BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 1398—1403 (1969)

Synthetic Studies of the Flavone Derivatives. X.*1 The Synthesis of 3,4′,5-Trihydroxy-3′,6,7-trimethoxyflavone and the Structures of Chrysosplenin and Chrysosplenetin

Kenji FUKUI, Takashi MATSUMOTO and Sachihiko TANAKA

Department of Chemistry, Faculty of Science, Hiroshima University, Higashi-sendamachi, Hiroshima

(Received September 28, 1968)

The acid-catalyzed isomerization of 4-benzyloxy-2′-hydroxy-3,4′,5′,6′-tetramethoxychalcone gave 4′-benzyloxy-3′,5,6,7-tetramethoxyflavanone, which was then converted by oxidation to 4′-benzyloxy-3-hydroxy-3′,5,6,7-tetramethoxyflavone. This, after debenzylation to 3,4′-dihydroxy-3′,5,6,7-tetramethoxyflavone, was partially demethylated with aluminum chloride or aniline hydrochloride to give 3,4′,5-trihydroxy-3′,6,7-trimethoxyflavone (I) (mp 213—214°C), the structure proposed previously for the chrysosplenetin (mp 177—178°C) isolated from *Chrysosplenium japonicum* Makino. However, the synthetic flavone was found to be different from natural chrysosplenetin by a mixed melting point determination and by a comparison of the spectra. Finally, the structures of chrysosplenetin and chrysosplenin were established by the spectroscopic studies to be 4′,5-dihydroxy-3,3′,6,7-tetramethoxyflavone (XIII) and its 4′-glucoside (XIV) respectively. The revised structure for chrysosplenetin has been fully confirmed by direct comparison with an authentic sample.

Chrysosplenin, yellow glycoside, has been isolated from the dried whole herb of *Chrysosplenium japonicum* Makino by Nakaoki and Morita.[1] The hydrolysis of this glycoside with dilute sulfuric acid afforded an aglycone, chrysosplenetin. On the basis of analytical and chemical studies, those authors proposed that structures of chrysosplenetin and chrysosplenin were 3,4′,5-trihydroxy-3′,6,7-trimethoxyflavone (I) and its 3-(or 5-)glucoside respectively.

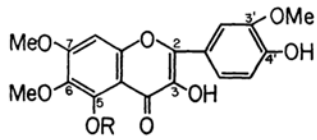
Although Mani and Venkataraman[2] reported a synthesis of I which involved a partial demethylation of the 5-methoxyl group of 3,4′-dihydroxy-3′,5,6,7-tetramethoxyflavone (II) with anhydrous aluminum chloride in ether, a similar selective demethylation of 3-hydroxy-5,7-dimethoxyflavone

*1 Part IX: K. Fukui, M. Nakayama and T. Horie, This Bulletin, in press.

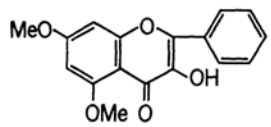
1) T. Nakaoki and N. Morita, *Yakugaku Zasshi* (*J. Pharm. Soc. Japan*), **76**, 320 (1956).

2) R. Mani and K. Venkataraman, *J. Sci. Ind. Res.* (*India*), **21B**, 477 (1962); *Chem. Abstr.*, **59**, 551g (1963).

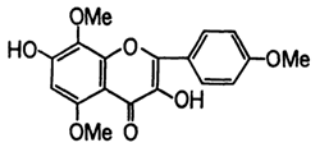
(III) in this laboratory was unsuccessful.[3] Recently, an unsuccessful demethylation of 3,7-dihydroxy-4′,5,8-trimethoxyflavone (IV) under similar reaction conditions has also been reported by Krishnamurti *et al.*[4]



I R = H
II R = Me



III



IV

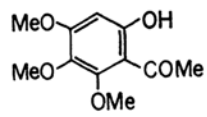
For this reason, it was thought worthwhile to study further the selective demethylation of the 5-methoxyl group of II.

The present paper will describe a synthesis of I, which was found to be different from the natural pigment, and will present revised structures for chrysosplenin and chrysosplenetin.

