Studies of the Selective *O*-Alkylation and Dealkylation of Flavonoids. VI.[1] Demethylation of 8-Hydroxy-5,7-dimethoxyflavones with Anhydrous Aluminum Chloride or Bromide in Acetonitrile

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The demethylation of seven 8-hydroxy-5,7-dimethoxyflavones with anhydrous aluminum chloride or bromide in acetonitrile was studied and the following results were obtained. (1) Anhydrous aluminum chloride in acetonitrile selectively split the 5-methoxyl group without cleavage of the 7-methoxyl group, and seven 5,8-dihydroxy-7-methoxyflavones were quantitatively synthesized by the demethylation. (2) In the demethylation with anhydrous aluminum bromide, the 5- and 7-methoxyl groups on 4′,5,7-trimethoxy- and 3′,4′,5,7-tetramethoxy-8-hydroxyflavone were selectively split to give the corresponding 5,7,8-trihydroxyflavones in good yield. However, the demethylation was not accessible to the synthesis of 5,7,8-trihydroxy-3′,4′,5′-trimethoxyflavone, 4′,5,7,8-tetrahydroxy-3′-methoxy-, and 3′,5,7,8-tetrahydroxy-4′-methoxyflavone, because of the cleavage of the methoxyl groups on the B ring. The synthesized flavones were employed for the identification of the two natural flavones, which were proposed to be 4′,5,8-trihydroxy-7-methoxyflavone and 4′,5,8-trihydroxy-3′,7-dimethoxyflavone. The former, salvitin, was revised to 4′,5,7-trihydroxy-6-methoxyflavone and the latter seemed to be 4′,5,7-trihydroxy-3′,8-dimethoxyflavone.

In 1975, Gupta *et al.*[2] identified salvitin, isolated from *Salvia plebeia*, as 4′,5,8-trihydroxy-7-methoxyflavone (**1b**) on the basis of the spectral data and the synthesis by the two methods: the nuclear oxidation of 4′,5-dihydroxy-7-methoxyflavone and the oxidative demethylation of 4′-benzyloxy-5,7,8-trimethoxyflavone with nitric acid *via* the corresponding 5,8-quinone derivative. On the basis of the UV and MS data, Whalen *et al.*[3] claimed that one of the natural flavones which were isolated from *Solanum* section *Androceras* was 4′,5,8-trihydroxy-3′,7-dimethoxyflavone (**1d**). Recently, two natural flavones, 5,7,8-trihydroxy-4′-methoxyflavone (**2a**)[4] and 4′,5,7,8-tetrahydroxy-3′-methoxyflavone (**2d**)[3] were also isolated in the form of glycosides. A convenient method for synthesizing 5,8-dihydroxy-7-methoxyflavones (**1**) and 5,7,8-trihydroxyflavones (**2**) such as the above natural flavones seems to be the oxidative demethylation[2,5] of 5,7,8-trioxygenated flavones using nitric acid. However, little 5,8-dihydroxy-4′,7-dimethoxyflavone (**1a**) was synthesized from 4′,5,7,8-tetramethoxyflavone[6] by use of this method.

On the other hand, we had reported that 5,6-dihydroxy-7-methoxyflavones (**4**) and 5,6,7-trihydroxyflavones (**5**) were synthesized from 6-hydroxy-5,7-dimethoxyflavones (**3**) by the demethylation with anhydrous aluminum chloride in acetonitrile.[7] The results suggest that **1** and **2** may be synthesized from 8-hydroxy-5,7-dimethoxyflavones (**6**), isomers of **3**. Hence the selective demethylation of **6** with anhydrous aluminum chloride or bromide was studied, and it was found that **1a**—**g** and **2a**, **c** were synthesized from the corresponding **6** in high yield. In this paper, we report on the demethylation of **6**, the characterization of **1** and **2**, and the identification of the two natural flavones which were proposed as 5,8-dihydroxy-7-methoxyflavones (**1b** and **1d**).

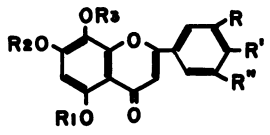
Results and Discussion

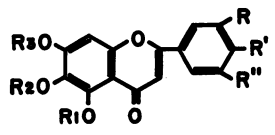
Syntheses of 8-Hydroxy-5,7-dimethoxyflavones (6). The 2-benzyloxyl group on 2,3-bis(benzyloxy)-4,6-dimethoxyacetophenone (**8**), which was easily derived from 2,3-dihydroxy-4,6-dimethoxyacetophenone (**7**),[8] was selectively split with hydrochloric acid in acetic acid to give 3-benzyloxy-2-hydroxy-4,6-dimethoxyacetophenone (**9**) in good yield. But the partial benzylation of **7** with benzyl chloride-anhydrous potassium carbonate in acetone or *N*,*N*-dimethylformamide did not give **9** in favorable yield because of the formation of by-products. The benzoates, derived from **9** with substituted benzoyl chlorides, were converted into the diketone derivatives (**10**) by the Baker-Venkataraman rearrangement with potassium hydroxide in anhydrous pyridine. Cyclization of **10** with anhydrous sodium acetate in acetic acid easily led to 8-benzyloxy-5,7-dimethoxyflavones (**11**) which were quantitatively converted into **6** by the hydrogenolysis with palladium on charcoal.

Demethylation of 8-Hydroxy-5,7-dimethoxyflavones (6) with Anhydrous Aluminum Chloride in Acetonitrile. In the previous paper,[9] we reported that the 5-methoxyl group on the acetates of 6-hydroxy-5,7,8-trimethoxyflavones was quantitatively split to give 5,6-dihydroxy-7,8-dimethoxyflavones with about 5% (w/v) anhydrous aluminum chloride in acetonitrile at 80 °C. But under the same conditions, few of the 5-methoxyl groups on **6a** and its acetate (**12a**) were split. On the other hand, the 7-methoxyl group on **6a** was not completely split with about 30% (w/v) anhydrous aluminum chloride in acetonitrile, in contrast to that of 6-hydroxy-5,7,8-trimethoxyflavones[9] and **3**.[7] Therefore, **1a**—**g** were easily synthesized from **6** in quantitative yield under the following conditions: about 10% (w/v) anhydrous aluminum chloride in acetonitrile at 70 °C for 10 h.

