{11}$: C, 59.26; H, 4.56. Found: C, 59.18; H, 4.57.

8-Benzyloxy-4′,5,6,7-tetramethoxyflavone (**37a**)[2)] was oxidized with dimethyldioxirane to give the flavone **38a**: mp 148—149 °C (from $CHCl_3$–MeOH); yield, 90%. *Anal.* Calcd for $C_{26}H_{24}O_8$: C, 67.23; H, 5.21. Found: C, 66.96; H, 5.20. 3,8-Dihydroxy-4′,5,6,7-tetramethoxyflavone (**13a**): mp 142—143 °C (from $CHCl_3$–hexane). *Anal.* Calcd for

$C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 60.73; H, 4.82. Its acetate (Ac-**13a**): mp 140—141 °C (from MeOH). *Anal.* Calcd for $C_{23}H_{22}O_{10}$: C, 60.26; H, 4.84. Found: C, 60.13; H, 4.82.

5,8-Dihydroxy-3,6,7-trimethoxyflavone (11e) A mixture of the flavone **39e**[2] (480 mg), $PhCH_2Cl$ (0.27 ml), and anhydrous K_2CO_3 (1.5 g) in *N*,*N*-dimethylformamide (5.0 ml) was heated with stirring at 150—160 °C for 10 min and then diluted with H_2O. The separated oily material was treated in a usual way to give the benzyl ether **40e**: mp 122—123 °C (from Me_2CO–MeOH); yield, 547 mg (93%). *Anal.* Calcd for $C_{31}H_{26}O_6$: C, 75.29; H, 5.30. Found: C, 75.28; H, 5.30. 5,8-Bis(benzyloxy)-3-hydroxy-6,7-dimethoxyflavone (**41e**): mp 140—141 °C (from $CHCl_3$–MeOH). *Anal.* Calcd for $C_{31}H_{26}O_7$: C, 72.93; H, 5.13. Found: C, 72.66; H, 5.08. Its methyl ether (**42e**): mp 172—173 °C (from $CHCl_3$–MeOH). *Anal.* Calcd for: $C_{32}H_{28}O_7$: C, 73.27; H, 5.38. Found: C, 73.03; H, 5.36. 5,8-Dihydroxy-3,6,7-trimethoxyflavone (**11e**): mp 206—207 °C (from EtOAc–MeOH). *Anal.* Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68. Found: C, 62.50; H, 4.63. Its acetate (Ac-**11e**): mp 162—163 °C (from MeOH). *Anal.* Calcd for $C_{22}H_{20}O_9$: C, 61.68; H, 4.71. Found: C, 61.56; H, 4.69.

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