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Synthetic Studies of the Flavone Derivatives. XVIII.[*1] The Syntheses of 5,7,3′-Trihydroxy-3,8,4′,5′-tetramethoxyflavone and Related Compounds

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Recently, a new pigment isolated from *Beyeria brevifolia* (Muell Arg.) Benth.[1] was identified as 5,7,3′-trihydroxy-3,8,4′,5′-tetramethoxyflavone (I).

The present paper will describe the syntheses of I and its related compounds from 3,ω-dimethoxy-2,4,6-trihydroxyacetophenone (II)[2] by a modification of a procedure reported earlier.[2-6]

According to the method of Allan-Robinson's flavone synthesis, the condensation of the ketone II with 3-benzyloxy-4,5-dimethoxybenzoic anhydride and potassium 3-benzyloxy-4,5-dimethoxybenzoate, followed by treatment with alcoholic potassium hydroxide, was expected to afford a mixture of 3′-benzyloxy-5,7-dihydroxy-3,6,4′,5′-tetramethoxyflavone (III) and the 3′-benzyl ether (IV) of I. The reaction mixture could be separated into two crystals, A (mp 159.5—160.5°C) and B (mp 126—127 and 135—135.5°C), by a fractional partition. The catalytic hydrogenolysis of A over Pd–C gave the 5,7,3′-trihydroxyflavone derivative (V), which was then converted into the triacetate (VI), triethyl (VII), and trimethyl ether (VIII) with usual methods. The properties of VIII were superimposable upon those of 3,5,6,7,3′,4′,5′-heptamethoxyflavone.[7,8] Further, in the NMR spectra data[*2]

[*1] Part XVII of this series: K. Fukui, M. Nakayama and T. Horie, This Bulletin, **43**, 1524 (1970).

1) P. W. Chow and P. R. Jefferies, *Aust. J. Chem.*, **21**, 2529 (1968).

2) K. Fukui, T. Matsumoto, S. Nakamura, M. Nakayama and T. Horie, *Experientia*, **24**, 108 (1968); This Bulletin, **41**, 1413 (1968).

3) K. Fukui, M. Nakayama and T. Horie, *Experientia*, **24**, 417 (1968); This Bulletin, **41**, 2805 (1968).

4) K. Fukui, M. Nakayama and T. Horie, *Experientia*, **24**, 769 (1968); This Bulletin, **42**, 1649 (1969).

5) T. Horie, *Experientia*, **24**, 880 (1968); This Bulletin, **42**, 2701 (1969).

6) K. Fukui, T. Matsumoto, M. Nakayama and T. Horie, *Experientia*, **25**, 349 (1969); *J. Sci. Hiroshima Univ. Series A-II*, **33**, 221 (1969).

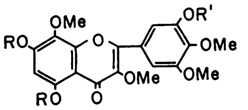
7) P. R. Jefferies, J. R. Knox and E. J. Middleton, *Aust. J. Chem.*, **15**, 532 (1962).

8) D. L. Dreyer, *J. Org. Chem.*, **33**, 3574 (1968).

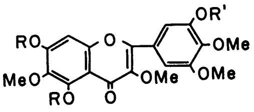
[*2] The NMR spectra were measured with a Hitachi R-20 spectrometer (60 MHz) in $CDCl_3$, using tetramethylsilane as the internal standard (δ, ppm): s, singlet; m, multiplet.

of VII and VIII, the chemical shift (δ *ca.* 6.70) of the singlet peak (1H) was very similar to that due to the C-8 proton of some flavones reported in the literature.[2-9] From the above results, A and V may be formulated as III and 5,7,3′-trihydroxy-3,6,4′,5′-tetramethoxyflavone respectively. On the other hand, the singlet peak at δ 6.46 (1H) of B can be assigned to the C-6 proton of the flavone nucleus. Thus, B is identified as the benzyl derivative (IV) of I. The hydrogenolysis of IV gave the desired flavone, I, which was then easily derived to triacetate (IX) and triethyl ether (X). The properties of the synthetic flavones (I, IX and X) were consistent with those described in an earlier report.[1]

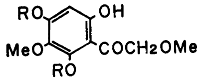
By a similar method, 5,7-dihydroxy-3,6,3′,4′,5′-pentamethoxyflavone (XI), which was easily converted into diacetate (XII) and diethyl ether (XIII), was prepared from II and 3,4,5-trimethoxybenzoic anhydride. XIII was also prepared by the reaction of the 4,6-diethoxy-5,ω-dimethoxy-2-hydroxyacetophenone (XIV)[2] with 3,4,5-trimethoxybenzoic anhydride. The dimethyl ether of XI was found to be identical with VIII by a direct comparison.



