4,6,7-Trimethoxy-5-methylchromen-2-one, a New Coumarin from *Leonotis nepetaefolia*

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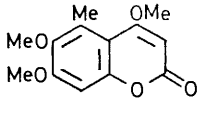
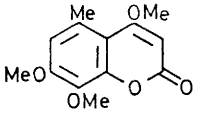
4,6,7-Trimethoxy-5-methylchromen-2-one (1) has been isolated from *Leonotis nepetaefolia* and its structure confirmed by synthesis of the hydrolysis product, 2′-hydroxy-4′,5′-dimethoxy-6′-methylacetophenone (4) from 2,3,5-trimethoxybenzaldehyde.

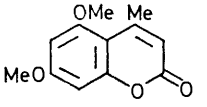
During work on the diterpenoid constituents of *Leonotis nepetaefolia* [1] we isolated a new coumarin, $C_{13}H_{14}O_5$, m.p. 209° [$\nu_{max.}$ (CCl_4) 1 727 cm^{-1}]. The n.m.r. spectrum revealed the presence of three methoxy-groups (δ 3.75, 3.91, and 3.94), an aromatic methyl group (δ 2.59), a vinylic proton [δ 5.53 (1 H, s)], and an aromatic proton [δ 6.68 (1 H, s)]. The similarity of the n.m.r. and u.v. [$\lambda_{max.}$ 225, 275infl, 287, 313, 327infl nm (ε 20 000, 8 800, 12 800, 15 000, and 11 000)] spectra to those of siderin (4,7-dimethoxy-5-methylchromen-2-one)[2] suggested two possible structures, (1) and (2), for this compound. A



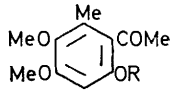
(1)



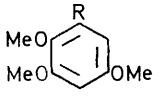
(2)



(3)



(4) R = H
(7) R = Me



(5) R = CHO
(6) R = Me

decision was facilitated by use of $Eu(fod)_3$-induced shifts, which have recently been shown [3] to provide a ready method for determining the substitution pattern in coumarins. The results strongly favoured structure (1): the shifts of the various protons relative to H-3 were: H-8, 0.30; 5-Me, 0.16; OMe, 0.17, 0.13, and 0.08 p.p.m. The corresponding shifts for the model compound (3) (5,7-dimethoxy-4-methylchromen-2-one) were: H-8, 0.29; H-6, 0.14; 4-Me, 0.21; OMe, 0.10 and 0.07 p.p.m. The size of the relative shift of the aromatic proton indicates [3] that it is attached to C-8.

The presence of the 4-methoxy-group in structure (1) was confirmed by alkaline hydrolysis followed by acidic hydrolysis, which resulted in decarboxylation to give the *o*-hydroxyacetophenone (4), m.p. 76—77° † [$\nu_{max.}$ (CCl_4) 3 400 and 1 620 cm^{-1}; δ 2.5 (ArMe), 2.62 (CH_3CO), 3.70 and 3.84 (2 OMe), 6.32 (1 H, s, aromatic), and 13.08 (1 H, s, phenolic OH)]. This compound, which has not been described previously, was synthesised in the following way. 2,3,5-Trimethoxybenzaldehyde (5) (prepared from *o*-vanillin; see Experimental section) was subjected to Wolff–Kishner reduction to afford the oily 2,3,5-trimethoxytoluene (6) [δ 2.17 (ArMe), 3.71 (6 H) and 3.80 (3 H) (3 OMe), and 6.27 and 6.33 (both d, *J* 3 Hz, H-4, and -6)]. Friedel–Crafts acylation of (6) with aluminium chloride and acetyl chloride took place regiospecifically at C-6 to yield 2′,4′,5′-trimethoxy-6′-methylacetophenone (7), m.p. 84° [δ 2.17 (ArMe), 2.45 (CH_3CO), 3.71, 3.80, and 3.88 (3 OMe), and 6.40 (1 H, s, H-3)]. The benzene-induced shifts of the methoxy-groups of (7) (0.60, 0.43, and 0.11 p.p.m.) support its assigned substitution pattern. Treatment of (7) with an excess of boron trichloride, a reagent for the specific demethylation of *o*-methoxyacylbenzenes,[5] readily afforded the *o*-hydroxyacetophenone (4), identical with the hydrolysis product of the natural compound (1). This synthesis confirms structure (1).

EXPERIMENTAL

For general details see ref. 1.

Isolation.—Dried powdered *L. nepetaefolia* (whole plant; 3 kg) was extracted with cold benzene. The extract was concentrated and left overnight. The precipitate of crude nepetaefolinol [1] was filtered off and the mother liquors were chromatographed over grade IV alumina. The chloroform eluate was rechromatographed and afforded a gum (100 mg) which solidified on trituration with ether. Crystallisation from methanol gave 4,6,7-*trimethoxy*-5-*methylchromen*-2-*one* (1), m.p. 209—210° (Found: C, 62.2; H, 5.4. $C_{13}H_{14}O_5$ requires C, 62.4; H, 5.65%).