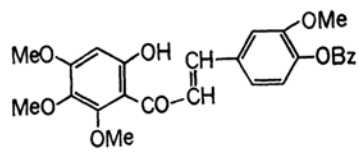
According to the method of Hörhammer *et al*,[5] 4′-benzyloxy-3-hydroxy-3′,5,6,7-tetramethoxyflavone (V) was prepared from 2-hydroxy-4,5,6-trimethoxyacetophenone (VI) *via* 4-benzyloxy-2′-hydroxy-3,4′,5′,6′-tetramethoxychalcone (VII); it was obtained in a yield of 83% (lit.[5] 49%). The flavonol (V) was also obtained by a similar oxidation of 4′-benzyloxy-3′,5,6,7-tetramethoxyflavanone (VIII), which had been prepared by the acid-catalyzed isomerization of VII. The catalytic debenzylation of V gave II; mp 236—237°C (lit.[2] mp 235°C).

Now, an attempt at the selective demethylation of the 5-methoxyl group of II with anhydrous aluminum chloride in ether, using the method of Mani and Venkataraman[2] or a modification of it, failed, but, not unexpectedly, it did lead to the recovery of the starting material. Therefore, the other effective methods were used on II; a) leaving it with anhydrous aluminum chloride in nitrobenzene at room temperature, and b) fusion with aniline hydrochloride.

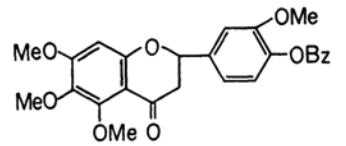
When II in nitrobenzene was treated with anhydrous aluminum chloride at room temperature for 5 hr, a demethylated flavone was isolated as yellow needles, mp 213—214°C, in a yield of 52%. The same flavone was also obtained in a yield of 19% by the fusion of II with aniline hydrochloride at 180°C for 1 hr. The mass spectrum of this demethylated flavone showed a molecular ion peak at *m/e* 360, supporting the molecular formula of $C_{18}H_{16}O_8$ (Mwt 360.31); the NMR spectrum in dimethyl sulfoxide-d_6 showed the presence of three methoxyl groups, at δ 3.74, 3.85, and 3.91 (each 3H singlet), three hydroxyl groups, at δ 9.47, 9.73, and 12.42 (each 1H singlet), and four aromatic protons, at δ 6.88 (C_8–H singlet), 6.95 ($C_{5'}$–H, doublet, J=9 cps), 7.77 ($C_{6'}$–H, double doublet, J=2 cps and 9 cps), and 7.81 ($C_{2'}$–H, doublet, J=2 cps). The demethylated flavone was also characterized as its triacetate (IX), which gave the original flavone (mp 213—214°C) (by acid hydrolysis), its dibenzyl ether (X), and its dimethyl ether, 5-hydroxy-3,3′,4′,6,7-pentamethoxyflavone (XI). The compound XI was further methylated to 3,3′,4′,5,6,7-hexamethoxyflavone (XII), which was identical with a sample prepared by the methylation of II. The structures of XI and XII were confirmed by direct comparisons with authentic sample[6]; this proved that there was no isomeric



VI



VII



VIII

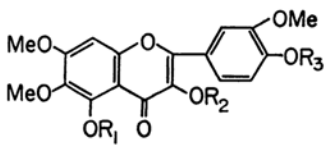
Bz = Benzyl

3) K. Fukui and T. Matsumoto, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **86**, 1079 (1965).

4) M. Krishnamurti, T. R. Seshadri and P. R. Shankaran, *Tetrahedron*, **22**, 941 (1966).

5) L. Hörhammer, H. Wagner, E. Graf and L. Farkas, *Chem. Ber.*, **98**, 548 (1965).

6) K. Fukui, T. Matsumoto, S. Nakamura, M. Nakayama and T. Horie, This Bulletin, **41**, 1413 (1968).



