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Synthetic Studies of the Flavone Derivatives. XXIV.[1] The Synthesis of 5-Hydroxy-7,8,3′,4′-tetramethoxyflavone, A Pigment from Bergamott Oil

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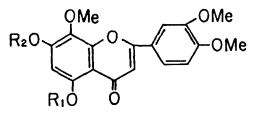
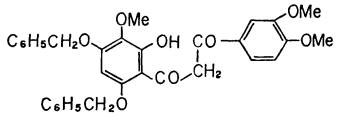
In 1968, 5-hydroxy-7,8,3′,4′-tetramethoxyflavone (I) was isolated from Bergamott oil by Farid.[2] In previous papers,[3,4] the present authors reported the syntheses of 5,7-dihydroxy-8-methoxyflavone derivatives from 4,6-dibenzyloxy-2-hydroxy-3-methoxyacetophenone (II). The present paper will describe the synthesis of I in a manner similar to that previously described.[3,4]





III

I R_1=H, R_2=Me,
IV R_1=R_2=$C_6H_5CH_2$,
V R_1=R_2=H,
VI R_1=R_2=Ac,
VII R_1=H, R_2=Et,
VIII R_1=Ac, R_2=Me,

By the Baker-Venkataraman transformation, 4,6-dibenzyloxy-2-hydroxy-3-methoxy-ω-(3,4-dimethoxybenzoyl)acetophenone (III) was obtained from II and 3,4-dimethoxybenzoyl chloride *via* the corresponding ester. The cyclodehydration of III with sodium acetate afforded 5,7-dibenzyloxy-8,3′,4′-trimethoxyflavone (IV). The catalytic hydrogenolysis of IV gave 5,7-dihydroxy-8,3′,4′-trimethoxyflavone (V). The flavone (V) was easily converted into a diacetate (VI) and a monoethyl ether (VII). The partial methylation of V yielded the desired flavone, I, which was then easily converted into an acetate (VIII). The properties of the flavone, I, and of VIII were found to be almost the same as those recorded in the literature.[2]

Experimental[5]

4,6-Dibenzyloxy-2-hydroxy-3-methoxy-ω-(3,4-dimethoxybenzoyl)-acetophenone (III). A mixture of II[3] (510 mg) and 3,4-dimethoxybenzoyl chloride (700 mg) in anhydrous pyridine (5 ml) was heated at 120°C for 2 hr. The cooled reaction mixture was then poured into diluted hydrochloric acid. The mixture was extracted with ether, and the ether layer was washed with a sodium carbonate solution and then water. The solvent was removed, and the resulting semi-solid was dried in a desiccator.

A mixture of the above crude ester, powdered potassium hydroxide (1.5 g), and anhydrous pyridine (12 ml) was heated at 60°C for 4 hr with stirring. The reaction mixture was acidified with diluted hydrochloric acid, and then extracted with ether. The ether layer was allowed to stand overnight in a refrigerator. The separated crystals were recrystallized from ethyl acetate to give III; mp 169.5—170.5°C (yellow needles); yield, 457 mg (60%). It gave a green color with ferric chloride in ethanol.

Found: C, 70.84; H, 5.62%. Calcd for $C_{32}H_{30}O_8$: C, 70.83; H, 5.57%.

5,7-Dibenzyloxy-8,3′,4′-trimethoxyflavone (IV). A mixture of III (400 mg), sodium acetate (1 g), and acetic acid (10 ml) was heated at 140°C for 1 hr. The reaction mixture was diluted with water, and then extracted with ether. The product was recrystallized from ethyl acetate-methanol (1: 1) to give IV; mp 157—158.5°C (colorless needles); yield, 350 mg (91%). UV: λ_{max}^{EtOH} nm (log ε); 249 (4.35), 273.5 (4.36), 343 (4.37). NMR:[5] ($CDCl_3$) 6.51_s (H-3); 6.62_s (H-6).

Found: C, 73.43; H, 5.41%. Calcd for $C_{32}H_{28}O_7$: C, 73.27; H, 5.38%.

