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Mass Spectral Analysis of Some Naturally Occurring Polymethoxyflavones

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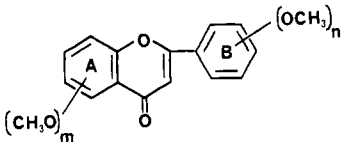
Ten polymethoxyflavones (PMFs) representative of a large class of naturally occurring compounds were prepared for mass spectral analysis. Intense peaks were observed at M^+ and $(M - CH_3)^+$, which could be used to identify and/or quantitate these or related compounds in foodstuffs or biological fluids. Characteristic peaks at m/z 167 and 139 were observed for certain 5,7,8-trimethoxy-PMFs, which may be of diagnostic value for structural recognition.

Flavones 1 containing one or more methoxy groups in



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rings A and B occur throughout nature (Venkataraman, 1975) and most frequently in a wide variety of citrus species (Horowitz and Gentili, 1977). The prominence of these compounds in citrus has resulted in several reports describing their separation and quantitation by high-performance liquid chromatography (HPLC) (Bianchini and Gaydou, 1983; Ting et al., 1979) and by HPLC coupled with combined UV and fluorescence detection (Rouseff and Ting, 1979). The analytical profile of polymethoxyflavones (PMFs) is sufficiently characteristic to allow the determination of one type of citrus juice in the presence of another (Ting et al., 1979).

The biochemical role of PMFs in plants is largely unknown; but in the case of nobiletin, the material appeared to function as a natural fungicide (Ben-Aziz, 1967). Citrus PMFs also produce physiological activities in animals (Robbins, 1980), namely, by reducing blood viscosity (Robbins, 1976) and by their ability to indirectly detoxify certain polycyclic carcinogens (Wattenberg et al., 1968). The reported biological effects suggested that dietary flavones may play an important role toward alleviating cancer and/or degenerative diseases in man.

In this report we describe the preparation and mass spectral (MS) analysis of 10 representative PMFs, several of which occur naturally in citrus and other plants. The purpose of the work was to provide more detailed MS data for future identification and/or quantitation of PMFs and to test the generality of the currently accepted MS fragmentation mechanism of flavones, summarized earlier by Kingston (1971).

The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45247.

Table I. Physical Properties of 2'-Hydroxychalcones

compound[a]	methoxy substituents	% yield	mp, °C	lit. mp, °C	TLC R_f
2a	3,3',4,4',5',6'	100	oil	116-117[b]	0.41[f]
2b	3,3',4,4'5,6'	34	170.5-172	169-170[c]	0.17
2c	2,3',4,4',6,6'	83	152.5-153.5	154[d]	0.14
2d	2,3,3',4,4',6'	68	164-166		0.21
2f	2,3,4,4',6'	34	134-135.5		0.39
2g	3,3',4,4',6'	84	141-142.5	146-148[c]	0.13
2h	3,4,4',6'	49	154-156	151[e]	0.33
2i	3',4,4',6'	89	138-140	144-145[c]	0.26

[a] Letters correspond to chalcones that were converted to flavones, 3a-i. Chalcone 2e corresponding to tangeretin was not synthesized. [b] Sastry and Row (1961). [c] Sherif et al. (1981). [d] Cummins et al. (1963). [e] Reidel et al. (1942). [f] Silica gel G plates; solvent was methyl *tert*-butyl ether.

Table II. Physical Properties of Polymethoxyflavones

structure no.	methoxy substituents	% yield	mp, °C	lit. mp, °C	TLC R_f
3a	5,6,7,8,3',4'	47	135-136	134[a]	0.78[e]
3b	5,7,8,3',4',5'	79	184.5-186.5	–[b]	0.82
3c	5,7,8,2',4',6'	32	246-247	–	0.82
3d	5,7,8,2',3',4'	46	178.5-181.5	180-182[c]	0.80
3e	5,6,7,8,4'		147-149.5	154[a]	0.82
3f	5,7,2',3',4'	32	156-159.5	–	0.84
3g	5,7,8,3',4'	51	194-195	197-198[a]	0.72
3h	5,7,3',4'	50	191-193	190-191[d]	0.84
3i	5,7,8,4'	65	206-210	211-213[a]	0.67
3j	7,3',4',5'	38	190-192	190-191[d]	0.87

[a] Horowitz and Gentili (1977). [b] mp not cited (DeSilva et al., 1980). [c] Govindachari et al. (1968). [d] Banerji and Goomer (1980). [e] Silica gel G plates; solvent was chloroform-methanol-water, 65:25:4.

