Communications to the Editor

[Chem. Pharm. Bull.
32(10)4217—4219(1984)]

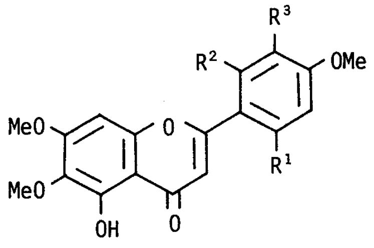
SYNTHESIS OF 5,6'-DIHYDROXY-2',3',4',6,7-PENTAMETHOXYFLAVONE

Munekazu Iinuma,* Kiyoshi Iwashima, Toshiyuki Tanaka
and Shin Matsuura
Gifu College of Pharmacy, 5-6-1 Mitahora-higashi, Gifu 502,
Japan

5,6'-Dihydroxy-2',3',4',6,7-pentamethoxy- (1), 2',5-dihydroxy-3',4',6,6',7-pentamethoxy- (2) and 3',5-dihydroxy-2',4',6,6',7-pentamethoxyflavone (3) were synthesized to compare with brickellin isolated from Brickellia veronicaefolia and B. chlorolepis. The spectral properties of these synthetic flavones were not consistent with those of brickellin.

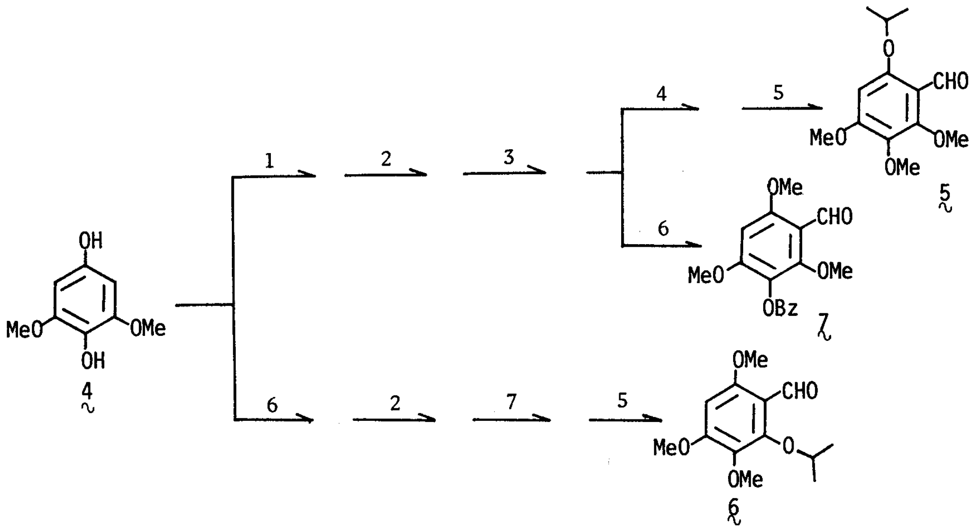
KEYWORDS —— flavone synthesis; 5,6'-dihydroxy-2',3',4',6,7-pentamethoxyflavone; 2',5-dihydroxy-3',4',6,6',7-pentamethoxyflavone; 3',5-dihydroxy-2',4',6,6',7-pentamethoxyflavone