I R=R'=H
IV R=H R'=C6H5CH2
IX R=R'=CH3CO
X R=R'=Et



III R=H R'=C6H5CH2
V R=R'=H
VI R=R'=CH3CO
VII R=R'=Et
VIII R=R'=Me
XI R=H R'=Me
XII R=CH3CO R'=Me
XIII R=Et R'=Me



II R=H
XIV R=Et

Experimental*3

3′-Benzyloxy-5,7-dihydroxy-3,6,4′,5′-tetramethoxyflavone (III) and 3′-Benzyloxy-5,7-dihydroxy-3,8,4′,5′-tetramethoxyflavone (IV). A mixture of II (2.5 g),[2] 3-benzyloxy-4,5-dimethoxybenzoic anhydride (25 g), and potassium 3-benzyloxy-4,5-dimethoxybenzoate (9 g) was heated at 175—180°C under reduced pressure for 10 hr; the mixture was then treated by a method analogous with those of previous reports[2-6] to give an oily flavone mixture (*ca.* 3.5 g).

The mixture was dissolved with a 5% aqueous potassium hydroxide solution (50 m*l*) and then allowed to stand in a refrigerator. The precipitate thus separated was collected to give potassium salt of flavone. After the mother liquor had been acidified with hydrochloric acid, the resulting oily material was repeatedly treated with a solution of potassium hydroxide (1.2 g) and potassium carbonate (3.0 g) in water (20 m*l*). The second crop of the potassium salt was thus obtained.

The mother liquor was acidified with hydrochloric acid and extracted with ether. After the solvent had been removed, the residue was dissolved with absolute ether (*ca.* 10 m*l*) and then allowed to stand in a refrigerator. The crystals thus separated were collected and recrystallized from aqueous methanol to give a hydrate of IV as pale yellow needles; mp 95—100°C (67—68°C sinter); yield, 240 mg (4.5%). This was recrystallized from absolute ether to give yellow needles; mp 126—127°C and 135—135.5°C. UV: λ_{max} mμ (log ε); (EtOH) 278 (4.33), 314 (4.17), 370$_{sh}$ (4.05);*4 (EtOH-AcONa) 286 (4.39), 364 (3.99); (EtOH-AlCl$_3$) 288.5 (4.27), 314 (4.17), 349 (4.18), 420 (3.87). NMR:*2 6.46$_s$ (C$_6$–H), 7.40—7.60$_m$ (7H; C$_{2'}$–H, C$_{6'}$–H and C$_6\underline{H}_5$CH$_2$).

Found: C, 64.90; H, 5.18%. Calcd for $C_{26}H_{24}O_9$: C, 64.99; H, 5.04%.

The combined potassium salt of flavone was treated with diluted hydrochloric acid and extracted with ether. After the solvent had then been removed, the residue was recrystallized from ethanol to give III as pale yellow needles; mp 159.5—160.5°C; yield, 700 mg (13%). UV: λ_{max} mμ (log ε); (EtOH) 275 (4.21), 339 (4.29); (EtOH-AcONa) 277.5 (4.35), 304 (4.12), 352 (4.14); (EtOH-AlCl$_3$) 258 (4.09). 284 (4.17), 355 (4.27). NMR:*2 6.57$_s$ (C$_8$–H), 7.35—7.60$_m$ (7H; C$_{2'}$–H, C$_{6'}$–H C$_{6'}$–H and C$_6\underline{H}_5$CH$_2$).

Found: C, 64.75; H, 4.94%. Calcd for $C_{26}H_{24}O_9$: C, 64.99; H, 5.04%.

5,7,3′-Trihydroxy-3,6,4′,5′-tetramethoxyflavone (V). A solution of III (325 mg) dissolved in a mixture of ethyl acetate and methanol (1 : 1 : 100 m*l*) was shaken with Pd–C (10% : 140 mg) in hydrogen. The product was recrystallized from methanol to give V as yellow needles; mp 163.5—164.5°C; yield, 237 mg (90%). UV: λ_{max} mμ (log ε); (EtOH) 275 (4.21), 343 (4.28); (EtOH-AcONa) 277 (4.45), 304 (4.14), 378 (4.22); (EtOH-AlCl$_3$) 283 (4.20), 358 (4.29).

Found: C, 58.70; H, 4.82%. Calcd for $C_{19}H_{18}O_9$: C, 58.46; H, 4.65%.

Triacetate (VI). Mp 126—127°C (colorless prisms from ether). UV: λ_{max}^{EtOH} mμ (log ε); 248 (4.31), 327 (4.31).

Found: C, 58.23; H, 4.76%. Calcd for $C_{25}H_{24}O_{12}$: C, 58.14; H, 4.68%.