EXPERIMENTAL SECTION

Materials. Tangeretin was purchased from the George F. Uhe Co. and recrystallized from ethanol before use; 3,4,5-trimethoxybenzoyl chloride, phloroacetophenone,

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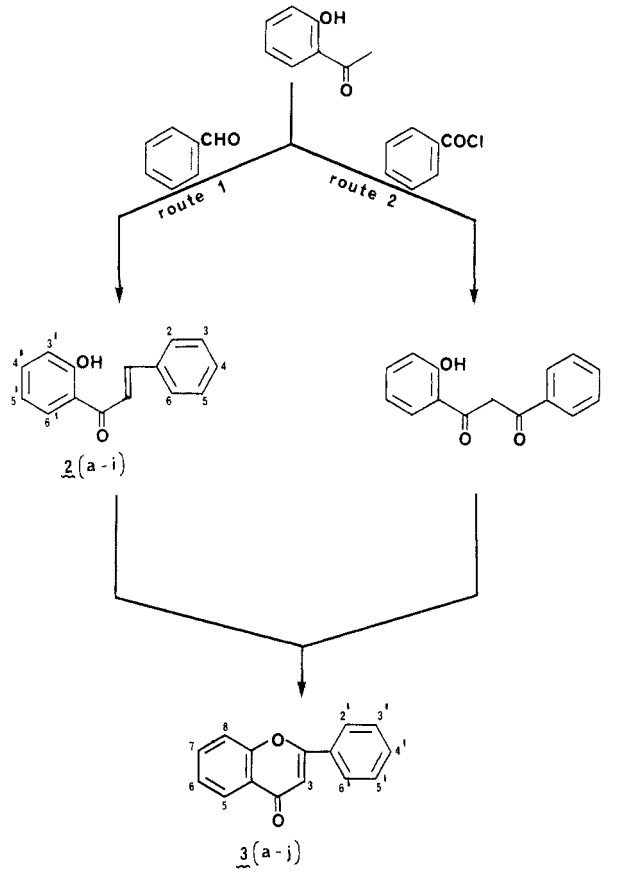

Figure 1. Synthetic routes to flavones. For clarity, methoxy groups are not shown.

2′-hydroxy-4′-methoxyacetophenone, 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, and 2,4,6-, 2,3,4-, and 3,4,5-trimethoxybenzaldehydes were purchased from Aldrich Chemical Co. and used as received; 4′,6′-dimethoxy-2′-hydroxyacetophenone; 2′-hydroxy-3′,4′,6′-trimethoxy- and 2′-hydroxy-3′,4′,5′,6′-tetramethoxyacetophenones were prepared according to literature procedures [Dave et al. (1960), Baker (1941), and Burnham et al. (1972), respectively].

Synthetic Procedures. Synthetic PMFs were prepared according to routes outlined in Figure 1. In route 1 appropriate methoxybenzaldehydes were reacted with 2′-hydroxymethoxyacetophenones to yield chalcones **2a–i** (Table I), which were subsequently oxidized with selenium dioxide to obtain the requisite PMFs **3a–i** (Swift, 1971) (Table II). Flavone **3j** was prepared via the Baker-Venkataraman reaction (route 2) starting with 3,4,5-trimethoxybenzoyl chloride and 2′-hydroxy-4′-methoxyacetophenone (Wagner and Farkas, 1975). Examples of routes 1 and 2 used to prepare chalcones and flavones are given below. Proton magnetic resonance (^{1}H NMR) spectra were obtained to corroborate the structures of the flavones (Table III).

