Chem. Pharm. Bull. 37(5) 1216—1220 (1989) Vol. 37, No. 5

Studies of the Selective O-Alkylation and Dealkylation of Flavonoids. XII.[1] A New, Convenient Method for Synthesizing 3,5-Dihydroxy-6,7-dimethoxyflavones from 3,5,6,7-Tetramethoxyflavones

Tokunaru HORIE,*,[a] Yasuhiko KAWAMURA,[a] Masao TSUKAYAMA[a] and Shiro YOSHIZAKI[b]

Department of Chemical Science and Technology, Faculty of Engineering, Tokushima University,[a] Minamijosanjima-cho, Tokushima 770, Japan and Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd.,[b] Otedori, Higashi-ku, Osaka 540, Japan. *Received October 7, 1988*

The 5-methoxy group on 3,5,6,7-tetramethoxyflavones and the 3-methoxy group on 3,6,7-trimethoxy-5-tosyloxyflavones were selectively cleaved with anhydrous aluminum bromide in acetonitrile under controlled conditions without the cleavage of benzyloxy groups on the B ring. By the application of these reactions, seven 3,5-dihydroxy-6,7-dimethoxyflavones were easily synthesized from the corresponding 3,5,6,7-tetramethoxyflavones which were synthesized from 3,6-dihydroxy-2,4,ω-trimethoxyacetophenone by means of the Allan–Robinson reaction followed by methylation.

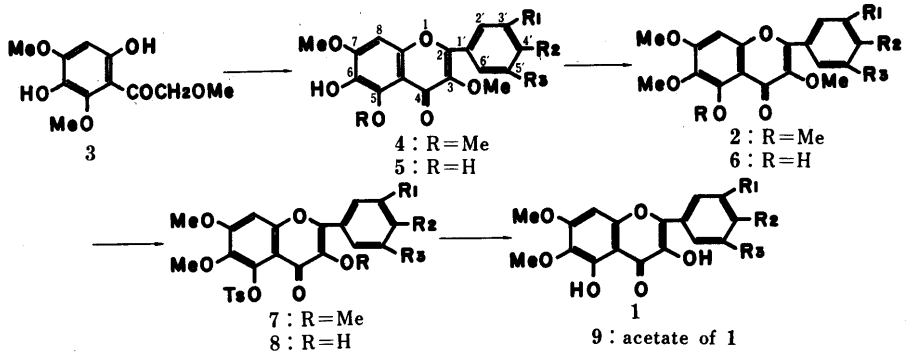
Keywords Allan–Robinson reaction; selective demethylation; 3,5,6,7-tetramethoxyflavone; 5-hydroxy-3,6,7-trimethoxyflavone; 6-hydroxy-3,5,7-trimethoxyflavone; 5-tosyloxyflavone; 5,6-dihydroxy-3,7-dimethoxyflavone; 3,5-dihydroxy-6,7-dimethoxyflavone, 3,5-diacetoxy-6,7-dimethoxyflavone

We have been studying the selective O-alkylation and dealkylation of flavonoids to establish new, convenient methods for synthesizing polyhydroxyflavones.[1] Concurrently, the inhibitory activities of the products toward three enzyme systems were studied and several potent inhibitors have already been found.[2-5] The flavones subjected to the screening have no free hydroxy group at the 3-position, although the activities of 3-hydroxyflavones are of great interest.[6,7] Consequently, we have examined the selective demethylation of the 3- and 5-methoxy groups in a flavone skeleton[8,9] and established a new, convenient method for synthesizing 3,5,7-trihydroxy-8-methoxyflavones[1] and 3,5-dihydroxy-7,8-dimethoxyflavones[10] from the corresponding 3,5-dimethoxyflavones. These results show that 3,5-dihydroxy-6,7-dimethoxyflavones (**1**) can be easily synthesized from the corresponding 3,5,6,7-tetramethoxyflavones (**2**). The naturally occurring flavones **1** have been synthesized from the corresponding chalcones *via* the 3-hydroxyflavones,[11-15] but their yields were not always high. Thus, the selective demethylation of 3- and 5-methoxy groups in **2** was studied in order to obtain 3-hydroxyflavones for a survey of their biological activities, and a convenient method for synthesizing 3,5-dihydroxy-6,7-dimethoxyflavones (**1**) was established. Though ultraviolet (UV) spectral data are widely applied in the structural elucidation of naturally occurring flavones, the details are not always clear. Therefore, we also examined the UV spectra of the products obtained here.

Results and Discussion

The demethylation of 7-hydroxy-3,5,8-trimethoxyflavones and their derivatives with anhydrous aluminum bromide in acetonitrile affords quantitatively a mixture of the corresponding 5- and 3-hydroxyflavones.[1,9,10] However, the cleavage of the 5-methoxy group in flavones with an oxygenated group at the 6-position was much easier than that of the 3-methoxy group.[16-18] For example, the demethylation of 3,4′,5,6,7-pentamethoxyflavones affords quantitatively the 5-hydroxyflavone only.[9] These facts show that the 3,5-dihydroxy-6,7-dimethoxyflavones (**1**) can be easily synthesized from the corresponding 3,5,6,7-tetramethoxyflavones (**2**) according to Chart 1.

