BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 2327—2330 (1969)

Synthetic Studies of the Flavone Derivatives. XII.*1 The Synthesis of 8,3'-Dimethoxy-5,7,4'-trihydroxyflavone

Kenji FUKUI and Mitsuru NAKAYAMA

Department of Chemistry, Faculty of Science, Hiroshima University, Higashi Sendamachi, Hiroshima

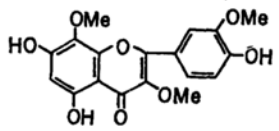
and Tokunaru HORIE

Department of Applied Chemistry, Faculty of Engineering, University of Tokushima, Tokushima

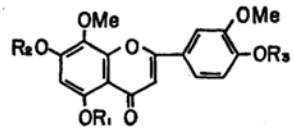
(Received December 28, 1968)

The partial benzylation of 3-methoxy-2,4,6-trihydroxyacetophenone gave a mixture of 2,4-dibenzyloxy-6-hydroxy- and 4,6-dibenzyloxy-2-hydroxy-3-methoxyacetophenone. The latter was esterified with 4-benzyloxy-3-methoxybenzoyl chloride, and the resulting ester was converted into 8,3'-dimethoxy-5,7,4'-tribenzyloxyflavone *via* the corresponding diketone. The catalytic debenzylation of the flavone gave 8,3'-dimethoxy-5,7,4'-trihydroxyflavone. Its diethyl ether was also prepared from 3,6-dimethoxy-4-ethoxy-2-hydroxyacetophenone by an unambiguous method.

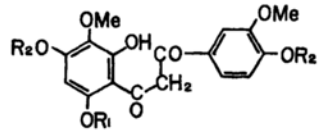
Recently, several new 5,7-dihydroxy-8-methoxyflavone derivatives have been isolated in nature[1] and their structures have been identified on the basis of spectral comparison with the known flavones. The synthesis of 3,8,3'-trimethoxy-5,7,4'-trihydroxyflavone (I) and related compounds have previously been reported.[2] It was considered useful to synthesize 8,3'-dimethoxy-5,7,4'-trihydroxyflavone (II), which may be expected to occur in nature, and to compare its properties with that of I and related compounds. The present paper will report on the synthesis of II from 3-methoxy-2,4,6-trihydroxyacetophenone (III).[3]



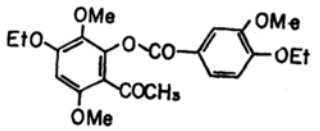
I



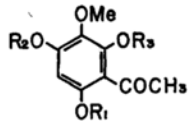
II $R_1=R_2=R_3=H$
VII $R_1=R_2=R_3=C_6H_5CH_2$
VIII $R_1=R_2=R_3=CH_3CO$
IX $R_1=H$, $R_2=R_3=Et$
XII $R_1=Me$, $R_2=R_3=Et$



VI $R_1=R_2=C_6H_5CH_2$
XIII $R_1=Me$, $R_2=Et$



XI



III $R_1=R_2=R_3=H$
IV $R_1=H$, $R_2=R_3=C_6H_5CH_2$
V $R_1=R_2=C_6H_5CH_2$, $R_3=H$
X $R_1=Me$, $R_2=Et$, $R_3=H$

When the III ketone was treated with benzyl chloride in the presence of anhydrous potassium carbonate in anhydrous acetone, two kinds of benzylated ketones, A (a crystalline fraction, mp 140—141°C) as the minor portion and B (an oily fraction) as the major portion, were separated from the reaction mixture. The former, A, shows

*1 Part XI of this series: K. Fukui, T. Matsumoto and S. Tanaka, This Bulletin, **42**, 2380 (1969).

1) C. A. Henrick and P. R. Jefferies, *Tetrahedron*, **21**, 3219 (1965); E. L. Ghisalberti, P. R. Jefferies and C. A. Stacey, *Australian J. Chem.*, **20**, 1049 (1967).

