

XANTHONE CONSTITUENTS OF *HYPERICUM ERICOIDES*

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ABSTRACT.—*Hypericum ericoides* contains 2,3,4-trimethoxyxanthone, 1,7-dihydroxyxanthone, 2-hydroxyxanthone, and a new compound which was identified as 2-hydroxy-5,6,7-trimethoxyxanthone by spectroscopic evidence.

Several xanthone derivatives have recently been isolated from *H. maculatum* (1), *H. androseum* (2) and *H. mysorensis* (3). As a contribution to the phytochemistry of the genus *Hypericum*, we now report the isolation and characterization of four xanthenes from the hitherto non-studied *H. ericoides*. Its stems, leaves and flowers are used in Valentian folk medicine. Among the compounds isolated, 2-hydroxy-5,6,7-trimethoxyxanthone (fig. 1) has not previously been reported from natural sources.

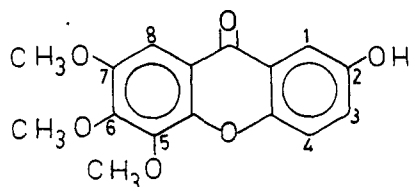


Figure 1

RESULTS AND DISCUSSION

An ether extract of the plant material was fractionated into neutral, phenolic and acidic fractions. 2,3,4-Trimethoxyxanthone, was obtained by silica gel chromatography of the neutral fraction, and was identified on the basis of ms, pmr and by comparison with an authentic sample (ir and mixed m.p.) (4). 1,7-Dihydroxyxanthone (euxanthone), was eluted first from the phenolic fraction and was identified on the basis of ms, pmr and uv utilizing shift reagents, confirmed by comparison with authentic sample (5). Compound C, 2-hydroxyxanthone, was eluted next from the phenolic fraction. It was identified on the basis of ms, pmr and uv utilizing shift reagents and was also confirmed by comparison with an authentic sample (5).

A new compound was eluted last from the phenolic fraction. Spectroscopic evidence pointed to its being 2-hydroxy-5,6,7-trimethoxyxanthone (fig. 1) on the following grounds. The molecular isotopic ions point to the formula $C_{16}H_{14}O_6$. Of the six oxygens, one is contained in an OH group (ir, 3200 cm^{-1} ; pmr δ 9.90), three are in methoxyl groups (pmr, three singlets at δ 3.98, 3.93 and 3.89 for 9H), and the other two belong to the xanthone skeleton as a carbonyl group (ir, 1640 cm^{-1}) and ether group (ir, 1235, 1200 and 1130 cm^{-1} respectively). The compound is a weak acid; its uv spectrum is not altered in methanol when recorded in the presence of sodium acetate; therefore the positions 3 or 6 would not be acceptable for the hydroxyl group (6). Positions 4 (or 5) in an otherwise unsubstituted ring are also improbable because the uv spectra of 4-hydroxyxanthone in the presence of sodium hydroxide and sodium acetate are very close and almost superimposable but different from its spectrum in methanol (7). Positions 1 (or 8) can also be excluded, because the uv spectra in methanol and in (methanol+ $AlCl_3$) are superimposable. Thus, the hydroxyl group is most probably situated at the 2 (or 7) position. The three methoxyl groups must be located in the other ring to explain

the proton singlet in the pmr spectra of the compound and its trimethylsilyl derivative alike. Two of them are probably at the 5 and 7 positions since the mass spectrum shows two dominant peaks, M-CH₃ and M-2CH₃, and it seems to be well established that the dominant fragmentation route of xanthenes thus methoxy-substituted begins with the loss of a methyl group (9). The third methoxyl group must be situated at the 6 position; location at the 8 position would give, upon electron impact, some peak resulting from the loss of elements of water (10), and this is not the case. Besides, in the pmr spectrum a proton in the 6 position should appear as a singlet at higher field (about δ 7.0), due the influence of two o-OCH₃ groups (8), than that seen at δ 7.33. The hydroxyl group may now be finally located. The chemical shift of H-1 suffers a para-magnetic change of 0.47 after trimethylsilylation of the compound; the only possible explanation is the situation of an OH group at the 2 (or 4) position, large paramagnetic shifts being produced by alkylation of *o*- and *p*-OH groups (8). The mentioned H-1 signal appears clearly as a doublet ($J=2$ Hz) showing slight splitting in the pmr spectrum of the trimethylsilyl derivative, which is consistent with the coupling it undergoes.