A convenient method for synthesizing 3,5,6,7-tetramethoxyflavones as a starting material is the Allan–Robinson reaction of 3,6-dihydroxy-2,4,ω-trimethoxyacetophenone (**3**)[19-23] or its 3-methyl ether,[24,25] but the yields in the condensation are not always high. In our investigation, however, all Allan–Robinson reactions of **3** with an anhydride of substituted benzoic acid in the presence of its potassium salt afforded the corresponding 6-hydroxy-3,5,7-trimethoxyflavone (**4**) and 5,6-dihydroxy-3,7-dimethoxyflavone (**5**); a mixture of the two products was easily ob-



a: $R_1=R_3=H$, $R_2=OMe$ **b**: $R_1=R_2=OMe$, $R_3=H$ **c**: $R_1=R_2=R_3=OMe$
d: $R_1=R_3=H$, $R_2=OH$ **e**: $R_1=OMe$, $R_2=OH$, $R_3=H$ **f**: $R_1=OH$, $R_2=OMe$, $R_3=H$
g: $R_1=R_2=OH$, $R_3=H$ **h**: $R_1=R_3=H$, $R_2=OCH_2Ph$ **i**: $R_1=OMe$, $R_2=OCH_2Ph$, $R_3=H$
j: $R_1=OCH_2Ph$, $R_2=OMe$, $R_3=H$ **k**: $R_1=R_2=OCH_2Ph$, $R_3=H$

Chart 1

tained in a favorable yield. The ratios of **4** and **5** were influenced by the reaction conditions, but the main product was **4**. The mixtures were converted into the corresponding 3,5,6,7-tetramethoxyflavones (**2**) by methylation without further purification, though the mixtures could easily be separated into each component by silica gel chromatography.

Generally the 5-methoxy group in 5,6,7-trioxygenated flavones or their acetates was selectively cleaved with 5% (w/v) anhydrous aluminum chloride in acetonitrile at 50 °C for 1 h to give quantitatively the corresponding 5-hydroxyflavones.[16,18] Actually, the demethylation of **2a**—**c** with no benzyloxy group under similar demethylating conditions afforded quantitatively the 5-hydroxyflavones (**6a**—**c**), but that of **2h** or **2i** with a benzyloxy group on the B ring produced the debenzylated product, **6d** or **6e**, along with **6h** or **6i**. On the other hand, the 3- or 5-methoxy group in 7-hydroxy-3,5,8-trimethoxyflavones and their derivatives is selectively cleaved with 5% (w/v) anhydrous aluminum bromide in acetonitrile at room temperature for 1 h to give a mixture of the corresponding 3- and 5-hydroxyflavones without cleavage of the benzyloxy groups on the B ring.[1,10] However, the demethylation of **2h** or **2i** under similar conditions was also accompanied with the formation of debenzylated products. The results show that the cleavage of the benzyloxy groups on the B ring was greatly influenced by the 6-oxygenated group on the A ring, and that much milder conditions are adequate for the demethylation of **2**. Therefore, the demethylation of the 5-methoxy group in **2** was reexamined and the following optimum conditions, under which the 5-hydroxyflavones (**6**) were quantitatively obtained without the formation of debenzylated products, were found: 2.5% (w/v) anhydrous aluminum bromide in acetonitrile at 0—5 °C for 15—20 min.

The 5-hydroxyflavones (**6**) were easily converted into the corresponding 5-tosyloxyflavones (**7**). The 3-methoxy group in **7** was selectively cleaved with 5% (w/v) anhydrous aluminum bromide in acetonitrile at room temperature for 1 h to give the corresponding 3-hydroxyflavones (**8**), suggesting that the tosyloxy group at the 5-position retarded the cleavage of benzyloxy groups on the B ring. The 5-tosyloxy group in **8** was smoothly hydrolyzed with anhydrous potassium carbonate in methanol to give the desired 3,5-dihydroxy-6,7-dimethoxyflavones (**1**). Hydrogenolysis of the benzyloxyflavones (**1h**—**k**) with palladium on charcoal afforded the corresponding hydroxyflavones (**1d**—**g**). The 3,5-dihydroxyflavones (**1a**—**g**) were converted into the corresponding acetates.

The UV and proton nuclear magnetic resonance (^{1}H-NMR) spectral data for the flavones synthesized here fully supported the assigned structures. The UV spectral data for **1b**, which has been synthesized from the corresponding chalcone *via* the 3-hydroxyflavone by Bhardwaj *et al.*,[12] however, are markedly different from those for our synthetic flavone **1b**. They have also reported that the same flavone **1b** can be synthesized from the 5-hydroxyflavone **6b** by the direct demethylation with hydrobromic acid in acetic acid,[26] but this result seems questionable. The cleavage of the 3-methoxy group in these flavones seems to be more difficult than that of the methoxy group at the 6- or 4′-position,[17,18] and the demethylated product is presumed to be the 5,6-dihydroxyflavone **5b** or 5,4′-dihydroxyflavone **6e**. Actually, the UV and ^{1}H-NMR spectral data for their synthesized flavones were identical with those for **5b**.