V R_1=Me, R_2=H, R_3=Bz
IX R_1=R_2=R_3= Ac
X R_1=H, R_2=R_3= Bz
XI R_1=H, R_2=R_3= Me
XII R_1=R_2=R_3= Me

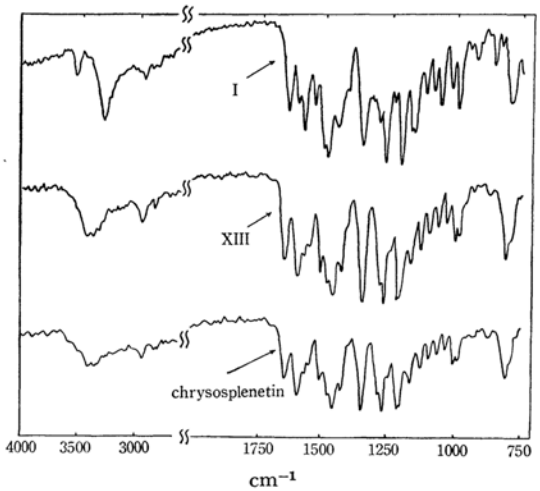


Fig. 1. Infrared spectra of I, XIII and chrysosplenetin in KBr.

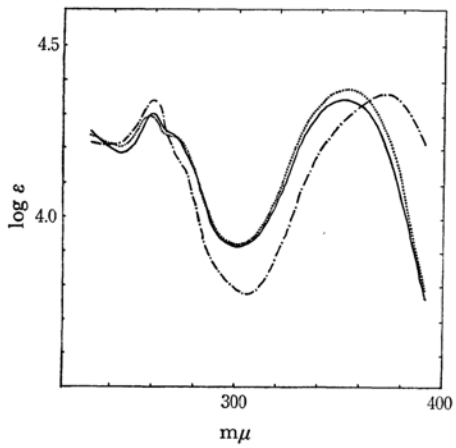


Fig. 2. Ultraviolet spectra of I (·—·—·), XIII (·····) and chrysosplenetin (——) in ethanol.

change during the demethylation of II. As is shown in Table 1, a long-wavelength band in the UV spectrum of X undergoes a bathochromic shift (29 mμ) upon the addition of aluminum chloride;[7] this shows the presence of a free 5-hydroxyl group.

From these facts, the structure of the demethylated flavone was established to be 3,4′,5-trihydroxy-3′,6,7-trimethoxyflavone (I); this identification was also supported by the UV spectra (see Table 1). The synthetic flavone (I) was found not to be identical with natural chrysosplenetin, mp 177—178°C*2 (lit.[1] mp 158—159°C) by a mixed-melting-point determination and by a comparison of their IR, UV, NMR, and mass spectra.

Consequently, the correct structures of chrysosplenetin and chrysosplenin*2 were studied further. We used spectroscopic methods because of the small amount of the natural sample available.

a) Chrysosplenetin. The NMR spectrum of chrysosplenetin in pyridine-d_5 showed the presence of four methoxyl groups, at δ 3.86 (6H singlet) and 4.01 (6H singelt), and four aromatic protons, at δ 6.87 (C_8–H, singelt), 7.37 ($C_{5'}$–H, doublet, J=9 cps), 7.93 ($C_{6'}$–H, double doublet, J=2 cps and 9 cps), and 8.00 ($C_{2'}$–H, doublet, J=2 cps). In the UV spectra (Table 1), a free 5-hydroxyl group is indicated by the bathochromic shift (31 mμ) of the long-wavelength band in the presence of aluminum chloride. The large bathochromic shift (67 mμ or 57 mμ) of the long-wavelength band in ethanol upon the addition of fused sodium acetate[8] or sodium hydroxide[7] suggests the presence of a free 4′-hydroxyl group. Chrysosplenetin is stable in an alkaline solution, for when the alkaline solution is acidified, the spectrum changes to the parent one in ethanol. This suggests the absence of a free 3,4′-dihydroxyl group. The absence of a free *o*-dihydroxyl group is also indicated by effects of the addition of boric acid and sodium acetate.[8,9] It has already been made clear that chrysosplenetin is a quercetagetin derivative.[1] Therefore, the structure of chrysosplenetin must be 4′,5-dihydroxy-3,3′,6,7-tetramethoxyflavone (XIII). In addition, the molecular ion peak in the mass spectrum of chrysosplenetin was observed at *m/e* 374, supporting the XIII structure, $C_{19}H_{18}O_8$ (Mwt 374.33). Finally, chrysosplenetin was compared with authentic XIII specimens which had previously been synthesized by Hörhammer *et al.*[5] and by Fukui *et al.*[6] by the different routes; all the samples were shown to be identical by a mixed-melting-point determination and by a comparison of their IR, UV, NMR, and mass spectra.