The benzyloxyl groups on **11** were also split to give **1** under the above conditions. However, the high performance liquid chromatograms (HPLC) of the demethylated products from the flavones (**6b**, **d**, **e**, and **f**) which had benzyloxyl groups on the B ring indicated the existence of by-products having longer retention time than that of **1**. Consequently, for the synthesis of **1**, the demethylation of **6** was better than that of **11**.

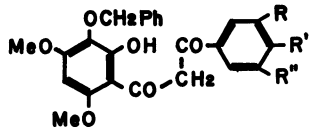
The ^{1}H NMR data for the hydroxyflavones (**1** and **6**) (in DMSO) and the acetates (**13**) of **1** (in $CDCl_3$) are shown in Tables 1 and 2. The C_3- and C_6-proton



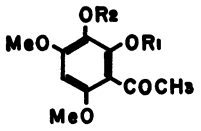


1 R_1=R_3=H, R_2=Me
2 R_1=R_2=R_3=H
6 R_1=R_2=Me, R_3=H
11 R_1=R_2=Me, R_3=CH_2Ph
12 R_1=R_2=Me, R_3=Ac
13 R_1=R_3=Ac, R_2=Me
14 R_1=R_2=H, R_3=Me
16 R_1=R_2=R_3=Ac

3 R_1=R_3=Me, R_2=H
4 R_1=R_2=H, R_3=Me
5 R_1=R_2=R_3=H
15 R_1=R_3=H, R_2=Me



10



7 R_1=R_2=H
8 R_1=R_2=CH_2Ph
9 R_1=H, R_2=CH_2Ph

1, 2, 3, 4, 5, 6, 14, and 15

a R=R"=H, R'=OMe
b R=R"=H, R'=OH
c R=R'=OMe, R"=H
d R=OMe, R'=OH, R"=H
e R=OH, R'=OMe, R"=H
f R=R'=OH, R"=H
g R=R'=R"=OMe
h R=R"=OMe, R'=OH
i R=R'=R"=OH

10 and 11

a R=R"=H, R'=OMe
b R=R"=H, R'=OCH_2Ph
c R=R'=OMe, R"=H
d R=OMe, R'=OCH_2Ph, R"=H
e R=OCH_2Ph, R'=OMe, R"=H
f R=R'=OCH_2Ph, R"=H
g R=R'=R"=OMe

12, 13, and 16

a R=R"=H, R'=OMe
b R=R"=H, R'=OAc
c R=R'=OMe, R"=H
d R=OMe, R'=OAc, R"=H
e R=OAc, R'=OMe, R"=H
f R=R'=OAc, R"=H
g R=R'=R"=OMe
i R=R'=R"=OAc

signals listed in these Tables were assigned on the basis of the NOE experiment for **1a** and **13a**: the integrated intensities of the singlets at δ 6.52 for **1a** and δ 6.67 for **13a** increased about 28 and 22% respectively, when the methoxyl groups were saturated by double irradiation. The C_6-proton on **1** is not affected by their substituents on the B ring and its signals are in the narrow range of δ 6.51 to 6.54, while the C_3-proton is slightly affected and its signals are in the slightly wider range of δ 6.65 to 7.02. These phenomena are also observed in the spectra for **6** and **13**. On the other hand, the signals for C_6-proton on **13** in $CDCl_3$ are in the range of δ 6.67 to 6.69 and the range shifts about 0.15 ppm lower than that of **1** in DMSO (δ 6.51—6.54). These δ values for **1** and **13** are distinct from those for 5,7-dihydroxy-8-methoxyflavones (**14**)[10-12] (C_6–H, $\delta\approx$6.3; acetates, $\delta\approx$6.8) or 5,7-dihydroxy-6-methoxyflavones (**15**)[13,14] (C_8–H, $\delta\approx$6.6; acetates, $\delta\approx$7.3).

In the UV spectra for **1**, Bands I and II are seen at about 330 and 280 nm respectively, as shown in Table 3. These bands undergo bathochromic shift by the addition of aluminum chloride and the spectra consist typically of four major absorption peaks. The properties are greatly different from those of 5,6,7-trihydroxyflavone derivatives such as **15**[13,14] or **4**[7,15] However, the UV data for the flavones (**1**) are essentially identical with those for the corresponding 5,7-dihydroxy-8-methoxyflavones (**14**),[10-12] the isomers of **1**, but a little differences were observed at 300—330 nm in the presence of aluminum chloride.

On the other hand, Bands I and II for the 5,7-dihydroxyflavones (**14**) are shifted bathochromically by the addition of sodium acetate,[10-12] but these bands for the 5,8-dihydroxyflavones (**1a**, **c**, **e**, and **g**) which have not the 4'-hydroxyl group do not show any bathochromic shift. In the UV spectra for the 5,8-dihydroxyflavones (**1b**, **d**, and **f**) having the 4'-hydroxyl group, Band II which associates with absorption involving the A ring benzoyl system do not also shift bathochromically by the addition of sodium acetate, but Band I undergoes a bathochromic shift and splits into two typical absorption peaks: one has the same wavelength as Band I and the other is in a range of 390—410 nm (Table 3).

*Demethylation of 8-Hydroxy-5,7-dimethoxyflavones (**6**) with Anhydrous Aluminum Bromide in Acetonitrile.* In the HPLC of 5,6,7-trioxygenated flavones, their retention times have been known to decrease with increasing numbers of hydroxyl groups except for 5-hydroxyl

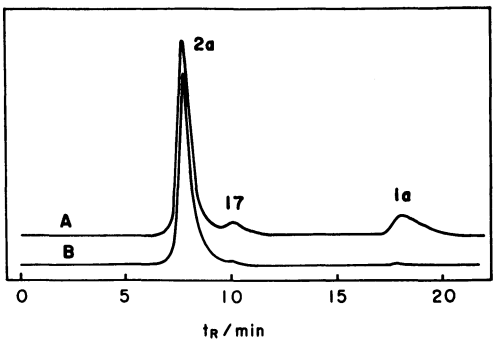


Fig. 1. HPLC of demethylated products from **6a** with anhydrous aluminum bromide in acetonitrile at 50 °C for 24 h (A) in air and 48 h (B) in nitrogen atmosphere. Flow rate, 0.5 ml/min. Temp, room temp.