TABLE I. UV Spectral Data for 3,5-Dihydroxy-6,7-dimethoxyflavones (**1**)[a]

		λ_{max} nm (log ε)			
1a	EtOH	257 (4.22)	272 (4.24)	361 (4.28)	
	EtOH–$AlCl_3$		273 (4.29)	367 (4.19)	418 (4.29)
	EtOH–NaOAc	258 (4.24)	270 (4.24)	364 (4.14)	415i (3.76)
1b	EtOH	258 (4.32)	271 (4.18)	366 (4.32)	
	EtOH–$AlCl_3$	265 (4.37)		382sh (4.19)	421 (4.35)
	EtOH–NaOAc	258 (4.32)	270i (4.23)	370 (4.21)	415i (3.76)
1c	EtOH	255 (4.19)	266sh (4.18)	360 (4.25)	
	EtOH–$AlCl_3$	265 (4.26)	277 (4.28)	371 (4.17)	420 (4.30)
	EtOH–NaOAc	259 (4.24)		370 (4.09)	415sh (3.90)
1d	EtOH	260 (4.24)	270 (4.24)	366 (4.33)	
	EtOH–$AlCl_3$		273 (4.33)	371 (4.18)	420 (4.36)
	EtOH–NaOAc	260 (4.27)	270 (4.27)	370 (4.26)	415i (3.83)
1e	EtOH	259 (4.33)		371 (4.35)	
	EtOH–$AlCl_3$	267 (4.36)		385i (4.15)	428 (4.38)
	EtOH–NaOAc	259 (4.33)		375 (4.27)	415i (3.85)
1f	EtOH	258 (4.34)		368 (4.33)	
	EtOH–$AlCl_3$	267 (4.39)		385i (4.21)	422 (4.37)
	EtOH–NaOAc	259 (4.32)		375 (4.21)	415i (3.85)
1g	EtOH	266 (4.27)		374 (4.28)	
	EtOH–$AlCl_3$	270 (4.38)		388i (4.18)	428 (4.40)
	EtOH–NaOAc	260 (4.28)		382 (4.20)	415i (3.97)

a) sh, shoulder; i, inflection point.

These results show that the selective demethylation of 3,5,6,7-tetraoxygenated flavones as shown in Chart 1 is generally applicable for the syntheses of 3,5-dihydroxyflavones with a oxygenated group at the 6-position and for their chemical modification.

General features of the UV spectra of the 3,5-dihydroxyflavones **1** in ethanol are as follows. Clear absorption maxima (log ε, 4.25—4.35) of band I are seen in the range of 361 to 371 nm, at shorter wavelengths than those of the isomeric 3,5-dihydroxy-7,8-dimethoxyflavones (380—388 nm).[10] Band II is affected by the oxygenated groups on the B ring and characteristic absorption maxima appear in the range of 255 to 272 nm as shown in Table I. Band I undergoes a bathochromic shift upon the addition of aluminum chloride and splits typically into two absorption peaks. These properties are greatly different from those of 3,5,7,8-tetraoxygenated flavones with 3- and 5-hydroxy groups.[1,10] In the presence of sodium acetate, bathochromic shifts of bands II are not observed, but bands I of all 3,5-dihydroxyflavones (**1**) undergo a typical bathochromic shift and the characteristic shift attributed to the 4′-hydroxy group is not observed in the flavones **1d**, **1e**, **1f**, and **1g**, as in the cases of 3,5-dihydroxy-7,8-dimethoxyflavones[10] and 3,5,7-trihydroxy-8-methoxyflavones.[1] These features of the UV spectra are relevant to the structural elucidation of 3,5-dihydroxy-6,7-dimethoxyflavones (**1**).

Experimental

All melting points were determined in glass capillaries and are uncorrected. ^{1}H-NMR spectra were recorded on a Hitachi R-24 spectrometer (60 MHz), using tetramethylsilane as an internal standard and chemical shifts were given in δ values. UV spectra were recorded on a Hitachi 124 spectrophotometer. Column chromatography was carried out on Kieselgel 60 (70—230 mesh; Merck). Elemental analyses were performed with a Yanaco CHN corder, model MT-2. Acetonitrile as a demethylating

solvent was obtained by distillation over CaH_2.