b) Chrysosplenin. The NMR spectrum of chrysosplenin in dimethyl sulfoxide-d_6 showed the presence of four methoxyl groups, at δ 3.75, 3.84,

7) L. Jurd, "The Chemistry of Flavonoid Compound," ed. by T. A. Geissman, Pergamon Press, Oxford (1962), Chap. 5.

*2 Natural samples were kindly supplied by Professor N. Morita; the melting points, after one crystallization, were observed in this laboratory.

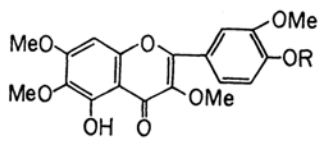
8) L. Jurd and R. M. Horowitz, *J. Org. Chem.*, **22**, 1618 (1957); B. Gentili and R. M. Horowitz, *Tetrahedron*, **20**, 2313 (1964).

9) L. Jurd, *Arch. Biochem. and Biophys.*, **63**, 376 (1956).

Table 1. Ultraviolet spectra of I, X, XIII, chrysosplenin and chrysosplenetin

	λ_{max} mμ (log ε)					
	EtOH	NaOAc*3	$AlCl_3$*4	NaOH*4	NaOH-HCl*5	NaOAc-H_3BO_3*3,*4
I	259 (4.34)	259.5(4.33)	270 (4.37)	326 (4.12)	269 (4.20)	259 (4.35)
	273*6(4.17)	271*6(4.26)	304*6(3.75)		297 (4.15)	273*6(4.20)
	370 (4.36)	378 (4.27)	390*6(4.23)			373 (4.34)
		420*6(3.82)	428 (4.38)			
X	258.5(4.33)	258.5(4.32)	269 (4.32)	293.5(4.32)	259 (4.36)	
	273 (4.29)	273.5(4.28)	284 (4.31)	380*6(3.69)	272*6(4.33)	
	347 (4.34)	346 (4.32)	376 (4.33)		348 (4.32)	
Chrysosplenin	255 (4.20)	256 (4.19)	264 (4.20)	292 (4.18)	256 (4.16)	255 (4.23)
	275 (4.24)	274 (4.25)	287.5(4.26)	380 (3.73)	274 (4.21)	274 (4.27)
	344 (4.30)	342 (4.28)	367 (4.31)		342 (4.19)	342 (4.30)
Chrysosplenetin	259 (4.28)	261 (4.26)	272*6(4.27)	271 (4.19)	259 (4.26)	262 (4.30)
	271*6(4.23)	271*6(4.25)	282 (4.27)	410 (4.34)	271*6(4.20)	271*6(4.27)
	353 (4.34)	358 (4.16)	384 (4.32)		353 (4.30)	358 (4.31)
		420 (4.15)				
XIII	258 (4.28)	259 (4.27)	268.5(4.25)	270 (4.29)	258 (4.29)	
	272*6(4.23)	272*6(4.23)	282 (4.27)	410 (4.42)	270*6(4.24)	
	353 (4.37)	353 (4.33)	380 (4.36)		353 (4.42)	
		420 (3.77)				

3.90, and 3.93 (each 3H singlet), of four aromatic protons, at δ 6.96—7.85 (multiplet), and one hydrogen-bonding hydroxyl group, at δ 12.58 (1H broad singelt), which latter suggests the presence of a 5-hydroxyl group. In the UV spectra (Table 1), a free 5-hydroxyl group is also supported by the bathochromic shift (23 mμ or 36 mμ) of the long-wavelength band upon the addition of aluminum chloride or sodium hydroxide. The absence of a free 3- or 4′- or 7-hydroxyl group, a free 3,4′-dihydroxyl group, and a free *o*-dihydroxyl group is also indicated by the spectra summarized in Table 1. The above spectral evidence leads to the identification of chrysosplenin as the 4′-glucoside (XIV) of chrysosplenetin.



