Studies of the Selective *O*-Alkylation and Dealkylation of Flavonoids. V.[1] The Synthesis of 5,6-Dihydroxy-3,4′,8-trimethoxyflavone and a Revised Structure for the Flavone from *Conyza stricta*

Tokunaru Horie,* Hiroki Kourai, Hideaki Osaka and Mitsuru Nakayama†

Department of Applied Chemistry, Technical College of Tokushima University, Minamijosanjima-cho, Tokushima 770

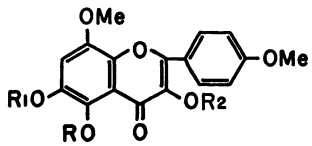
† *Department of Chemistry, Faculty of Science, Hiroshima University, Higashisenda-machi, Naka-ku, Hiroshima 730*

(Received December 24, 1981)

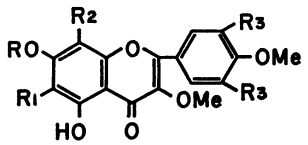
5,6-Dihydroxy-3,4′,8-trimethoxyflavone, which was the proposed structure of the pigment occuring in *Conyza stricta*, was synthesized from 2,3,5,6-tetramethoxyacetophenone in six steps. The natural pigment was identical not with the synthesized flavone, but with 5,7-dihydroxy-3,4′,8-trimethoxyflavone, an isomer of the former.

Two new flavones (**A**) and (**B**) were isolated from *conyza stricta* by Sen *et al.*;[2] their structures were proposed to be 5,6-dihydroxy-3,4′,8-trimethoxyflavone (**1**) and 5,7-dihydroxy-3,3′,4′,5′,8-pentamethoxyflavone (**2**) on the basis of their spectroscopic data and degradation studies. The properties of natural flavone (**A**), however, did not agree with those of synthesized 5,6-dihydroxy-3,4′,8-trimethoxyflavone (**1**). A close inspection of the properties of natural flavone (**A**) and of the isomers of **1** indicated that those of the former were identical with those of 5,7-dihydroxy-3,4′,8-trimethoxyflavone (**3**),[3] an analogue of **2**. This paper will describe the synthesis of 5,6-dihydroxy-3,4′,8-trimethoxyflavone (**1**) and a revised structure, 5,7-dihydroxy-3,4′,8-trimethoxyflavone (**3**), for the natural flavone (**A**).

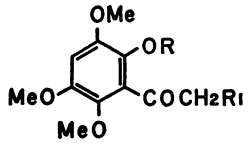
The outline of the synthesis was as follows. 2,3,5,6-Tetramethoxyacetophenone (**4**)[4] was brominated with copper(II) bromide, according to the method of Malik *et al.*;[5] then the resulting ω-bromo-2,3,5,6-tetramethoxyacetophenone (**5**) was converted into 2,3,5,6-tetramethoxy-ω-(*p*-methoxybenzoyloxy)acetophenone (**6**) with potassium *p*-methoxybenzoate in *N*,*N*-dimethylformamide. The benzoate (**6**) was demethylated with anhydrous aluminium chloride in acetonitrile to give 2-hydroxyacetophenone (**7**) in a good yield.



1 R=R$_1$=H, R$_2$=Me
8 R=R$_1$=Me, R$_2$=H
9 R=R$_1$=Me, R$_2$=Ac
10 R=R$_1$=R$_2$=Me
11 R=H, R$_1$=R$_2$=Me
12 R=Ac, R$_1$=R$_2$=Me
13 R=R$_1$=Ac, R$_2$=Me



