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# 2′,5,6,7-TETRAMETHOXYFLAVONE AND THE STRUCTURE OF ZAPOTIN

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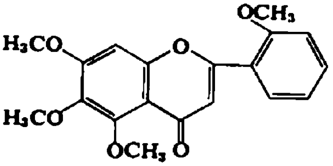
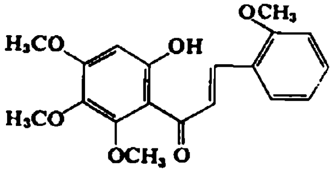
**Abstract**—2′,5,6,7-Tetramethoxyflavone, synthesized by two methods has been found to be different from zapotin.

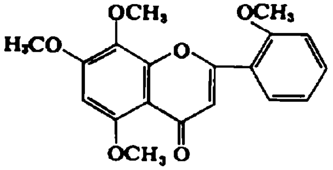
THE flavone zapotin was isolated by Sondheimer *et al.* from the seeds[1] and root bark[2] of the tree *Casimiroa edulis* Llave et Lex. On the basis of degradative evidence and colour reactions, this new flavone was considered to be 2′,5,6,7-tetramethoxyflavone[3] (I). Recently a synthesis of 2′,5,6,7-tetramethoxyflavone and its non-identity with zapotin was reported by Farkas and Nogradi.[4] In connection with our work[5] on the 2′-oxygenated flavones, we had occasion to synthesize 2′,5,6,7-tetramethoxyflavone and we wish to report here two more syntheses of this flavone carried out in this laboratory simultaneously with the Hungarian workers.



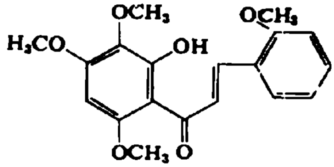
I



II



III



IV

Condensation of 2-hydroxy-4,5,6-trimethoxyacetophenone[6] with *o*-anisaldehyde in the presence of alkali gave 2′-hydroxy-2,4′,5′,6′-tetramethoxychalcone (II) as a reddish-yellow gum which could not be induced to crystallize. It was purified by chromatography over silica gel and oxidized to the flavone I by means of selenium dioxide.

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[1] F. A. Kincl, J. Romo, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4163 (1956).

[2] F. A. Kincl. J, Iriarte, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4170 (1956).

[3] F. Sondheimer and A. Meisels, *Tetrahedron* **9**, 139 (1960).

[4] L. Farkas and M. Nogradi, *Chem. Ber.* **98**, 164 (1965).

[5] T. R. Govindachari, P. C. Parthasarathy, B. R. Pai and P. S. Subramaniam, *Tetrahedron* **21**, 3237 (1965).

[6] V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.* **23A**, 262 (1946).

Alternatively, 2′,5,7,8-tetramethoxyflavone (III) was subjected to a Wessely-Moser rearrangement[7] by demethylation with hydriodic acid. The resulting 2′,5,6,7-tetrahydroxyflavone on complete methylation yielded 2′,5,6,7-tetramethoxyflavone (I) identical with the specimen obtained above. The 2′,5,7,8-tetramethoxyflavone (III) required in this synthesis was readily obtained by oxidizing 2′-hydroxy-2,3′,4′,6′-tetramethoxychalcone (IV) with selenium dioxide.

Our 2′,5,6,7-tetramethoxyflavone has m.p. 96° and $\lambda_{\max}^{\text{EtoH}}$ 234 (sh), 262 and 322 mμ (log ε 4·20, 4·20 and 4·21)[8] whereas zapotin has been reported[1] to have m.p. 150–151° and $\lambda_{\max}^{\text{EtoH}}$ 230, 255 and 324 mμ (log ε 4·45, 4·20, 3·83). It is thus evident that the structure of zapotin needs revision.