2′-Hydroxy-2,3,3′,4,4′,6′-hexamethoxychalcone (**2d**). A mixture containing 2,3,4-trimethoxybenzaldehyde (5.15 g, 0.0262 mol), 2′-hydroxy-3′,4′,6′-trimethoxyacetophenone (3.96 g, 0.0175 mol), and ethanol (50 mL) was stirred at ca. 24 °C and treated with 50 mL of saturated, aqueous NaOH solution in an argon atmosphere. After 18.5 h ethanol was removed in vacuo and the residue was dissolved in water (300 mL). The aqueous phase was extracted with ether (150 mL) to remove unreacted aldehyde and saturated with gaseous CO_2 to precipitate the chalcone. The crude product was filtered off, washed with ice–water, and dried in a vacuum desiccator. Recrystallization from

Table III. Proton NMR Data of Polymethoxyflavones

structure no.	ring protons[a]							methoxy groups[b]
	H-3	H-5	H-6	H-8	H-2′	H-3′	H-5′	H-6′	
3a	6.67 s				7.92 d (8)	7.05 d (8)	7.05 d (8)	7.92 d (8)	3.93, 4.05, 4.08, 4.15
3b	6.67 s		6.47 s		7.20 s			7.20 s	3.93, 3.98, 4.02, 4.03
3c	6.40 s		6.22 s			6.17 s	6.17 s		3.80, 3.87, 3.98
3d	6.87 s		6.43 s				6.77 d (8)	7.60 d (8)	3.97, 4.00, 4.02
3e	6.67 s				7.92 d (8)	7.05 d (8)	7.05 d (8)	7.92 d (8)	3.93, 4.05, 4.08, 4.15
3f	6.83 s		6.37 d (2)	6.50 d (2)			6.80 d (9)	7.50 d (9)	3.93, 3.97
3g	6.58 s		6.42 s		7.53 dd (2, 9)		6.93 d (9)	7.37 d (2)	3.97, 4.00
3h	6.62 s		6.40 d (2)	6.60 d (2)	7.33 d (2)		6.97 d (8)	7.53 dd (2, 8)	3.95, 4.03
3i	6.60 s		6.47 s		7.90 d (9)	7.03 d (9)	7.03 d (9)	7.90 d (9)	3.90, 4.00, 4.03
3j	6.67 s	8.10 d (10)	7.15 dd (2, 10)	6.93 d (2)	7.08 s			7.08 s	3.93, 3.97

[a] Chemical shifts in parts per million downfield from $(CH_3)_4Si$; $CDCl_3$ solvent; multiplicity indicated by s = singlet, d = doublet, dd = doublet of doublets, etc.; coupling constants J (hertz) given in parentheses; all peak assignments agreed with area integrals; not all CH_3Os were resolved. [b] All singlets.

methanol gave 4.84 g (68% yield) of **2d** as orange-gold crystals: mp 164–166°C; ^{1}H NMR δ 3.85, 3.90, and 3.97 (18 H, s, 6 × OCH_3), 6.00 (1 H, s, H-5′), 6.68 (1 H, d, J = 8 Hz, H-5), 7.30 (1 H, d, J = 8 Hz, H-6), 7.90 (2 H, s, Hα and Hβ), and 14.00 (1 H, s, 2′-OH). Calcd for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 61.98; H, 5.97.

2′-Hydroxy-2,3,4,4′,6′-pentamethoxychalcone (**2f**). This compound was prepared in a manner analogous to **2d** starting with 2,3,4-trimethoxybenzaldehyde (2.94 g, 0.015 mol) and 4′,6′-dimethoxy-2′-hydroxyacetophenone (1.96 g, 0.010 mol). Recrystallization of the crude product from ethanol gave 1.29 g of yellow crystals (34% yield): mp 134–135.5 °C; ^{1}H NMR δ 3.83, 3.97, and 3.93 (15 H, s, 5 × OCH_3), 5.95 (1 H, d, J = 2 Hz, 5′-H), 6.10 (1 H, d. J = 2 Hz, H-3′), 6.68 (1 H, d, J = 9 Hz, H-5), 7.33 (1 H, d, J = 9 Hz, H-6), 7.93 (2 H, s, Hα and Hβ), and 14.43 (1 H, s, 2′-OH). Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.26; H, 5.99.