2) K. Fukui, M. Nakayama and T. Horie, *Experientia*, **24**, 417, 769 (1968); K. Fukui, T. Matsumoto, M. Nakayama and T. Horie, This Bulletin, **41**, 2805 (1968); T. Horie, *Experientia*, **24**, 880 (1968).

3) P. S. Phadke, A. V. Rama Rao and K. Venkataraman, *Indian J. Chem.*, **5**, 131 (1967).

the analytical data for $C_{23}H_{22}O_5$ corresponding to the dibenzyl ether of III and a positive ferric chloride reaction. The latter, B, could not be crystallized, but it was identified as crude 2,4-dibenzyloxy-6-hydroxy-3-methoxyacetophenone (IV) on the basis of further experiments.[4] Consequently, the structure of A was postulated to be 4,6-dibenzyloxy-2-hydroxy-3-methoxyacetophenone (V).

The V dibenzyloxyketone was esterified with 4-benzyloxy-3-methoxybenzoyl chloride in the presence of anhydrous pyridine, and then the resulting ester was converted into 4,6-dibenzyloxy-2-hydroxy-3-methoxy-ω-(4-benzyloxy-3-methoxybenzoyl)-acetophenone (VI) by Baker-Venkataraman transformation.[5] The cyclodehydration of the VI diketone with anhydrous sodium acetate in acetic acid afforded a flavone, mp 149.5—150.5°C, which gave a red color when treated with magnesium and hydrochloric acid. The NMR spectrum[*2] of the flavone indicated the presence of two methoxyl groups, three benzyloxy groups, and five aromatic protons (Table 1). Further, a set of proton signals at 6.51 and 6.64 (each 1 H, singlet) in the aromatic region could, by the application of the study of Farid,[6] be assigned to the C-6 and C-3 protons[*3] respectively. Therefore, this flavone may be formulated as 8,3'-dimethoxy-5,7,4'-tribenzyloxyflavone (VII). The debenzylation of VII with hydrogen gave the desired flavone II, which was then easily derived to triacetate (VIII) by the usual method.

In order to establish the structure of the trihydroxyflavone (II), the diethyl derivative (IX) of II was also synthesized by the following unambiguous method. 2-Hydroxy-3,6-dimethoxy-4-ethoxyacetophenone (X),[7] when esterified with 4-ethoxy-3-methoxybenzoyl chloride, yielded 2-(4-ethoxy-3-methoxybenzoyloxy)-3,6-dimethoxy-4-ethoxyacetophenone (XI). The subsequent reaction of the XI ester gave 7,4'-diethoxy-5,8,3'-trimethoxyflavone (XII) *via* the corresponding diketone, XIII. The partial demethylation of XII with anhydrous aluminum chloride afforded 7,4'-diethoxy-8,3'-dimethoxy-5-hydroxyflavone, which was found to be identical with the IX mentioned above by a mixed-melting-point determination and by infrared spectra comparison. The NMR spectra of VIII and IX (Table 1) show one proton signal corresponding to the C-6 proton at 6.86 and 6.40 respectively; these spectra were in accordance with those of the flavone derivatives described in earlier reports.[1,6,8]

Table 1. NMR data of flavones[*2,*4]

Proton	Compounds		
	VII	VIII	IX
C-3	6.64_s	6.68_s	6.58_s
C-6	6.51_s	6.86_s	6.40_s
C-2'	$6.8—8.1_m$	7.50_{bs}	7.43_d
C-5'		$7.22_{d'}$	$6.98_{d'}$
C-6'		7.57_q	7.69_q

[*4] s, singlet; bs, broad singlet; d, doublet (J_{meta}=2.5 Hz); d', doublet (J_{ortho}=9.0 Hz); q, quartet (J_{ortho}=9.0 Hz, J_{meta}=2.5 Hz); m, multiplet.