As the third instance of the naturally occurring flavones, tetra-oxygenated in ring B, brickellin was isolated by Roberts *et al.* from Brickellia veronicaefolia and B. chlorolepis, and the structure was proposed by them to be 5,6'-dihydroxy-2',3',4',6,7-pentamethoxyflavone (1) by spectroscopic evidence.[1] In order to confirm the structure (1) proposed for brickellin, we synthesized the flavone (1) along with its isomers, 2',5-dihydroxy-3',4',6,6',7-pentamethoxy- (2) and 3',5-dihydroxy-2',4',6,6',7-pentamethoxyflavone (3) as shown in Chart 1. The respective aldehydes necessary for preparation of the ring B moieties of these flavones, *i.e.*, 6-isopropyloxy-2,3,4-trimethoxy- (5), 2-isopropyloxy-3,4,6-trimethoxy- (6), and 3-benzyloxy-2,4,6-trimethoxybenzaldehyde (7)[2] were synthesized from 2,5-dihydroxy-1,3-dimethoxybenzene (4) in the way shown in Chart 2. A debenzylation of 3,6-dibenzyloxy-2,4-dimethoxybenzaldehyde (procedure 3) gave a mixture of monophenol and diphenol compounds. The phenols were separated by silica gel chromatography (eluent: $CHCl_3$). A partial demethylation of 2,3,4,6-tetramethoxy-benzaldehyde (procedure 7) gave mere 2-hydroxy-3,4,6-trimethoxybenzaldehyde selectively. The aldehydes (5, 6 and 7) were condensed with 2-hydroxy-4,5,6-trimethoxyacetophenone in the usual way to give 2'-hydroxy-6-isopropyloxy-2,3,4,4',5',6'-hexamethoxy- (8), 2'-hydroxy-2-isopropyloxy-3,4,4',5',6,6'-hexamethoxy- (9) and 3-benzyloxy-2'-hydroxy-2,4,4',5',6,6'-hexamethoxychalcone (10), respectively.[3] These chalcones were oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dry dioxane into the corresponding flavones (8', 9' and 10'). The



1 ; R^1 = OH, R^2 = R^3 = OMe
2 ; R^2 = OH, R^1 = R^3 = OMe
3 ; R^3 = OH, R^1 = R^2 = OMe

Chart 1



1; BzCl-K_2CO_3/DMF, 2; $POCl_3$-DMF, 3; Pd-C,H_2/AcOEt, 4; CH_3J-K_2CO_3/$(CH_3)_2CO$,
5; $(CH_3)_2CHBr$,K_2CO_3/DMF, 6; $(CH_3)_2SO_4$-KOH, 7; BCl_3/CH_2Cl_2 Bz: $-CH_2C_6H_5$

Chart 2

resulting flavones were derived into **1**, **2** and **3** by partial demethylation and simultaneous deisopropylation (**8**' and **9**') with BCl_3, or by the usual debenzylation followed by partial demethylation (**10**'). Table I shows the physical and spectral properties of the flavones thus obtained.

Table I. Physical and Spectral Properties of **1**, **2**, **3** and Brickellin

	1	**2**	**3**	Brickellin
mp (°C)	177-178	187-188	198-199	197
^{1}H NMR ($CDCl_3$) δ	6.39 6.46 6.53	6.12 6.37 6.45	6.32 6.35 6.45	6.35 6.45 6.88
MS m/z (rel. int.)	404(M^+)(100), 389(72), 375(17), 361(8), 359(17), 209(17), 181(28), 153(21)	404(M^+)(100), 389(81), 375(24), 361(11), 359(24), 209(16), 181(19), 153(21)	404(M^+)(100), 389(86), 375(19), 361(8), 359(17), 209(13), 181(18), 153(19)	404(M^+)(100), 403(14), 389(85), 372(60), 361(1), 296(1), 208(31), 181(33), 153(29)

Table II. UV Spectral Data of **1**, **2**, **3** and Brickellin by Use of Shift Reagents

	1	**2**	**3**	Brickellin
λ_{max}^{MeOH} nm (log ε)	262, 326 (4.3)(4.1)	264, 321 (4.2)(4.1)	262, 300, 331sh (4.3)(4.0)(4.0)	262, 345
+$AlCl_3$	275, 293sh, 368	276, 295sh, 344	276, 326, 379	272, 322sh, 394
+$AlCl_3$ + HCl	275, 296sh, 356	276, 295sh, 344	276, 322, 371	272, 318sh, 386
+NaOMe	264, 380	291sh, 340	269, 360	254, 402
+NaOAc	262, 326	264, 321	262, 300, 330	260, 344