Synthesis of a Mixture of 6-Hydroxy-3,5,7-trimethoxyflavones (4) and 5,6-Dihydroxy-3,7-dimethoxyflavones (5) as Starting Materials A mixture of 3,6-dihydroxy-2,4,ω-trimethoxyacetophenone (**3**) (2.4 g, 10 mmol), substituted benzoic anhydride (35 mmol), and potassium benzoate (15 mmol) was heated at 170—180 °C for 6—8 h under reduced pressure and then the mixture was dissolved in MeOH–Me_2CO–H_2O (*ca.* 3:2:1, 200—300 ml). The solution was refluxed with a solution of KOH (7.0 g, 125 mmol) in water (30 ml) for 15—25 min under a nitrogen atmosphere, diluted with water, and then saturated with CO_2. Organic solvents were evaporated off under reduced pressure and separated phenolic products were collected by filtration and by extraction with EtOAc. The combined products were crystallized from EtOAc–Et_2O or $CHCl_3$–Et_2O and recrystallized to give a mixture of **4** and **5**. Pure products **4** and **5** were obtained from the oily phenolic materials recovered from the mother liquor by silica gel chromatography with $CHCl_3$–EtOAc (10:1 or 10:2) (Table II).

In the case of a mixture of 3′,4′-bis (benzyloxy) flavones (**4k** and **5k**), the crude products were recrystallized from $CHCl_3$ in order to remove 3,4-bis (benzyloxy) benzoic acid, and the soluble materials were treated with hot EtOAc to give a mixture of **4k** and **5k**, since the crude products contained a large amount of the acid which did not dissolve in $NaHCO_3$ solution. The following data are total yields of **4** and **5**.

A mixture of **4a** and **5a** was recrystallized from EtOAc–MeOH; yield, 2.21 g (62—64%): **4b** and **5b**, from EtOAc, 2.57 g (67—69%): **4c** and **5c**, from EtOAc, 2.74 g (66—68%): **4h** and **5h**, from EtOAc–MeOH, 2.1 g (49—50%): **4i** and **5i**, from $CHCl_3$–Et_2O, 2.52 g (55—56%): **4j** and **5j**, from EtOAc, 2.94 g (64—65%): **4k** and **5k**, from $CHCl_3$–MeOH, 3.6 g (67—69%).

3,5,6,7-Tetramethoxyflavones (2) A mixture (*ca.* 3 mmol) of flavones **4** and **5** was refluxed with dimethyl sulfate (1 ml, 8 mmol) and powdered anhydrous K_2CO_3 (5 g, 35 mmol) in Me_2CO (50 ml) under stirring for 2.5—4 h and then water was added. The mixture was additionally refluxed for 20—30 min, then the organic solvent was evaporated off. The separated oily materials were extracted with EtOAc and the extract was recrystallized to give **2** quantitatively as colorless needles or prisms (Table II).

5-Hydroxy-3,6,7-trimethoxyflavones (6) Cold solutions of 5% (w/v) anhydrous $AlBr_3$ in MeCN (35 ml, 16.5 mmol) and a flavone **2** (2 mmol) in MeCN (35 ml) were mixed under stirring (the solution became turbid owing to the separation of an aluminum complex) and allowed to stand at 0—5 °C for 15—20 min. The mixture was poured into 1—2% HCl and heated at 70—80 °C for 20—30 min. The solvent was evaporated off under reduced pressure, and the separated crystals were collected and recrystallized to give **6** as yellow needles or prisms (Table III).

3,6,7-Trimethoxy-5-tosyloxyflavones (7) A mixture of a flavone **6** (1 mmol), *p*-toluenesulfonyl chloride (285 mg, 1.5 mmol), and powdered anhydrous K_2CO_3 (2 g, 14 mmol) in Me_2CO (30—50 ml) was refluxed under stirring till the starting material disappeared (2—4 h). The mixture was poured into diluted HCl and then concentrated under reduced pressure. The separated precipitate was collected and recrystallized to give **7** as colorless needles or prisms (Table III).

3-Hydroxy-6,7-dimethoxy-5-tosyloxyflavones (8) A flavone **7** (1 mmol) was dissolved in a solution of 5% (w/v) anhydrous $AlBr_3$ in MeCN (20—25 ml, 3.5—4.5 mmol) and the solution was allowed to stand at room temperature (20—30 °C) for 1 h. The reaction mixture was poured into 1—2% HCl, heated at 70—80 °C for 20—30 min, and diluted with water. The separated crystals were collected and recrystallized to give **8** as yellow needles or prisms (Table III).

