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^{13}C-Nuclear Magnetic Resonance (NMR) Spectral Studies on Polysubstituted Flavonoids. I. ^{13}C-NMR Spectra of Flavones

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The ^{13}C-NMR spectra of 61 flavone derivatives were measured in dimethyl sulfoxide. By consideration of the chemical shifts of skeletal carbons, the parameters (α and β values) and correction factor (o value) necessary for calculating their carbon shifts were deduced. The skeletal carbons of polysubstituted flavones and flavonols could easily be assigned by the use of these values and SCS of OMe or OH. The ^{13}C-NMR spectra were confirmed to give useful information that could not be obtained from other spectral data. The data were applied for the structure elucidation of unknown polysubstituted flavones.

Keywords——^{13}C-NMR spectra; polysubstituted flavones; α value; β value; o value; extensive additivity rule

Several papers have already been published on ^{13}C-NMR spectral studies on flavonoids,[2] but the flavonoids dealt with in these studies were limited in the number of substituents (OMe and OH), and in the substitution patterns. Therefore, these studies are not particularly helpful in identifying naturally occurring unknown flavones, such as flavones with 5,6,8-,[3] 5,7,8-, and 5,6,7-trisubstituted ring A structures, or with unusual substitution patterns in ring B, such as 2′,4′-,[4] 2′,6′-,[5] and 2′,3′,5′-[6] trisubstituted flavones. We systematically measured the ^{13}C-NMR spectra of various flavone (**1**—**61**) to develop extensive additivity rules for methoxyl and hydroxyl groups in flavones, and calculated two parameters and correction value necessary for the assignment of the skeletal carbons of flavones. The accuracy of these values was confirmed by repeated experiments. Attempts were made to apply them to the structure elucidation of unknown flavones.

Substituent Chemical Shifts (SCS) of the Ether Moiety and Benzopyrone Moiety (α and β Values)

Comparison of the chemical shifts of skeletal carbons of an unsubstituted flavone (**1**) with those of monomethoxyflavones[2a] (**2**—**8**) indicated that the chemical shifts of the carbons in ring A are not affected by a methoxyl group in ring B, and also that the skeletal carbons of ring B are not affected by the position of a methoxyl group substituted in ring A. Therefore, it was thought that the ether moiety at the 1-position (the flavone numbering system) directly contributed to the chemical shift of each of the carbons in ring B, and similarly the benzopyrone moiety at the 1′-position contributed to those of ring B. By taking the carbonyl moiety at C-4 to be $COCHCH_2$, the α value was calculated from the SCS of $COCHCH_2$ and the chemical

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Table I. SCS of the Ether Moiety (α value) and Benzopyrone Moiety (β value) in Flavones

	C-9	C-8, 10	C-5, 7	C-6
α value	+28.5	−11.6	−2.6	−3.2

	C-1′	C-2′, 6′	C-3′, 5′	C-4′
β value	+2.5	−2.2	0	+2.6

(ppm)

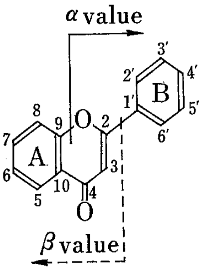

Table II. ^{13}C-NMR Chemical Shifts of an Unsubstituted Flavone (**1**) and Monomethoxyflavones (**2**—**8**)

Position of OMe		2	3	4	5	6	7	8	9	10
None	(**1**)	163.0	107.3	178.0	125.4	124.9	133.5	117.9	156.0	123.7
5	(**2**)	160.2	108.1	176.3	159.0 (154.8)	109.8 (108.5)	133.8 (128.5)	107.4 (106.7)	157.3 (155.7)	113.8 (109.2)
6	(**3**)	162.4	105.8	176.6	105.2 (109.1)	156.5 (154.2)	122.6 (113.0)	119.5 (115.6)	150.1 (146.8)	123.8 (124.7)
7	(**4**)	163.5	106.4	176.2	125.8 (124.6)	114.0 (108.5)	162.5 (158.7)	100.6 (100.1)	157.1 (155.7)	116.8 (115.8)
8	(**5**)	162.4	107.1	176.9	115.8 (115.7)	124.7 (124.7)	107.1 (113.0)	149.1 (145.8)	— (140.2)	125.2 (124.2)
2′	(**6**)	160.5	112.3	177.0	124.8	124.4	133.2	117.9	155.6	122.8
3′	(**7**)	162.2	106.9	176.9	125.1	124.4	133.8	118.0	155.3	123.0
4′	(**8**)	162.6	105.2	176.6	124.8	124.4	133.5	117.8	155.3	123.0

