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Flavonoids Syntheses. II.[1] Synthesis of Flavones with a 2′,3′,6′-Trioxygenated Ring B

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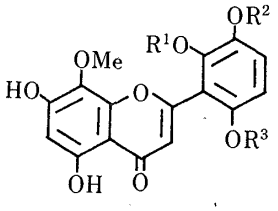
3′,5,6′,7-Tetrahydroxy-2′,8-dimethoxyflavone (**1**) and its isomers (**2**, **3** and **4**) were synthesized to confirm the proposed structure for a flavone isolated from *Scutellaria baicalensis* and *S. rehderiana*.

Keywords——flavone synthesis; 2′,3′,6′-trioxygenated flavone; 3′,5,6′,7-tetrahydroxy-2′,8-dimethoxyflavone; 2′,5,6′,7-tetrahydroxy-3′,8-dimethoxyflavone; 2′,3′,5,7-tetrahydroxy-6′,8-dimethoxyflavone; 3′,5,6′,7-tetrahydroxy-2′,6-dimethoxyflavone

Flavones with a trioxygenated ring B, having an apparent hydroquinone structure, are of interest because of their stability and occurrence in nature. The syntheses and the spectral properties of the flavones with 2′,3′,5′- and 2′,4′5′-trioxygenated moieties in ring B were dealt with in our previous papers (2′,3′,5′-,[2] 2′,4′,5′-[3]). The only known naturally occurring flavone with a 2′,3′,6′-trioxygenated B ring is 3′,5,6′,7-tetrahydroxy-2′,8-dimethoxyflavone (**1**) isolated from *Scutellaria baicalensis* by Tomimori *et al.*[4] and from *S. rehderiana* by Liu *et al.*[5] In this paper, we describe syntheses of **1**, together with 2′,5,6′,7-tetrahydroxy-3′,8-dimethoxy- (**2**) and 2′,3′,5,7-tetrahydroxy-6′,8-dimethoxyflavone (**3**) as isomers of ring B, and 3′,5,6′,7-tetrahydroxy-2′,6-dimethoxyflavone (**4**) as an isomer of ring A, in order to confirm the proposed structure.



1: $R^2=R^3=H$, $R^1=Me$
2: $R^1=R^3=H$, $R^2=Me$
3: $R^1=R^2=H$, $R^3=Me$

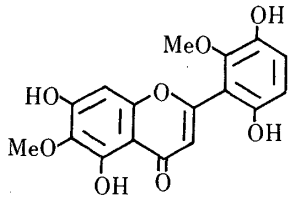


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Chart 1

The requisite aldehydes for preparation of the above flavones, 3,6-diisopropyloxy-2-methoxy- (**5**), 2,6-diisopropyloxy-3-methoxy- (**6**), and 2,3-diisopropyloxy-6-methoxybenzaldehyde (**7**), were synthesized from 1,4-diisopropyloxy-2-methoxy- (**8**), 2,4-diisopropyloxy-1-methoxy- (**9**), and 1,2-diisopropyloxy-4-methoxybenzene (**10**) by metalation with *n*-butyl lithium followed by treatment with *N*,*N*-dimethylformamide (DMF). These aldehydes were condensed with 2-hydroxy-4-isopropyloxy-3,6-dimethoxyacetophenone (**11**)[6] in the presence of piperidine in pyridine to give 2′-hydroxy-3,4′,6-triisopropyloxy-2,3′,6′-trimethoxy- (**12**), 2′-hydroxy-2,4′,6-triisopropyloxy-3,3′,6′-trimethoxy- (**13**) and 2′-hydroxy-2,3,4′-triisopropyloxy-3′,6,6′-trimethoxychalcone (**14**), respectively. The resulting chalcones