Triethyl Ether (VII). Mp 111.5—112.5°C (colorless needles from ether). UV: λ_{max}^{EtOH} mμ (log ε); 267$_{sh}$ (4.19), 328 (4.39). NMR:*2 6.72$_s$ (C$_8$–H), 7.37$_s$ (2H; C$_{2'}$–H and C$_{6'}$–H).

Found: C, 63.19; H, 6.43%. Calcd for $C_{25}H_{30}O_9$: C, 63.28; H, 6.37%.

Trimethyl Ether (3,5,6,7,3′,4′,5′-Heptamethoxyflavone) (VIII). Mp 153—154°C (colorless needles from methanol) (lit, mp 155—156°C,[7] 156—157°C[8]). UV: λ_{max}^{EtOH} mμ (log ε); 267$_{sh}$ (4.22), 327.5 (4.35). NMR:*2 6.74$_s$ (C$_8$–H), 7.38$_s$ (2H; C$_{2'}$–H and C$_{6'}$–H).

Found: C, 60.90; H, 5.51%. Calcd for $C_{22}H_{24}O_9$:

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9) C. A. Henrick and P. R. Jefferies, *Aust. J. Chem.*, **17**, 934 (1962); J. Massicot and J-P. Marthe, *Bull. Soc. Chim. Fr.*, **1962**, 1962; **1963**, 2712.

*3 All the melting points are uncorrected.

*4 sh=shoulder.

C, 61.10; H, 5.59%.

5, 7, 3′-Trihydroxy-3, 8, 4′, 5′-tetramethoxyflavone (I). IV (195 mg) was debenzylated by the method described for III; mp 213—214°C (yellow prisms from methanol) (lit, mp 214—216°C1)); yield, 140 mg (91%). UV: λ_{max} mμ (log ε); (EtOH) 279 (4.38), 314 (4.21), 355_{sh} (4.15); (EtOH–AcONa) 286 (4.55), 310_{sh} (4.27), 395 (4.11); (EtOH–$AlCl_3$) 284 (4.34), 314 (4.23), 350 (4.25), 407 (3.93).

Found: C, 58.35; H, 4.66%. Calcd for $C_{19}H_{18}O_9$: C, 58.46; H, 4.65%.

Triacetate (IX). Mp 126—127°C (colorless needles from methanol). UV: λ_{max}^{EtOH} mμ (log ε); 246.5 (4.31), 338 (4.20).

Found: C, 58.05; H, 4.56%. Calcd for $C_{25}H_{24}O_{12}$: C, 58.14; H, 4.68%.

Triethyl Ether (X). Mp 115—116°C (colorless needles from absolute ether). UV: λ_{max}^{EtOH} mμ (log ε); 275 (4.30), 313 (4.16), 350 (4.22).

Found: C, 63.39; H, 6.15%. Calcd for $C_{25}H_{30}O_9$: C, 63.28; H, 6.37%.

5, 7-Dihydroxy-3, 6, 3′, 4′, 5′-pentamethoxyflavone (XI). A mixture of II (1.8 g), 3,4,5-trimethoxybenzoic anhydride (13 g), and potassium 3,4,5-trimethoxybenzoate (5.3 g) was heated at 180°C under reduced pressure for 8 hr. The product was recrystallized from methanol to give XI as yellow needles; mp 189—190°C; yield, 260 mg (8%). UV: λ_{max} mμ (log ε); (EtOH) 275 (4.12), 340 (4.29); (EtOH–AcONa) 278 (4.41), 371 (4.14); (EtOH–$AlCl_3$) 284 (4.17), 358 (4.25).

Found: C, 59.21; H, 4.94%. Calcd for $C_{20}H_{20}O_9$: C, 59.40; H, 4.99%.

Diacetate (XII). Mp 148.5—149.5°C (colorless prisms from methanol). UV: λ_{max}^{EtOH} mμ (log ε); 252_i (4.18).[*5] 356 (4.04).

Found: C, 58.82; H, 4.74%. Calcd for $C_{24}H_{24}O_{11}$: C, 59.01; H, 4.95%.

Dimethyl Ether. Mp 153—154°C. It was undepressed on admixture with the sample of VIII.

Diethyl Ether (XIII). *a) From XI.* Mp 144—145°C (colorless needles from methanol). UV: λ_{max}^{EtOH} mμ (log ε); 265 (4.20), 342 (4.22).

Found: C, 62.37; H, 5.81%. Calcd for $C_{24}H_{28}O_9$: C, 62.60; H, 6.13%.

b) From XIV. A mixture of XIV (1.0 g), 3,4,5-trimethoxybenzoic anhydride (3.5 g), and triethylamine (2 m*l*) was heated at 170°C for 8 hr under a stream of nitrogen. The mixture was then treated by a usual method; mp 144.5—145.5°C; yield, 500 mg (31%). It was undepressed on admixture with the sample of a).

[*5] i=inflection point.