XIII R = H

XIV R = Glucosyl

*3 Saturated with fused sodium acetate.

*4 0.002 mol/*l*.

*5 The alkaline solution was acidified with dilute hydrochloric acid.

*6 Inflection.

Experimental*7

4-Benzyloxy-2′-hydroxy-3,4′,5′,6′-tetramethoxychalcone (VII). A mixture of 2-hydroxy-4,5,6-trimethoxyacetophenone (VI)[10] (5.5 g), 4-benzyloxy-3-methoxybenzaldehyde (13.5 g), aqueous sodium hydroxide (50%, 140 g), and ethanol (400 m*l*) was treated by a method similar to that of Hörhammer *et al.*[5] The crude product was recrystallized from a benzene-methanol mixture to give VII, mp 158—159°C, which gave a brown ferric chloride reaction in ethanol; yield 9.0 g (83%) (lit.[5] mp 158—159°C, yield 49%).

Found: C, 69.58; H, 5.61%. Calcd for $C_{26}H_{26}O_7$: C, 69.32; H, 5.82%.

4′-Benzyloxy-3′, 5, 6, 7-tetramethoxyflavanone (VIII). A mixture of VII (16.0 g) and ethanolic sulfuric acid (3%: 1.6 *l*) was refluxed for 9 hr. Most of the solvent was evaporated under a vacuum, and the residue was poured into water (2 *l*). The precipitate was collected, washed with water, and then treated with methanol. From the sparingly-soluble part, the starting material (VII) (6.6 g, 41%) was recovered; the soluble part was recrystallized from methanol to give VIII as colorless needles, mp 126°C, which gave a negative

*7 All melting points are uncorrected. The NMR spectra were taken on a Hitachi Model R-20 NMR spectrometer (60 Mc/sec), using tetramethylsilane as the internal standard; their chemical shifts are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, dd: double doublet, m: multiplet.

10) V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **23A**, 262 (1946).

ferric chloride reaction; yield 6.4 g (40%).

Found: C, 69.47; H, 5.79%. Calcd for $C_{26}H_{26}O_7$: C, 69.32; H, 5.82%.

4'-Benzyloxy-3-hydroxy-3',5,6,7-tetramethoxyflavone (V). To a boiling solution of VIII (0.6 g) in methanol (50 ml) there were added hydrogen peroxide (30%: 3.0 ml) and then aqueous potassium hydroxide (20%: 10 ml). After the refluxing had been continued for 1.5 min, the mixture was poured onto ice (200 g), and the alkaline solution was acidified with dilute hydrochloric acid. The yellow precipitate was collected, washed with water, and then recrystallized from acetone to give V as yellow needles, mp 201—202°C, which gave a brown ferric chloride reaction in ethanol; yield 0.1 g (16%). This substance was identical with a sample (mp 201—202°C) (lit.[5] mp 202°C) prepared by the method of Hörhammer *et al.*[5] UV: λ_{max}^{EtOH} mμ (log ε); 237*[6] (4.29), 255 (4.37), 360 (4.39).

Found: C, 67.34; H, 5.25%. Calcd for $C_{26}H_{24}O_8$: C, 67.23; H, 5.21%.

Benzyl Ether of V. A mixture of V (460 mg), benzyl chloride (140 mg), anhydrous potassium carbonate (700 mg), and dimethylformamide (4.0 ml) was gently refluxed for 1 hr. After the mixture had been poured into water, the precipitate was collected, washed with water, and then recrystallized from ethanol to give colorless needles, mp 105.5—106.5°C, which gave a negative ferric chloride reaction; yield 490 mg (88%).

Found: C, 71.63; H, 5.50%. Calcd for $C_{33}H_{30}O_8$: C, 71.47; H, 5.45%.