The demethylated products of **7i** and **7k** were not homogeneously

TABLE II. 3,5,6,7-Tetramethoxyflavones (**2**), 6-Hydroxy-3,5,7-trimethoxyflavones (**4**), and 5,6-Dihydroxy-3,7-dimethoxyflavone (**5**)

Compd.	mp (°C) (lit.)	Recrystn. solvent	^{1}H-NMR[a] C_8-H	Formula	Found (%)		Calcd (%)	
					C	H	C	H
2a	153—154 (153—154)[19]	$CHCl_3$–MeOH	6.69 s	$C_{20}H_{20}O_7$	64.27	5.30	64.51	5.41
2b	140—141 (141—142)[19]	MeOH	6.69 s	$C_{21}H_{22}O_8$	62.88	5.48	62.68	5.51
2c	147—148 (150—151, 154—155)[19,24]	$CHCl_3$–MeOH	6.73 s	$C_{22}H_{24}O_8$	61.15	5.46	61.10	5.59
2h	137—138 (152.5—154)[28]	MeOH	6.68 s	$C_{26}H_{24}O_7$	69.84	5.25	69.63	5.39
2i	132.5—133.5 (136—137)[29]	MeOH	6.68 s	$C_{27}H_{26}O_8$	67.50	5.62	67.77	5.48
2j	115—116 (120.5—121.5)[30]	EtOH	6.62 s	$C_{27}H_{26}O_8$	67.61	5.44	67.77	5.48
2k	52—54, 97—98	MeOH	6.57 s	$C_{33}H_{30}O_8$	71.66	5.28	71.47	5.45
4a	201—203 (199—200)[19]	$CHCl_3$–MeOH	7.04 s[b]	$C_{19}H_{18}O_7$	63.93	5.22	63.68	5.06
4b	232—233 (209—210)[19]	Me-cellosolve	7.08 s[b]	$C_{20}H_{20}O_8$	61.53	5.38	61.85	5.19
4c	188—189 (193—194)[19]	MeOH	6.72 s	$C_{21}H_{22}O_9$	60.12	5.08	60.28	5.30
4h	132—133, 153—154 (133)[20]	$CHCl_3$–MeOH	6.75 s	$C_{25}H_{22}O_7$	69.19	5.18	69.11	5.10
4i	134—134.5 (132.5—134)[21]	EtOAc	6.70 s	$C_{26}H_{24}O_8$	67.45	5.18	67.23	5.21
4j	175—176 (168—169)[22]	EtOAc	6.67 s	$C_{26}H_{24}O_8$	67.20	5.17	67.23	5.21
4k	185—186	$CHCl_3$–MeOH	6.68 s	$C_{32}H_{28}O_8$	70.80	4.97	71.10	5.22
5a	180—180.5 (176—177)[27]	$CHCl_3$–EtOAc	6.82 s[b]	$C_{18}H_{16}O_7$	62.52	4.64	62.79	4.68
5b	220—222 (220—221)[27]	$CHCl_3$–EtOAc	6.83 s[b]	$C_{19}H_{18}O_8$	61.00	5.04	60.96	4.85
5c	193—193.5	$CHCl_3$–EtOAc	6.86 s[b]	$C_{20}H_{20}O_9$	59.68	4.95	59.40	4.99
5h	157—157.5	$CHCl_3$–MeOH	6.50 s	$C_{24}H_{20}O_7$	68.80	4.84	68.56	4.80
5i	161—162.5	$CHCl_3$–EtOAc	6.46 s	$C_{25}H_{22}O_8$	66.44	4.77	66.66	4.92
5j	140—141, 167—168	$CHCl_3$–MeOH	6.42 s	$C_{25}H_{22}O_8$	66.57	4.76	66.66	4.92
5k	182—183.5 (183—184)[23]	$CHCl_3$–MeOH	6.45 s	$C_{31}H_{26}O_8$	70.99	4.86	70.71	4.98

a) δ-Value in $CDCl_3$; s, singlet. *b*) Measured in DMSO-d_6.

TABLE III. 5-Hydroxy-3,6,7-trimethoxyflavones (**6**), 3,6,7-Trimethoxy-5-tosyloxyflavones (**7**), and 3-Hydroxy-6,7-dimethoxy-5-tosyloxyflavones (**8**)