Experimental[*5]

4,6-Dibenzyloxy-2-hydroxy-3-methoxyacetophenone (V). A mixture of the acetophenone III[3] (2.5 g), anhydrous potassium carbonate (7.0 g), and benzyl chloride (3.5 g) in anhydrous acetone (50 m*l*) was refluxed for 16 hr and then diluted with water (150 m*l*). After the solution had been concentrated in a vacuum to *ca.* 50 m*l*, the residue was extracted with ether. The ether layer was washed with a 3% sodium hydroxide solution and with water, and the solvent was removed. After the oily residue had then been dissolved with methanol-ether (20 : 1), the mixture was kept overnight in a refrigerator. The resulting precipitate was collected, washed with methanol, and recrystallized from ethyl acetate to give V as pale yellow prisms, mp 140—141°C, which gave a dark brown color with ferric chloride; yield, 290 mg (6%). UV: λ_{max} mμ (log ε); 289.5 (4.24), 322 (3.53).

Found: C, 72.94; H, 5.70%. Calcd for $C_{23}H_{22}O_5$: C, 73.00 H, 5.86%.

The acetate: acetic anhydride-pyridine method; mp 87—88°C (colorless needles from aqueous methanol). UV: λ_{max} mμ (log ε); 263.5 (3.85), 302 (3.71).

Found: C, 71.64; H, 5.52%. Calcd for $C_{25}H_{24}O_6$: C, 71.41; H, 5.75%.

The solvent of the mother liquor was removed by evaporation to give crude 2,4-dibenzyloxy-6-hydroxy-3-methoxyacetophenone (IV) (*ca.* 1.5 g), which had been converted into some 5,7-dihydroxy-6-methoxyflavone derivatives in a previous paper.[4]

4,6-Dibenzyloxy-2-hydroxy-3-methoxy-ω-(4-benzyloxy-3-methoxybenzoyl)-acetophenone (VI). A mixture of V (0.5 g) and 4-benzyloxy-3-methoxybenzoyl

4) K. Fukui, M. Nakayama and T. Horie, *Experientia*, **25**, 355 (1969).

5) W. Baker, *J. Chem. Soc.*, **1933**, 1381; K. Venkataraman and H. S. Mahal, *ibid.*, **1934**, 1767.

[*2] All the NMR spectra in this paper were measured with a Hitachi R-20 spectrometer (60 MHz), using tetramethylsilane as the internal standard (δ-value in $CDCl_3$).

6) S. Farid, *Tetrahedron*, **24**, 2121 (1968).

[*3] The C-6 proton signal is broader than that of the C-3 proton.[6]

7) T. Horie, M. Masumura and S. Okumura, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **83**, 468 (1962).

8) C. A. Henrick and P. R. Jefferies, *Australian J. Chem.*, **17**, 934 (1964); J. Massicot and J-P. Marthe, *Bull. Soc. Chim. France*, **1962**, 1962; J. Massicot, J-P. Marthe and S. Heitz, *ibid.*, **1963**, 2712.

[*5] All the melting points are uncorrected. The ultraviolet spectra were measured in ethanol.

chloride (0.8 g) in pyridine (6 ml) was heated for 2 hr in an oil bath at 120°C. The cooled reaction mixture was poured into diluted hydrochloric acid. The mixture was extracted with ether, and the ether layer was washed with a sodium carbonate solution and then with 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 (1.0 g), and pyridine (10 g) was heated for 4 hr at 60°C with stirring. The reaction mixture was acidified with diluted hydrochloric acid and then solidified by the addition of ether. The resulting precipitate was collected and recrystallized from ethyl acetate to give VI as yellow needles; mp 146.5—148°C; yield, 330 mg (40%). From the ether layer, VI was also obtained according to the ordinary procedure; yield, 135 mg (17%). It gave a green color with ferric chloride. UV: λ_{max} mμ (log ε); 301 (4.17), 390 (4.44), 408_{sh} (4.39).*6

Found: C, 73.96; H, 5.68%. Calcd for $C_{38}H_{34}O_8$: C, 73.77, H, 5.54%.

