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On the Structure of Zapotin and Zapotinin. II.[1] The Synthesis of Zapotin.

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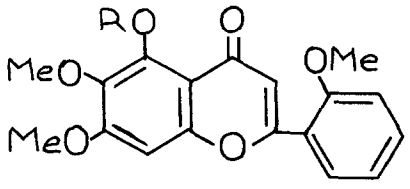
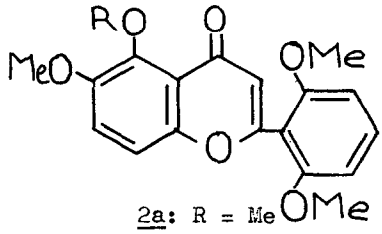
To zapotin and zapotinin, two closely related and interconvertible flavonoids from Casimiroa edulis Llave et Lex.[2] the structures 1a and 1b were assigned on grounds of spectroscopic and degradative evidences in 1960 by Sondheimer and Meisels.[3]



1a: R = Me
1b: R = H



2a: R = Me
2b: R = H

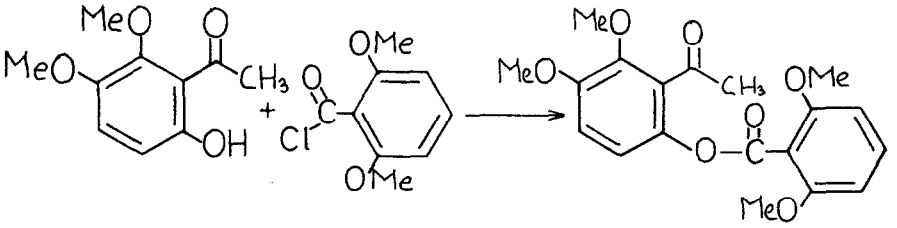
By an unambigous synthesis of 2',5,6,7-tetramethoxyflavone /1a/ and 5-hydroxy-2',6,7-trimethoxyflavone /1b/, that both were different from the corresponding natural products, we have demonstrated /see preceeding paper[1]/ the incorrectness of this assumption. Our results were confirmed by similar investigations of two Indian groups[4,5], as well as by Scheinmann and Sondheimer[6].

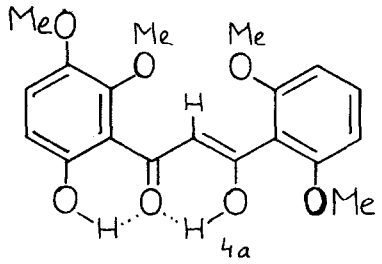
A reinvestigation of the problem by NMR-spectroscopy by Garrat, Scheinmann and Sondheimer[7], and independently by Dreyer and Bertelli[8] led to the revised structures 2',5,6,6'-tetramethoxyflavone /2a/ and 5-hydroxy-2',6,6'--trimethoxyflavone /2b/ for zapotin and zapotinin resp.

The unique structure of the B-ring in zapotin on one hand, and discrepancy between the new formula and the isolation of salycilic acid as a major degradation product of demethylated zapotin on the other, prompted us to

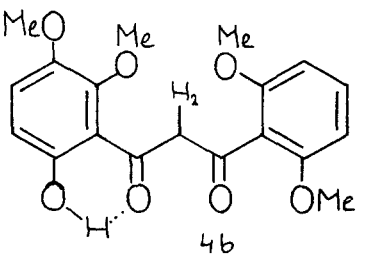
carry out the synthesis of 2a. An attempt for the synthesis of 2a has been reported by Dreyer et al.[8] In view of the considerable steric repulsion imposed by the o,o-disubstitution of ring B, it was evident, that only intermediates, which can be prepared under forcing condition are suitable precursors in a synthesis leading to 2a.

In this way 2-hydroxy-5,6-dimethoxyacetophenone[9] was treated with 2,6-dimethoxybenzoylchloride[10] in hot pyridine to afford 2-/2,6-dimethoxybenzoyloxy/-5,6-dimethoxyacetophenone /3/ in moderate yield. Sodium hydride induced rearrangement of 3 gave the diketone 4. Cyclodehydration of 4 in ethanol containing a trace of sulphuric acid yielded 2',5,6,6'-tetramethoxyflavone /2a/ identical in every respect /m.p., m.m.p., UV and IR spectra/ with natural zapotin.[11] The conversion of zapotin to zapotinin has been reported earlier,[3] thus the synthesis of 2a involves also that of 2b.





