Synthetic Studies of the Flavone Derivatives. VIII.[*1] The Synthesis of 5,7,4′-Trihydroxy-3,8,3′-trimethoxyflavone[*2]

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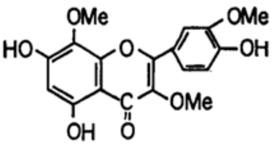
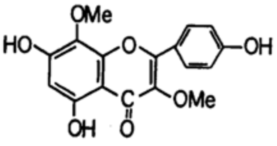
Recently, two new pigments were isolated from the leaves and terminal branches of *Cyanostegia angustifolia* Turcz. by Ghisalberti *et al.*1) On the basis of spectral and chemical studies, they established the structures of these pigments to be 5,7,4′-trihydroxy-3,8,3′-trimethoxyflavone (I) and 5,7,4′-trihydroxy-3,8-dimethoxyflavone (II).



I

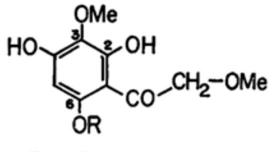


II

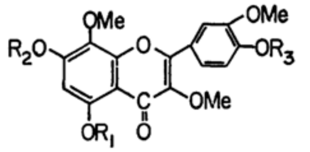
The present paper will deal with two different syntheses of I and will confirm the proposed structure.

According to Allan-Robinson's flavone synthesis, the condensation of 2,4-dihydroxy-3,6,ω-trimethoxyacetophenone (III)2) with *O*-benzoylvanillic anhydride, followed by treatment with alcoholic potassium hydroxide, afforded 7,4′-dihydroxy-3,5,8,3′-tetramethoxyflavone (IV), which was then converted to the dibenzyl ether (V) with benzyl chloride. The oxidative demethylation3) of V with nitric acid gave 7,4′-dibenzyloxy-3,3′-dimethoxyflavone-5,8-quinone (VI) as an intermediate; this was easily reduced to the corresponding 5,8-dihydroxy compound (VII). The partial methylation of VII with diazomethane gave 7,4′-dibenzyloxy-5-hydroxy-3,8,3′-trimethoxyflavone (VIII), which was then debenzylated to I by catalytic hydrogenolysis over palladium-charcoal.

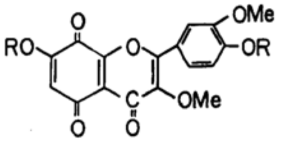
An alternative synthesis of I was carried out as follows. In a previous paper,4) 2,4,6-trihydroxy-3,ω-dimethoxyacetophenone (IX) was reacted with *O*-benzylvanillic anhydride to give 4′-benzyloxy-5,7-dihydroxy-3,6,3′-trimethoxyflavone (X). Investigating this reaction further, we found that 4′-benzyloxy-5,7-dihydroxy-3,8,3′-trimethoxyflavone (XI), an isomer of X, was produced as a by-product. Each product could be successfully separated by fractional recrystallization from



III $R=Me$
IX $R=H$



IV $R_1=Me$, $R_2=R_3=H$
V $R_1=Me$, $R_2=R_3=C_6H_5CH_2$
VIII $R_1=H$, $R_2=R_3=C_6H_5CH_2$
XI $R_1=R_2=H$, $R_3=C_6H_5CH_2$



VI $R=C_6H_5CH_2$

[*1] Part VII: K. Fukui, T. Matsumoto, S. Nakamura, M. Nakayama and T. Horie, This Bulletin, **41**, 1413 (1968).

[*2] A part of this work has been briefly communicated: *Experimentia*, **24**, 417 (1968).

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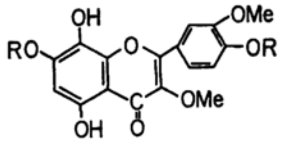
1) E. L. Ghisalberti, P. R. Jefferies and C. I. Stacey, *Australian J. Chem.*, **20**, 1049 (1967).