8,3′-Dimethoxy-5,7,4′-tribenzyloxyflavone (VII). A mixture of VI (225 mg) and anhydrous sodium acetate (1.0 g) in acetic acid (10 ml) was heated for 2 hr at 140°C. The reaction mixture was then diluted with water and extracted with ether. The ether layer was washed with a sodium carbonate solution and with water, and allowed to stand overnight in a refrigerator. The separating crystals were collected, and recrystallized from ethyl acetate to give VII as colorless needles, mp149.5—150.5°C, which gave a negative ferric chloride reaction; yield, 155 mg (71%). IR: 1635 cm^{-1} (KBr). UV: λ_{max} mμ (log ε); 247_i (4.36),*7 272 (4.37), 338 (4.40). NMR:*2,*4 5.28_s (2H); 5.19_s (4H) (C_6H_5-$C\underline{H}_2$); 3.99_s (6H, $C\underline{H}_3O$); (Table 1).

Found: C, 76.20; H, 5.16%. Calcd for $C_{38}H_{32}O_7$: C, 75.98; H, 5.37%.

8,3′-Dimethoxy-5,7,4′-trihydroxyflavone (II). A solution of VII (130 mg) in ethyl acetate - methanol (1 : 1; 50 ml) was submitted to catalytic hydrogenolysis at room temperature in the presence of Pd-C (10%: 75 mg). After the catalyst had been filtered, the filtrate was evaporated under a vacuum. The residue was recrystallized from diluted ethanol to give II as yellow plates, mp 274—276°C, which gave a dark green color with ferric chloride; yield, 60 mg (91%). IR: 3540, 3470, 3400, 1649, 1613, 1578, 1556, 1508 cm^{-1} (KBr). UV: λ_{max} mμ (log ε); 244.5 (4.18), 253 (4.19), 276 (4.27), 343 (4.28).

Found: C, 61.61; H, 4.10%. Calcd for $C_{17}H_{14}O_7$: C, 61.82; H, 4.27.

The triacetate (VIII): hot acetic anhydride - pyridine method; mp 196—196.5°C (colorless needles from ethanol). IR: 1762, 1644 cm^{-1} ($CHCl_3$). UV: λ_{max} mμ (log ε); 241 (4.35), 263 (4.28), 316 (4.28). NMR:*2,*4 4.05_s, 3.94_s (each 3H, $OC\underline{H}_3$); 2.45_s, 2.40_s 2.36_s (each 3H, $OCOC\underline{H}_3$); (Table 1).

Found: C, 60.79; H, 4.40%. Calcd for $C_{23}H_{20}O_{10}$: C, 60.52; H, 4.42%.

2-(4-Ethoxy-3-methoxybenzoyloxy)-3,6-dimethoxy-4-ethoxyacetophenone (XI). A mixture of X[7] (2.5 g), 4-ethoxy-3-methoxybenzoyl chloride (2.8 g), and anhydrous pyridine (8.0 ml) was heated in an oil bath at 110°C for 2.5 hr. The cooled mixture was poured into ice-cold dilute hydrochloric acid and then solidified by the addition of ether. The resulting precipitate was collected and recrystallized from ethanol to give XI as colorless plates; mp 132.5—133.5°C; yield, 2.75 g (63%). From the ether layer, XI was also obtained according to the ordinary procedure; yield, 0.75 g (17%). UV: λ_{max} mμ (log ε); 265 (4.17), 300 (3.99).

Found: C, 63.30; H, 6.38%. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26%.

3,6-Dimethoxy-4-ethoxy-2-hydroxy-ω-(4-ethoxy-3-methoxybenzoyl)-acetophenone (XIII). A mixture of the XI ester (2.3 g), powdered potassium hydroxide (4.0 g), and pyridine (16 g) was treated by the procedure described for VI. The product was then recrystallized from ethanol to give XIII as pale yellow needles, mp 145—146°C, which gave a green color with ferric chloride; yield, 1.65 g (72%). UV: λ_{max} mμ (log ε); 298 (4.31), 387 (4.17), 405_{sh} (4.10).*6

Found: C, 63.32; H, 6.28%. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26%.