5,7,8,2′,3′,4′-Hexamethoxyflavone (**3d**). A mixture of **2d** (4.59 g, 0.0114 mol), SeO_2 (5.68 g, 0.0512 mol) and *n*-pentanol (55 mL) was stirred and heated under reflux for 18 h. The cooled mixture was diluted with chloroform (ca. 100 mL), filtered to remove selenium, and concentrated in vacuo to remove solvents. Recrystallization of the residue from ethyl acetate gave 2.10 g of **3d** (46% yield), mp 170–174 °C. A second recrystallization from the same solvent gave the analytically pure flavone as pale yellow crystals, mp 178.5–181.5 °C (^{1}H NMR, Table III). Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51. Found: C, 62.67; H, 5.81.

7,3′,4′,5′-Tetramethoxyflavone (**3j**). A solution containing 2′-hydroxy-4′-methoxyacetophenone (1.00 g, 0.0060 mol) in acetone (20 mL) was treated sequentially with anhydrous K_2CO_3 (4.0 g) and 3,4,5-trimethoxybenzoyl chloride (1.57 g, 0.0068 mol). The mixture was stirred and most of the acetone was removed by slow distillation during 64 h. Water was added and the β-diketone product was extracted with ethyl acetate. Crude β-diketone (1.51 g of yellow solid obtained on evaporation of ethyl acetate) was dissolved in benzene (50 mL), treated with 0.80 g of *p*-toluene sulfonic acid, and distilled to azeotropically remove water (ca. 4 h). When the volume of benzene reached 20 mL, distillation was interrupted and the mixture was refluxed another 16.5 h. Benzene was replaced by ethyl acetate (200 mL), and after being cooled to 0 °C and washed with 10% aqueous NaOH and saturated brine, the solution was dried (Na_2SO_4) and evaporated to obtain 0.782 g of **3j** (38% yield). Recrystallization from ethyl acetate gave colorless needles, mp 190–192 °C (^{1}H NMR, Table III).

Analytical Procedures. Mass spectra were determined via electron impact at 70 eV with a Hewlett-Packard Model 5985B instrument, source temperature, 200 °C. The probe temperature was programmed as follows: 24–150 °C (ballistically), 150 °C (1 min), and 150–325 °C at 25 °C/min.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained at 60 MHz by using a Varian T-60 spectrometer. Compounds were analyzed in chloroform-*d* containing 1% tetramethylsilane as the internal reference standard. Chemical shift assignments were made in view of accepted generalizations (Markham and Mabry, 1975) and by interrelating spectral data of known and previously unreported compounds (Table III).

Thin-layer chromatography (TLC) was done on 5 × 20 cm Merck precoated silica gel 60 (F-254) plates with 0.25 mm layer thickness. Solvent systems used were methyl *tert*-butyl ether for chalcones and 65:25:4 chloroform–methanol–water, v/v/v, for flavones. Visualization of spots was either by iodine vapor or ultraviolet light.

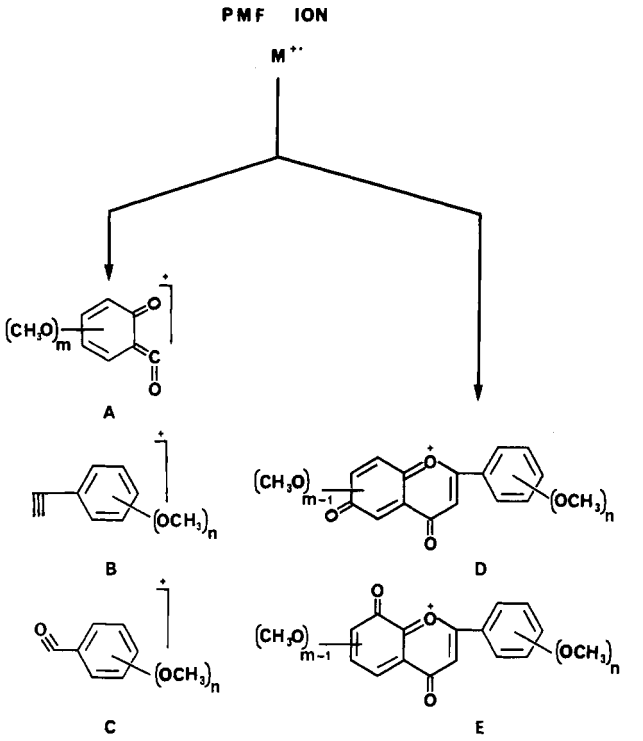

Figure 2. Mass spectral fragmentation of polymethoxyflavones.