Position of OMe		1′	2′	3′	4′	5′	6′	OCH_3
None	(**1**)	131.5	126.0	128.8	131.3	128.8	126.0	
5	(**2**)	130.7	125.6	128.6	131.1	128.6	125.5	56.0
6	(**3**)	131.0	125.8	128.7	131.3	128.7	125.8	55.5
7	(**4**)	131.1	125.8	128.7	131.1	128.7	125.8	55.6
8	(**5**)	131.6	126.4	129.1	131.6	129.1	126.4	55.8
2′	(**6**)	120.0 (115.7)	157.4 (156.7)	111.2 (113.2)	132.4 (131.3)	120.5 (119.8)	128.7 (126.5)	55.6
3′	(**7**)	132.2 (131.2)	111.4 (111.0)	159.5 (158.9)	117.3 (115.8)	129.9 (128.7)	118.3 (117.6)	55.1
4′	(**8**)	123.0 (122.3)	127.7 (126.5)	114.3 (113.2)	161.8 (161.5)	114.3 (113.2)	127.7 (126.5)	55.1

The values calculated from the α and β values and SCS of OMe are given in parentheses.

shift of benzene (128.7 ppm). On the other hand, the β value was calculated from the observed chemical shifts by regarding benzopyrone itself as a substituent attached to benzene (B ring). The values obtained in this way are listed in Table I. The chemical shifts of the skeletal carbons carrying OMe (**2**—**5**) in ring A and (**6**—**8**) in ring B were calculated for the parameters and SCS of OMe. Comparison of the calculated and observed values showed that they were in very good agreement (Table II). Therefore, the assignment of skeletal carbons could be easily carried out by calculation.

Table III. ^{13}C-NMR Chemical Shifts of Flavones with Various Substituents in Ring B

Position of OMe		2	3	4	5	6	7	8	9	10
2′, 3′	(**9**)	161.7	—	177.6	125.4	124.5	134.3	118.3	155.9	123.0
2′, 4′	(**10**)	162.7	112.2	176.6	124.5	124.3	133.4	117.8	155.3	122.7
2′, 5′	(**11**)	160.0	113.6	176.9	125.1	124.4	133.9	117.6	155.6	122.8
2′, 6′	(**12**)	160.4	113.6	176.6	124.8	124.7	133.9	118.2	156.2	123.1
3′, 5′	(**13**)	161.7	106.9	176.4	124.7	124.1	133.4	117.8	155.1	122.8
2′, 3′, 4′	(**14**)	160.9	110.0	176.6	124.4	124.0	133.8	118.0	155.9	122.8
2′, 4′, 6′	(**15**)	160.2	113.7	176.3	124.5	124.5	133.3	117.7	155.9	122.8
3′, 4′, 5′	(**16**)	162.0	106.3	176.6	124.9	124.3	133.5	118.0	155.2	123.0
2′, 3′, 5′, 6′	(**17**)	159.9	113.3	176.3	125.1	124.6	133.8	117.9	155.9	122.9
2′, 3′, 4′, 5′, 6′	(**18**)	159.6	113.2	176.6	125.1	124.7	133.9	117.9	156.1	123.0

Position of OMe		1′	2′	3′	4′	5′	6′	OCH_3
2′, 3′	(**9**)	111.2 (115.7)	147.1 (148.0)	153.0 (153.4)	111.2 (115.8)	120.5 (119.8)	116.0 (117.6)	60.2(2′) 55.9(3′)
2′, 4′	(**10**)	109.9 (106.8)	159.1 (156.7)	98.7 (97.7)	160.9 (161.5)	105.8 (104.3)	129.7 (126.5)	55.5(2′) 55.1(4′)
2′, 5′	(**11**)	120.2 (115.7)	151.6 (147.8)	114.0 (113.2)	118.3 (115.8)	152.9 (150.0)	111.5 (111.0)	56.1(2′) 55.4(5′)
2′, 6′	(**12**)	110.4 (110.2)	157.7 (156.7)	104.1 (104.3)	132.3 (131.3)	104.1 (104.4)	157.7 (156.7)	55.8(2′, 6′)
3′, 5′	(**13**)	132.6 (131.6)	104.0 (102.1)	160.4 (158.9)	103.1 (100.3)	160.4 (158.9)	104.0 (102.1)	55.0(3′, 5′)
2′, 3′, 4′	(**14**)	108.0 (106.8)	152.0 (151.2)	141.9 (137.9)	155.6 (156.0)	108.0 (104.0)	118.0 (117.6)	60.9(2′) 60.2(3′) 55.8(4′)
2′, 4′, 6′	(**15**)	103.7 (100.2)	158.6 (156.7)	91.0 (88.8)	162.7 (161.5)	91.0 (88.8)	158.6 (156.7)	55.7 55.0(2′, 4′, 6′)
3′, 4′, 5′	(**16**)	126.0 (122.3)	104.1 (102.1)	152.9 (153.4)	140.8 (140.5)	152.9 (153.4)	104.1 (102.1)	59.4(4′) 56.1(3′, 5′)
2′, 3′, 5′, 6′	(**17**)	102.2 (100.2)	139.7 (142.3)	148.5 (144.5)	112.9 (100.3)	148.5 (144.5)	139.7 (142.9)	60.7(2′, 6′) 56.4(3′, 5′)
2′, 3′, 4′, 5′, 6′	(**18**)	116.2	142.5	146.8	149.4	146.8	142.5	61.1 60.6(2′, 3′, 4′, 5′, 6′)

