BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 2380—2382 (1969)

Synthetic Studies of the Flavone Derivatives. XI.*[1] The Synthesis of 4′,5,7-Trihydroxy-3,8-dimethoxyflavone, A Pigment from *Cyanostegia angustifolia* Turcz.

Kenji FUKUI, Takashi MATSUMOTO and Sachihiko TANAKA

Department of Chemistry, Faculty of Science, Hiroshima University, Higashi-sendamachi, Hiroshima

(Received December 17, 1968)

Recently, Ghisalberti *et al.*[1)] reported the isolation of two new pigments from the leaves and terminal branches of *Cyanostegia angustifolia* Turcz.; they proposed, on the basis of chemical and spectral studies, that the structures of these pigments were 4′,5,7-trihydroxy-3,3′,8-trimethoxyflavone (I) and 4′,5,7-trihydroxy-3,8-dimethoxyflavone (II).

In a previous paper,[2)] we reported on the total synthesis of I and its identity with a natural pigment. The present paper will describe a total synthesis of II. The experimental details of the present work are essentially the same as those of the previous paper,[2)] involving an oxidative demethylation[3)] of the 5,8-dimethoxyflavone derivative with nitric acid.

According to Allan-Robinson's flavone synthesis,[4)] the condensation of 2,4-dihydroxy-3,6,ω-trimethoxyacetophenone[5)] (III) with 4-benzyloxybenzoic anhydride[6)] (IV) gave 4′-benzyloxy-7-hydroxy-3,5,8-trimethoxyflavone (V), which was then benzylated to the 7-benzyl ether (VI). The compound VI was also obtained by a similar condensation of 4-benzyloxy-2-hydroxy-3,6,ω-trimethoxyacetophenone[5)] (VII) with IV. The oxidative demethylation of VI with nitric acid gave the 5,8-quinone derivative (VIII) as an intermediate; this was then easily reduced to the corresponding 5,8-dihydroxy compound (IX). The partial methylation of IX with diazomethane gave 4′,7-dibenzyloxy-5-hydroxy-3,8-dimethoxyflavone (X), which was then debenzylated to give the desired flavone (II), mp 247—249°C and 257—258°C, by catalytic hydrogenolysis over Pd-C. The synthetic flavone (II) was shown to be identical with the natural pigment by a mixed-melting-point determination and by a comparison of their IR and UV spectra.

We next turned our attention to an investigation of another effective method. Since it is well known that 3,5-dimethoxyflavone derivatives are demethylated at the 5-position with anhydrous aluminum chloride in ether,[7)] a partial demethylation of 4′,7-dihydroxy-3,5,8-trimethoxyflavone (XI), prepared from V, with anhydrous aluminum chloride in ether was carried out in the hope of obtaining the 5-hydroxy compound (II). The product obtained was yellow crystals, mp above 300°C, which were characterized as triacetate, mp 173—175°C,*[2] and trimethylated ether (XIII). The flavone (XIII) was also obtained by the methylation of XI with diazomethane; this proved that there was no isomeric change during the demethylation of XI.

The physical properties of the demethylated flavone did not agree with those of the natural pigment. The NMR spectrum of the demethylated flavone in dimethyl sulfoxide-d_6 showed the presence of two methoxyl groups, at δ 3.84 and 3.87 (each a 3H singlet); of five aromatic protons, at δ 6.51 (singlet, C_6–H), 7.01 (doublet, $C_{3'}$–H and $C_{5'}$–H) and 8.12 (doublet, $C_{2'}$–H and $C_{6'}$–H), and three hydroxyl groups, at δ 8.74, 10.04, and 10.50 (each a 1H singlet). In the UV spectra summarized in Table 1, a long-wavelength band of the demethylated flavone in ethanol undergoes a large bathochromic shift (59 mμ) upon the addition of aluminum chloride;[8)] this shows the presence of a free 3-hydroxyl group. The demethylated flavone is unstable in an alkaline solution, for when

---

*[1] Part X: K. Fukui, T. Matsumoto and S. Tanaka, This Bulletin, **42**, 1398 (1969). Parts of this work have been briefly communicated: K. Fukui, T. Matsumoto, M. Nakayama and T. Horie, *Experientia*, **25**, 349 (1969).

1) E. L. Ghisalberti, P. R. Jefferies and C. I. Stacey, *Australian J. Chem.*, **20**, 1049 (1967).

2) K. Fukui, T. Matsumoto, M. Nakayama and T. Horie, This Bulletin, **41**, 2805 (1968).

3) M. Krishnamurti, T. R. Seshadri and P. R. Shankaran, *Tetrahedron*, **22**, 941 (1966), and the references cited therein.

4) J. Allan and R. Robinson, *J. Chem. Soc.*, **1924**, 2192.

5) V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **24A**, 238 (1946).

6) S. E. Flores, J. Herran and H. Menchace, *Tetrahedron*, **4**, 132 (1958).