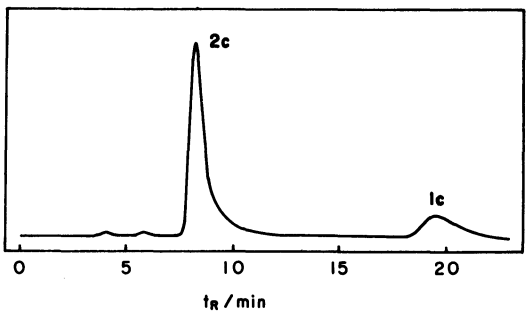


Fig. 2. HPLC of demethylated product from **6c** with anhydrous aluminum bromide in acetonitrile at 50 °C for 24 h in nitrogen atmosphere.
Same conditions as in Fig. 1.

Table 1. ^{1}H NMR data for 5,8-dihydroxy-7-methoxyflavones(**1**), 5,7,8-trihydroxyflavones(**2**), and 8-hydroxy-5,7-dimethoxyflavones(**6**) in DMSO

Compd	Arom. H						OMe		5-OH
	C_3–H	C_6–H	$C_{3'}$–H	$C_{5'}$–H	$C_{2'}$–H	$C_{6'}$–H			
1a	6.80s	6.52s	7.10d (2H)		8.07d (2H)		3.85s (3H)	3.90s (3H)	12.42s
1b	6.74s	6.53s	6.94d (2H)		8.00d (2H)		3.91s (3H)		12.45s
1c	6.90s	6.51s	—	7.11d	7.59d′	7.75q	3.85s (3H)	3.87s (3H)	12.40s
							3.89s (3H)		
1d	6.87s	6.53s	—	6.95d	7.60d′	7.77q	3.90s (6H)		12.45s
1e	6.72s	6.53s	—	7.08d	7.53d′	7.61q	3.86s (3H)	3.91s (3H)	12.46s
1f	6.65s	6.53s	—	6.90d	7.53d′	7.47q	3.91s (3H)		12.46s
1g	7.02s	6.54s	—	—	7.40s (2H)		3.77s (3H)	3.91s (9H)	12.33s
1h	6.96s	6.54s	—	—	7.41s (2H)		3.89s (9H)		12.46s
1i	6.55s	6.55s	—	—	7.09s (2H)		3.93s (3H)		12.53s
2a	6.79s	6.28s	7.13d (2H)		8.12d (2H)		3.86s (3H)		12.32s
2b	6.70s	6.26s	6.92d (2H)		7.99d (2H)		—		12.35s
2c	6.88s	6.27s	—	7.10d	7.62d′	7.77q	3.85s (3H)	3.88s (3H)	12.32s
2f	6.60s	6.26s	—	6.88d	7.35—7.6m (2H)		—		12.36s
2g	6.98s	6.28s	—	—	7.41s (2H)		3.76s (3H)	3.90s (6H)	12.26s
2i	6.50s	6.29s	—	—	7.08s (2H)		—		12.52bs
17	6.89s	—	7.08d (2H)		8.17d (2H)		3.85s (3H)		13.20s
6a	6.59s	6.67s	7.06d (2H)		8.02d (2H)		3.83s (6H)	3.95s (3H)	—
6b	6.55s	6.67s	6.93d (2H)		7.93d (2H)		3.85s (3H)	3.97s (3H)	—
6c	6.72s	6.69s	—	7.12d	7.59d′	7.73q	3.85s (6H)	3.89s (3H)	—
							3.97s (3H)		
6d	6.63s	6.63s	—	6.90d	7.45—7.7m (2H)		3.82s (3H)	3.88s (3H)	—
							3.95s (3H)		
6e	6.50s	6.67s	—	7.05d	7.46d′	7.54q	3.83s (3H)	3.86s (3H)	—
							3.97s (3H)		
6f	6.45s	6.68s	—	6.89d	7.48d′	7.42q	3.83s (3H)	3.97s (3H)	—
6g	6.82s	6.69s	—	—	7.37s (2H)		3.76s (3H)	3.85s (3H)	—
							3.90s (6H)	3.98s (3H)	—

s: singlet, d: doublet (J=8.5 Hz), d′: doublet(J=2.5 Hz), q: quartet (J=8.5, 2.5 Hz), m: multiplet.

Table 2. ^{1}H NMR data for 5,8-diacetoxy-7-methoxyflavones(**13**) and 5,7,8-triacetoxyflavones(**16**) in $CDCl_3$

Compd	Arom. H						OMe		OAc	
	C_3–H	C_6–H	$C_{3'}$–H	$C_{5'}$–H	$C_{2'}$–H	$C_{6'}$–H				
13a	6.47s	6.67s	6.97d (2H)		7.69d (2H)		3.85s (3H)	3.92s (3H)	2.44s (6H)	
13b	6.51s	6.69s	7.20d (2H)		7.76d (2H)		3.92s (3H)		2.32s (3H)	2.43s (6H)
13c	6.48s	6.68s	—	6.94d	7.24d′	7.39q	3.92s (9H)		2.43s (6H)	
13d	6.51s	6.69s	—	7.10d	7.30d′	7.36q	3.88s (3H)	3.92s (3H)	2.32s (3H)	2.41s (3H)
									2.43s (3H)	
13e	6.45s	6.67s	—	7.02d	7.43d′	7.63q	3.89s (3H)	3.91s (3H)	2.34s (3H)	2.43s (6H)
13f	6.49s	6.69s	—	7.30d	7.5—7.75m (2H)		3.93s (3H)		2.31s (6H)	2.43s (6H)
13g	6.49s	6.69s	—	—	6.98s (2H)		3.90s (12H)		2.43s (6H)	
16a	6.54s	6.93s	6.98d (2H)		7.70d (2H)		3.87s (3H)		2.34s (3H)	2.44s (6H)
16b	6.55s	6.93s	7.20d (2H)		7.73d (2H)		—		2.32s (6H)	2.41s (6H)
16c	6.53s	6.93s	—	6.93d	7.23d′	7.37q	3.93s (6H)		2.33s (3H)	2.42s (6H)
16f	6.54s	6.94s	—	7.29d	7.5—7.75m (2H)		—		2.30s (6H)	2.32s (3H)
									2.41s (6H)	
16g	6.55s	6.95s	—	—	6.98s (2H)		3.91s (9H)		2.35s (3H)	2.42s (6H)
16i	6.52s	6.93s	—	—	7.50s (2H)		—		2.30s (9H)	2.32s (3H)
									2.41s (6H)	
Acetate of **17**	6.53s	—	6.97d (2H)		7.67d (2H)		3.86s (3H)		2.41s (3H)	2.43s (3H)
									2.48s (3H)	

s: singlet, d: doublet (J=8.5 Hz), d′: doublet (J=2.5 Hz), q: quartet (J=8.5, 2.5 Hz), m: multiplet.