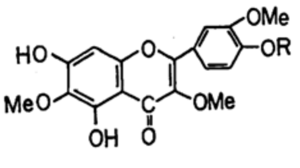
2) V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **24A**, 238 (1946).

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

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



VII $R=C_6H_5CH_2$



X $R=C_6H_5CH_2$

aqueous alcohol. This suggests that the ring-closure of the ketone IX proceeds in two directions, that is, toward the 2- and 6-hydroxyl group positions with respect to the ketonic group, and that it eventually affords X and XI. The benzyl protective group for the phenolic hydroxyl of XI was eliminated by catalytic hydrogenolysis over palladium-charcoal to yield I, which was identical with the sample described above. The physical properties of synthetic I were in good accordance with those of the natural pigment. Synthetic I was also characterized as triacetate and triethyl ether.

Experimental*4

7,4′-Dihydroxy-3,5,8,3′-tetramethoxyflavone (IV). A mixture of III (2.4 g), *O*-benzoylvanillic anhydride (14.0 g), and potassium *O*-benzoylvanillate (9.0 g) was ground together and heated at 180°C under a vacuum for 5 hr. The reaction mixture was then powdered, refluxed with a solution of aqueous potassium hydroxide (40%: 50 g) and ethanol (170 m*l*) for 20 min, and evaporated under a vacuum to dryness. The residue was dissolved in water, and the alkaline solution, after the removal of a small amount of an insoluble material, was acidified with dilute hydrochloric acid. The precipitate was collected, washed successively with aqueous sodium bicarbonate and water, and then recrystallized from aqueous ethanol to give yellow needles of IV, mp 250—252°C, which gave a green ferric chloride reaction in ethanol; yield, 1.0 g.

Found: C, 61.05; H, 4.73%. Calcd for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85%. UV: λ_{max}^{EtOH} mμ (log ε); 253.5 (4.30), 271.5 (4.30), 353 (4.30).

The Diacetate. Hot acetic anhydride - pyridine method; mp 158—160°C (pale yellow needles from aqueous methanol).

Found: C, 60.03; H, 4.80%. Calcd for $C_{23}H_{22}O_{10}$: C, 60.26; H, 4.84%.

7,4′ - Dibenzyloxy - 3,5,8,3′ - tetramethoxyflavone (V). A mixture of IV (1.2 g), benzyl chloride (980 mg), anhydrous potassium carbonate (2.3 g), and dimethylformamide (2.0 m*l*) was heated at 160—165°C in an oil bath for 1 hr. The reaction mixture was then diluted with water (*ca.* 30 m*l*), and the precipitate was collected, washed with water, and then recrystallized from ethanol to give pale yellow microneedles of V, mp 161—163°C; yield, 1.6 g.

Found: C, 71.47; H, 5.49%. Calcd for $C_{33}H_{30}O_8$: C, 71.47; H, 5.45%. UV: λ_{max}^{EtOH} mμ (log ε); 253.5 (4.38), 272.5 (4.36), 354 (4.32).

7,4′-Dibenzyloxy-5,8-dihydroxy-3,3′-dimethoxyflavone (VII). A suspension of V (1.0 g) in nitric acid (45%: 25 m*l*) was stirred vigorously at 40°C in a water bath for 20 min. After the mixture had cooled, the precipitate was collected, washed with water, and then recrystallized once from acetone to give crude 7,4′-dibenzyloxy-3,3′-dimethoxyflavone-5,8-quinone (VI), mp 194—196°C, as brown microneedles; yield, 0.3 g.

When a solution of crude VI (0.3 g) in hot acetic acid (10 m*l*) was treated with sodium sulfite heptahydrate (1.5 g), the solution turned from deep red to bright yellow.

The reaction mixture was heated on a steam bath for 1 min and then diluted with water. After the mixture had cooled, the yellow precipitate was collected, washed with water, and then recrystallized from ethyl acetate to give yellow microneedles of VII, mp 198—200°C, which gave a green ferric chloride reaction in ethanol; yield, 220 mg.