The aromatic protons (H-3, 5' and 8) of the flavone with one hydroxyl and three methoxyl groups at either position of C-2', 3', 4' and 6' had their chemical shifts in the field higher than 6.88 ppm1) assigned to C-5' in brickellin (Table I). In UV spectra (Table II), the absorption bands based on band I of the synthesized flavones were all observed in ca 321-331 nm, but the corresponding band was obseved at 345 nm in the case of brickellin. The present UV absorption results are generally in agreement with those of 4',5,6'-trihydroxy-2',3',6,7-tetramethoxyflavone and its isomers.4) The bathochromic shifts of band I of the present flavones by the use of shifts reagents were also very similar to the results of our previous studies.5) Furthermore, in the ^{13}C NMR spectrum of **1**,6) the chemical shifts of skeletal carbons were utterly different from those of brickellin. The assignment was based on 2', 3', 4', 5, 6, 6', 7-heptamethoxyflavone described in our preceding paper.7) The carbon signals of methoxyl groups of **1** located at C-2', 3' and 6 were in the field as low as 61.7-60.9 ppm and those located at C-4' and 7 were in 56.4 and 56.1 ppm. However, in brickellin the signals of two methoxyl groups were at 61.7 and 60.5 ppm and three methoxyls at 56.5, 56.1 and 55.7 ppm. On the basis of the physical and spectral comparison of the synthesized flavones with those of brickellin, the proposed structure (**1**) for brickellin is not correct.

REFERENCES AND NOTES

1) M.F. Roberts, B.N. Timmermann, T.J. Mabry, R. Brown, and S.A. Matlin, Phytochemistry, 23, 163 (1984).

2) **5**; A yellow oil. ^1H NMR (CCl_4) δ : 3.66 (3H, s, OCH_3), 3.80 (6H, s, $2xOCH_3$), 6.23 (1H, s, H-5), 10.12 (1H, s, CHO). MS m/z : 254 (M^+). **6**; A yellow oil. ^1H NMR (CCl_4) δ : 3.69, 3.80, 3.89 (3H, each s, OCH_3), 6.26 (1H, s, H-5), 10.15 (1H, s, CHO). MS m/z : 254 (M^+). **7**; A colorless oil. ^1H NMR (CCl_4) δ : 3.80 (3H, s, OCH_3), 3.84 (6H, s, $2xOCH_3$), 6.15 (1H, s, H-5), 10.12 (1H, s, CHO). MS m/z : 302 (M^+).

3) **8**; An orange-yellow oil. ^1H NMR ($CDCl_3$) δ : 6.27, 6.31 (1H, each s, H-3',5), 8.10 (1H, d, J= 15.6 Hz, H-β), 8.42 (1H, d, J= 15.6 Hz, H-α), 13.81 (1H, s, OH). **9**; A reddish oil. ^1H NMR ($CDCl_3$) δ : 6.12, 6.20 (1H, each s, H-3',5), 8.12 (2H, H-α and β), 13.80 (1H, s, OH). **10**; mp 142-143°C (MeOH), orange-yellow needles. ^1H NMR ($CDCl_3$) δ : 6.11, 6.20 (1H, each s, H-3', 5), 7.94 (1H, d, J= 16.0 Hz, H-β), 8.21 (1H, d, J= 16.0 Hz, H-α), 13.78 (1H, s, OH).

4) M. Iinuma, T. Tanaka, and S. Matsuura, Heterocycles, 20, 2425 (1983).

5) M. Iinuma, T. Tanaka, ans S. Matsuura, Chem. Pharm. Bull., 32, 2296 (1984).

6) **1**; ^{13}C NMR ($CDCl_3$) δ : 182.9 (4), 162.0 (2), 159.0 (7), 156.6 (4'), 154.2 (2'), 152.6 (6'), 151.9 (5 and 9), 136.0 (3'), 132.4 (6), 112.0 (3), 106.7 (1'), 105.9 (10), 96.8 (8), 91.0 (5'), 61.7, 61.2, 60.9 (CH_3O at C-2',3',6), 56.4, 56.1 (CH_3O at C-4',7).

7) M. Iinuma, T. Tanaka, and S. Matsuura, Chem. Pharm. Bull., accepted.

(Received August 3, 1984)