7) J. Gripenberg, "The Chemistry of Flavonoid Compound," ed. by T. A. Geissman, Pergamon Press, Oxford (1962), Chap. 13.

*[2] The natural pigment gave triacetate; mp 167—168°C.[1)]

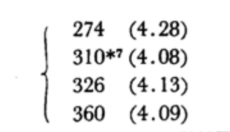
8) L. Jurd, Ref. 7, Chap. 5.

TABLE 1. ULTRAVIOLET SPECTEA OF XII, SYNTHETIC AND NATURAL II

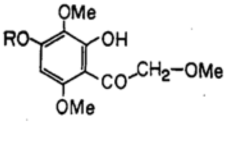
	λ_{max} mμ (log ε)				
	EtOH	AlCl$_3$*3	NaOH*4	NaOH-HCl*5	NaOAc*6
XII	270 (4.25)	267 (4.35)	297 (4.22)	269 (4.25)	280 (4.33)
	294 (3.98)	341 (3.79)	316 (4.24)	295*7 (4.04)	381 (4.15)
	369 (4.24)	428 (4.28)	340 (4.23)		
Synthetic II	274 (4.36)	284 (4.30)	284 (4.42)	274 (4.18)	284 (4.42)
	310*7 (4.16)	313 (4.19)	334 (4.15)	310*7 (3.89)	304*7 (4.23)
	326 (4.19)	352 (4.25)	412 (4.42)	330 (4.21)	371 (4.06)
	360 (4.15)	417 (4.02)		361 (4.00)	
Natural II	274 (4.28)	284 (4.23)	284 (4.38)	274 (4.26)	281 (4.31)
	310*7 (4.08)	313 (4.13)	335 (4.08)	310*7 (4.04)	304*7 (4.14)
	326 (4.13)	352 (4.20)	412 (4.36)	328 (4.10)	369 (4.00)
	360 (4.09)	417 (3.95)		360 (4.08)	

*3 0.002 mol/*l*.
*4 Added one drop of aqueous sodium hydroxide (4%).
*5 The alkaline solution was acidified with dilute hydrochloric acid.
*6 Saturated with fused sodium acetate.
*7 Inflection.

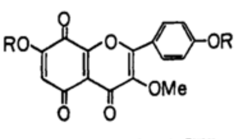
the alkaline solution is acidified, the long-wavelength band of the parent spectrum in ethanol disappears. This suggests the presence of a free 3,4'-dihydroxyl group.[8] The presence of a free 7-hydroxyl group is also indicated by the bathochromic shift (10 mμ) of the short-wavelength band in the presence of fused sodium acetate.[8] From this spectral evidence, the structure of the demethylated flavone was established to be 3,4',7-trihydroxy-5,8-dimethoxyflavone (XII).



II $R_1=R_4=Me$, $R_2=R_3=R_5=H$
V $R_1=R_2=R_4=Me$, $R_3=H$, $R_5=C_6H_5CH_2$
VI $R_1=R_2=R_4=Me$, $R_3=R_5=C_6H_5CH_2$
IX $R_1=Me$, $R_2=R_4=H$, $R_3=R_5=C_6H_5CH_2$
X $R_1=R_4=Me$, $R_2=H$, $R_3=R_5=C_6H_5CH_2$
XI $R_1=R_2=R_4=Me$, $R_3=R_5=H$
XII $R_1=R_3=R_5=H$, $R_2=R_4=Me$
XIII $R_1=R_2=R_3=R_4=R_5=Me$



III R=H
VII R=$C_6H_5CH_2$



VIII R=$C_6H_5CH_2$

Experimental*8

4'-Benzyloxy-7-hydroxy-3,5,8-trimethoxyflavone (V). A mixture of III (7.2 g), IV (33.0 g), and potassium 4-benzyloxybenzoate (16 .0 g) was ground together and heated at 180°C in an oil bath for 5 hr. The reaction mixture was cooled, powdered, and then refluxed for 30 min with a solution of ethanol (300 m*l*) and potassium hydroxide (30 g) in water (60 m*l*). The solvent was removed under a vacuum and washed with water; then the residue was again treated with an ethanolic alkaline solution as described above. The crude product was washed with hot water and hot acetone successively. The acetone-insoluble part was recrystallized from acetic acid to give yellow needles of V; mp 240—242°C; yield 2.0 g.

Found: C, 68.85; H, 4.97%. Calcd for $C_{25}H_{22}O_7$: C, 69.11; H, 5.10%.

4',7-Dibenzyloxy-3,5,8-trimethoxyflavone (VI). *a) From V.* The compound V (30 mg) was benzylated to give colorless needles of VI, mp 149—150°C (from aqueous methanol), which gave a negative ferric chloride reaction in ethanol; yield, 20 mg.