Flavones Having Various Substitution Patterns in Ring B and Correction Value for *o*-Dimethoxyl Group (*o* Value)

The chemical shifts of carbons with two isolated methoxyl groups in ring B (**10**, **11**, **12**, and **13**) can be simply calculated from the β value and SCS of OMe (Table III). The calculated values agreed with those observed, but the carbons carrying adjacent methoxyl groups as in **9** were 10 ppm further downfield than expected. Such a phenomenon was observed not only in ring B (**14** and **16**) but also in ring A (**26** and **27**). Consequently a correction for these shifts became necessary, and an *o* value of +7 to +10 ppm was obtained as a result of calculation (flavones **9**, **14**, **26**, and **27**). This *o* value can be applied to trimethoxyflavones (**14** and **16**). The calculation of chemical shifts, for example **14**, can be done by considering that another methoxyl group is attached to C-4′ of **9**, and the *o* value and SCS of OMe are added to each carbon. Similarly, tetramethoxyflavone (**17**) can be regarded as two methoxyl groups attached to C-5′ and C-6′ of **9**, or C-3′ and C-5′ of **12**. The assignment was easily made in the same way as above. In the case of pentamethoxyflavone (**18**), a methoxyl group may be considered as attached to C-4′ of **17**, and the chemical shift of each of the carbons can be calculated by taking the new *o* effect into consideration.

As mentioned above, the skeletal carbons of flavones with various substitutions in ring B can be assigned by calculation. The shift of C-3 is usually between 103 and 106 ppm, but when methoxyl group is attached to C-2′ or C-6′, a downfield shift occurs to between 110 and 114 ppm.

Table IV. ^{13}C-NMR Chemical Shifts of the 3′,4′-Disubstituted Flavones

Position of OMe or OH		2	3	4	5	6	7	8	9	10
5, 6, 7, 3′, 4′	(**19**)	160.2	106.2	175.5	153.6	139.7	157.2	97.0	151.4	111.9
3′/5, 6, 7, 4′[a]	(**20**)	160.6	105.7	175.6	153.7	139.5	157.2	96.9	151.4	111.8
4′/5, 6, 7, 3′	(**21**)	160.7	105.7	175.6	153.7	139.7	157.3	96.9	151.4	111.9
3′, 4′/5, 6, 7	(**22**)	160.0	105.4	175.8	153.8	139.6	157.3	96.9	151.5	111.7
5, 3′/6, 7, 4′	(**23**)	163.7	103.2	182.0	152.5	131.9	158.5	91.2	152.0	111.9
5, 3′, 4′/6, 7	(**24**)	164.2	103.0	181.9	152.5	131.9	158.5	91.2	151.9	111.9

Position of OMe or OH		1′	2′	3′	4′	5′	6′	OCH$_3$
5, 6, 7, 3′, 4′	(**19**)	123.0 (122.3)	109.5 (111.0)	148.9 (148.4)	151.6 (151.0)	111.9 (113.2)	119.4 (117.6)	61.5(5) 61.0(6) 56.2 55.9(7, 3′, 4′)
3′/5, 6, 7, 4′[a]	(**20**)	121.8 (125.1)	109.9 (113.9)	147.9 (140.1)	149.9 (148.9)	115.6 (115.0)	119.7 (118.6)	61.6(5) 60.7(6) 56.2(7, 4′)
4′/5, 6, 7, 3′	(**21**)	121.9 (123.0)	110.1 (112.0)	150.1 (148.3)	147.9 (146.9)	115.8 (116.1)	119.7 (119.4)	61.6 60.7(5, 6) 56.0(7, 3′)
3′, 4′/5, 6, 7	(**22**)	121.9 (125.0)	113.1 (115.7)	145.5 (143.0)	148.9 (145.6)	115.9 (117.9)	118.4 (120.4)	61.8(5) 60.8(6) 56.3(7)
5, 3′/6, 7, 4′	(**23**)	122.8	105.0	146.7	151.2	112.9	118.0	60.1(6) 56.3 55.8(7, 4′)
5, 3′,4′/6, 7	(**24**)	121.5	113.4	145.6	149.7	116.0	119.0	59.9(6) 56.3(7)

a) The numbers before the diagonal line indicate the substitution positions of hydroxyl groups.

In many flavones found in nature, OMe and/or OH are attached at C-3′ and C-4′, and different assignments of carbons at C-1′ and C-6′ in these flavones have been made by different workers.[2c,2d] Therefore, these flavones (**19**—**24**) were examined (Table IV). The carbon shifts at C-1′ and C-6′ calculated by considering *β* and *o* values showed the former (122 ppm) to be more downfield than the latter (119 ppm). The chemical shifts of carbons at C-1′ and C-6′, consequently, should be assigned according to Ternai and Markham.[2c] Discrimination between **20** and **21** seemed possible by such calculations, but the spectra of the two flavones showed very similar signal patterns. It may be easier to examine the acylation shift[7] rather than to study the native form.