Compd.	mp (°C) (lit.)	Recrystn. solvent	Yield (%)	^{1}H-NMR[a] C_8-H	Formula	Found (%)		Calcd (%)	
						C	H	C	H
6a	168—169 (168—169)[9]	$CHCl_3$–MeOH	93	6.43 s	$C_{19}H_{18}O_7$	63.39	4.92	63.68	5.06
6b	160.5—161 (161—162)[31]	MeOH	95	6.44 s	$C_{20}H_{20}O_8$	62.04	5.09	61.85	5.19
6c	174—176 (175—177)[24]	$CHCl_3$–MeOH	90	6.44 s	$C_{21}H_{22}O_9$	60.28	5.09	60.28	5.30
6h	123—125 (141—143, 124—125)[28,32]	$CHCl_3$–MeOH	88	6.46 s	$C_{25}H_{22}O_7$	69.27	4.93	69.11	5.10
6i	166.5—167 (167.5—168.5)[31]	$CHCl_3$–MeOH	86	6.43 s	$C_{26}H_{24}O_8$	66.99	5.04	67.23	5.21
6j	114.5—115	MeOH	86	6.37 s	$C_{26}H_{24}O_8$	67.10	5.02	67.23	5.21
6k	152—153 (151.5—153)[33]	$CHCl_3$–MeOH	90	6.37 s	$C_{32}H_{28}O_8$	71.25	5.10	71.10	5.22
7a	174—175	$CHCl_3$–MeOH	89	6.86 s	$C_{26}H_{24}O_9S$	60.67	4.93	60.93	4.69
7b	184—185	$CHCl_3$–MeOH	95	6.83 s	$C_{27}H_{26}O_{10}S$	59.88	4.80	59.77	4.83
7c	170—171	$CHCl_3$–MeOH	82	6.82 s	$C_{28}H_{28}O_{11}S$	58.51	4.64	58.73	4.93
7h	225—226	$CHCl_3$–EtOAc	82	6.83 s	$C_{32}H_{28}O_9S$	65.36	4.64	65.29	4.80
7i	197.5—198	$CHCl_3$–MeOH	89	6.80 s	$C_{33}H_{30}O_{10}S$	63.94	4.92	64.07	4.89
7j	90—91	$CHCl_3$–Et_2O	96	6.76 s	$C_{33}H_{30}O_{10}S$	63.90	4.79	64.07	4.89
7k	149—150	$CHCl_3$–MeOH	99	6.76 s	$C_{39}H_{34}O_{10}S$	67.20	4.71	67.42	4.93
8a	123—124	$CHCl_3$–MeOH	88	6.88 s	$C_{25}H_{22}O_9S$	60.00	4.35	60.23	4.44
8b	138—139	$CHCl_3$–MeOH	91	6.85 s	$C_{26}H_{24}O_{10}S$	59.30	4.51	59.08	4.58
8c	195—197	$CHCl_3$–MeOH	86	6.85 s	$C_{27}H_{26}O_{11}S$	57.96	4.86	58.06	4.69
8h	223—224	$CHCl_3$–MeOH	91	6.89 s	$C_{31}H_{26}O_9S$	64.60	4.31	64.80	4.56
8i	206—207	$CHCl_3$–MeOH	89	6.85 s	$C_{32}H_{28}O_{10}S$	63.37	4.66	63.56	4.67
8j	181—182	$CHCl_3$–MeOH	96	6.80 s	$C_{32}H_{28}O_{10}S$	63.24	4.53	63.56	4.67
8k	122—123	EtOAc–MeOH	90	6.79 s	$C_{38}H_{32}O_{10}S$	66.82	4.80	67.05	4.74

a) δ-Value in $CDCl_3$.

TABLE IV. 3,5-Dihydroxy-6,7-dimethoxyflavones (**1**) and Their Acetates (**9**)

Compd.	mp (°C) (lit.)	Recrystn. solvent	Yield (%)	^{1}H-NMR[a] C_8-H	Formula	Found (%)		Calcd (%)	
						C	H	C	H
1a	210—212 (212—214, 222—223)[11,25]	MeOH	80	6.80 s[b]	$C_{18}H_{16}O_7$	62.57	4.52	62.79	4.68
1b	235—235.5	$CHCl_3$–MeOH	88	6.94 s[b]	$C_{19}H_{18}O_8$	60.96	4.72	60.96	4.85
1c	228—228.5	$CHCl_3$–MeOH	84	6.86 s[b]	$C_{20}H_{20}O_9$	59.52	4.87	59.40	4.99
1d	286—288 (291—292)[13]	EtOAc–MeOH	85	6.84 s[b]	$C_{17}H_{14}O_7$	61.77	4.14	61.82	4.27
1e	213.5—214 (213—214)[15]	EtOAc–MeOH	89	6.82 s[b]	$C_{18}H_{16}O_8$	59.78	4.59	60.00	4.48
1f	238—239 (242—243, 244.5—245.5)[13,14]	EtOAc–MeOH	92	6.80 s[b]	$C_{18}H_{16}O_8$	59.79	4.24	60.00	4.48
1g	278—279 (285—287)[13]	EtOAc–MeOH	94	6.77 s[b]	$C_{17}H_{14}O_8$	58.86	3.81	58.96	4.08
1h	195—196	EtOAc	86	6.93 s[b]	$C_{24}H_{20}O_7$	68.76	4.60	68.56	4.80
1i	215—216	$CHCl_3$–MeOH	95	6.83 s[b]	$C_{25}H_{22}O_8$	66.44	4.92	66.66	4.92
1j	170—171	$CHCl_3$–MeOH	95	6.78 s[b]	$C_{25}H_{22}O_8$	66.55	4.81	66.66	4.92
1k	199.5—200	$CHCl_3$–MeOH	87	6.78 s[b]	$C_{31}H_{26}O_8$	70.50	4.82	70.71	4.98
9a	178.5—180 (187—189)[11]	MeOH		6.82 s	$C_{22}H_{20}O_9$	61.67	4.61	61.68	4.71
9b	177.5—178 and 197	MeOH		6.82 s	$C_{23}H_{22}O_{10}$	60.33	4.63	60.26	4.84
9c	214—214.5	$CHCl_3$–MeOH		6.83 s	$C_{24}H_{24}O_{11}$	58.82	4.99	59.01	4.95
9d	208—209 (210—211)[13]	EtOAc–MeOH		6.89 s	$C_{23}H_{20}O_{10}$	60.48	4.44	60.52	4.42
9e	233.5—234 (228—230)[15]	$CHCl_3$–MeOH		6.80 s	$C_{24}H_{22}O_{11}$	59.39	4.63	59.26	4.56
9f	215—216 (219—221, 218—220)[13,14]	$CHCl_3$–MeOH		6.82 s	$C_{24}H_{22}O_{11}$	59.04	4.41	59.26	4.56
9g	195.5—196 (199—200)[13]	$CHCl_3$–MeOH		6.81 s	$C_{25}H_{22}O_{12}$	58.15	4.11	58.37	4.31