3,4'-Dihydroxy-3',5,6,7-tetramethoxyflavone (II). A solution of V (700 mg) in ethyl acetate (700 ml) was submitted to catalytic hydrogenolysis at room temperature in the presence of Pd-C (5%; 700 mg). After the catalyst had been filtered off, the filtrate was evaporated, and then the residue was recrystallized from ethyl acetate to give II as yellow needles, mp 236—237°C (lit.[2] mp 235°C), which gave a brown ferric chloride reaction in ethanol; yield 510 mg (91%). UV: λ_{max}^{EtOH} mμ (log ε); 237*[6] (4.24), 255 (4.33), 364 (4.37). NMR in DMSO-d_6: 3.78 (s, MeO), 3.86 (s, 2MeO), 3.95 (s, MeO), 6.97 (d, J_{ortho}=9 cps, $C_{5'}$–H), 7.17 (s, C_8–H), 7.73 (dd, J_{ortho}=9 cps, J_{meta}=2 cps, $C_{6'}$–H), 7.79 (d, J_{meta}=2 cps, $C_{2'}$–H), 8.94 (bs) and 9.63 (bs) (C_3–OH and $C_{4'}$–OH). Mass spectrum: *m/e* 374 (M^+).

Found: C, 61.04; H, 4.87%. Calcd for $C_{19}H_{18}O_8$: Mwt, 374.33; C, 60.96; H, 4.85%.

Diacetate of II. Hot acetic anhydride-pyridine method; mp 169—170°C (from ethanol). NMR in $CDCl_3$: 2.35 (s, 2AcO), 3.89 (s, 2MeO), 3.98 (s, 2MeO), 6.75 (s, C_8–H), 7.15 (d, J_{ortho}=9 cps, $C_{5'}$–H), 7.41 (m, $C_{2'}$–H and $C_{6'}$–H).

Found: C, 60.13; H, 4.88%. Calcd for $C_{23}H_{22}O_{10}$: C, 60.26; H, 4.84%.

3,4',5-Trihydroxy-3',6,7-trimethoxyflavone (I). *a) With Aluminum Chloride in Nitrobenzene.* The flavone (II) (400 mg) was added to a mixture of anhydrous aluminum chloride (4.0 g) and dry nitrobenzene (40 ml). After the mixture had stood at room temperature for 5 hr, ice (25 g) and then concentrated hydrochloric acid (25 ml) were stirred into the mixture and cooled in an ice-water bath. The nitrobenzene was removed by steam distillation, and the residual precipitate was collected, washed with water, and then recrystallized from methanol to give I as yellow needles, mp 213—214°C, which gave a dark green ferric chloride reaction in ethanol; yield 200 mg (52%). The mixed melting point with natural chrysosplenetin (mp 177—178°C) was 163—174°C.

Found: C, 60.20; H, 4.41%. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48%.

b) With Aniline Hydrochloride. A mixture of II (700 mg) and aniline hydrochloride (1.50 g) was heated at 180°C for 1 hr, and then cooled. After the addition of water (40 ml), the precipitate was collected, washed with water, and recrystallized from methanol to give yellow needles, mp 213—214°C, which was shown to be identical with that of the sample of a) by a mixed-melting-point determination and by a comparison of the IR spectra; yield 130 mg (19%).

c) Hydrolysis of IX. A mixture of IX (200 mg), concentrated hydrochloric acid (20 ml), and ethanol (80 ml) was refluxed for 1.5 hr. After the evaporation of the solvent under a vacuum, the residue was poured into an ice-water mixture (*ca.* 80 ml). The precipitate was collected, washed with water, and then recrystallized from methanol to give yellow needles, mp 213—214°C, which was identical with that of the sample of a); yield 105 mg (71%).