Disubstituted Flavones in Ring A

The carbon shifts of flavone with two adjacent methoxyl groups in ring A can be calculated from the *α* value and *o* value, and the SCS of OMe (Table V). In the case of **26**, for example, three methods can be applied: one is to consider OMe attached to C-6 of **2**, the second is to con-

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Table V. ^{13}C-NMR Chemical Shifts of Flavones with Various Substituents in Ring A

Position of OMe or OH	2	3	4	5	6	7	8	9	10
5, 7, 4′ (**25**)	160.1	106.4	175.4	158.8	95.9	163.4	93.2	159.7	108.1
2′/5, 6 (**26**)	158.6	113.1	176.5	150.5	146.4	133.6	117.4	149.1	111.0
7, 8 (**27**)	161.7	106.1	176.1	117.6	110.5	156.0	136.2	149.5	119.6
2/3, 5, 6[a] (**28**)			201.7	143.8	139.9	122.2	144.4	139.1	103.5
2/3, 4, 6[a] (**29**)			202.8	150.8	93.9	158.0	121.6	156.8	105.8
2/4, 5, 6[a] (**30**)			202.5	159.3	134.2	159.8	95.9	154.2	108.4
5, 6, 8 (**31**)	159.9	106.9	176.3	144.9	139.9	118.5	149.0	138.4	103.3
5, 7, 8 (**32**)	159.2	108.0	175.5	150.8	93.9	156.1	130.0	155.3	107.4
5, 6, 7 (**33**)	159.9	107.2	175.2	153.5	139.6	157.2	96.7	151.2	111.8
2′/5, 6, 8 (**34**)	158.2	111.2	176.4	144.7	139.0	118.9	148.6	139.0	104.3
2′/5, 7, 8 (**35**)	157.3	112.3	175.2	150.8	93.9	155.7	129.9	155.1	107.9
2′/5, 6, 7 (**36**)	157.9	111.4	175.4	151.0	139.4	153.6	96.7	157.0	111.4
5, 2′/6, 8 (**37**)	161.6	108.4	183.0	141.1	139.2	116.8	141.7	139.2	107.5
5, 2′/7, 8 (**38**)	161.2	108.6	181.8	148.6	95.4	157.9	127.8	156.1	103.6
5, 2′/6, 7 (**39**)	161.5	108.6	182.3	151.8	132.9	158.6	91.5	151.8	105.0
5, 7, 8, 4′ (**40**)	162.1	106.7	175.8	151.4	95.1	156.6	130.8	155.3	—
5, 7, 8, 2′ (**41**)	157.7	112.4	175.9	151.9	94.2	156.2	130.2	155.4	108.1
5, 6, 7, 4′ (**42**)	161.6	105.8	175.4	153.6	139.5	157.1	96.7	151.2	111.8

Position of OMe or OH	1′	2′	3′	4′	5′	6′	OCH_3
5, 7, 4′ (**25**)	122.8	127.2	114.2	161.5	114.2	127.2	55.8 55.5 55.1
2′/5, 6 (**26**)	117.9	156.0	116.6	131.7	119.1	127.9	56.3
7, 8 (**27**)	131.0	125.7	128.7	131.0	128.7	125.7	60.8(8) 55.8(7)
2/3, 5, 6[a] (**28**)							60.7 56.7 56.4 31.8[b]
2/3, 4, 6[a] (**29**)							60.6 56.1 32.0[b]
2/4, 5, 6[a] (**30**)							60.8 60.3 55.9 31.5[b]
5, 6, 8 (**31**)	130.8	125.6	128.8	131.2	128.8	125.6	60.5(5) 56.6(6, 8)
5, 7, 8 (**32**)	130.0	125.4	128.7	130.9	128.7	125.4	60.6(8) 56.1(5, 7)
5, 6, 7 (**33**)	130.9	125.4	128.4	130.9	128.4	125.4	61.3(5) 60.6(6) 56.1(7)
2′/5, 6, 8 (**34**)	117.5	156.0	116.6	131.7	118.9	127.8	60.6(5) 56.7(8) 55.7(6)
2′/5, 7, 8 (**35**)	118.9	155.7	116.5	131.7	118.9	127.8	60.3(8) 55.9(5, 7)
2′/5, 6, 7 (**36**)	117.3	156.0	116.6	131.6	118.8	127.8	61.3(5) 60.5(6) 55.9(7)
5, 2′/6, 8 (**37**)	119.2	156.4	116.8	132.4	119.2	128.0	57.2(8) 56.8(6)
5, 2′/7, 8 (**38**)	117.1	156.4	116.7	132.3	119.1	128.7	60.6(8) 56.1(7)
5, 2′/6, 7 (**39**)	119.4	156.7	116.9	131.6	119.4	128.4	59.9(6) 56.3(7)
5, 7, 8, 4′ (**40**)	123.7	127.7	114.9	159.9	114.9	127.7	61.2(8) 56.8(7) 55.1(5, 4′)
5, 7, 8, 2′ (**41**)	120.2	157.3	112.2	132.1	120.6	128.4	60.7(8) 56.2(7) 55.7(5)
5, 6, 7, 4′ (**42**)	122.8	127.3	114.2	160.2	114.2	127.3	61.4 60.6(5, 6) 56.2 55.7(7, 4′)