Melting points were determined on a Fisher-Johns hot-stage apparatus and were not corrected.

Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

RESULTS AND DISCUSSION

Electron impact mass spectrometry (EIMS) has been used extensively in structural studies of flavonoids and related plant phenolics (Mabry and Ulubelen, 1980; Mabry and Markham, 1975). The primary fragmentation pathways for aglyconic flavones during EIMS are shown in Figure 2. The flavone molecular ion M^+ can split into charged species A, B, or C via pyrone ring fragmentations. The splitting of M^+ into A and B is believed to occur by a retro Diels-Alder (RDA) reaction. Further loss of smaller molecular fragments from M, A, B, and C gives rise to frequently observed daughter decay products whose structures have been verified by high-resolution MS (Kingston, 1971). Methoxyflavones with substituents at C-6 or C-8 are especially prone to loss of methyl leading to stable quinoid ions D and E, $(M - CH_3)^+$.

EIMS data for compounds **3a–j** are shown in Tables IV and V. Table IV lists the five most intense ions observed for each compound while Table V presents the analysis of each mass spectrum in terms of prevalent parent–daughter decay ions found in the spectra of 24 related flavones (Kingston, 1971).

Intense molecular ions (M^+) were observed for PMFs with one to three A-ring methoxy groups [56–100% of base peak (BP)], e.g., **3b–d** and **3f–j**. However, compounds with completely substituted A-rings like nobiletin **3a** and tangeritin **3e** gave relatively weak molecular ions, 22 and 17% of BP, respectively.

$(M - 1)^+$ peaks were usually weak (0–15% BP) except for the two 5,7-dimethoxyflavones **3f** and **3h** (66 and 67% BP, respectively).

All flavones with methoxy groups at C-6 or C-8 exhibited intense $(M - CH_3)^+$ peaks, and as expected, compounds lacking these substituents, i.e., **3f**, **3h**, and **3j**, showed less evidence for loss of methyl.

Table IV. Five Most Intense Ions in MS of Flavones

compound	M_r	mass data, m/z (intensity as % of BP)
3a	402	387 (100), 402 (22), 388 (22), 344 (19), 197 (19)
3b	402	387 (100), 402 (75), 167 (32), 358 (29), 139 (21)
3c	402	387 (100), 402 (62), 167 (52), 195 (40), 139 (26)
3d	402	387 (100), 402 (70), 167 (46), 195 (27), 139 (23)
3e	372	357 (100), 358 (22), 372 (17), 182 (17), 314 (16)
3f	372	372 (100), 371 (66), 326 (45), 151 (36), 343 (32)
3g	372	357 (100), 372 (56), 167 (35), 328 (32), 139 (25)
3h	342	342 (100), 341 (67), 296 (30), 313 (28), 325 (18)
3i	342	327 (100), 342 (84), 298 (29), 167 (24), 139 (19)
3j	342	342 (100), 327 (44), 151 (20), 157 (18), 142 (18)

Recent work (Goudard et al., 1979) suggested that the propensity for methyl loss was greater for 5,6,7,8-tetramethoxyflavones than for 5,7,8-trimethoxyflavones. In their study the $(M - CH_3)^+$ ion was the base peak in spectra of six 5,6,7,8- and 5,6,7-PMFs, suggesting highly facile loss of the C-6 methoxy methyl. Less evidence was found for C-8 methoxy methyl loss, and in three examples of 5,7,8-trimethoxy PMFs cited the M^+ ions were the base peaks (BP) in their spectra.

In our work, a facile methyl loss was observed in 5,7,8-tri- and 5,6,7,8-tetramethoxyflavones. For 5,6,7,8-tetramethoxyflavones **3a** and **3e** the $(M - CH_3)^+$ ion was the base peak with M^+ at 22 and 17% of BP, respectively. In addition, five examples of 5,7,8-trimethoxy-PMFs, **3b–d**, **3g**, and **3i**, also gave $(M - CH_3)^+$ as the base peak with M^+ ranging from 56 to 84% of BP. The enhanced loss of C-8 methoxy methyls in our work is understandable considering instrumental differences, but one is cautioned toward using MS to assign structures to unknown PMFs unless comparable positional isomers are available for calibration. Stated another way, ambiguity can exist in MS structural distinction of 5,6,7,(8)-tetramethoxy- and 5,7,8-trimethoxy-PMFs unless conditions for the loss of a methyl group from C-8 happen to be minimal.