3,4',5-Triacetoxy-3',6,7-trimethoxyflavone (IX). A mixture of I (300 mg), acetic anhydride (4.0 ml), and dry pyridine (6.0 ml) was refluxed for 1.5 hr. The crude product was then recrystallized from acetone to give the triacetate (IX) as colorless needles, mp 228—230°C, which gave a negative ferric chloride reaction; yield 320 mg (79%). UV: λ_{max}^{EtOH} mμ (log ε); 241 (4.29), 308 (4.13). NMR in $CDCl_3$: 2.30 (s, AcO), 2.33 (s, AcO), 2.46 (s, AcO), 3.84 (s, MeO), 3.87 (s, MeO), 3.97 (s, MeO), 6.88 (s, C_8–H), 7.14 (d, J_{ortho}=9 cps, $C_{5'}$–H), 7.40 (overlap, $C_{2'}$–H), 7.42 (dd, J_{ortho}=9 cps, J_{meta}=2 cps, $C_{6'}$–H). Mass spectrum: *m/e* 486 (M^+).

Found: C, 59.20; H, 4.67%. Calcd for $C_{24}H_{22}O_{11}$: Mwt., 486.42; C, 59.26; H, 4.56%.

3,4'-Dibenzyloxy-5-hydroxy-3',6,7-trimethoxyflavone (X). A mixture of I (90 mg), benzyl chloride (145 mg), anhydrous potassium carbonate (1.5 g), and dry acetone (30 ml) was refluxed for 15 hr. The crude product was then recrystallized from methanol to give the dibenzyl ether (X) as yellow needles, mp 141—142°C, which gave a green ferric chloride reaction in ethanol; yield 32 mg (24%).

Found: C, 71.05; H, 5.17%. Calcd for $C_{32}H_{28}O_8$: C, 71.10; H, 5.22%.

5-Hydroxy-3,3',4',6,7-pentamethoxyflavone (XI). To a solution of I (800 mg) in acetone (100 ml), an ethereal diazomethane solution was added; then the mixture was allowed to stand at room temperature for 3.5 hr. After the solvent had been evaporated, the residue was recrystallized from methanol to give XI as yellow needles, mp 161—162°C, which gave a green ferric chloride reaction in ethanol; yield 600 mg (70%). The melting point was undepressed on admixture with an authentic sample[6] (mp 161—162°C). UV: λ_{max}^{EtOH} mμ (log ε); 239 (4.12), 255.5 (4.27), 272.5 (4.23), 345 (4.35). NMR in $CDCl_3$: 3.85 (s, MeO), 3.90 (s, MeO), 3.95 (s, 3MeO), 6.51 (s, C_8–H), 7.00 (d, J_{ortho}=9 cps, $C_{5'}$–H), 7.75 (dd, J_{ortho}=9 cps, J_{meta}=2 cps, $C_{6'}$–H), 7.71 (d, J_{meta}=2 cps, $C_{2'}$–H), 12.60 (s, C_5–OH).

Found: C, 61.70; H, 5.33%. Calcd for $C_{20}H_{20}O_8$: C, 61.85; H, 5.19%.

3,3′,4′,5,6,7-Hexamethoxyflavone (XII). *a) From II.* A mixture of II (300 mg), dimethyl sulfate (200 mg), anhydrous potassium carbonate (2.0 g), and dry acetone (250 m*l*) was refluxed for 15 hr. After the mixture had been filtered, the filtrate was evaporated, washed successively with aqueous sodium hydroxide, and water, and then recrystallized from methanol to give XII as colorless needles; mp 142—143°C, which was identical with that of an authentic sample[6] (mp 142—143°C); yield 210 mg (65%). It gave a negative ferric chloride reaction. NMR in $CDCl_3$: 3.84 (s, MeO), 3.89 (s, MeO), 3.94 (s, 3MeO), 3.99 (s, MeO), 6.75 (s, C_8–H), 6.98 (d, J_{ortho}=9 cps, $C_{5'}$–H), 7.71 (dd, J_{ortho}=9 cps, J_{meta}=2 cps, $C_{6'}$–H), 7.70 (d, J_{meta}=2 cps, $C_{2'}$–H).

Found: C, 62.54; H, 5.37%. Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51%.

b) From XI. A mixture of XI (370 mg), dimethyl sulfate (150 mg), anhydrous potassium carbonate (2.0 g), and dry acetone (150 m*l*) was refluxed for 60 hr. The reaction mixture was then treated by the method of a) to give XII; mp 142—143°C, which was identical with that of the sample of a); yield 280 mg (73%).