a) δ-Value in $CDCl_3$; s, singlet. *b*) Measured in DMSO-d_6.

dissolved in $CHCl_3$ because of the incomplete decomposition of the aluminum complexes. Therefore, the products were warmed with a mixture of 5% HCl and $CHCl_3$ at 60—70 °C under stirring till the precipitates dissolved in $CHCl_3$. The $CHCl_3$ was evaporated off and the separated crystals were recrystallized to give **8i** and **8k**.

3,5-Dihydroxy-6,7-dimethoxyflavones (1a—c and 1h—k) A mixture of a flavone **8** (1 mmol) and anhydrous K_2CO_3 (2 g) in MeOH (30—40 ml) was refluxed under stirring for 1—2 h and then poured into diluted hydrochloric acid. The solvent was evaporated off under reduced pressure and the separated crystals were collected and recrystallized to give **1** as yellow needles or prisms (Table IV). **1b**: ^{1}H-NMR ($CDCl_3$): 3.94, 3.98, 3.99, 4.00 (each 3H, s, OMe), 6.57 (1H, s, C_8-H), 7.01 (1H, d, J=8.5 Hz, $C_{5'}$-H), 7.80 (1H, d, J=2.5 Hz, $C_{2'}$-H), 7.83 (1H, dd, J=8.5, 2.5 Hz, $C_{6'}$-H), 11.68 (1H, s, C_5-OH). The ^{1}H-NMR and UV spectral data are not consistent with those for **1b** synthesized by Bhardwaj *et al.*[12,26] [lit. mp 214 °C. ^{1}H-NMR($CDCl_3$): 3.85 (3H), 3.96 (9H), 6.55 (1H), 6.99 (1H), 7.68 (2H). UV λ_{max}^{MeOH} nm: 280, 345; ($AlCl_3$) 295, 375; (NaOAc) 280, 345]; their compound seems to be identical with our synthesized flavone **5b** [^{1}H-NMR ($CDCl_3$): 3.91 (3H), 4.01 (6H), 4.03 (3H), 6.55 (1H), 6.95 (1H), 7.67 (1H, $C_{2'}$-H), 7.72 (1H, $C_{6'}$-H), 12.38 (1H). UV λ_{max}^{EtOH} nm (log ε): 283 (4.26), 347 (4.38); ($AlCl_3$) 296 (4.29), 374 (4.41); (NaOAc) 285 (4.26), 343 (4.36)]. **1c**: ^{1}H-NMR($CDCl_3$): 3.90 (6H), 3.92 (6H), 3.93 (3H) (s, OMe), 6.50 (1H, s, C_8-H), 7.43 (2H, s, $C_{2',6'}$-H).

3,5-Dihydroxy-6,7-dimethoxyflavones (1d—g) with Hydroxy Groups on the B Ring The benzyloxyflavones (**1h—k**) (300—400 mg) were hydrogenated over palladium on charcoal (10%; 200 mg) in EtOAc–MeOH (1 : 1; 200—300 ml) till the hydrogen uptake ceased. The catalyst was filtered off, the filtrate was evaporated and the residue was recrystallized to give **1** (Table IV).

Acetates (9a—g) of 1 A flavone **1** (30—40 mg) was dissolved in acetic anhydride–pyridine (5 : 1; 0.5 ml) and allowed to stand at room temperature (25—30 °C) for a day. The mixture was treated with water to give quantitatively the corresponding **9** as colorless needles (Table III). **9b**: ^{1}H-NMR ($CDCl_3$): 2.29, 2.45 (each 3H, s, OAc), 3.80 (3H), 3.90 (6H), 3.93 (3H) (s, OMe), 6.82 (1H, s, C_8-H), 6.89 (1H, d, J=8.5 Hz, $C_{5'}$-H), 7.29 (1H, d, J=2.5 Hz, $C_{2'}$-H), 7.38 (1H, dd, J=8.5, 2.5 Hz, $C_{6'}$-H). **9c**: ^{1}H-NMR ($CDCl_3$): 2.29, 2.44 (each 2H, s, OAc), 3.81 s (3H), 3.86 (6H), 3.89 (3H), 3.95 (3H) (s, OMe), 6.83 (1H, s, C_8-H), 6.98 (2H, s, $C_{2',6'}$-H).