An attempt was made to correlate the fragmentation of **3a–j** in terms of ions previously observed in the mass spectra of 24 related flavones (Table V) (Kingston, 1971). Besides M^+, $(M - 1)^+$, and $(M - CH_3)^+$ already mentioned, only a few ions were of sufficient intensity to merit diagnostic value. The $(M - CHO)^+$, $(M - CH_3O)^+$, and $(M - CH_2O_2)^+$ ions were somewhat more intense in 5,7-dimethoxyflavones, **3f** and **3h**, but the significance of this result was not immediately apparent. RDA fragmentation led to no highly stable ions as shown by relatively weak A, B, and C peaks. Secondary breakdown of RDA ions did, however, lead to more stable species, some of which had useful diagnostic value.

Two types of numerical ambiguities were noted among the RDA-breakdown ions of PMFs when the same number of substituents were present in both the A- and B-rings. For example, the nominal m/z 167 ion observed in the spectra of **3b–d** could represent $(A - CH_3CO)^+$ ($C_8H_7O_4$: 167.03429) or $(C - CO)^+$ ($C_9H_{11}O_3$: 167.070814). Also, in **3b–d** $(A - CH_3)^+$ ($C_9H_7O_5$: 195.029343) would appear to coincide with C ($C_{10}H_{11}O_4$: 195.065728) in conventional low-resolution MS. Instances where these ambiguities are possible are indicated in Table V.

All five 5,7,8-trimethoxy-PMFs displayed relatively intense and apparently unique ions at m/z 167 and 139. We propose that the appearance of these peaks in conjunction with strong M^+ and $(M - CH_3)^+$ ions could provide diagnostic evidence for identification of certain 5,7,8-trimethoxy-PMFs. Structures for m/z 167 and 139 can be postulated in view of established flavone fragmentation routes. The constancy of m/z 167 in five PMFs suggested $(A - CH_3CO)^+$, but some ambiguity with $(C - CO)^+$ exists for **3b–d**. A lesser influence of the B-ring fragment $(C - CO)^+$ on total m/z 167 ion intensity was evidenced by comparing two nonisomeric compounds with identical B-rings, i.e., **3f** vs. **3d**. In **3f** where $(C - CO)^+$ can be unambiguously

Table V. Ion Intensities in Mass Spectra of Flavones[a]

compound	M	M − 1	M − CH_3	M − OH	M − OH_2	M − OH_3	M − CO	M − CHO	M − CH_3O	M − CH_3CO	M − CH_2O_2
3a	22		100	1				3	6	6	5
3b	75	12	100	5			3	14	5	13	4
3c	62	12	100	2			3	13	7	12	4
3d	70	11	100	3			3	14	6	8	3
3e	17		100	1			2	7	3	7	5
3f	100	66	9	11	5	2	8	32	30	6	45
3g	56	15	100	5			3	15	6	21	6
3h	100	67	2	18	3		5	28	13	2	30
3i	84	10	100	4			3	16	7	16	5
3j	100		44					1		7	

compound	A + H	A	A − H	A − CH_3	A − CO	A − CH_3CO	B	B − CH_3	C	C − CO	M − CO/ 2^b
3a			1	6		19	8	5	8	3	2
3b	1	1	4	12[c]		32[d]	3	6	12	32	7
3c	3	5	6	40[c]	2	52[d]	8	4	40	52	16
3d	3	3	6	27[c]	2	46[d]	6	7	27	46	13
3e			1	5		14	9	6	7	2	4
3f	18	6	17	11	12	18	9	15	19	20	11
3g	5	4	3	12	2	35	5	5	16	9	7
3h	2			3[c]	2	6[d]	10	8	3	6	14
3i	2	1	4	11		24	11	7	12	4	18
3j	20	3	11	3	3	5	2	5	1	3	17

[a] Intensities of positive ions expressed as percent of base peak; data presented in the convention adopted by Kingston (1971). [b] Doubly charged ion. [c] Peak not distinguishable from C at low resolution. [d] Peak not distinguishable from C − CO at low resolution.