† The isomeric 2′-hydroxy-3′,4′-dimethoxy-6′-methylacetophenone has m.p. 94°.[4]

[1] K. K. Purushothaman, S. Vasanth, and J. D. Connolly, *J.C.S. Perkin I*, 1974, 2661.
[2] K. K. Chexal, C. Fouweather, and J. S. E. Holker, *J.C.S. Perkin I*, 1975, 554.
[3] A. I. Gray, R. D. Waigh, and P. G. Waterman, *J.C.S. Chem. Comm.*, 1974, 632.
[4] W. Baker and H. Raistrick, *J. Chem. Soc.*, 1941, 670.
[5] F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Letters*, 1966, 4153.

2'-Hydroxy-4',5'-dimethoxy-6'-methylacetophenone (4).—The coumarin (1) (90 mg) was refluxed with methanolic 5% potassium hydroxide (10 ml) for 2 h. The methanol was removed *in vacuo* and the residue acidified with 5M-hydrochloric acid, heated for 5 min, and extracted with ether. Crystallisation from cold hexane yielded the *product* (4), m.p. 76—77°, $\lambda_{max.}$ 220, 234, 277, and 318 nm (ε 10 500, 8 500, 5 600, and 3 500) (Found: C, 62.6; H, 6.8. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.7%).

2,3,5-Trimethoxybenzaldehyde (5).—*o*-Veratraldehyde (12 g), prepared by methylation of *o*-vanillin under standard conditions with sodium hydride and methyl iodide in dimethyl sulphoxide, was nitrated with concentrated nitric acid.[6,7] The product (11.7 g), an equimolar mixture of the 5- and 6-nitro-derivatives, was reduced and diazotised by the method of Smith and Laforge.[7] Fortuitiously, the crude product (2.9 g) consisted mainly of the desired 2,3-dimethoxy-5-hydroxybenzaldehyde. It crystallised from methanol as long needles (1.92 g), m.p. 141—144° (lit.,[8] 137°) [δ 3.85 and 3.88 (2 OMe), 6.67 and 6.76 (both d, *J* 3 Hz, H-4 and -6), and 10.28 (1 H, s, CHO)]. Methylation, as above, afforded 2,3,5-trimethoxybenzaldehyde (5) (1.4 g), which crystallised from aqueous methanol as long needles, m.p. 67° (lit.,[8] 71°) [δ 3.80, 3.85, and 3.88 (3 OMe), 6.73 and 6.83 (both d, *J* 3 Hz, H-4 and -6), and 10.38 (1 H, s, CHO)].

2,3,5-Trimethoxytoluene (6).—The aldehyde (5) (1 g) in diethylene glycol was heated on an oil-bath at 150 °C for 2 h with an excess of hydrazine hydrate. An excess of solid potassium hydroxide was added and the mixture heated at 180 °C for 3 h. Water was added and the solution extracted with ether. Preparative t.l.c. of the crude product (0.57 g) gave 2,3,5-*trimethoxytoluene* (6) as an oil (100 mg), *m/e* 182, $\lambda_{max.}$ 228 (ε 5 300) and 283 nm (2 250).

2',4',5'-Trimethoxy-6'-methylacetophenone (7).—2,3,5-Trimethoxytoluene (100 mg) was dissolved in an ethereal solution of an excess of aluminium chloride, and an excess of acetyl chloride was added dropwise.[4] The mixture was stirred at room temperature overnight, acidified with 5M-hydrochloric acid, and heated on a steam-bath for ½ h. Extraction with ether and recrystallisation from hexane afforded 2',4',5'-*trimethoxy-6'-methylacetophenone* (7) (90 mg), m.p. 84°, $\nu_{max.}$ (CCl_4) 1 697 cm^{-1}, $\lambda_{max.}$ 224, 268, and 295 nm (ε 10 700, 4 000, and 3 500) (Found: C, 64.35; H, 7.25. $C_{12}H_{16}O_4$ requires C, 64.25; H, 7.2%).

2'-Hydroxy-4',5'-dimethoxy-6'-methylacetophenone (4).—The trimethoxyacetophenone (7) (30 mg) in dichloromethane was stirred at 0 °C for 5 min with a large excess of boron trichloride. Water was added and the organic layer separated. The crude product was crystallised from cold hexane to give 2'-hydroxy-4',5'-dimethoxy-6'-methylacetophenone (4) (24 mg), m.p. 76—77°, identical with the hydrolysis product of (1).

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[6] W. H. Perkin and R. Robinson, *J. Chem. Soc.*, 1914, 2376.
[7] W. H. Perkin, R. Robinson, and F. W. Stoyle, *J. Chem. Soc.*, 1924, 2355.
[8] L. E. Smith and F. B. Laforge, *J. Chem. Soc.*, 1931, 3072.

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