References

1) Part XI of this series: T. Horie, M. Tsukayama, Y. Kawamura, M. Seno and S. Yamamoto, *Bull. Chem. Soc. Jpn.*, **61**, 441 (1988).
2) J. Okuda, I. Miwa, K. Inagaki, T. Horie and M. Nakayama, *Biochem. Pharmacol.*, **31**, 3807 (1982); *idem, Chem. Pharm. Bull.*, **32**, 767 (1984).
3) T. Yoshimoto, M. Furukawa, S. Yamamoto, T. Horie and S. Watanabe-Kohno, *Biochem. Biophys. Res. Commun.*, **116**, 612 (1983).
4) T. Horie, M. Tsukayama, H. Kourai, C. Yokoyama, M. Furukawa, T. Yoshimoto, S. Yamamoto, S. Watanabe-Kohno and K. Ohata, *J. Med. Chem.*, **29**, 2256 (1986).
5) I. Miwa, J. Okuda, T. Horie and M. Nakayama, *Chem. Pharm. Bull.*, **34**, 838 (1986).
6) E. L. Wheeler and D. L. Berry, *Carcinogenesis*, **7**, 33 (1986).
7) G. Klopman and M. L. Dimayuga, *Mol. Pharmacol.*, **34**, 218 (1988).
8) T. Horie, M. Tsukayama, Y. Kawamura and S. Yamamoto, *Chem. Pharm. Bull.*, **35**, 4465 (1987).
9) T. Horie, M. Tsukayama, Y. Kawamura and M. Seno, *J. Org. Chem.*, **52**, 4702 (1987).
10) T. Horie, M. Tsukayama, Y. Kawamura and S. Yamamoto, *Phytochemistry*, **27**, 1491 (1988).
11) H. Wagner, L. Hörhammer, R. Höer and L. Farkas, *Chem. Ber.*, **100**, 1768 (1967).
12) D. K. Bhardwaj, S. C. Jain and G. C. Sharma, *Indian J. Chem., Sec. B*, **15B**, 860 (1977).
13) H. Wagner, L. Farkas, G. Flores and J. Strelisky, *Chem. Ber.*, **107**, 1049 (1974).
14) K. Fukui, T. Matsumoto and S. Imai, *Bull. Chem. Soc. Jpn.*, **44**, 1698 (1971).
15) K. Fukui, T. Matsumoto and S. Tanaka, *Bull. Chem. Soc. Jpn.*, **42**, 1398 (1969).
16) T. Horie, H. Kourai, M. Tsukayama, M. Masumura and M. Nakayama, *Yakugaku Zasshi*, **105**, 232 (1985).
17) T. Horie, H. Kourai and N. Fujita, *Bull. Chem. Soc. Jpn.*, **56**, 3773 (1983).
18) T. Horie, H. Kourai, H. Osaka and M. Nakayama, *Bull. Chem. Soc. Jpn.*, **55**, 2933 (1982).
19) L. R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **23A**, 23 (1946).
20) H. Wagner, I. Maurer, L. Farkas and J. Strelisky, *Tetrahedron*, **33**, 1411 (1977).
21) M. Nakayama, K. Fukui, T. Horie and M. Masumura, *Nippon Kagaku Zasshi*, **91**, 739 (1970).
22) R. N. Goel, A. C. Jain and T. R. Seshadri, *J. Chem. Soc.*, **1956**, 1369.
23) H. Wagner, I. Maurer, L. Farkas and J. Strelisky, *Tetrahedron*, **33**, 1405 (1977).
24) P. R. Jefferies, J. R. Knox and E. T. Middleton, *Aust. J. Chem.*, **18**, 532 (1962).
25) K. Y. Sim, *J. Chem. Soc. (C)*, **1967**, 976.
26) D. K. Bhardwaj, R. K. Jain, S. C. Jain and C. K. Manchanda, *Proc. Indian Natl. Sci. Acad., Part A*, **51**, 4 (1985).
27) A. C. Jain, T. R. Seshadri and K. R. Sreenivasan, *J. Chem. Soc.*, **1955**, 3908.
28) L. Farkas, B. Vermes and M. Nógrádi, *Chem. Ber.*, **99**, 3222 (1966).
29) L. Hörhammer, H. Wagner, E. Graf and L. Farkas, *Chem. Ber.*, **98**, 548 (1965).
30) L. Hörhammer, H. Wagner, H. Rösler, E. Graf and L. Farkas, *Chem. Ber.*, **97**, 2857 (1964).
31) K. Fukui, T. Matsumoto, S. Nakamura, M. Nakayama and T. Horie, *Bull. Chem. Soc. Jpn.*, **41**, 1413 (1968).
32) T. Horie, *J. Sci. Hiroshima Univ. Ser. A-II*, **33**, 221 (1969).
33) K. Fukui, M. Nakayama and T. Horie, *Bull. Chem. Soc. Jpn.*, **42**, 1649 (1969).