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SYNTHESIS OF 6,7,2',3'-TETRAMETHOXY-5,4',6'-TRIHYDROXYFLAVONE

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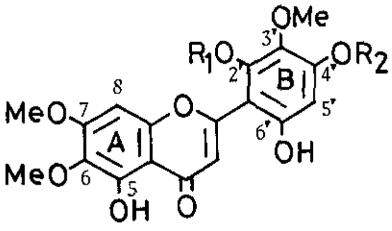
Abstract — 6,7,2',3'-Tetramethoxy-5,4',6'-trihydroxyflavone and its positional isomers were synthesized, and any of them were not identical with the flavone isolated from *Notholaena aschenborniana*.

The structure of hepta-substituted flavone, isolated from *Notholaena aschenborniana* KL. (Polypodiaceae) was concluded to be 6,7,2',3'-tetramethoxy-5,4',6'-trihydroxyflavone (1) by spectroscopic methods by Wollenweber *et al.*[1] We called attention to the structure of this flavone, because it was the first reported flavone having tetra-O-substituted B ring, and was was homospecies flavone[2] which had the same substitutional patterns between in ring A and in ring B in the corresponding β-diketone (3). For preparation of 1, the problem was how to prepare B ring moiety,



1 $R_1 = Me$, $R_2 = H$
2 $R_1 = H$, $R_2 = Me$

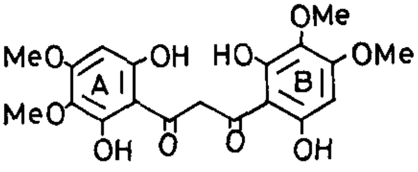


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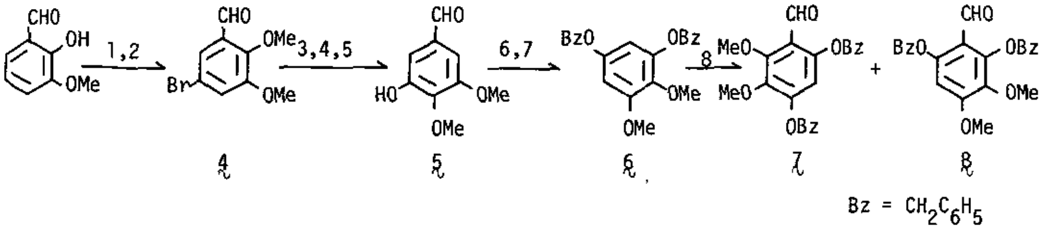
Chart 1

2,4-dibenzyloxy-5,6-dimethoxybenzaldehyde (7). 3-Hydroxy-4,5-dimethoxybenzaldehyde (irininaldehyde) (5), which was the important synthetic intermediate as precursor for 7 and had not yet been prepared successfully, was able to be synthesized by our new method from o-vanillin by five steps as shown in chart 2, [5; ^{1}H NMR

($CDCl_3$) δ : 3.88, 3.96 (6H, each s, 2xOC$\underline{H}_3$), 6.98 (O$\underline{H}$), 7.03, 7.10 (2H, each d, J= 2.3 Hz, H-2,6), 9.75 (C$\underline{H}$O)]. After 5 was subjected to the Baeyer-Villiger reaction, the resulting diphenol was benzylated with benzyl chloride and K_2CO_3 in DMF to give



1: Br_2/AcOH, 2: Me_2SO_4/acetone, 3: HCO_3H/HCO_2H, 4: CuCN/DMF,
5: Raney Ni/HCO_2H, 6: HCO_3H/HCO_2H, 7: BzCl, K_2CO_3/DMF, 8: $POCl_3$/DMF.

