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A NEW FLAVONE FROM BERGAMOTT OIL

WEAK COUPLING IN NMR BETWEEN RING AND METHOXYL PROTONS

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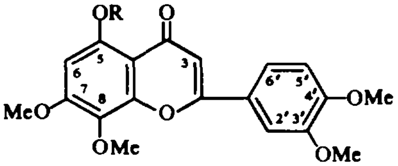
Abstract—A new natural flavone (5-hydroxy-7,8,3′,4′-tetramethoxyflavone, I) has been isolated from bergamott oil. A flavone previously isolated from *Ammi visnaga* has been identified as rhamnazin. Evidence for a weak spin coupling between ring and OMe protons in flavone derivatives is given.

A NUMBER of coumarin derivatives have been isolated from bergamott oil.[1] In addition to bergapten, bergamottin and citropten, a new flavone has, m.p. 210–212°, been isolated and identified as 5-hydroxy-7.8.3′.4′-tetramethoxyflavone by application of the systematic study of Massicot and Marthe[2] which involves the substituent effect on the chemical shift of protons in flavonic compounds. (NMR data, Table 1).



I–III

TABLE 1. IR AND NMR DATA OF I–III

Compound	$\nu_{C=O}$	τ^a (in $CDCl_3$)					
	[cm^{-1}] (KBr)	3-H	6-H	2′-H	5′-H	6′-H	OH/OMe/OAc
I R = H	1657	3.40	3.55	2.54	2.98	2.40	−2·6 5-OH 6·005 6.02 OMe 6·035 (2)
II R = Me	1639	3.37	3.53	2.54	2.97	2.40	5.98 6.00 6·01–6·02 (2) OMe 6·03
III R = Ac	1635 1766	3.44	3.30	2.55	2.98	2.41	5·98 6·02–6·03 (2) OMe 6·05 7·57 5-OAc

[a] In I–III: $J_{5'6'} = 8·7$; $J_{2'6'} = 2·2$; $J_{2'5'} = 0·5$ c/s

The signal at $-2{\cdot}6\ \tau$ indicates the presence of an OH group in position 5. This can also be concluded from the red shift in UV on addition of $AlCl_3$ to an ethanolic solution[3]. The singlet at $3{\cdot}40\ \tau$ is in accord with a 3-unsubstituted flavone; an isoflavone structure is thus excluded. The aromatic proton spectrum of I is consistent with the presence of a 1,2,4-trisubstituted and a pentasubstituted ring (cf. Table 1). Ring A, which has an OH group in position 5, must therefore be the one bearing only one aromatic proton. The chemical shifts of the three protons in ring B [$\tau = 2{\cdot}40$ (*o*- and *m*-coupling), $\tau = 2{\cdot}54$ (*m*- and *p*-coupling) and $\tau = 2{\cdot}98$ (*o*- and *p*-coupling)] show that the two OMe groups of this ring are located at the 3′- and 4′-positions. This and the 5,7,8-oxygenation pattern of ring A was confirmed by methylation of I to yield 5,7,8,3′,4′-pentamethoxyflavone (II), identical with an authentic sample.[4] This oxygenation pattern has not been found, as far as is known, among natural flavones.

A trihydroxy-dimethoxyflavone,* previously isolated from *Ammi visnaga* (L.),[5] has now been identified as rhamnazin (3,5,4′-trihydroxy-7,3′-dimethoxyflavone). This follows from the identity of its IR spectrum with that of an authentic sample, identity of UV spectra[5,6] and methylation to quercetin pentamethylether (identical IR[7] and NMR[2]).

Coupling between ring and methoxyl protons. It appears striking, that in the NMR spectrum of I the 6-H signal is broader than that of the 3-H (line widths at half height: 0·85 and 0·6 c/s, respectively), although the latter may be expected to be broadened due to weak coupling with 2′- and 6′-H. The correctness of the assignment of the signals at $\tau = 3{\cdot}40$ and $3{\cdot}54$ to 3-H and 6-H, respectively, in I follows, however, from NMR data of other flavones[2] and from the spectrum of the acetyl derivative III, in which the "broad signal" is shifted 0·25 ppm to lower field while the "sharp" one is shifted only 0·04 ppm to higher field. A downfield shift of 0·18 to 0·53 is to be expected[2] on replacing an *ortho* OH or Me group by acetyl. It seems probable that the broadening of the 6-H signal is due to long range coupling with OMe protons. This is consistent with the OMe absorption in III, since the line width of the OMe-signal at $5{\cdot}98\ \tau$ is larger (0·85 c/s) than that of the signal at $6{\cdot}05\ \tau$ (0·57 c/s). The latter is presumably due to the 8-OMe group. Further support for this view is the fact that in II the 6-H (with two OMe groups in *o*-positions) shows a much greater broadening relative to the 3-H, when compared with the analogous absorption in I and III. (cf. Fig. 1).