[a] The numbering system of acetophenones corresponds to that of flavones.
[b] $CO\underline{C}H_3$.

sider OMe attached to C-5 of **3**, and the third is to consider OMe removed from C-8 of 5,6,8-trimethoxyflavone (**31**). The values obtained by these three methods were similar, and agreed with those observed. The shifts for skeletal carbons of 7,8-dimethoxyflavone (**27**) were similarly calculated from **4**, **5**, and **32**. On the other hand, those for the 5,7-dimethoxyflavone derivative (**25**) can be calculated directly without using the *o* value, because methoxyl group are present in *meta* position. The carbon shifts of 5,8- and 6,7-dimethoxyflavones were not measured in this experiment but can probably be calculated in a similar way.

Trisubstituted Flavones in Ring A

It is difficult to distinguish clearly the substitution patterns of trisubstituted flavones in ring A by means of proton magnetic resonance (PMR)[8,9] or other spectral data. Discrimination between 5,6,7- and 5,7,8-trioxygenated flavones has been reported in a few papers dealing with mass spectra[10] and NOE of PMR,[11] but 5,6,8-trioxygenated flavone has not been distinguished from the former two. It was found that these flavones have characteristic signal patterns in ^{13}C-NMR spectra, which may be used to distinguish these species. In order to assign skeletal carbons of trimethoxyflavones, the carbons of acetophenones, *i. e.*, 2-OH-3,5,6-$(OCH_3)_3$-(**28**),[8] 2-OH-3,4,6-$(OCH_3)_3$- (**29**), and 2-OH-4,5,6-$(OCH_3)_3$- (**30**) acetophenone were examined. The signal pattern of 5,6,8-trimethoxyflavone (**31**) was entirely different from those of 5,7,8- (**32**) and 5,6,7- (**33**) trimethoxyflavones, and the differences of **32** and **33** were very clear. Therefore, it seems possible to distinguish these flavones from ^{13}C-NMR spectral data. Furthermore, the chemical shifts of methoxyl groups are indicative of structure. The carbon shifts of methoxyl groups usually appear between 55.0 and 56.6 ppm, but when another OMe is in the *ortho*-position, they are observed further downfield, between 59.5 and 63.6 ppm. The present experiment showed that the carbon shifts of methoxyl groups appeared at 60.5 (C-5) and 56.6 (C-6,8) ppm in **31**, 60.6 (C-8) and 56.1 (C-5,7) ppm in **32**, and at 61.3 (C-5), 60.6 (C-6) and 56.7 (C-7) ppm in **33**. They are characteristic of the substitution positions of methoxyl groups.

Thus, **31**, **32**, and **33** were distinguished not only by the chemical shifts of skeletal carbons but also by those of the methoxy carbons. In the case of skullcapflavone I and related flavones[8] (**34**—**39**), all carbon shifts were characteristic of their structures. The carbon signals of the trimethoxyflavones (**40**, **41**, and **42**), which have different substitution patterns in ring B, can be easily assigned by comparison with those of the flavones mentioned above.

Tetrasubstituted Flavones in Ring A

The carbon shifts of a flavone fully substituted in ring A may be calculated by assuming that another OMe is attached to C-7 in **31**, to C-6 in **32**, or to C-8 in **33** (Table VI). In the case of flavones isolated from the peels of *Citrus reticulata*.[12] tangeritin (**44**), nobiletin (**45**), 5-de-

Table VI. ^{13}C-NMR Chemical Shifts of the 5,6,7,8-Tetrasubstituten Flavones

Position of OMe or OH		2	3	4	5	6	7	8	9	10
5, 6, 7, 8	(**43**)	160.3	107.3	175.6	143.7 (144.6)	137.5 (139.6)	150.2 (151.7)	137.5 (136.9)	147.0 (145.7)	113.2 (111.8)
5, 6, 7, 8, 4′	(**44**)	162.3	106.4	175.8	143.8	138.0	151.1	138.0	147.7	115.0
5, 6, 7, 8, 3′, 4′	(**45**)	160.7	106.8	176.2	144.0	138.1	151.4	138.1	148.0	114.7
5/6, 7, 8, 4′	(**46**)	163.6	106.0	182.1	144.9	135.8	152.1	132.5	148.1	114.6
5/6, 7, 8, 3′, 4′	(**47**)	163.2	105.9	182.0	144.7	135.6	152.0	132.3	148.2	114.6