TABLE 3. UV DATA FOR 5,8- DIHYDROXY-7-METHOXYFLAVONES(**1**) AND 5,7,8-TRIHYDROXYFLAVONES(**2**)

Compd	λ_{max}/nm (log ε)											
	EtOH				EtOH–$AlCl_3$				EtOH–NaOAc			
1a	282	308	325 i	363 i	288	318	343 i	407	282	308	325 i	363 i
	(4.34)	(4.39)	(4.28)	(3.85)	(4.25)	(4.43)	(4.28)	(3.77)	(4.34)	(4.40)	(4.29)	(3.84)
1b	279	309	326sh	367 i	285	319	345sh	406	278	309	326sh	391
	(4.32)	(4.33)	(4.27)	(3.96)	(4.25)	(4.37)	(4.31)	(3.87)	(4.30)	(4.26)	(4.21)	(4.09)
1c	281		335		288	330	350	415	283		335	
	(4.32)		(4.26)		(4.25)	(4.27)	(4.29)	(3.82)	(4.30)		(4.28)	
1d	279		340		286	328sh	356	412	277		341	410
	(4.26)		(4.24)		(4.21)	(4.19)	(4.28)	(3.93)	(4.24)		(4.14)	(4.12)
1e	279	298 i	339		286	307	354	416	279	298 i	337	
	(4.34)	(4.21)	(4.24)		(4.29)	(4.23)	(4.28)	(3.87)	(4.33)	(4.22)	(4.25)	
1f	278	301	345		284	310	358	417	275	299sh	347	390sh
	(4.27)	(4.15)	(4.23)		(4.25)	(4.13)	(4.21)	(3.98)	(4.26)	(4.10)	(4.13)	(4.05)
1g	283	307	330 i		292	319	345 i	416	285	307	330 i	
	(4.31)	(4.29)	(4.19)		(4.26)	(4.32)	(4.19)	(3.74)	(4.30)	(4.31)	(4.22)	
1h	279	318sh	346		288	332sh	361	415sh	268	313	345	430
	(4.23)	(4.14)	(4.28)		(4.20)	(4.17)	(4.31)	(3.90)	(4.21)	(4.01)	(4.08)	(4.20)
1i	278	312	350		283	324	365	433	267	310	353 i	417
	(4.22)	(4.06)	(4.22)		(4.25)	(4.03)	(4.16)	(4.14)	(4.22)	(3.93)	(4.03)	(4.14)
2a	287 i	304		367 i	293sh	316	345 i	402		297		
	(4.37)	(4.41)		(3.83)	(4.27)	(4.41)	(4.22)	(3.88)		(4.39)		
2b	286 i	306	335 i		289	317	343sh	412		304		375
	(4.32)	(4.38)	(4.15)		(4.24)	(4.39)	(4.27)	(3.75)		(4.30)		(4.05)
2c	286		317		292	327	347sh	405sh		298sh	317	
	(4.30)		(4.28)		(4.24)	(4.28)	(4.26)	(3.77)		(4.28)	(4.31)	
2f	284		334		287	305sh	358	402sh		303 i	327	386
	(4.23)		(4.23)		(4.23)	(4.17)	(4.21)	(3.98)		(4.12)	(4.14)	(4.10)
2g		300			298sh	317	350 i	405		300		
		(4.35)			(4.28)	(4.35)	(4.15)	(3.69)		(4.29)		
2i	282	318sh	336		288	323	367	405sh			330	398
	(4.14)	(4.22)	(4.24)		(4.21)	(4.05)	(4.16)	(4.13)			(4.05)	(4.13)
17		304				306 i	325			306		
		(4.47)				(4.37)	(4.47)			(4.39)		

sh: shoulder, i: inflection point.

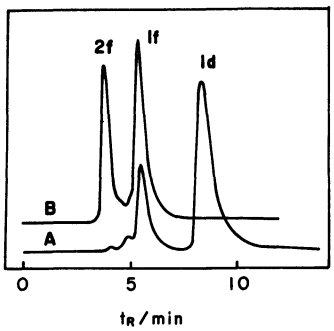


Fig. 3. HPLC of demethylated products from **6d** with anhydrous aluminum bromide in acetonitrile at 50 °C for 2 h (A) and 12 h (B).
Same conditions as in Fig. 1.

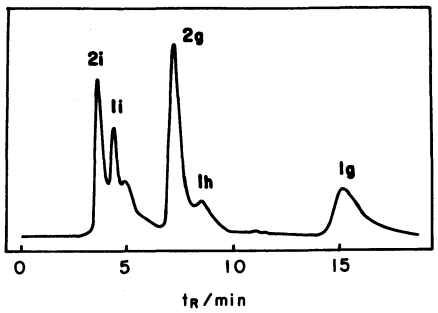


Fig. 4. HPLC of demethylated product from **6g** with anhydrous aluminum bromide in acetonitrile at 50 °C for 12 h.
Same conditions as in Fig. 1.

group.[16] The high performance liquid chromatography may be very useful for the separation of the demethylated products. Therefore, the demethylation of **6** with anhydrous aluminum bromide in acetonitrile was investigated in order to find a suitable method for the syntheses of 5,7,8-trihydroxyflavones (**2**) by the chromatography. The HPLC obtained are shown in Figs. 1—4.

The HPLC of the demethylated products from **6a** in the atmosphere showed the presence of three components (Fig. 1, Curve A). These components were identified as 5,7,8-trihydroxy-4′-methoxyflavone (**2a**), 6-bromo-5,7,8-trihydroxy-4′-methoxyflavone (**17**), and **1a** respectively, on the basis of the ^1H NMR and UV data (Tables

1—3). The amount of the bromoflavone (**17**) increased with increasing reaction time, but apparently decreased in nitrogen atmosphere (Fig. 1, Curve B). The 4'-methoxyl group of **6a** was stable under these demethylation conditions, so that 4',5,7,8-tetrahydroxyflavone (**2b**)[17] in the demethylated products was not detected by the high performance liquid chromatography. These results show that the 5- and 7-methoxyl groups of **6a** are selectively split with anhydrous aluminum bromide in nitrogen atmosphere to give **2a** in good yield.