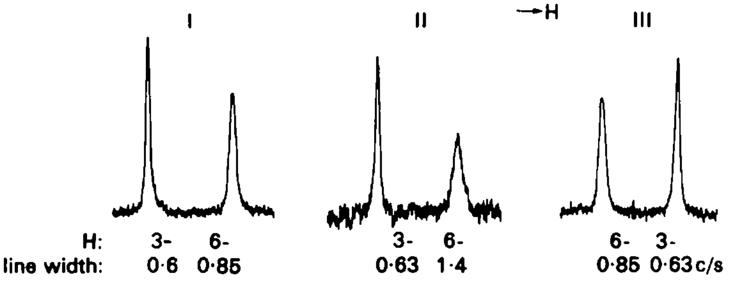


FIG. 1. NMR-signals of the 3-H and 6-H in I–III (measured at 60 Mc/s; sweep width 100 c/s)

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* m.p. 217–219° (from toluene).

EXPERIMENTAL

Isolation of the components of bergamott oil. 1 kg of the residue remaining after distillation of the volatile fraction from bergamott oil was suspended in 4 l. ether, warmed, cooled to room temp, decanted and the insoluble part twice more extracted in the same way with ether. The insoluble part (30 g crystalline material, m.p. 178–183°) was crystallized from alcohol, dissolved in alc. KOH, diluted with water, filtered from insoluble amorphous material, acidified and extracted with $CHCl_3$ to afford after two recrystallizations from EtOH 15 g bergapten, m.p. 187–188° (Lit.[1] 187–188°). The combined ethereal soln was distilled, the residue diluted with pet. ether and repeatedly extracted with a total of 6 l. of 70–80% EtOH. The residue after distillation was dissolved in EtOH and cooled to room temp to yield 9·1 g crystalline material, m.p. 144–147°. Recrystallization from EtOH gave 7 g citropten, m.p. 146–148° (Lit.[1] 146–147°). Further cooling of the mother liquor for 4 days at 5–10° afforded 2·5 g of a yellow crystalline compound, m.p. 207–210°. After recrystallization from benzene, 2 g of I were obtained as yellow needles, m.p. 210–212° (Found: C, 63·46; H, 4·86; OMe, 33·59; act. H, 0·31; M.W. 363 (in campher). Calc. for $C_{19}H_{18}O_7$ (358·4): C, 63·68; H, 5·06; 4(OMe), 34·6; act. H, 0·28%). I is soluble in conc HCl, and insoluble in 10% NaOHaq. With Mg/HCl in EtOH I gives a red colour and with $FeCl_3$ a green colour.

UV (EtOH); 338, 290 (sh), 275 and 253 mμ (ε, 17,500, 11,800, 18,400, 16,400). The 338 mμ max has the appearance of two overlapping bands; on addition of $AlCl_3$ the spectrum shows a shift of about 9 mμ to larger wavelengths (slight alterations of ε) and a new max appears at 402 mμ (ε 9500).

Upon further cooling of the alcoholic mother liquor and dilution with water ca. 10 g of crystalline material was precipitated. This was repeatedly extracted with pet. ether (b.p. 50–70°) from which 3 g bergamottin, m.p. 57–60° (from pet. ether) (Lit.[1] 59–61°) were obtained.

5,7,8,3′,4′-Pentamethoxyflavone (II). 200 mg I, 2 ml MeI and 5 g K_2CO_3 in 20 ml acetone were heated under reflux for 4 hr. The colourless soln was filtered, distilled and the residue crystallized from MeOH—water giving 120 mg II, m.p. 193–194° (Lit.[4] 192–193°). The mixed m.p. with an authentic sample of II was undepressed and IR spectral comparison confirmed their identity.

5-Acetoxy-7,8,3′,4′-tetramethoxyflavone (III). 200 mg I were acetylated with Ac_2O and pyridine in the usual manner and gave after crystallization from acetone–pet. ether 150 mg III, m.p. 178–180°.

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