Position of OMe or OH		1′	2′	3′	4′	5′	6′	OCH_3
5, 6, 7, 8	(**43**)	130.9	125.6	128.7	130.9	128.7	125.6	61.4(5, 6, 7, 8)
5, 6, 7, 8, 4′	(**44**)	123.6	128.0	115.0	160.7	115.0	128.0	62.0 61.8(5, 6, 7, 8) 55.8(4′)
5, 6, 7, 8, 3′, 4′	(**45**)	119.8	109.7	149.5	152.3	112.5	123.7	62.3 61.9(5, 6, 7, 8) 56.3(3′, 4′)
5/6, 7, 8, 4′	(**46**)	122.7	128.0	114.6	162.4	114.6	128.0	61.1 60.2(6, 7, 8) 55.3(4′)
5/6, 7, 8, 3′, 4′	(**47**)	119.8	109.3	148.9	152.0	111.9	122.5	61.4 60.2(6, 7, 8) 55.5(3′, 4′)

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methyltangeritin (**46**), 5-demethylnobiletin (**47**), the signal patterns of ring A carbons were similar to those of **43**. On the other hand, carbon shifts relating to ring B were comparable with those of **8** or **19**. In the case of 5-demethylflavones such as **23**, **24**, **46**, and **47**, the carbon

Table VII. ^{13}C-NMR Chemical Shifts of Flavones Containing a Methyl Group in Ring A

		2	3	4	5	6	7	8	9	10
6-Me	(**48**)	162.4	106.5	176.8	117.6 (116.2)	134.8 (133.1)	123.8 (124.1)	117.6 (115.4)	153.6 (152.5)	122.7 (124.5)
7-Me	(**49**)	162.4	107.3	176.9	118.0 (115.4)	126.9 (124.6)	145.2 (142.6)	118.0 (116.2)	156.1 (155.5)	121.5 (126.6)
6-Me-7-OMe	(**50**)	162.5	107.3	176.4	125.7 (126.5)	125.3 (123.2)	162.5 (163.2)	99.3 (100.5)	156.5 (154.2)	117.0 (116.7)
8-Me-7-OMe	(**51**)	162.4	106.5	176.9	123.6 (122.9)	113.8 (113.9)	161.4 (163.2)	109.6 (109.8)	154.8 (157.8)	117.6 (116.7)

		1′	2′	3′	4′	5′	6′	OCH_3	CH_3
6-Me	(**48**)	131.2	125.8	128.7	131.2	128.7	125.8		20.1
7-Me	(**49**)	131.7	126.4	129.2	131.7	129.2	126.4		22.4
6-Me-7-OMe	(**50**)	131.6	126.4	129.2	131.8	129.2	126.4	56.4	15.6
8-Me-7-OMe	(**51**)	131.4	126.2	129.2	131.9	129.2	126.2	56.4	8.1

Table VIII. ^{13}C-NMR Chemical Shifts of Polysubstituted Flavones

Position of OMe or OH		2	3	4	5	6	7	8	9	10
4′/5, 6, 7, 8	(**52**)	161.4	106.0	176.3	144.1	138.4	151.4	138.4	148.1	116.7
5, 7,4′/6, 8, 3′	(**53**)	163.1	102.7	182.0	145.1	131.3	150.5	127.7	148.1	115.7
5, 6, 7, 8, 2′, 6′	(**54**)	162.1	114.0	175.2	143.2	137.3	150.7	137.3	147.3	114.4
2′/5, 6, 7, 8, 6′	(**55**)	162.0	114.4	175.5	143.2	137.4	150.7	137.4	147.3	114.4
5, 2′/6, 7, 8, 6′	(**56**)	162.1	111.7	182.2	146.0	135.5	152.2	132.2	148.2	118.9
5, 6, 2′/7, 8, 6′	(**57**)	161.8	111.3	182.2	142.9	133.9	147.9	133.9	147.9	118.8
2′/5, 3′, 4′, 5′, 6′	(**58**)	157.9	114.9	176.0	144.4	138.4	151.7	138.4	148.2	114.9
5, 6, 7, 8, 2′, 3′, 4′, 5′, 6′	(**59**)	157.9	114.9	176.0	144.4	138.4	151.7	138.4	148.2	114.9
5/3, 6, 7, 3′, 4′	(**60**)	148.2	137.6	177.9	151.2	131.3	154.9	91.0	158.2	111.5
5, 3′/3, 6, 7, 4′	(**61**)	146.0	137.6	177.9	151.4	131.2	155.1	90.8	158.2	111.4