Chart 2

6 as a colorless oil [^{1}H NMR ($CDCl_3$) δ : 3.71, 3.76 (6H, each s, 2xOC$\underline{H}_3$), 4.88, 4.99 (4H, each s, 2xOC$\underline{H}_2$Ph), 6.20 (2H, s, H-4,6), 7.30 (10H, 2xPh). MS m/z: 350 (M^+)]. Compound (6) was subjected to the Vilsmeier reaction to obtain two aldehydes, 7 and 8 [4] which were separated by chromatography on silica gel (eluent: C_6H_6). The difference of these positional isomers was clearly recognized by NOE technique in their ^{1}H NMR spectra. NOE of the aldehyde proton in 7 was observed 23% when methoxy protons were irradiated, but in the case of 8, NOE could not be observed by the similar irradiation. These aldehydes were condensed with 2-hydroxy-4,5,6-trimethoxyacetophenone (9) respectively in pyridine containing small amounts of piperidine to obtain 2'-hydroxy-2,4-dibenzyloxy-5,6,4',5',6'-pentamethoxychalcone (10) [mp 137-139°C, ^{1}H NMR (CCl_4) δ : 8.10 (1H, d, J=16 Hz, H-β), 8.46 (1H, d, J= 16 Hz, H-α)], and 2'-hydroxy-2,6-dibenzyloxy-3,4,4',5',6'-pentamethoxychalcone (11) [mp 136-137°C, ^{1}H NMR (CCl_4) δ : 8.08 (1H, d, J=16 Hz, H-β), 8.13 (1H, d,

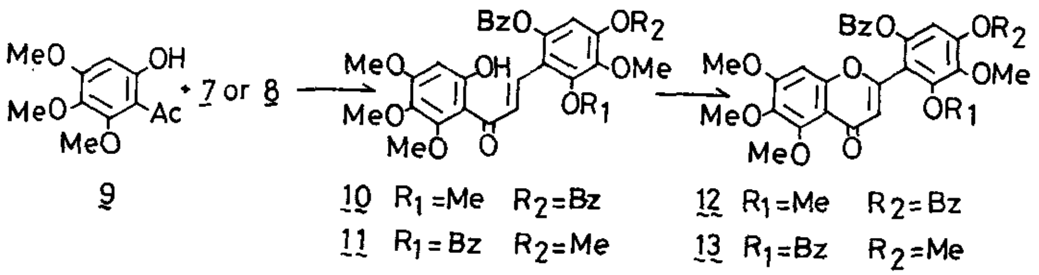


Chart 3

J=16 Hz, H-α)]. It is generally difficult to convert the chalcones substituted with more than two benzyloxyl groups into the corresponding flavanones. Therefore, **10** and **11** *were directly oxidized with DDQ in dioxane*[6] *into the respective flavones;* 4',6'-dibenzyloxy-5,6,7,2',3'-pentamethoxyflavone (**12**) and 2',6'-dibenzyloxy-5,6,7,3',4'-pentamethoxyflavone (**13**).[7] Debenzylation of **12** by catalytic hydrogenation with 10% Pd-C afforded 4',6'-dihydroxy-5,6,7,2',3'-pentamethoxyflavone (**14**) [mp 222-224°C (decomp.), ^{1}H NMR (DMSO-d6) δ : 3.81, 3.83, 3.85, 3.95 (15H, each s, 5x $OC\underline{H}_3$), 6.05, 6.30, 6.69 (3H, each s, H-3,8,5'); MS m/z: 404 (M^+), 389 (M^+-CH_3) (100%)], which was partially demethylated with BCl_3 in dichloromethane at -70°C[8] to provide **1** as a pale yellow powder [mp 281°C (AcOEt-C_6H_{14}), ^{1}H NMR (DMSO-d6) δ : 3.74, 3.79, 3.85, 3.95 (12H, each s, 4x$OC\underline{H}_3$), 6.28, 6.33, 6.75 (3H, each s, H-3,8, 5'); MS m/z: 390 (M^+), 375 (M^+-CH_3), 195; UV λ_{max}^{MeOH} (nm): 263, 329. λ^{+AlCl_3} : 275, 298sh, 365. λ^{+AlCl_3+HCl}: *275, 297sh, 362.* λ^{+NaOMe}: *263, 295sh, 390]. The flavone* (**2**) was also obtained from **13** in the same manner as **1**. However, the synthesized 6,7,2',3'-tetramethoxy-5,4',6'-trihydroxyflavone (**1**) was not identical with the naturally occurring flavone by comparison of co-TLC. Therefore, the proposed structure for the flavone was not correct. For further investigation of the structure, the plausible positional isomers, that is, 6,7,2',4'-tetramethoxy-5,3',6'-trihydroxyflavone (**15**), 6,7,3',6'-tetramethoxy-5,2',4'-trihydroxyflavone (**16**), and 7,8,3',6'-tetramethoxy-5,2',4'-trihydroxyflavone (**17**) were synthesized. The requisite starting materials, 3,6-dibenzyloxy-2,4-dimethoxybenzaldehyde (**18**), 2,4-dibenzyloxy-3,6-dimethoxybenzaldehyde (**19**) and 2-hydroxy-3,4,6-trimethoxyacetophenone (**20**) were prepared by the usual ways. After condensation of **9** with **18**, **9** with **19**, and **19** with **20**, the resulting chalcones were converted into **15**, **16** and **17** by the same way described above. The physical and spectral properties of the flavones thus obtained were summarized in Table I. Each of these properties was not agreed with that of the reported flavone.