The 5- and 7-methoxyl groups of **6c** were also selectively split under the above conditions to give **2c** as a main product. However, the HPLC of the demethylated product from **6c** showed small peaks which had shorter retention times than that of **2c** (Fig. 2). These small peaks are presumed to be those of the demethylated products of **2c**.

In the HPLC of the demethylated product from **6d**, the components of main peaks (R_t 3.8, 5.4, and 8.2 min) were identified as 3',4',5,7,8-pentahydroxyflavone (**2f**),[18] **1f**, and **1d** respectively, and the small peak (R_t 4.9 min) which is observed as a shoulder peak is estimated to be that of 4',5,7,8-tetrahydroxy-3'-methoxyflavone (**2d**) (Fig. 3). These results indicate that the 3'-methoxyl group is more easily split than the 7-methoxyl group and that the methoxyl groups of **6d** are split in the following order: 5, 3', and 7.

Similarly **6e**, an isomer of **6d**, was demethylated to **2f** *via* **1f**, but the 4'-methoxyl group was more easily split than the 3'-methoxyl group on **1d**. These results indicate that the hydroxyl group promotes the cleavage of adjacent methoxyl group. The cleavage of the methoxyl group with anhydrous aluminum bromide seems to proceed *via* the formation of a cyclic aluminum complex between the hydroxyl group and the methoxyl oxygen atom adjacent to each other.[19] However, the cleavage of 7-methoxyl group was clearly slower than that on the B ring of **1d** or **1e**, even though both of the methoxyl groups have an adjacent hydroxyl group. One of the causes of the difficulty in the cleavage of 7-methoxyl group may be that the 8-hydroxyl group has a tendency to form the cyclic aluminum complex with the ether oxygen atom at 1 position on the flavone nucleus.

On the other hand, the HPLC of the demethylated product from **6g** which has three methoxyl groups adjacent to each other showed the presence of many components (Fig. 4). The five main components were identified as 3',4',5,5',7,8-hexahydroxyflavone (**2i**), 3',4',5,5',8-pentahydroxy-7-methoxyflavone (**1i**), 5,7,8-trihydroxy-3',4',5'-trimethoxyflavone (**2g**), 4',5,8-trihydroxy-3',5',7-trimethoxyflavone (**1h**), and **1g** respectively (Tables 1—3). These results suggest that **6g** is demethylated to form **2i** *via* **1g** by the following two pathways because of a small difference of the rate of cleavage between the 7- and 4'-methoxyl groups: **6g**→**1g**→**2g**→**2i** and **6g**→**1g**→**1h**→**1i**→**2i**. Therefore, it seems that the flavones, **1g**, **2g**, **1i**, and **2i**, in the HPLC are observed as main peaks and that the flavones having the methoxyl groups adjacent to a hydroxyl group on the B ring such as **1h** are observed as small peaks.

From these results, it is suggested that the 5,7,8-trihydroxyflavones (**2**) which had one or two methoxyl groups on the B ring were easily synthesized by the demethylation of **6** with anhydrous aluminum bromide in acetonitrile.

The C_6-proton signals of the ^{1}H NMR for 5,7,8-trihydroxyflavones (**2**) and its acetates (**16**) appear at δ 6.26—6.29 and δ 6.93—6.95 respectively (Tables 1 and

Table 4. Comparison of salvitin and the two trihydroxyflavones (**1b** and **15b**)

		Salvitin[2]	**1b**	**15b**[13]
Mp θ_m/°C		304—305	277—279	298.5—300.5
(Triacetate)		(170)	(265—266)	(168.5—169.5)
UV: λ_{max}/nm	in MeOH	276 335	in EtOH 279 309 326sh 367i	in EtOH 275 336
	($AlCl_3$)	301 354	285 319 345sh 406	304 358
	(NaOAc)	276 347	278 309 326sh 391	277 340
^{1}H NMR of triacetate in $CDCl_3$ (δ)	OAc	2.34 2.42 2.53	2.32 2.43(6H)	2.34 2.40 2.51
	C_3–H	6.68	6.51	6.63
	C_6– or C_8–H	7.40	6.69	7.32

sh: shoulder, i: inflection point.

Table 5. Comparison of UV data for the natural flavone and the two 5,7,8-trioxygenated flavones (**1d** and **14d**)

Compd		λ_{max}/nm (log ε)				
Natural flavone[3]	in MeOH	254	272	292sh	342	
	($AlCl_3$)	266sh	279	305	358	402
	(NaOAc)	260 266sh	295sh			410
1d	in EtOH	255(4.13)	279(4.26)		340(4.24)	
	($AlCl_3$)	260sh(4.08)	286(4.21)	328sh(4.19)	356(4.28)	412(3.93)
	(NaOAc)		277(4.24)		341(4.14)	410(4.12)
14d[12]	in EtOH	255(4.21)	276.5(4.29)		343(4.26)	
	($AlCl_3$)	263(4.12)	285(4.24)	302sh(4.09)	360(4.29)	402(4.10)
	(NaOAc)		286(4.37)	328(4.09)		414(4.34)

sh: shoulder.

2). These chemical shifts resemble those of the C_6-proton for 5,7-dihydroxy-8-methoxyflavones (**14**)[10-12] ($\delta \approx 6.3$) and its acetates ($\delta \approx 6.8$), but differ apparently from those of the C_8-proton for 5,6,7-trihydroxyflavones (**5**)[7] ($\delta \approx 6.6$) and its acetates ($\delta \approx 7.45$).

The UV spectra for **2** in ethanol or ethanol–aluminum chloride are similar to those for the corresponding **1**. However, Bands I and II in ethanol for **2** approach more closely to each other than those for the corresponding **1**. Therefore, in the presence of sodium acetate, the bathochromic shift of Band II which is associated with the 7-hydroxyl group on **2** is not clearly observed because of the overlap with neighboring Band I (Table 3).