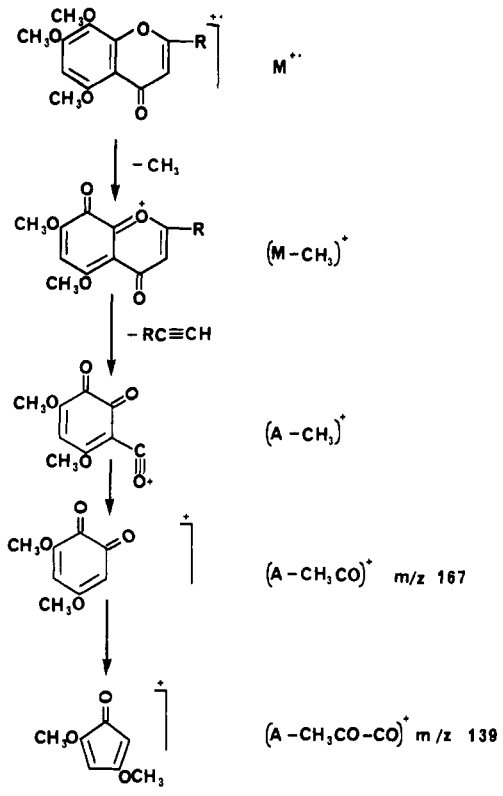

Figure 3. MS fragmentation of 5,7,8-trimethoxyflavones.

assigned, the intensity of m/z 167 (20%) is significantly lower than that observed in **3b–d**.

The common occurrence of m/z 167 and 139 ions in **3b–d**, **3g** and **3i** suggested they were related by loss of carbon monoxide (m/z 28). A possible scheme depicting the formation of ions m/z 167 and 139 during MS fragmentation of 5,7,8-trimethoxy-PMFs is shown in Figure 3. Breakdown of $(M - CH_3)^+$ ions via the RDA route can give rise to $(A - CH_3)^+$, a pathway that has been confirmed by metastable ion measurements in C-6 methoxyflavones (Kingston, 1971). Subsequent loss of CO from $(A - CH_3)^+$ can then give rise to m/z 167 and m/z 139.

The mass spectra of 10 PMFs were well explained by the generalizations of Kingston (1971). In particular, intense ions at M^+, $(M - CH_3)^+$, and sometimes $(M - 1)^+$ were observed that could be useful for structural recognition and/or quantitation.

ACKNOWLEDGMENT

We thank John Pryne for assistance in obtaining the PMF mass spectra.

Registry No. **2a**, 78417-27-3; **2b**, 78224-96-1; **2c**, 89121-56-2; **2d**, 89121-57-3; **2f**, 89121-58-4; **2g**, 63878-51-3; **2h**, 10496-67-0; **2i**, 5453-02-1; **3a**, 478-01-3; **3b**, 80324-51-2; **3c**, 89121-54-0; **3d**, 21315-69-5; **3e**, 481-53-8; **3f**, 89121-55-1; **3g**, 17290-70-9; **3h**, 855-97-0; **3i**, 6601-66-7; **3j**, 3044-57-3; 3,4,5-trimethoxybenzoyl chloride, 4521-61-3; 2′-hydroxy-4′-methoxyacetophenone, 552-41-0; 2′-hydroxy-3′,4′,6′-trimethoxyacetophenone, 7507-98-4; 2′-hydroxy-3′,4′,5′,6′-tetramethoxyacetophenone, 3162-28-5; 4-methoxybenzaldehyde, 123-11-5; 3,4-dimethoxybenzaldehyde, 120-14-9; 2,4,6-trimethoxybenzaldehyde, 830-79-5; 2,3,4-trimethoxybenzaldehyde, 2103-57-3; 3,4,5-trimethoxybenzaldehyde, 86-81-7; 4′,6′-dimethoxy-2′-hydroxyacetophenone, 90-24-4.

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