TABLE I. Physical and Spectral Data for **1**, **2**, **3** and **4**

	1	**2**	**3**	**4**
mp (°C)	252—254 (dec.) (lit.[4] 255)	163—164 (dec.)	272—274 (dec.)	212—213
^{1}H-NMR δ (DMSO-d_6)	6.20 (s, H-3), 6.26 (s, H-6), 6.50, 6.88 (d, J=9 Hz, H-5′ and H-4′)	6.15 (s, H-3), 6.23 (s, H-6), 6.31, 6.90 (d, J=8.5 Hz, H-5′ and H-4′)	6.14 (s, H-3), 6.23 (s, H-6), 6.35, 6.85 (d, J=9 Hz, H-5′ and H-4′)	6.20 (s, H-3), 6.45 (s, H-8), 6.52, 6.83 (d, J=9 Hz, H-5′ and H-4′)
	3.79, 3.81 (2)[a]	3.68, 3.70 (2)[a]	3.62, 3.67 (2)[a]	3.70, 3.75 (2)[a]
IR ν_{max}^{KBr} cm^{-1}	3400, 1660, 1610	3350, 1660, 1620	3450, 1660, 1630, 1605	3400, 1660, 1610
MS m/z (rel. int.)	346 (M^+, 69), 331 (100), 316, 303, 288, 167, 139	346 (M^+, 56), 331 (100), 316, 303, 288, 167, 139	346 (M^+, 60), 331 (100), 316, 303, 167, 139	346 (M^+, 100), 331 (78), 328, 167, 139
UV λ_{max}^{MeOH} nm	265, 310sh, 340	265, 310sh, 340sh	266, 312sh, 340	262, 306, 340inf.
+$AlCl_3$	276, 318sh, 385	275, 295sh, 326, 390	275, 297sh, 335, 386	273, 325, 370sh
+$AlCl_3$+HCl	276, 318sh, 385	276, 295sh, 323, 390	277, 298sh, 320sh, 386	273, 322, 370sh
+NaOMe	275, 356	275, 303sh, 368	275, 360sh	268, 350
+AcONa	274, 340	274, 340sh	273, 335sh	264, 345

a) The number of methoxyl groups.

were oxidized in the usual way to the corresponding flavones (**12a**, **13a** and **14a**), which were treated with boron trichloride[6] to afford the desired flavones, **1**, **2** and **3**.

On the other hand, the aldehyde (**5**) was condensed with 2-hydroxy-4,6-diisopropyloxy-5-methoxyacetophenone (**15**)[6] to give 2′-hydroxy-3,4′,6,6′-tetraisopropyloxy-2,5′-dimethoxychalcone (**16**), which was led to **4** in the same manner as described above. The mp and spectral properties of the flavones thus obtained are listed in Table I. On the basis of direct comparison with the present synthetic flavones (co-thin layer chromatography and spectral data), the natural flavone from *S. baicalensis* and *S. rehderiana* was confirmed to be 3′,5,6′,7-tetrahydroxy-2′,8-dimethoxyflavone.

Experimental

Flavone synthesis *via* the chalcone and the apparatus used were described in the previous paper.[2]

3′,5,6′,7-Tetrahydroxy-2′,8-dimethoxyflavone (1)——An ethereal solution of 1,4-diisopropyloxy-2-methoxybenzene (**8**) (4.3 g) was added dropwise to 15% *n*-BuLi hexane solution (30 ml) and the mixture was refluxed for 3 h, then allowed to cool. DMF (3 ml) was added to the reaction mixture and the whole was heated for a further 1 h, poured into 5% HCl (200 ml) and extracted with ether. The ethereal extract was concentrated under reduced pressure to give **5** (3.5 g) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.35, 1.38 (6H, each d, J=6 Hz, $(C\underline{H}_3)_2CH$), 3.90 (3H, s, OCH_3), 4.50 (2H, m, 2×C$\underline{H}$<), 6.65, 7.13 (1H, each d, J=9 Hz, H-4, 5), 10.63 (1H, s, CHO). Condensation of **5** (700 mg) with **11** (500 mg) in pyridine containing piperidine (1 ml) gave **12** (900 mg), as a red oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30, 1.35, 1.40 (6H, each d, J=6 Hz, $(C\underline{H}_3)_2CH$), 3.78 (3H, s, OCH_3), 3.83 (6H, s, 2×OCH_3), 4.50 (3H, m, 3×C$\underline{H}$<), 5.95 (1H, s, H-5′), 6.55, 6.85 (1H, each d, J=9 Hz, H-4,5), 8.05, 8.35 (1H, each d, J=15.6 Hz, H-β, α). The chalcone (**12**) (500 mg) was oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone to afford **12a** (320 mg), as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 6.22 (1H, s, H-3), 6.38 (1H, s, H-6), 6.58 (1H, d, J=9 Hz, H-5′), 6.92 (1H, d, J=9 Hz, H-4′). The resulting flavone (320 mg) gave **1** (180 mg) as pale yellow needles (AcOEt–C_6H_{14}) on treatment with BCl_3.[6]