Position of OMe or OH		1′	2′	3′	4′	5′	6′	OCH_3
4′/5, 6, 7, 8	(**52**)	122.0	128.5	114.9	161.4	114.9	128.5	62.4(5, 6, 7, 8)
5, 7, 4′/6, 8,3′	(**53**)	121.4	109.7	150.5	147.8	115.7	119.9	61.0 59.8(6, 8) 56.0(3′)
5, 6, 7, 8, 2′, 6′	(**54**)	110.0	157.8	104.1	132.3	104.1	157.8	61.5 61.3(5, 6, 7, 8) 55.7(2′, 6′)
2′/5, 6, 7, 8, 6′	(**55**)	108.6 (103.1)	156.4 (153.4)	106.1 (107.2)	131.8 (131.3)	102.1 (105.3)	158.2 (158.5)	61.4(5, 6, 7, 8) 55.7(6′)
5, 2′/6, 7, 8, 6′	(**56**)	108.6	156.4	106.1	132.2	101.9	158.1	61.4(7, 8) 60.2(6) 55.8(6′)
5, 6, 2′/7, 8, 6′	(**57**)	108.6	156.4	106.1	132.2	102.1	158.1	61.5 60.7(7, 8) 55.7(6′)
2′/5, 3′, 4′, 5′, 6′	(**58**)	116.9	143.4	147.8	150.3	146.8	143.4	61.8 61.5(5, 4′, 5′, 6) 55.7(3′)
5, 6, 7, 8, 2′, 3′, 4′, 5′, 6′	(**59**)	116.9	143.4	147.8	150.3	146.8	143.4	62.2 61.6
5/3, 6, 7, 3′, 4	(**60**)	121.6	105.3	148.2	151.2	111.5	121.6	59.5(6) 55.9 55.4
5, 3′/3, 6, 7, 4′	(**61**)	122.0	105.3	146.0	149.9	114.7	120.1	59.7(6) 56.0 55.4

at C-4 shifts downfield (+6.5 ppm) while the carbon at C-8 shifts upfield (−5.5 ppm), since there is a hydrogen bond between OH (C-5) and CO (C-4).

Flavones with Methyl Group in Ring A

The carbon shifts of flavones such as **48**, **49**, **50**, and **51** were assigned by calculation, using the α value and SCS of OMe and Me (Table VII). In the case of **50** and **51**, methyl and methoxyl groups are adjacent to each other, and it is necessary to take the *o* value into consideration. The great difference in the chemical shifts of methyl carbon in **50** and **51** will give useful information in connection with the Wassely-Moser rearrangement, C-glycosides (vitexin and isovitexin), and biflavones (cupressflavone, agatisflavone, and amentoflavone).

The flavones **52** and **53** were newly isolated from the peels of *Citrus reticulata*.[12] The substitution pattern of **52**, with four methoxyl groups and one hydroxyl group, was similar to that of tangeritin as regards the PMR data. The signal patterns of skeletal carbons were also similar to those of tangeritin (Table VIII), but the position of the hydroxyl group was not clear from the other spectral data. On the other hand, the signal of OMe carbons was at 62.4 ppm (tangeritin: 62.0, 61.8, and 55.8 ppm). This showed that isolated methoxyl groups were not present in this flavone and therefore that the hydroxyl group must be located at C-4′. Thus, the structure of **52** was concluded to be 4′-hydroxy-5,6,7,8-tetramethoxyflavone. The substitution pattern of ring B in **53** was thought to be similar to that of **21** by comparison with **19**—**24**, and two hydroxyl groups should be located at C-5 and C-7 in ring A in view of the chemical shifts of C-5 carbon (+6.6 ppm) and C-8 carbon (−11.0 ppm). Further consideration of the shifts of OMe (61.0, 59.8, and 56.0 ppm) indicated **53** to be sudachitin(5,7,4′-trihydroxy-6,8,3′-trimethoxyflavone).[13] In the case of the permethylether of skullcapflavone II[8] (**56**), the skeletal carbons were easily assigned by comparison with **43** and **12**, except that the signal of C-3 was shifted downfield by 8 ppm because of the effect of OMe at C-2′ and C-6′. In the case of **55**, the carbon shifts of ring B were assigned on the basis of the β value and SCS of OH and OMe. The flavone[8] **57** was a by-product obtained from **55** during demethylation. The ^{13}C-NMR data showed **57** to be demethylated at C-6, *i. e.*, 5,6,2′-trihydroxy-7,8,6′-trimethoxyflavone. The flavone[8] **58** was an abnormal product formed during the dehydrative cyclization of 2′-benzyloxy-2-hydroxy-3,4,5,6,6′-pentamethoxydibenzoylmethane in the presence of conc. H_2SO_4. The signal pattern of ring A was very similar to that of 5-methoxyflavone (**2**), and the substitution pattern of ring B was confirmed to be 2-OH-3′,4′,5′,6′-$(OCH_3)_4$ based on the extensive additivity rule described above. Therefore, **58** was concluded to be 2′-hydroxy-5,3′,4′,5′,6′-pentamethoxyflavone. The flavone **59** was fully substituted by methoxyl groups in all positions except C-3. Their skeletal carbons were assigned by comparison with **43** and **18**. The carbon signals of methoxyl groups appeared at 62.2 and 61.6 ppm because of the effects of adjacent positions.

In the case of polysubstituted flavonols (**60** and **61**) isolated from the seeds of *Vitex trifolia*, all the carbon signals corresponded to those of flavones except for C-2 (148.2 or 146 ppm) and C-3 (137.6 ppm). It thus appears that the extensive additivity rule mentioned above can also be applied to flavonols.