It is of interest to note that this is the first 2-hydroxytrimethoxyxanthone to be reported. All the hydroxytrimethoxyxanthenes mentioned in the literature are 1-hydroxytrimethoxyxanthenes (11-19), one 3-hydroxytrimethoxyxanthone (natural) (20) and one 4-hydroxytrimethoxyxanthone (synthetic) (21).

EXPERIMENTAL¹

EXTRACTION AND FRACTIONATION.—The plant material was collected and classified in "Tabernes de Valldigna" of Valencia by Dr. Mansanet, Prof. of Botany of University of Valencia. Powdered and dried stems, leaves and flowers of *Hypericum ericoides* (5 kg) were extracted successively with petroleum ether, ether and alcohol. The ether extract (35 g) was fractionated with the aid of Na₂CO₃ and NaOH solutions into neutral (15.7 g), phenolic (11.3 g) and acidic (1 g) fractions. Neutral and phenolic fractions were chromatographed on silica gel 60 (Merck) columns. The neutral fraction yielded with benzene-ether (100-1), a crystalline product 2,3,4-trimethoxyxanthone (25 mg). From the phenolic fraction four crystalline products, 1,7-dihydroxyxanthone (4 mg), 2-hydroxyxanthone (28 mg), a flavonoid (7 mg), and 2-hydroxy-5,6,7-trimethoxyxanthone (12 mg) were successively eluted with benzene-ether (100/1), (100/5), (100/10) and (100/15), respectively. The flavonoid will be reported separately later.

2,3,4-TRIMETHOXYXANTHONE.—2,3,4-Trimethoxyxanthone exhibited the following data: mp 149-150° (from EtOH); analysis: found, C, 66.93; H, 4.80; calculated for C₁₅H₁₄O₅: C, 67.13; H, 4.89; uv λ max (log ϵ) (MeOH) nm 247 (4.42), 279 (3.83), 305 (3.88), 353 (3.68); ir (KBr) cm⁻¹ 3030, 2930, 2840, 1660, 1615, 1590, 1520, 1460, 1375, 1320, 1280, 1260, 1250, 1230, 1130, 750, 650; ms *m/e* (relative intensity) 286 (100, M⁺), 271 (27.5), 256 (14.7), 241 (16.1), 228 (29.5), 200 (5.4); pmr (CDCl₃, 90 MHz) δ 8.38 (2dd, $J=8$, 1.6 and 0.8 Hz, H-8), 7.7 (3d, $J=8$ and 1.6 Hz, H-6), 7.59 (2dd, $J=8$, 1.6 and 0.8 Hz, H-5), 7.50 (s, H-1), 7.40 (3d, $J=8$ and 1.6 Hz, H-7), 4.12 and 4.2 (2s, 3 OCH₃). This nice separation of protons was only obtained in the expanded spectrum at 90 MHz and was tested by internuclear double resonance. This final identification was confirmed by comparison with an authentic specimen kindly given to us by Dr. O. R. Gottlieb (4).

1,7-DIHYDROXYXANTHONE (EUXANTHONE).—1,7-Dihydroxyxanthone exhibited the following properties: mp 237-238° (from EtOH); uv λ max (MeOH) nm (log ϵ) 234 (4.42), 260 (4.47), 288 (3.91), 320sh, 390 (3.80); λ max (MeOH+NaOH) nm 259, 281sh, 430; λ max (MeOH+NaOAc) nm 240sh, 261, 293sh, 393; λ max (MeOH+AlCl₃) nm 235, 279, 311, 453, these maxima do not change in (MeOH+AlCl₃+HCl); ir (KBr) cm⁻¹ 3300, 1635, 1605, 1575, 1480, 1360, 1235, 1050, 825, 805; ms *m/e* (relative intensity) 228 (100, M⁺), 200 (10.8, M-CO), 171 (3.5, M-CO-CHO), 144 (4.7, M-3 CO); pmr (DMSO-d₆, 80 MHz) δ 11.10 (s, OH-1), 10.04 (s, OH-7), 7.66 (t, $J=10$ Hz, H-3), 7.56 (s, H-8), 6.53 (d, $J=10$ Hz, H-2), 7.42 (m, H-5 and H-6). This final identification was confirmed by comparison with a specimen of euxanthone obtained from Dr. O. R. Gottlieb (5).