Found: C, 70.89; H, 5.01%. Calcd for $C_{31}H_{26}O_8$: C, 70.71; H, 4.98%.

7,4′ - Dibenzyloxy - 5 - hydroxy-3,8,3′ - trimethoxyflavone (VIII). VII (140 mg) in acetone (30 m*l*) was treated with an excess of diazomethane in ether. After standing at room temperature for 3 hr, the mixture was evaporated under a vacuum to dryness. The residue was recrystallized from an acetone-ethanol mixture to give yellow microneedles of VIII, mp 172—173°C, which gave a green ferric chloride reaction in ethanol; yield, 120 mg.

Found: C, 71.07; H, 5.20%. Calcd for $C_{32}H_{28}O_8$: C, 71.10; H, 5.22%.

4′ - Benzyloxy - 5,7 - dihydroxy - 3,8,3′ - trimethoxyflavone (XI). The reaction of the ketone (IX) (3.0 g) with *O*-benzylvanillic anhydride (27.0 g) was carried out in a manner previously reported.[4] The crude product was dissolved in hot aqueous ethanol, after which the solution was allowed to stand overnight at room temperature. The precipitate gave 4′-benzyloxy-5,7-dihydroxy-3,6,3′-trimethoxyflavone (X)[4], mp 180—181.5°C; yield, 1.2 g (20%). The solvent of the mother liquor was removed by evaporation to afford a yellowish residue, which was washed with hot acetone and then recrystallized from methyl ethyl ketone to give 4′-benzyloxy-5,7-dihydroxy-3,8,3′-trimethoxyflavone (XI), mp 206—208°C (golden yellow prisms), which gave a green ferric chloride reaction in ethanol; yield, 0.55 g (9%).

Found: C, 66.91; H, 4.70%. Calcd for $C_{25}H_{22}O_8$: C, 66.66; H, 4.92%. UV: λ_{max}^{EtOH} mμ (log ε); 257 (4.23), 276 (4.29); 340 (4.18).

5,7,4′-Trihydroxy-3,8,3′-trimethoxyflavone (I). *a) From VIII.* A solution of VIII (60 mg) in ethyl acetate (20 m*l*) was submitted to catalytic hydrogenolysis at room temperature in the presence of Pd-C (10%: 100 mg). After the catalyst had been filtered, the

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*4 All melting points are uncorrected.

filtrate was evaporated under a vacuum; the residue was then recrystallized from methanol to give yellow plates of I, mp 217—219°C, (lit.[1]) mp 215—217°C), which gave a green ferric chloride reaction in ethanol; yield, 25 mg.

Found: C, 59.87; H, 4.56%. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48%. UV: λ_{max}^{EtOH} mμ (log ε); 260 (4.23), 276.5 (4.29), 340^{sh} (4.17), 365 (4.21).

b) From XI. By a reaction similar to that described above, XI (284 mg), Pd-C (10%: 300 mg), and ethyl acetate (100 m*l*) gave I (mp 213.5—215°C), which was identical with a sample derived by the above described method a); yield, 185 mg.

The Triacetate. Mp 140—141°C, after resolidifying 147—148.5°C (colorless needles from methanol) (lit.[1]) mp 146—147°C).

Found: C, 59.25; H, 4.63%. Calcd for $C_{24}H_{22}O_{11}$: C, 59.26; H, 4.56%.

The Triethyl Ether. Mp 104.5—105.5°C (colorless needles from aqueous ethanol) (lit.[1]) mp 110—111°C).

Found: C, 62.34; H, 6.49%. Calcd for $C_{24}H_{28}O_8 \cdot H_2O$: C, 62.49; H, 6.22%. Drying at 100°C/0.1 mmHg for 3 hr, mp 121—121.5°C (104.5°C sinter).

Found: C, 64.59; H, 6.18%. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35%.

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