4′,5-Dihydroxy-3,3′,6,7-tetramethoxyflavone(XIII). The flavone (XIII: mp 181—182°C) was prepared by the method of Hörhammer *et al.*[5]; it was proved to be identical with a sample prepared by the method of Fukui *et al.*.[6] NMR in pyridine-d_5: 3.86 (s, 2MeO), 4.01 (s, 2MeO), 6.87 (s, C_8–H), 7.37 (d, J_{ortho}=9 cps, $C_{5'}$–H), 7.93 (dd, J_{ortho}=9 cps, J_{meta}=2 cps, $C_{6'}$–H), 8.00 (overlap, $C_{2'}$–H). NMR in DMSO-d_6: 3.73 (s, MeO), 3.82 (s, MeO), 3.88 (s, MeO), 3.92 (s, MeO), 6.90 (s, C_8–H), 6.99 (d, J_{ortho}=9 cps, $C_{5'}$–H), 7.65 (dd, J_{ortho}=9 cps, J_{meta}=2 cps, $C_{6'}$–H), 7.72 (overlap, $C_{2'}$–H), 9.87 (bs, $C_{4'}$–OH), 12.62 (s, C_5–OH). Mass spectrum: *m/e* 374 (M^+).

Found: C, 60.79; H, 4.76%. Calcd for $C_{19}H_{18}O_8$: Mwt., 374.33; C, 60.96; H, 4.85%.

The mixed melting point of XIII with natural chrysosplenetin (mp 177—178°C) was 178—180.5°C.

Diacetate of XIII. Mp 191—192°C, identical with that of an authentic sample[6] (mp 191—192°C). NMR in $CDCl_3$: 2.31 (s, AcO), 2.47 (s, AcO), 3.77 (s, MeO), 3.83 (s, MeO), 3.87 (s, MeO), 3.95 (s, MeO), 6.85 (s, C_8–H), 7.16 (d, J_{ortho}=9 cps, $C_{5'}$–H), 7.65 (dd, J_{ortho}=9 cps, J_{meta}=2 cps, $C_{6'}$–H), 7.74 (overlap, $C_{2'}$–H). Mass spectrum: *m/e* 458 (M^+).

Found: C, 60.03; H, 4.76%. Calcd for $C_{23}H_{22}O_{10}$: Mwt., 458.41; C, 60.26; H, 4.84%.

Chrysosplenetin. Mp 177—178°C*[2]. Mass spectrum: *m/e* 374 (M^+) ($C_{19}H_{18}O_8$: Mwt=374.33). NMR in pyridine-d_5: 3.86 (s, 2MeO), 4.01 (s, 2MeO), 6.87 (s, C_8–H), 7.37 (d, J_{ortho}=9 cps, $C_{5'}$–H), 7.93 (dd, J_{ortho}=9 cps, J_{meta}=2 cps, $C_{6'}$–H), 8.00 (d, J_{meta}=2 cps, $C_{2'}$–H). UV: λ_{max}^{EtOH} mμ (log ε); 259 (4.28), 271*[6] (4.23), 353 (4.34).

The authors are grateful to Professor N. Morita, Toyama University, for his gifts of natural chrysosplenetin and chrysosplenin. Thanks are also due to the Toyo Soda Co., Ltd., for the mass spectral measurements. This work was supported by a grant-in-aid from the Ministry of Education.

Appendix. Since this paper had been submitted, Shimizu and Morita reported on the structure of chrysosplenin in a communication form (*Chem. Pharm. Bull. Japan*, **16**, 2310 (1968)), and those authors concluded that chrysosplenin was a mixture of 4′,5-dihydroxy-3,3′,6,7-tetramethoxyflavone-4′-monoglucoside (XIV, chrysosplenoside-B) and 3′ or 4′-monoglucoside of 3′,4′,5-trihydroxy-3,6,7-trimethoxyflavone (chrysosplenoside-D) in a 68 : 32 ratio.