Experimental

^{13}C-NMR spectra were recorded on a JEOL FX-60 Fourier transform spectrometer operating at 21.15 MHz (spectral width 4000 Hz, 4096 data points). Dimethyl sulfoxide was used as a solvent. The deuterium signal of D_2O was used as the lock signal.

The melting points (uncorrected) of flavones used for measurement were as follows: **1**, mp 98—99°; **2**, mp 125—127°; **3**, mp 162—164°; **4**, mp 99—101°; **5**, mp 200—202°; **6**, mp 102—103°; **7**, mp 128—130°; **8**, mp 158—159°; **9**, mp 80—83°; **10**, mp 93—94°; **11**, mp 108—110°; **12**, mp 147—148°; **13**, mp 135—136°; **14**, mp 90—91°; **15**, mp 153—155°; **16**, mp 174—176°; **17**, mp 132—133°; **18**, mp 97—98°; **19**, mp 176—177°;

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13) T. Horie, M. Masumura, and S. Okumura, *Nippon Kagaku Zasshi*, **83**, 465 (1962).

20, mp 175°; **21**, mp 205—206°; **22**, mp 251—252°; **23**, mp 196—198°; **24**, mp 279°; **25**, mp 156—158°; **26**, mp 255—256°; **27**, mp 146—149°; **28**, mp 45—47°; **29**, mp 111—113°; **30**, mp 143°; **31**, mp 155—157°; **32**, mp 166—168°; **33**, mp 166—167°; **34**, mp 239—241°; **35**, mp 276—279°; **36**, mp 241—245°; **37**, mp 250°; **38**, mp 255—256°; **39**, mp 255°; **40**, mp 211—212°; **41**, mp 140—141°; **42**, mp 158°; **43**, mp 110—111°; **44**, mp 153—154°; **45**, mp 138°; **46**, mp 176—178°; **47**, mp 143—145°; **48**, mp 118—120°; **49**, mp 121—122°; **50**, mp 152—154°; **51**, mp 97—99°; **52**, mp 196—198°; **53**, mp 210—212°; **54**, mp 98—99°; **55**, mp 175—177°; **56**, mp 178—179°; **57**, mp 223—226°; **58**, mp 148—151°; **59**, mp 115—116°; **60**, mp 161—162°; **61**, mp 169—170°.

Synthesis of 2′,3′,5′,6′-Tetramethoxyflavone (**17**)——After metalation of 1,2,4,5-tetramethoxybenzene with n-BuLi, treatment with solid CO_2 gave 2,3,5,6-tetramethoxybenzoic acid (**62**), mp 135—137°. Condensation of **62** with 2-hydroxyacetophenone, and subsequent Baker-Venkataraman rearrangement and dehydrative cyclization in the presence of conc. H_2SO_4 afforded **17** as colorless needles. PMR ($CDCl_3$) δ: 3.79, 3.92 (12H, each s, $2\times2\times OCH_3$), 6.46 (1H, s, H-3), 6.71 (1H, s, H-4′), 7.29—7.85 (3H, m, H-6,7,8), 8.20—8.38 (1H, m, H-5).

Synthesis of 2′,3′,4′,5′,6′-Pentamethoxyflavone (**18**)——After methylation of 2-hydroxy-3,4,5,6-tetramethoxyacetophenone, obtained from nobiletin (**45**) by alkaline degradation, the haloform reaction[14] afforded 2,3,4,5,6-pentamethoxybenzoic acid (**63**), mp 89—90°. The procedures described above, using **63** and 2-hydroxyacetophenone as starting materials, gave **18** as colorless needles. PMR ($CDCl_3$) δ: 3.83 (6H, s, $2\times OCH_3$), 3.89 (6H, s, $2\times OCH_3$), 3.99 (3H, s, OCH_3), 7.37—7.42 (2H, m, H-6,7), 7.64 (1H, dd, $J=5.8$, 2.0 Hz, H-8), 8.28 (1H, dd, $J=5.8$, 2.0 Hz, H-5).

Synthesis of 5,6,7,8,2′,3′,4′,5′,6′-Nonamethoxyflavone (**59**)——Condensation of 2-hydroxy-3,4,5,6-tetramethoxyacetophenone with **63** gave 2-(2′,3′,4′,5′,6′-pentamethoxybenzoyl)-3,4,5,6-tetramethoxyacetophenone (**64**) mp 118—119°. **64** was converted into 2-hydroxy-3,4,5,6,2′,3′,4′,5′,6′-nonamethoxydibenzoylmethane (**65**), mp 116—117° by Baker–Venkataraman rearrangement. Dehydrative cyclization of **65** gave **59** as colorless prisms. PMR ($CDCl_3$) δ: 3.85 (6H, s, $2\times OCH_3$), 3.91 (9H, s, $3\times OCH_3$), 3.96 (6H, s, $2\times OCH_3$), 4.01 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 6.25 (1H, s, H-3).

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