Identification of the Two Natural Flavones. The structure of salvitin, isolated from *Salvia plebeia*, has been confirmed to be 4′,5,8-trihydroxy-7-methoxyflavone (**1b**) on the basis of the spectral data and the synthesis.[2] The properties of salvitin, however, were not identical with those of **1b** synthesized by us (Table 4). The singlet peak at δ 7.4 in the ^{1}H NMR for salvitin triacetate is assigned to the C_8-proton on 5,7-diacetoxy-6-methoxyflavones[13,14] or 5,6,7-triacetoxyflavones.[7] In addition, the UV data for salvitin are similar to those of 4′,5,7-trihydroxy-6-methoxyflavone[13] (**15b**). These results suggest that the structure of salvitin is **15b**, an isomer of **1b**. The physical data of salvitin and its triacetate are shown to be identical with those of **15b** and its triacetate[13] as shown in Table 4. Consequently, the structure of salvitin was found to be 4′,5,7-trihydroxy-6-methoxyflavone (dinatin[20]) (**15b**).

Whalen *et al.*[3] have proposed that the structure of one of the natural flavones, isolated from *Solanum* section *Androceras*, is 4′,5,8-trihydroxy-3′,7-dimethoxyflavone (**1d**) on the basis of the UV and MS data. They claimed that the structure of the natural flavone was not 4′,5,7-trihydroxy-3′,8-dimethoxyflavone (**14d**) but **1d** on the basis of the following facts: "Substitution of the C_7-hydroxyl group was demonstrated by the failure of Band II to show a bathochromic shift in NaOAc relative to MeOH". However, in the presence of sodium acetate, the bathochromic shift of Band II for **1d** synthesized is not exhibited, and the UV data are obviously different from those for the natural flavone as shown in Table 5. Moreover, the UV data for the natural flavone in the presence of aluminum chloride are similar to those for **14d**[12] rather than those for **1d**. These results suggest that the natural flavone is **14d**.

Experimental

All the melting points were determined in glass capillaries and were uncorrected. The ^{1}H NMR spectra were measured with a Hitachi R-24 spectrometer (60 MHz), using tetramethylsilane as an internal standard, and chemical shifts were presented in δ values. The UV spectra were taken on a Hitachi 124 spectrophotometer. The high performance liquid chromatographic analysis carried out with a Hitachi 635 instrument, using a column (2.1×500 mm) packed with Hitachi gel # 3011, methanol as a eluent, and a UV monitor at 338 nm.[16] For the separation of the demethylated products, a column (20×600 mm) packed with Hitachi gel # 3019 using methanol was employed.

3-Benzyloxy-2-hydroxy-4,6-dimethoxyacetophenone(9). A mixture of the acetophenone (**7**)[8] (10 g), benzyl chloride (30 ml), and anhydrous potassium carbonate (56 g) in *N,N*-dimethylformamide (60 ml) was gently refluxed for 3 h, and then water was added to the reaction mixture. After the excess of benzyl chloride was removed by steam distillation under reduced pressure, the oily material was extracted with ether. The ethereal solution was washed with water. The solvent was completely evaporated to give crude dibenzyl ether (**8**) as brown oil.

The crude dibenzyl ether was dissolved in acetic acid (100 ml) containing concentrated hydrochloric acid (10 ml) and then allowed to stand for 85 min at room temperature. After the solution was diluted with water, separated crystals were

Table 6. 3-Benzyloxy-2-hydroxy-4,6-dimethoxy-ω-benzoylacetophenones (**10**)

Compd	Mp θ_m/°C	Cryst. form	Recrystn. solvent	Yield/%	Formula	Found (%)		Calcd (%)	
						C	H	C	H
10a	158—159	Yellow needles	EtOAc	74	$C_{25}H_{24}O_7$	68.71	5.58	68.80	5.54
10b	188—189	Pale Yellow needles	EtOAc	71	$C_{31}H_{28}O_7$	72.38	5.30	72.64	5.51
10c	173—174	Yellow needles	$CHCl_3$–MeOH	82	$C_{26}H_{26}O_8$	66.70	5.41	66.94	5.62
10d	131—132	Yellow needles	EtOAc	62	$C_{32}H_{30}O_8$	70.63	5.67	70.83	5.57
10e	177—179	Pale yellow needles	EtOAc	80	$C_{32}H_{30}O_8$	70.61	5.66	70.83	5.57
10f	123—124	Yellow needles	EtOAc	60	$C_{38}H_{34}O_8$	74.02	5.40	73.77	5.54
10g	149—150	Yellow needles	EtOAc	84	$C_{27}H_{28}O_9$	65.03	5.69	65.31	5.68

Table 7. 8-Benzyloxy-5,7-dimethoxyflavones (**11**)

Compd	Mp θ_m/°C	Cryst. form	Recrystn. solvent	Yield/%	Formula	Found (%)		Calcd (%)	
						C	H	C	H
11a	149—150	Colorless needles	MeOH	98	$C_{25}H_{22}O_6$	71.99	5.15	71.76	5.30
11b	148—150	Pale yellow needles	$CHCl_3$–MeOH	98	$C_{31}H_{26}O_6$	75.40	5.12	75.29	5.30
11c	164—165	Pale yellow needles	$CHCl_3$–MeOH	97	$C_{26}H_{24}O_7$	69.83	5.27	69.63	5.39
11d	179—181	Pale yellow needles	$CHCl_3$–MeOH	98	$C_{32}H_{28}O_7$	73.43	5.20	73.27	5.38
11e	161—162	Pale yellow needles	$CHCl_3$–MeOH	98	$C_{32}H_{28}O_7$	73.48	5.08	73.27	5.38
11f	173—174	Colorless needles	$CHCl_3$–EtOAc	96	$C_{38}H_{32}O_7$	75.91	5.19	75.98	5.37
11g	206—207	Colorless needles	$CHCl_3$–MeOH	86	$C_{27}H_{26}O_8$	67.71	5.55	67.77	5.48

collected, washed with ether–hexane (1 : 1), and then recrystallized from methanol as pale yellow prisms, mp 95—97 °C; yield 11.4 g (80%). Found: C, 67.58; H, 5.99%. Calcd for $C_{17}H_{18}O_5$: C, 67.59; H, 6.00%.

*3-Benzyloxy-2-hydroxy-4,6-dimethoxy-ω-benzoylacetophenones (**10a**—**g**).* A mixture of **9** (3.0 g; 9.9 mmol) and the substituted benzoyl chloride (11—12 mmol) in pyridine (6 ml) was heated at 120 °C for 2 h. The cooled reaction mixture was poured into a mixture of ice, hydrochloric acid, and ether, and then stirred till the separated oily material changed into a precipitate. The precipitate was collected, washed with water, and dried to give crude benzoate.