4a



4b

The structure of intermediates 3 and 4 was wholly supported by their spectral properties.

The NMR-spectrum of 3 showed a 3 proton singlet at = 2.53 p.p.m. for the $COCH_3$ group, the four methoxy groups gave a single peak at = 3.88 p.p.m. The absorption pattern of the aromatic reagion was closely resemblant to that of zapotin.

The dibenzoylmethane 4 gave a single carbonyl absorption at = 1615 cm^{-1} /chelated C=O/ indicating that in the solid state it is the

enol-form /4a/. The NMR-spectrum /δ values in p.p.m./, taken immediately after dissolving the sample in $CDCl_3$ also indicated the presence of the pure enol-form: enolic-OH 15.63, chelated 2-OH 11.40, -CH = C/OH/ 6.90, no $COCH_2CO$ absorption. In solution equilibration with the keto-form /4b/ was soon established and indicated by the diminution of the characteristic enol--peaks, further by the appearance of $-COCH_2CO$ absorption at 4.62, and the peak of the chelated 2-OH of the keto-form at 11.80. These assignments are supported by detailed studies on the keto-enol equilibrium of 2-hydroxy-dibenzoylmethanes, published elsewhere[12].

Experimental

2,6-Dimethoxybenzoic acid.

Methyl 2,6-dimethoxybenzoate[13] /10 g/ was boiled for 3 hrs. with a mixture of dimethylsulphoxide /60 ml/ and 40% aq.KOH /16 ml/. After cooling, the potassium salt of the acid was filtered off and decomposed with conc. aq.HCl. The crude acid was recrystallized from H_2O; yield: 6 g /65%/, m.p. 189-190°, /Lit.[13] 190°/.

2-/2,6-Dimethoxybenzoyloxy/-5,6-dimethoxyacetophenon /3/.

2-Hydroxy-5,6-dimethoxyacetophenone[9] /3 g/ and 2,6-dimethoxybenzoyl chloride[10] /4.5 g/ was heated in dry pyridine /13 ml/ for 10 hrs. at 100°. The dark solution was poured into 20% aq.AcOH and the precipitate extracted with $CHCl_3$. The $CHCl_3$ solution was washed with dil. aq.NaOH and water, dried and evaporated. The residue was chromatographed on silica with C_6H_6:EtAc 10:1 to yield 3 g /55%/ of the ester, that was recrystallized from EtOAc. Colorless needles of m.p. 136-137°. /Found: C, 63.07; H, 5.51. $C_{19}H_{20}O_7$ requires: C, 63.33; H, 5.59/.

1-/2-Hydroxy-5,6-dimethoxyphenyl/-3-/2,6-dimethoxyphenyl/-1,3-propandion /4/:

Ester 3 /3 g/ was stirred in dry toluene /45 ml/ with NaH /0.75 g/ at 90° for 4 hrs. The product was extracted from the toluene with 10% aq.NaOH, the

aqueous solution acidified and extracted with $CHCl_3$. Evaporation of the solvent and recrystallization of the residue from MeOH afforded 4 as yellow plates of m.p. 129-130°. /Found: C, 63.27; H, 5.60. $C_{19}H_{20}O_7$ requires: C, 63.33; H, 5.59/. UV: λ_{max}^{EtOH} /log ε/ 222 /sh/ /4.28/, 274 /3.87/ and 335 /4.07/.

2',5,6,6'-Tetramethoxyflavon, zapotin.

Crude 4 /0.35 g/ was boiled for 30 min. with ethanol /10 ml/ containing 5 drops of concd. H_2SO_4. The neutralized solution was evaporated and the residue chromatographed on a small column of SiO_2 with benzene-pyridine 8:1 as eluant. Evaporation of the corresponding fraction and repeated recrystallization of the residue from MeOH gave 1a as colorless prisms of m.p. 149-150° /lit. 150-151° [2] and 147° [8]/. M.m.p. with a sample of natural zapotin 150°. UV: δ_{max}^{EtOH} /log ε/ 233 /4.45/, 255 /4.19/ and 326 /3.84/. /Lit.[2] λ_{max}^{EtOH} /log ε/ 230 /4.45/, 255 /4.20/ and 324 /3.83/./

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