2 R=R$_1$=H, R$_2$=R$_3$=OMe
3 R=R$_1$=R$_3$=H, R$_2$=OMe
14 R=Me, R$_1$=OH, R$_2$=R$_3$=H



4 R=Me, R$_1$=H
5 R=Me, R$_1$=Br
6 R=Me, R$_1$=OCOC$_6$H$_4$OMe(*p*)
7 R=H, R$_1$=OCOC$_6$H$_4$OMe(*p*)

According to the Allan-Robinson method of flavone synthesis, the condensation of the 2-hydroxyacetophenone (**7**) with *p*-methoxybenzoic anhydride and potassium *p*-methoxybenzoate, followed by treatment with methanolic potassium hydroxide, gave 3-hydroxyflavone (**8**), which was easily converted into the acetate (**9**). The ^{1}H-NMR spectra for **8** and **9** showed a singlet peak corresponding to the C-7 proton at δ 6.87 and 6.90 respectively (Table 1). The methylation of the flavone (**8**) with dimethyl sulfate gave 3,4′,5,6,8-pentamethoxyflavone (**10**). The flavone (**10**) was demethylated with a 5—10%(w/v) anhydrous aluminium chloride–acetonitrile solution to give a 5-hydroxyflavone (**11**) in a quantitative yield. On the other hand, demethylation with an about 30%(w/v) anhydrous aluminium chloride–acetonitrile solution containing 0.5% (v/v) water at 70 °C for 48 h[1] gave the desired 5,6-dihydroxy-3,4′,8-trimethoxyflavone (**1**). The strontium chloride-coloration test of the flavone (**1**) indicated the presence of two hydroxyl groups adjacent to each other.[6] The ^{1}H-NMR data for the synthesized flavones are shown in Table 1. The chemical shifts of the C-7 proton on the flavones and their acetates appeared in the narrow range of δ 6.87—6.99, in contrast to those of the aromatic protons on the A ring of 5,7-dihydroxy-6- or 8-methoxyflavones and their acetates. The 3-methoxyflavone (**1**) and **11** showed also characteristic UV spectra, which failed to show Band II (Table 2).

The 5,6-dihydroxyflavone (**1**) and its diacetate (**13**) are not identical with the natural flavone (**A**) and its diacetate, which were sent us by Sen. However, the ^{1}H-NMR data of the natural flavone diacetate are similar to that of the synthesized (**13**), and the singlet peak at δ 6.89 can be attributed to the C-6 or C-8 proton on the acetate of 5,7-dihydroxy-3,4′,8-trimethoxyflavone (**3**)[3] or 5,6-dihydroxy-3,4′,7-trimethoxyflavone (**14**)[7] (Table 3). The results indicated that the structure of **A** is either **3** or **14**. Since the UV data of the natural flavone (**A**) are similar to those

TABLE 1. ^{1}H-NMR DATA OF 3,4′,5,6,8-PENTAHYDROXYFLAVONE DERIVATIVES (δ)[a]

Compd	Solvent	C_7-H	$C_{3',5'}$-H	$C_{2',6'}$H	OMe	OH	OAc
8	$CDCl_3$	6.87 s	7.00 d	8.22 d	3.86 s (3H), 3.91 s (6H) 3.98 s (3H)	6.85 b	
9	$CDCl_3$	6.90 s	6.97 d	7.88 d	3.86 s (3H), 3.89 s (3H) 3.91 s (3H), 3.95 s (3H)		2.35 s (3H)
10	$CDCl_3$	6.87 s	7.00 d	8.16 d	3.87 s (6H), 3.94 s (6H) 3.97 s (3H)		
11	$CDCl_3$	6.92 s	7.00 d	8.13 d	3.87 s (6H), 3.92 s (6H)	12.00 s	
12	$CDCl_3$	6.87 s	6.97 d	8.09 d	3.80 s (3H), 3.87 s (6H) 3.97 s (3H)		2.46 s (3H)
1	$CDCl_3$	6.91 s	6.99 d	8.13 d	3.88 s (6H), 3.90 s (3H)	11.77 s	
	DMSO	6.99 s	7.10 d	7.99 d	3.80 s (3H), 3.86 s (6H)	11.6 b	
13	$CDCl_3$	6.91 s	6.99 d	8.09 d	3.79 s (3H), 3.85 s (3H) 3.94 s (3H)		2.31 s (3H) 2.42 s (3H)

a) s: Singlet, b: broad, d: doublet(J=8.5 Hz).