2-HYDROXYXANTHONE.—2-Hydroxyxanthone gave the following data: mp 238-239° (from EtOH); uv λ max (log ϵ) (MeOH) nm 238 (4.86), 251 (4.77), 270sh, 303 (3.93), 365 (4.07); these maxima do not change in (MeOH+AlCl₃) and in (MeOH+NaOAc); λ max (MeOH+NaOH) nm 251, 277sh, 315, 412; ir (KBr) cm⁻¹ 3220, 1635, 1610, 1590, 1480, 1455, 1340, 1230, 760; ms *m/e* (relative intensity) 212 (100, M⁺), 184 (21.15, M-CO), 155 (6.89, M-CO-CHO), 128 (11.2,

¹The melting points were determined on a Reichert apparatus. The ultraviolet spectra were measured on a Perkin-Elmer Ultraviolet-Visible Spectrophotometer, model 575. The infrared spectra were recorded in KBr pellets on a Perkin-Elmer 281 spectrophotometer. Pmr spectra were recorded in the stated solvents on a Perkin-Elmer R-32 (90 MHz) or Varian CST-20 (80 MHz) instrument with tetramethylsilane as internal standard. Mass spectra were taken with a Hitachi Perkin Elmer RMU-6L Spectrometer at 70 eV.

M-3 CO); pmr (DMSO- d_6 , 80 MHz) δ 9.90 (s, OH), 8.14 (2d, $J=8$ and 1.8 Hz, H-8), 7.63-7.32 (complex m, 6H). Final identification was made by comparison with an authentic sample obtained from Dr. O. R. Gottlieb (5).

2-HYDROXY-5,6,7-TRIMETHOXYXANTHONE.—2-Hydroxy-5,6,7-trimethoxyxanthone crystallized as yellow needles. It exhibited the following properties: mp 206° (from EtOH); uv λ max (log ϵ) (MeOH) nm 240 (4.64), 261 (4.57), 285sh, 322 (4.12), 373 (3.97); these maxima do not change in (MeOH+AlCl₃); and in (MeOH+NaOAc); λ max (MeOH+NaOMe) nm 255, 280sh, 338, 410; λ max (MeOH+NaOH) nm, 255, 275sh, 336, 412; Gibbs test is negative; ir (KBr) cm⁻¹ 3200, 2940, 2830, 1635, 1610, 1590, 1460, 1420, 1380, 1300, 1240, 1200, 1130, 1045, 815, 775; ms m/e (relative intensity) 302 (100, M⁺), 287 (23.9, M-CH₃), 272 (18.09, M-2 CH₃), 259 (14.5, M-CH₃-CO) 244 (23.5), 201 (7.2, M-OH-3 CO); pmr (DMSO- d_6 , 80 MHz) δ 7.56 (d, $J=8.6$ Hz, H-4), 7.42 (d, $J=2.5$ Hz, H-1), 7.33 (s, H-8), 7.25 (2d, $J=8.0$ and 2.5 Hz, H-3), 3.98 (s, 3 H, OCH₃), 3.93 (s, 3 H, OCH₃), 3.89 (s, 3H, OCH₃).

TRIMETHYLSILYLDERIVATIVE OF 2-HYDROXY-5,6,7-TRIMETHOXYXANTHONE.—This derivative gave the following data: pmr (CDCl₃, 80 MHz), 7.89 (d, $J=2.2$ Hz, H-1), 7.60 (2d, $J=9$ and 2.4 Hz, H-3), 7.45 (s, H-8), 7.36 (d, $J=9$ Hz, H-4), 4.05 and 3.95 (2s, 9H, 3 OCH₃).

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