## EXPERIMENTAL[9]

*2′-Hydroxy-2,4′,5′,6′-tetramethoxychalcone* (II). A mixture of 2-hydroxy-4,5,6-trimethoxyacetophenone (2 g), *o*-methoxybenzaldehyde (3 g) and NaOH (4 g in 4 ml. water) and EtOH (10 ml) was refluxed with stirring, for ½ hr in an atm of $N_2$. Acidification of the well cooled solution to congo red resulted in the separation of a red gum. It was extracted with ether, washed successively with sat. $NaHCO_3$ aq sat. $NaHSO_3$ aq and then with water. After drying ($Na_2SO_4$), the solvent was distilled off and the residual reddish gummy material was purified by chromatography over silica gel in benzene when it was obtained as a reddish-yellow viscous oil (1·6 g) which could not be induced to crystallize; $\lambda_{\max}^{\text{EtoH}}$ 210, 315 and 374 mμ. (Found: C, 67·30; H, 5·97; $C_{19}H_{20}O_6$ requires: C, 66·5; H, 5·85%.)

2′,5,6,7-*Tetramethoxyflavone* (I). A mixture of the foregoing chalcone (1 g) freshly sublimed $SeO_2$ (1 g) and n-amyl alcohol (25 ml) was refluxed gently for 20 hr. After being filtered, amyl alcohol was steam distilled, the residual reddish brown gum was separated from water by decantation and dried *in vacuo*. Chromatography of the dried residue over alumina in benzene and elution with ethyl acetate followed by repeated crystallization from benzene–pet. ether (b.p. 40–60°) gave 2′,5,6,7-tetramethoxyflavone as colourless cubes (220 mg) m.p. 96°; $\lambda_{\max}^{\text{EtoH}}$ 234 (sh), 262 and 322 mμ (log ε 4·20, 4·20 and 4·21). (Found: C, 66·78; H, 5·66. $C_{19}H_{18}O_6$ requires: C, 66·67; H, 5·30%.)

*2′-Hydroxy-2,3′,4′,6′-tetramethoxychalcone* (IV). 2-Hydroxy-3,4,6-trimethoxyacetophenone[10] (3 g), *o*-methoxybenzaldehyde (3 g), NaOH (6 g in 6 ml water) and EtOH (12 ml) were refluxed for ½ hr with stirring, in an atm of $N_2$. Acidification of the well cooled mixture gave the chalcone as a yellow precipitate which was collected, washed thoroughly with water and dried. Recrystallization from alcohol gave yellow plates (3 g), m.p. 170–172°. (Found: C, 66·45; H, 5·55. $C_{19}H_{20}O_6$ requires: C, 66·5; H, 5·85%.)

2′,5,7,8-*Tetramethoxyflavone* (III). The foregoing chalcone (1 g), $SeO_2$ (1 g) and n—amyl alcohol (30 ml) were heated under reflux for 18 hr. After working up as above, the flavone was obtained as colourless prisms by repeated crystallization from ethyl acetate, m.p. 184–186°; lit.[4] m.p. 186–188°; $\lambda_{\max}^{\text{EtoH}}$ 267 and 333 mμ (log ε 4·47, 4·14). (Found: C, 67·06; H, 5·06. $C_{19}H_{18}O_6$ requires: C, 66·67; H, 5·30%.)

*Rearrangement of* 2′,5,7,8-*tetramethoxyflavone*. A mixture of 2′,5,7,8-tetramethoxyflavone (1 g), HI (10 ml) and acetic anhydride (10 ml) was refluxed gently for 3 hr. After being cooled and poured into sat. $NaHSO_3$ aq, the yellow precipitate was collected, washed thoroughly with ice water and dried (0·5 g). It was once crystallized from dil. alcohol (m.p. 264–270°) and directly subjected to methylation without further purification. The tetrahydroxyflavone (0·4 g), dimethyl sulphate (2 ml), anhydrous $K_2CO_3$ (2 g) and acetone (60 ml) were refluxed for 32 hr. After being worked up in the usual manner the crude gummy product was chromatographed over alumina in benzene. Elution with benzene–ethyl acetate (1:1) gave 2′,5,6,7-tetramethoxyflavone (120 mg) in the first few fractions, m.p. and mixed m.p. 94–96°.

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[7] F. Wessely and G. H. Moser, *Monatsh.* **56**, 97 (1930).

[8] Farkas and Nogradi (Ref 4) reported m.p. 97° and $\lambda_{\max}^{\text{MeOH}}$ 213, 234, 261 and 230 mμ (log ε 4·31, 4·11, 4·11 and 4·12).

[9] M.p. are uncorrected.

[10] W. Baker, *J. Chem. Soc.* 662 (1941).