TABLE 2. UV DATA OF 3,4′,5,6,8-PENTAHYDROXYFLAVONE DERIVATIVES[a]

Compd		λ_{max}/nm (log ε)			
1	EtOH		308 (4.29)	335sh (4.16)	
	EtOH-$AlCl_3$	289i (3.98)	328 (4.33)	360 (4.27)	
8	EtOH	272 (4.22)	292i (4.02)	345 (4.24)	375sh (4.16)
	EtOH-$AlCl_3$	261 (4.32)	282sh (4.23)	395i (4.25)	433 (4.33)
10	EtOH	273i (4.20)	295 (4.29)	329 (4.30)	
11	EtOH	280i (4.11)	308 (4.36)	338 (4.28)	
	EtOH-$AlCl_3$	290sh (4.04)	330 (4.36)	355 (4.35)	

a) sh: Shoulder, i: inflection point.

TABLE 3. COMPARISON BETWEEN ^{1}H-NMR DATA OF DIACETATES OF NATURAL AND ITS ISOMERIC FLAVONES IN $CDCl_3$ (δ)[a]

Compd	Arom. H			OMe			OAc	
13	6.91 s	6.99 d	8.09 d	3.79 s	3.85 s	3.94 s	2.31 s	2.42 s
Diacetate of **A**(Nat.)[2]	6.86 s	7.11 d	8.20 d	3.89 s	3.95 s	4.06 s	2.41 s	2.49 s
Diacetate of **3**[3]	6.75 s	7.00 d	7.08 d	3.80 s	3.88 s	3.98 s	2.36 s	2.43 s
Diacetate of **14**[b]	6.86 s	6.98 d	7.99 d	3.77 s	3.88 s	3.90 s	2.32 s	2.45 s

a) s: Singlet, d: doublet (J=8.5—9 Hz). b) Synthesized from 6-hydroxy-3,4′5,7-tetramethoxyflavone.[9]

of **13**, and not to those of **14**, the structure of **A** is preferable to that of **3** (Table 4). In conclusion, the natural flavone (**A**) is confirmed to be 5,7-dihydroxy-3,4′,8-trimethoxyflavone (**3**), analogous to **2**, on the basis of the following results: the melting points of the natural flavone (**A**) and its diacetate are undepressed on mixing with the synthesized (**3**) and its diacetate respectively (Table 5), and the UV and IR spectra of these natural flavones are also superimposable on each other.

These two substances, **2** and **3**, were also isolated from the same plant by Tandon *et al.* in 1977.[8]

Experimental

All the melting points were determined in glass capillaries and are uncorrected. The ^{1}H-NMR spectra were measured with a Hitachi R-24 spectrometer (60 MHz), using tetramethylsilane as the internal standard, and the chemical shifts are presented in terms of the δ values. The UV and IR spectra were taken on Hitachi 124 and 215 spectrophotometers.

*ω-Bromo-2,3,5,6-tetramethoxyacetophenone (**5**).* To a solution of 2,3,5,6-tetramethoxyacetophenone (**4**) (4 g) in chloroform–ethyl acetate (each 25 ml), copper(II) bromide (7.6 g) was added, after which the mixture was stirred for 24 h at room temperature. The precipitate was then filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ether, washed with water, and dried. After the removal of the ether, the residue was recrystallized from ether–hexane to give pale yellow prisms; mp 91—93 °C; NMR ($CDCl_3$) δ 3.80, 3.88 (each 6H, s, OCH_3), 4.37 (2H, s, $-CH_2-$), 6.63 (1H, s, Arom. H); yield, 4 g (75%). Found: C, 45.28; H, 4.82%. Calcd for $C_{12}H_{15}O_5Br$: C, 45.16; H, 4.74%.