A mixture of the crude benzoate and powdered potassium hydroxide (4 g) in pyridine (15 ml) was stirred for 4 h at 60 °C, and then poured into a mixture of ice and hydrochloric acid. The separated precipitate was treated with a sodium carbonate solution and then recrystallized to give **10a**—**g** (Table 6).

*8-Benzyloxy-5,7-dimethoxyflavones (**11a**—**g**).* A mixture of **10** (3 g) and anhydrous sodium acetate (4 g) in acetic acid (20 ml) was heated at 140 °C for 4h, and then water was added to the mixture. The separated precipitate was recrystallized to give **11a**—**g** (Table 7).

*8-Hydroxy-5,7-dimethoxyflavones (**6a**—**g**).* Flavone (**11**) (500 mg) was hydrogenated over palladium on charcoal (10%; 200 mg) in ethyl acetate (150 ml)–methanol (150 ml) till the uptake of hydrogen ceased. After the catalyst was filtered off, the filtrate was evaporated. The residue was recrystallized to give **6a**—**g** (Table 8).

*8-Acetoxy-4′,5,7-trimethoxyflavone (**12a**):* colorless needles from methanol, mp 205—206 °C. Found: C, 64.58; H, 4.79% Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90%.

*5,8-Dihydroxy-7-methoxyflavones (**1a**—**g**).* A mixture of **6** (100 mg) and anhydrous aluminum chloride (1 g) in acetonitrile (10 ml) was heated at 70 °C for 10 h, and then a 0.5% hydrochloric acid (50 ml) was added to the reaction mixture. The mixture was warmed at 60 °C for 1—2 h, and then allowed to stand overnight in a refrigerator. The separated precipitate was recrystallized to give **1a**—**g** (Table 9).

Table 8. 8-Hydroxy-5,7-dimethoxyflavones (**6**)

Compd	Mp θ_m/°C	Cryst. form	Recrystn. solvent	Yield/%	Formula	Found (%)		Calcd (%)	
						C	H	C	H
6a	233—234	Yellow needles	MeOH	84	$C_{18}H_{16}O_6$	65.85	4.84	65.85	4.91
6b	293—295	Yellow needles	MeOH	97	$C_{17}H_{14}O_6$	65.08	4.50	64.96	4.49
6c	221—223	Yellow needles	MeOH	91	$C_{19}H_{18}O_7$	63.74	5.13	63.68	5.06
6d	227—228	Yellow needles	MeOH	80	$C_{18}H_{16}O_7$	62.61	4.45	62.79	4.68
6e	263—264	Yellow needles	MeOH	98	$C_{18}H_{16}O_7$	62.69	4.75	62.79	4.68
6f	296—297	Yellow needles	MeOH–EtOAc	93	$C_{17}H_{14}O_7$	61.56	4.24	61.82	4.27
6g	227—228	Yellow needles	MeOH	92	$C_{20}H_{20}O_8$	61.86	4.97	61.85	5.19

Table 9. 5,8-Dihydroxy-7-methoxyflavones (**1**)

Compd	Mp θ_m/°C	Cryst. form	Recrystn. solvent	Yield/%	Formula	Found (%)		Calcd (%)	
						C	H	C	H
1a	260—262	Yellow needles	MeOH	98	$C_{17}H_{14}O_6$	65.00	4.26	64.97	4.49
1b	277—279	Yellow needles	MeOH	98	$C_{16}H_{12}O_6$	64.25	4.30	64.00	4.03
1c	250—251	Yellow needles	MeOH	91	$C_{18}H_{16}O_7$	62.65	4.67	62.79	4.68
1d	280—281	Yellow needles	EGME[a)]	96	$C_{17}H_{14}O_7$	61.65	4.53	61.82	4.27
1e	245—246	Yellow needles	MeOH	97	$C_{17}H_{14}O_7$	61.75	4.07	61.82	4.27
1f	291—292	Yellow needles	MeOH	80	$C_{16}H_{12}O_7$	60.98	4.00	60.76	3.82
1g	216—217	Yellow needles	MeOH	98	$C_{19}H_{18}O_8$	60.68	4.85	60.96	4.85

a) Ethylene glycol monomethyl ether.

Table 10. Demethylated products of 8-hydroxyflavones (**6**) with anhydrous aluminum bromide in acetonitrile

Compd	Mp θ_m/°C	Cryst. form	Recrystn. solvent	Formula	Found (%)		Calcd (%)	
					C	H	C	H
2a	268—270[a)]	Yellow needles	MeOH	$C_{16}H_{12}O_6$	64.12	4.00	64.00	4.03
17	246[a)]	Yellow needles	MeOH	$C_{16}H_{11}O_6Br$	50.40	3.04	50.68	2.92
2b[17,b)]	293—295[a)]	Yellow needles	aq MeOH	$C_{15}H_{10}O_6 \cdot H_2O$	59.13	4.11	59.21	3.98
2c	251—252	Yellow needles	aq MeOH	$C_{17}H_{14}O_7 \cdot H_2O$	58.59	4.66	58.62	4.63
2f[18)]	>300	Yellow needles	aq MeOH	$C_{15}H_{10}O_7 \cdot 2H_2O$	53.46	4.27	53.26	4.17
1h	267—268	Yellow prisms	aq MeOH	$C_{18}H_{16}O_8 \cdot 2.5H_2O$	53.06	5.30	53.33	5.19
1i	>300	Yellow needles	MeOH	$C_{16}H_{12}O_8$	57.82	3.56	57.83	3.64
2g	268—270	Yellow needles	aq MeOH	$C_{18}H_{16}O_8$	59.77	4.39	60.00	4.48
2i	>300	Yellow needles	MeOH	$C_{15}H_{10}O_8 \cdot H_2O$	53.91	3.62	53.58	3.60

a) Decomposition point. b) This was synthesized from 4′,5,7,8-tetramethoxyflavone[6)] by the demethylation with anhydrous aluminum bromide in benzene at 50 °C for 24 h.