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REFERENCES AND FOOTNOTES

1. M. Jay, J. Favre-Bonvin, B. Boirin, M-S. Virecel, and E. Wollenweber,

Phytochemistry, 20, 2307 (1981).

2. The flavones derived from the β-diketones possessing the same substitutional patterns in ring A and B were especially called homospecies flavones. The most simplest homospecies flavone then 2'-oxygenated flavone: M. Iinuma and S. Matsuura, Yakugaku Zasshi, 100, 657 (1980).
3. M. Iinuma, T. Tanaka, and S. Matsuura, Yakugaku Zasshi, in press.
4. 7: ^{1}H NMR ($CDCl_3$) δ : 3.78 (6H, s, 2x$OC\underline{H}_3$), 5.10 (4H, s, 2x$OC\underline{H}_2Ph$), 6.29 (1H, s, H-5), 7.38 (10H, s, 2xPh), 10.38 (1H, s, $C\underline{H}O$); MS m/z: 378 (M^+), 278, 181. 8: ^{1}H NMR ($CDCl_3$) δ : 3.80, 3.93 (6H, each s, 2x$OC\underline{H}_3$), 5.04, 5.10 (4H, each s, 2x$OC\underline{H}_2Ph$), 10.30 (1H, s, $C\underline{H}O$); MS m/z: 378 (M^+), 278, 181.
5. By a usual method of chalcone synthesis, an o-hydroxyacetophenone was tried to condense with benzaldehyde in the presence of KOH. However, no reaction occurred in the case of 7 and 8.
6. In preparation.
7. 13: ^{1}H NMR ($CDCl_3$) δ : 3.86, 3.88, 3.90, 3.95, 4.04 (15H, each s, 5x$OC\underline{H}_3$), 5.11, 5.15 (4H, each s, 2x$OC\underline{H}_2Ph$), 6.28, 6.43, 6.53 (3H, each s, H-3,5,8), 7.21, 7.31 (10H, each br s, 2xPh).
8. D.M. Dean, J. Goodchild, L.E. Houghton, J.A. Martin, R.B. Morton, B. Parton, A.W. Price, and N. Somvichien, Tetrahedron Letters, 4153, 1966.

Table I Physical and Spectral Properties of 2, 15, 16 and 17

	mp (°C)	^{1}H NMR (DMSO-d6)	MS m/z (rel. int.)
2	239 (decomp.)	6.19 (H-5') 6.28 (H-3) 6.73 (H-8)	390 (M^+)(100) 375 (83)
15	232-233	6.28 (H-3) 6.36 (H-5') 6.75 (H-8)	390 (M^+)(100) 375 (75)
16	241	6.13 (H-5') 6.21 (H-3) 6.74 (H-8)	390 (M^+)(100) 375 (60)
17	220 (decomp.)	6.11 (H-5') 6.20 (H-3) 6.53 (H-6)	390 (M^+)(63) 375 (100)

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