2′,5,6′,7-Tetrahydroxy-3′,8-dimethoxyflavone (2)——The same procedure as described above was used. An aldehyde (**6**) (3.8 g) was derived from **9** (4 g) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30, 1.35 (6H, each d, J=6 Hz, 2×$(C\underline{H}_3)_2CH$), 3.88 (3H, s, OCH_3), 4.40 (2H, m, 2×C$\underline{H}$<), 6.48, 6.90 (2H, d, J=9 Hz, H-4,5), 10.25 (1H, s, CHO). **13**: An orange-yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28, 1.33, 1.40 (6H, each d, J=6 Hz, $(C\underline{H}_3)_2CH$), 3.75 (6H, s, 2×OCH_3), 3.80 (3H, s, OCH_3), 4.50 (3H, m, 3×C$\underline{H}$<), 5.95 (1H, s, H-5′), 6.53, 6.80 (1H, each d, J=9 Hz, H-4,5), 7.05, 7.38 (1H, each d, J=15.8 Hz, H-β,α), 14.08 (1H, s, OH). **13a**: A brown oil. ^{1}H-NMR ($CDCl_3$) δ: 6.20 (1H, s, H-3), 6.36 (1H, s, H-6), 6.55 (1H, d, J=9 Hz, H-5′), 6.89 (1H, d, J=9 Hz, H-4′). On treatment with BCl_3, **13a** (350 mg) gave **2** (200 mg) as yellow needles (AcOEt–C_6H_{14}).

2′,3′,5,7-Tetrahydroxy-6′,8-dimethoxyflavone (3)——The same procedure as described above was used. Compound **10** (4 g) was led to **7** (3.5 g), a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (12H, d, J=6 Hz, 2×(CH_3)$_2$CH), 1.38 (6H, d, J=6 Hz, (CH_3)$_2$CH), 3.75 (3H, s, OCH_3), 3.81 (6H, s, 2×OCH_3), 4.43—4.63 (3H, m, 3×CH<), 5.93 (1H, s, H-5′), 6.35, 6.85 (1H, each d, J=9 Hz, H-5), 8.02, 8.40 (1H, each d, J=15.8 Hz, H-β,α), 14.06 (1H, s, OH). **14a**: A pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 6.24 (1H, s, H-3), 6.39 (1H, s, H-6), 6.55 (1H, d, J=9 Hz, H-5′), 6.93 (1H, d, J=9 Hz, H-4′). A flavone **14a** (350 mg) afforded **3** (200 mg) as yellow prisms (AcOEt–C_6H_{14}) on treatment with BCl_3.

3′,5,6′,7-Tetrahydroxy-2′,6-dimethoxyflavone (4)——Condensation of **5** (1 g) with **15** (700 mg) gave **16** (1.1 g) as a red oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23, 1.30, 1.38, 1.43 (6H, each d, (CH_3)$_2$CH), 3.75, 3.86 (3H, each s, OCH_3), 4.50 (4H, m, 4×CH<), 6.21 (1H, s, H-3), 6.55, 6.88 (1H, each d, J=9 Hz, H-4,5), 8.00, 8.48 (1H, each d, J=16 Hz, H-β,α), 13.23 (1H, s, OH). **16a**: ^{1}H-NMR (CCl_4) δ: 5.99 (1H, s, H-8), 6.52 (1H, d, J=9 Hz, H-5′), 6.88 (1H, d, J=9 Hz, H-4′). On treatment with BCl_3, **16a** (200 mg) gave **4** (100 mg) as yellow prisms (AcOEt–C_6H_{14}).

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