TABLE 11. 5,8-DIACETOXY-7-METHOXYFLAVONES(**13**) AND 5,7,8-TRIACETOXYFLAVONES(**16**)

Compd	Mp θ_m/°C	Cryst. form	Recrystn. solvent	Formula	Found (%)		Calcd (%)	
					C	H	C	H
13a	240—240.5	Colorless needles	$CHCl_3$–MeOH	$C_{21}H_{18}O_8$	63.31	4.67	63.31	4.55
13b	265—266	Colorless needles	$CHCl_3$–MeOH	$C_{22}H_{18}O_9$	62.09	4.40	61.97	4.26
13c	198—199	Colorless needles	$CHCl_3$–MeOH	$C_{22}H_{20}O_9$	61.66	4.65	61.68	4.71
13d	256—257	Colorless needles	$CHCl_3$–MeOH	$C_{23}H_{20}O_{10}$	60.71	4.35	60.53	4.42
13e	238—240	Colorless needles	$CHCl_3$–MeOH	$C_{23}H_{20}O_{10}$	60.52	4.52	60.53	4.42
13f	255—257	Colorless needles	$CHCl_3$–MeOH	$C_{24}H_{20}O_{11}$	59.35	4.18	59.51	4.16
13g	240—240.5	Colorless needles	$CHCl_3$–MeOH	$C_{23}H_{22}O_{10}$	60.36	4.98	60.26	4.84
16a	246—248	Colorless needles	$CHCl_3$–MeOH	$C_{22}H_{18}O_9$	61.96	4.24	61.97	4.26
16b	246—247	Colorless needles	$CHCl_3$–MeOH	$C_{23}H_{18}O_{10}$	60.75	3.98	60.79	3.99
16c	214—215	Colorless needles	$CHCl_3$–MeOH	$C_{23}H_{20}O_{10}$	60.55	4.34	60.52	4.42
16f	224—225	Colorless needles	$CHCl_3$–MeOH	$C_{25}H_{20}O_{12}$	58.59	3.92	58.60	3.93
16g	191—192	Colorless needles	MeOH	$C_{24}H_{22}O_{11}$	59.13	4.65	59.26	4.56
16i	265—266	Colorless needles	$CHCl_3$–MeOH	$C_{27}H_{22}O_{14}$	56.85	3.92	56.87	3.89
Acetate of **17**	249—251	Colorless needles	$CHCl_3$–MeOH	$C_{22}H_{17}O_9Br$	52.25	3.40	52.29	3.39

Acetates (**13a—g**) of **1a—g** were synthesized by a hot acetic anhydride–pyridine method (Table 11).

*Demethylation of 8-Hydroxy-5,7-dimethoxyflavones (**6a**, **c**, **d**, **e**, and **g**) with Anhydrous Aluminium Bromide in Acetonitrile.* Flavone (**6**) (100 mg) was dissolved in a solution of anhydrous aluminum bromide (2 g)–acetonitrile (5 ml) and heated at 50 °C for 12—48 h. To the reaction mixture, a 0.5—1% hydrochloric acid (*ca.* 50 ml) solution was added, and the mixture was warmed at 60—70 °C for 10—20 min. The separated precipitate was extracted with ethyl acetate. The extract was washed with water and evaporated. The residue was analyzed by a high performance liquid chromatograph and then separated into each component (Tables 9 and 10).

Acetates (**16**) of **2** were synthesized by a hot acetic anhydride-pyridine method (Table 11).

References

1) Part V of this series; T. Horie, H. Kourai, H. Osaka, and M. Nakayama, *Bull. Chem. Soc. Jpn.*, **55**, 2933 (1982).

2) H. C. Gupta, K. N. N. Ayengar, and S. Rangaswami, *Indian J. Chem.*, **13**, 215 (1975).

3) M. D. Whalen and T. J. Mabry, *Phytochemistry*, **18**, 263 (1979).

4) V. M. Chari, R. J. Grayer-Barkmeijer, J. B. Harborne, and Bengt-Göran Österdahl, *Phytochemistry*, **20**, 1977 (1981).

5) K. Venkateswara Rao, K. Visveswara Rao, and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **25A**, 427 (1947); M. Krishnamurti, T. R. Seshadri, and P. R. Shankaran, *Tetrahedron*, **22**, 941 (1966).

6) V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **24A**, 243 (1946).

7) T. Horie, *Nippon Kagaku Kaishi*, **1978**, 748.

8) K. Nakazawa and C. Isoma, "Yukikagobutsu-goseiho," ed by the Society of Synthetic Organic Chemistry, Japan, Gihodo, Tokyo (1970), Vol. 20, pp. 61—64.

9) T. Horie, H. Kourai, M. Nakayama, M. Tsukayama, and M. Masumura, *Nippon Kagaku Kaishi*, **1980**, 1397.

10) M. Nakayama, T. Horie, Chun-Nan Lin, M. Arisawa, M. Shimizu, and N. Morita, *Yakugaku Zasshi*, **103**, 675 (1983).

11) M. Nakayama, S. Hayashi, K. Fukui, T. Horie, and M. Masumura, *Bull. Chem. Soc. Jpn.*, **45**, 2202 (1972).

12) K. Fukui, M. Nakayama, and T. Horie, *Bull. Chem. Soc. Jpn.*, **42**, 2327 (1969); M. Nakayama, K. Fukui, T. Horie, Y. Shimizu, and M. Masumura, *Nippon Kagaku Zasshi*, **91**, 1174 (1970).

13) K. Fukui, M. Nakayama, and T. Horie, *J. Sci. Hiroshima Univ., Ser. A-II*, **33**, 305 (1969).

14) K. Fukui, M. Nakayama, and T. Horie, *Bull. Chem. Soc. Jpn.*, **43**, 1524 (1970).

15) K. Fukui, M. Nakayama, T. Matsui, M. Masumura, and T. Horie, *Nippon Kagaku Zasshi*, **90**, 1270 (1969).

16) M. Nakayama, T. Horie, M. Makino, S. Ganno, and A. Narita, *Nippon Kagaku Kaishi*, **1978**, 1390.

17) S. C. Chhabra, S. R. Gupta, T. R. Seshadri, and N. D. Sharma, *Indian J. Chem.*, **14B**, 651 (1976).

18) J. B. Harborne and H. T. Clifford, *Phytochemistry*, **8**, 2071 (1969).

19) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968); K. S. Bhide, R. B. Mujumdar, and A. V. Rama Rao, *Indian J. Chem.*, **14B**, 168 (1976).

20) S. Rangaswamy and E. Venkata Rao, *Proc. Indian Acad. Sci.*, **54A**, 51 (1961); G. O. P. Doherty, N. B. Haynes, and W. B. Whalley, *J. Chem. Soc.*, **1963**, 5577.