5,7-Dihydroxy-8,3′,4′-trimethoxyflavone (V). A mixture of IV (300 mg) and palladium-charcoal (Pd: 10%; 90 mg) in a mixed solvent of ethyl acetate and methanol was shaken in an atmosphere of hydrogen for 4 hr. The product was recrystallized from ethyl acetate to give V; mp 217—218°C (yellow prisms); yield, 170 mg (86%). It gave a green color with ferric chloride in ethanol. UV: λ_{max} nm (log ε); (EtOH) 252.5_{sh} (4.20),[5] 278.5 (4.32), 336 (4.26); (EtOH–AcONa) 286.5 (4.46), 315 (4.24), 383 (4.05); (EtOH–$AlCl_3$) 286 (4.28), 349 (4.30), 400_{sh} (3.92). NMR: (DMSO) 3.79_s (3×MeO); 6.28_s (H-6); 6.95_s (H-3); 7.05_d (J=9) (H-5′); 7.46_{bs} (H-2′); 7.59_q (J=2.5, 9) (H-6′); 10.7_{bs}, 12.63_s (2×OH).

Found: C, 63.04; H, 4.52%. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68%.

Diacetate (VI): mp 163—164°C (colorless needles from aqueous methanol). UV: λ_{max}^{EtOH} nm (log ε); 247 (4.39), 262_{sh} (4.21), 341 (4.39). NMR: ($CDCl_3$) 6.59_s (H-3); 6.79_s (H-6).

Found: C, 61.84; H, 4.66%. Calcd for $C_{22}H_{20}O_9$: C, 61.68; H, 4.71%.

Monoethyl ether (VII): mp 184.5—185.5°C (yellow needles from ethanol). UV: λ_{max} nm (log ε); (EtOH) 256.5 (4.18), 292 (4.27), 359 (4.42); (EtOH–$AlCl_3$) 262.5 (4.17), 286.5 (4.31), 353 (4.30), 406 (4.09). NMR: ($CDCl_3$) 6.42_s (H-3); 6.60_s (H-6).

Found: C, 64.21; H, 5.40%. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41%.

1) Part XXIII: T. Horie, M. Tsukayama, M. Masumura, K. Fukui, and M. Nakayama, This Bulletin, **44**, 3198 (1971).
2) S. Farid, *Tetrahedron*, **24**, 2121 (1968).
3) K. Fukui, M. Nakayama, and T. Horie, This Bulletin, **42**, 2327 (1969).
4) M. Nakayama, K. Fukui, T. Horie, Y. Shimizu, and M. Masumura, *Nippon Kagaku Zasshi*, **91**, 1174 (1970).
5) All the melting points are uncorrected. The NMR spectra were measured with a Hitachi R-20 spectrometer (60 MHz), using tetramethylsilane as the internal standard (δ, ppm): s, singlet; d, doublet; q, quartet; b, broad. sh=shoulder.

5-Hydroxy-7,8,3′,4′-tetramethoxyflavone (I). V (36 mg) was methylated with diazomethane, and the product was recrystallized from ethyl acetate to give I; mp 209—210°C (lit,[2] mp 210—212°C) (yellow needles); yield, 30 mg (81%). It gave a green color with ferric chloride in ethanol. UV: λ_{max} nm (log ε); (EtOH) 254.5 (4.27), 276 (4.31), 294.5_{sh} (4.14), 343 (4.30); (EtOH–$AlCl_3$) 263 (4.16), 285.5 (4.28), 350 (4.31), 405 (4.04). NMR: ($CDCl_3$) 3.97_s (6H), 4.00_s (6H) (4×MeO); 6.47_s (H-6); 6.62_s (H-3); 7.04_d (J=9) (H-5′); 7.49_d (J=2.5) (H-2′); 7.56_q (J=2.5, 9) (H-6′); 12.6_{bs} (OH).

Found: C, 63.65; H, 5.06%. Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06%.

Acetate (VIII): mp 178—180°C (lit,[3] mp 178—180°C) (colorless needles from methanol). UV: λ_{max}^{EtOH} nm (log ε); 245 (4.36), 262_{sh} (4.23), 338 (4.37). NMR: ($CDCl_3$) 6.57_s (H-3), 6.71_s (H-6).

Found: C, 62.83; H, 5.05%. Calcd for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04%.