*2,3,5,6-Tetramethoxy-ω-(p-methoxybenzoyloxy)acetophenone (**6**).* A mixture of **5** (4 g) and potassium *p*-methoxybenzoate (5 g) in *N,N*-dimethylformamide (15—20 ml) was heated at 140—150 °C for 2 h. After the addition of water to the reaction mixture, the precipitate separated was collected, washed with water, and recrystallized from methanol to

Table 4. Comparison between UV spectral data of natural and its isomeric flavones[a)]

Compd	λ_{max}/nm (log ε)				
1	EtOH		308 (4.29)		335sh (4.16)
	EtOH-$AlCl_3$	289i (3.98)	328 (4.33)		360 (4.27)
	EtOH-AcONa	290i (4.18)	308 (4.20)		335i (4.12)
A(Nat.)	EtOH	276 (4.38)	304sh (4.23)		362 (4.07)
	EtOH-$AlCl_3$	284 (4.30)	311 (4.25)	345 (4.26)	412 (3.89)
	EtOH-AcONa	284 (4.50)	304i (4.29)		382 (4.00)
3	EtOH	276 (4.38)	304sh (4.23)		362 (4.08)
	EtOH-$AlCl_3$	284 (4.30)	311 (4.25)	344 (4.25)	408 (3.87)
	EtOH-AcONa	284 (4.50)	304i (4.30)		382 (4.00)
14	EtOH	283 (4.33)			339 (4.38)
	EtOH-$AlCl_3$	298 (4.36)			364 (4.42)
	EtOH-AcONa	285 (4.32)			339 (4.36)
13	EtOH	267 (4.21)	285i (4.08)		337 (4.35)
Acetate of **A**(Nat.)	EtOH	260 (4.22)			338 (4.29)
Acetate of **3**	EtOH	260 (4.23)			338 (4.30)

a) All the UV spectra were measured in our laboratory: i; inflection point, sh; shoulder.

Table 5. Melting points of dihydroxyflavones and their derivatives (°C)

Compd	Dihydroxyflavones		Diacetates	Monomethyl ether	Dimethyl ether
1	183.5—184.5	188.5—189.5[a)]	173—174	163—164	124—126
A(Nat.)	178—179[2)]	178—179[a)]	170—171[2)]	170—171[2)]	158—159[2)]
3	171—172[3)]	178—179[a)]	166.5—167.5[3)]	168—169[3)]	156—158[10)]
14	187—189	176—177[7)]	178—180 170—172[7)]	168—170[3)]	153—154[7)]

a) The melting points were measured with a Yanagimoto micro-melting apparatus.

give colorless prisms; mp 118—120 °C; NMR ($CDCl_3$) δ 3.80 (6H, s, OCH_3), 3.84 (9H, s, OCH_3), 5.22 (2H, s, $-CH_2-$), 6.61 (1H, s, Arom. H), 6.90, 8.04 (each 2H, d, J=9 Hz, Arom. H); yield, 3.69 g (81%). Found: C, 61.80; H, 5.83%. Calcd for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68%.

2-Hydroxy-3,5,6-trimethoxy-ω-(p-methoxybenzoyloxy)acetophenone (7). To a solution of anhydrous aluminium chloride (12 g) in acetonitrile (40 ml), **6** (3.82 g) was added, and the mixture was heated at 60 °C for 3 h. The reaction mixture was then poured into a mixture of hydrochloric acid and ice under stirring. The precipitate was collected and recrystallized from methanol to give yellow prisms (2.50 g); mp 120—121 °C; NMR ($CDCl_3$) δ 3.86 (9H, s, OCH_3), 3.98 (3H, s, OCH_3), 5.49 (1H, s, Arom. H), 6.92, 8.08 (each 2H, d, J=9 Hz, Arom. H), 11.84 (1H, s, OH). The precipitate recovered (1 g) from the mother liquor of recrystallization was repeatedly demethylated by the above-described method; an additional 0.8 g of **7** was thus obtained; total yield, 3.3 g (90%). Found: C, 60.61; H, 5.42%. Calcd for $C_{19}H_{20}O_8$: C, 60.63; H, 5.36%.