7,4′-Diethoxy-5,8,3′-trimethoxyflavone (XII). To a solution of XIII (1.17 g) in acetic acid (15 ml), a solution of acetic acid - concentrated sulfuric acid (5 : 1; 6 ml) was added, and then the mixture was heated at 70°C for 3 min. The cooled mixture was diluted with water (200 ml) and then heated on a steam-bath for 10 min. The resulting precipitate was collected and recrystallized from ethyl acetate to give XII as colorless prisms; mp 158—159°C; yield, 930 mg (83%). IR: 1652 cm^{-1} (Nujol). UV: λ_{max} mμ (log ε); 249 (4.21), 271.5 (4.23), 339 (4.25). NMR:*2,*4 7.59_q (C-6′); 7.46_d (C-2′); $6.99_{d'}$ (C-5′); 6.63_s (C-6); 6.46_s (C-3); 4.26_q, 4.19_q (each 2H, $CH_3C\underline{H}_2$, J=7.0 Hz); 3.97_s (9H, $C\underline{H}_3O$); 1.52_t (6H, $C\underline{H}_3CH_2$, J=7.0 Hz).

Found: C, 66.05; H, 6.06%. Calcd for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04%.

7,4′-Diethoxy-8,3′-dimethoxy-5-hydroxyflavone (IX). *a) From II.* A mixture of II (33 mg), anhydrous potassium carbonate (500 mg), and diethyl sulfate (200 mg) in anhydrous acetone (15 ml) was refluxed for 6 hr and then diluted with water (50 ml). The resulting precipitate was collected and recrystallized from ethanol to give IX as colorless needles, mp 178—179.5°C, which gave a green color with ferric chloride; yield, 25 mg (65%). IR: 1663, 1613 cm^{-1} (Nujol). UV: λ_{max} mμ (log ε); 253.5 (4.26), 275 (4.32), 339 (4.31). NMR:*2,*4 12.6_{bs} ($O\underline{H}$); 4.19_q (4H, $CH_3C\underline{H}_2$, J=7.0 Hz); 3.96_s, 3.93_s (each 3H, $C\underline{H}_3O$); 1.51_t (6H, $C\underline{H}_3CH_2$, J=7.0 Hz); (Table 1).

Found: C, 65.19; H, 5.80%. Calcd for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74%.

b) From XII. To a solution of XII (760 mg) in anhydrous nitrobenzene (8 g), a solution of anhydrous aluminum chloride (4 g) in ether (12 g) was added. The mixture was heated at 47°C for 3 hr. After the mixture had then been poured into 1% hydrochloric acid (250 ml), the solution was concentrated in a vacuum to 150 ml. The resulting precipitate was collected and recrystallized from ethanol to give IX, mp 178—179.5°C; yield, 360 mg (49%), which was identical with that of the sample a.

Found: C, 65.33; H, 5.82%. Calcd for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74%.

The acetate: hot acetic anhydride - pyridine method; mp 175.5—176.5°C (colorless needles from ethyl acetate).

*6 sh=Shoulder.

*7 i=Inflection point.

IR: 1753, 1645 cm^{-1} (Nujol). UV: λ_{max} mμ (log ε); 246 (4.39), 263.5 (4.27), 340 (4.41). NMR:[*2,*4] 7.67_q (C-6′); 7.43_d (C-2′); $6.98_{d'}$ (C-5′): 6.67_s (C-3); 6.55_s (C-6); 4.20_q (4H, $CH_3C\underline{H}_2$, J=7.0 Hz); 4.02_s, 3.96_s (each 3H, $C\underline{H}_3O$); 2.44_s ($OCOC\underline{H}_3$); 1.52_t (6H, $C\underline{H}_3CH_2$, J=7.0 Hz).

Found: C, 64.63; H, 5.74%. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65%.