Found: C, 73.12; H, 5.39%. Calcd for $C_{32}H_{28}O_7$: C, 73.27; H, 5.38%.

b) From VII. A mixture of VII (1.9 g), IV (4.0 g), and potassium 4-benzyloxybenzoate (2.5 g) was treated by a method similar to that used for V. The crude product was recrystallized from methanol to give VI mp 149—150°C, which was undepressed on admixture with the sample of a); yield, 0.5 g.

4',7-Dibenzyloxy-5,8-dihydroxy-3-methoxyflavone (IX). A suspension of VI (320 mg) in nitric acid (45%: 7.0 m*l*) was stirred vigorously at 40°C for 10 min. After the mixture had been cooled, the dark brown precipitate (VIII) was collected, washed with water, and dissolved in acetic acid (10 m*l*). The solution was heated on a steam bath with sodium sulfite heptahydrate (1.5 g) for 1 min, and then diluted with water. The yellow precipitate was collected, washed

---

*8 All the melting points are uncorrected. The NMR spectra were taken on a Hitachi Model R-20 NMR spectrometer (60 Mc/sec), using tetramethylsilane as the internal standard; their chemical shifts are presented in terms of δ values; s: singlet, d: doublet.

with water, and recrystallized from acetone to give yellow needles of IX, mp 201—203°C, which gave a green ferric chloride reaction in ethanol; yield, 180 mg.

Found: C, 72.39; H, 4.68%. Calcd for $C_{30}H_{24}O_7$: C, 72.57; H, 4.87%.

4′,7-Dibenzyloxy-5-hydroxy-3,8-dimethoxyflavone (X). The flavone IX (120 mg) was methylated with diazomethane to give yellow needles of X, mp 161—162°C (from acetone-methanol), which gave a green ferric chloride reaction in ethanol; yield, 100 mg.

Found: C, 73.19; H, 5.11%. Calcd for $C_{31}H_{26}O_7$: C, 72.93; H, 5.13%.

4′,5,7-Trihydroxy-3,8-dimethoxyflavone (II). A solution of X (80 mg) in ethyl acetate (25 m*l*) was submitted to catalytic hydrogenolysis at room temperature in the presence of Pd-C (10%: 100 mg). The product was recrystallized from aqueous methanol to give yellow needles of II, mp 247—249°C and 257—258°C, which gave a green ferric chloride reaction in ethanol; yield, 35 mg. This flavone was shown to be identical with the natural pigment (mp 246—248°C and 256—258°C)[*9] by a mixed-melting-point determination and by a comparison of their IR and UV spectra.

Found: C, 61.82; H, 4.39%. Calcd for $C_{17}H_{14}O_7$: C, 61.82; H, 4.27%.

4′,7-Dihydroxy-3,5,8-trimethoxyflavone (XI). A mixture of V (1.8 g), Pd-C (5%: 1.5 g), and acetic acid (350 m*l*) was treated by a method similar to that used for II. The crude product was recrystallized from acetic acid to give XI, mp 290—292°C; yield, 1.0 g.

Found: C, 62.67; H, 4.55%. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68%.

3,4′,7-Trihydroxy-5,8-dimethoxyflavone (XII). A mixture of XI (600 mg), anhydrous aluminum chloride (5.0 g), and dry ether (60 m*l*) was refluxed for 8 hr. The mixture was poured into dilute hydrochloric acid (3 N: 200 m*l*). After the ether had been removed, the precipitate was collected, washed with water, and then recrystallized from aqueous pyridine to give pale yellow needles of XII, mp above 300°C, which gave a brown ferric chloride reaction in ethanol; yield, 250 mg.

Found: C, 62.12; H, 4.33%. Calcd for $C_{17}H_{14}O_7$: C, 61.82; H, 4.27%.

Triacetate of XII. Hot acetic anhydride-pyridine method; mp 173—175°C (from aqueous methanol); the substance gave a negative ferric chloride reaction.

Found: C, 60.30; H, 4.29%. Calcd for $C_{23}H_{20}O_{10}$: C, 60.52; H, 4.42%.

3,4′,5,7,8-Pentamethoxyflavone (XIII). The compound XI was methylated with diazomethane to give colorless needles of XIII, mp 157—159°C (from aqueous methanol) (lit,[9]) 156—158°C), which gave a negative ferric chloride reaction. This compound was also obtained by the methylation of XII. NMR in $CDCl_3$: 3.92, 3.97 and 4.03 (each s, 5MeO), 6.49 (s, C_6-H), 7.10 (d, J=9.5 cps, $C_{3'}$-H and $C_{5'}$-H), 8.26 (d, J=9.5 cps, $C_{2'}$-H and $C_{6'}$-H).

Found: C, 64.43; H, 5.35%. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41%.

The authors are grateful to Professor P. R. Jefferies, the University of Western Australia, for his gift of the natural pigment. This work was supported by a grant-in-aid from the Ministry of Education.

[*9] The melting point was observed in this laboratory.

9) S. Rangaswami, P. S. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **9A**, 133 (1939).