3-Hydroxy-4',5,6,8-tetramethoxyflavone (8). A mixture of **7** (2.35 g), *p*-methoxybenzoic anhydride (10 g), and potassium *p*-methoxybenzoate (6.6 g) was heated at 170—180 °C under reduced pressure for 10 h. The mixture was then refluxed with a solution of potassium hydroxide (6.3 g) in 80% aqueous methanol (about 200 ml) under a nitrogen atmosphere for 30 min. The solvent was removed under reduced pressure, and water was added to the residue. The solution was saturated with carbon dioxide and then allowed to stand overnight in a refrigerator. The separated precipitate was collected and recrystallized from chloroform–methanol to give yellow prisms; mp 184—186 °C; yield, 0.67 g (30%). Found: C, 63.45; H, 5.04%. Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06%.

Acetate (9): Colorless needles from methanol; mp 201—203 °C. Found: C, 62.74; H, 4.99%. Calcd for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04%.

3,4',5,6,8-Pentamethoxyflavone (10). A mixture of **8** (500 mg), dimethyl sulfate (0.62 ml), and anhydrous potassium carbonate (1.2 g) in acetone (50 ml) was refluxed for 8 h. The reaction mixture was again refluxed for 30 min after the addition of water; then a part of the acetone was evaporated off. The resulting precipitate was recrystallized from methanol to give pale yellow needles; mp 124—126 °C; yield, 490 mg (94%). Found: C, 64.33; H, 5.41%. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41%.

5-Hydroxy-3,4',6,8-tetramethoxyflavone (11). To a solution of anhydrous aluminium chloride (0.52 g) in acetonitrile (10 ml), **10** (110 mg) was added, after which the mixture was heated at 60 °C for 1.5 h. After the addition of diluted hydrochloric acid, the mixture was heated on a steam-bath for 30 min and the acetonitrile was evaporated. The precipitate separated was recrystallized from methanol to give yellow needles; mp 163—164 °C; yield, 96 mg (91%). Found: C, 63.40; H, 5.01%. Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06%.

Acetate (12): Colorless needles from methanol; mp 194—196 °C. Found: C, 62.68; H, 5.14%. Calcd for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04%.

5,6-Dihydroxy-3,4',8-trimethoxyflavone (1). A mixture of **10** (180 mg) and anhydrous aluminium chloride (2 g) in 0.5% (v/v) aqueous acetonitrile (6 ml) was heated at 70

°C for 48 h, and after which the reaction mixture was treated by the method described for **11** to give a brownish-yellow precipitate. The precipitate was separated by preparative HPLC with a column packed with Hitachi gel #3019 using methanol, and then recrystallized from methanol to give orange-yellow needles; mp 183.5—184.5 °C; yield, 90 mg (54%). Found: C, 62.85; H, 4.72%. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68%.

*Diacetate (**13**)*: Colorless needles from methanol; mp 173—174 °C. Found: C, 61.45; H, 4.62%. Calcd for $C_{22}H_{20}O_9$: C, 61.68; H, 4.71%.

The authors are grateful to Dr. A. K. Sen, Indian Institute of Chemical Biology, for offering the samples of natural flavone and its acetate.

References

1) Part IV of this series; T. Horie, H. Kourai and H. Osaka, *Nippon Kagaku Kaishi*, **1982**, 1270.
2) A. K. Sen, S. B. Mahato, and N. L. Dutta, *Indian J. Chem.*, **14B**, 849 (1976).
3) T. Horie, *J. Sci. Hiroshima Univ., Series A-II*, **33**, 221 (1969).
4) T. Horie, M. Tsukayama, M. Masumura, M. Nakayama, and S. Hayashi, *Bull. Chem. Soc. Jpn.*, **52**, 2950 (1979).
5) M. L. Malik and S. K. Grover, *Indian J. Chem.*, **14B**, 513 (1976).
6) M. Shimizu and N. Morita, *Yakugaku Zasshi*, **88**, 1450 (1968).
7) A. C. Jain, T. R. Seshadri, and K. R. Sreenivasan, *J. Chem. Soc.*, **1955**, 3908.
8) S. Tandon and R. P. Rastogi, *Phytochemistry*, **16**, 1455 (1977).
9) L. R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **23A**, 23 (1946).
10) M. Ahuja, M. Bandophdhyay, and T. R. Seshadri, *Indian J. Chem.*, **13**, 1134 (1975).