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THE SYNTHESIS OF 2-HYDROXY-5,6,7-TRIMETHOXYXANTHONE: A CONFIRMATION OF STRUCTURE

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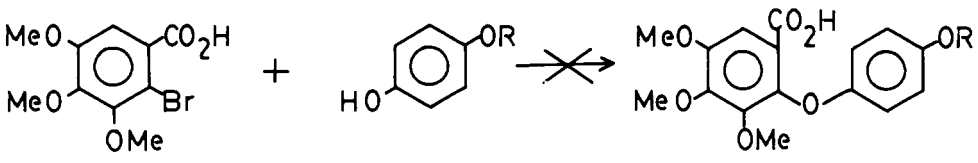
Hypericum ericoides L. (Guttiferae) is a small shrub that grows exclusively in eastern and southeastern Spain and in North Africa and is used in folk medicine (1-3). From this plant a new xanthone was isolated, which was identified as 2-hydroxy-5,6,7-trimethoxyxanthone [**10**] on the basis of its spectral data (4).

The known antiallergic and bronchus-expander properties of xanthones (5) make their syntheses highly valuable. The present paper describes the synthesis of 2-hydroxy-5,6,7-trimethoxyxanthone [**10**] in order to confirm the assigned structure.

In an attempt to devise an unambiguous synthesis of **10**, we attempted the preparation of diaryl ethers **3a** and **3b** from the *p*-hydroquinone derivatives **2a** or **2b** and 2-bromo-3,4,5-trimethoxybenzoic acid [**1**] (6,7), but no conversion was observed, the unaltered reactants being recovered (Scheme 1).



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2a R=H
2b R=CH_2Ph

3a R=H
3b R=CH_2Ph

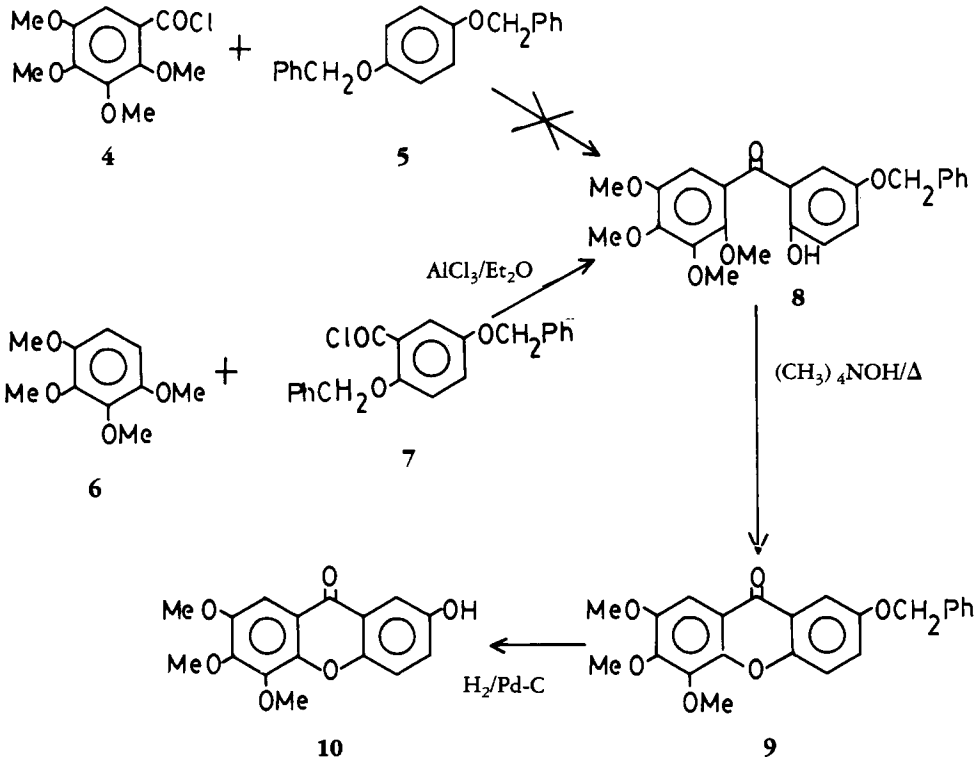
SCHEME 1

The successful synthesis was performed from the new benzophenone precursor **8** (Scheme 2). The synthesis of benzophenones under Friedel Crafts conditions has been effective in the preparation of 1,7-dioxygenated xanthones from 1,4-dimethoxybenzene and 2,6-dimethoxybenzoyl chloride (8). However, when we tried to obtain benzophenone **8** from 1,4-dibenzyloxybenzene [**5**] and 2,3,4,5-tetramethoxybenzoyl chloride [**4**], the unaltered reagents were recovered under mild conditions, but mixtures of esters (tlc, ir) resulted when higher temperatures and reaction times were used.

Compound **8** was prepared by Friedel Crafts acylation of 1,2,3,4-tetramethoxybenzene [**6**] (prepared from 1,2,3-trihydroxybenzene) (9) with 2,5-dibenzyloxybenzoyl chloride [**7**] prepared in situ from 2,5-dibenzyloxybenzoic acid and oxalyl chloride (10). The structure of the benzophenone **8** was confirmed spectroscopically. The mass spectrum shows peaks at *m/z* 424, 333, 225, 198, and 135 consistent with Scheme 3; this confirms that selective debenzylation at C-2 occurred in preference to the alternative demethylation at C-2′ (11), which occurs when both substituents are methoxyls.

When heated with Me_4NOH (8,12) 5-benzyloxy-2-hydroxy-2′,3′,4′,5′-tetramethoxybenzophenone [**8**] underwent cyclisation to 2-benzyloxy-5,6,7-trimethoxyxanthone [**9**]. The structure of this new xanthone was confirmed by spectral data (ir, uv, ^1H nmr, ms).

Hydrogenolysis of **9** with H_2/Pd-C(11,13) finally afforded 2-hydroxy-5,6,7-trimethoxyxanthone [**10**], identical to the natural xanthone (4) (mp, ir, uv, ^1H nmr, ms).



SCHEME 2

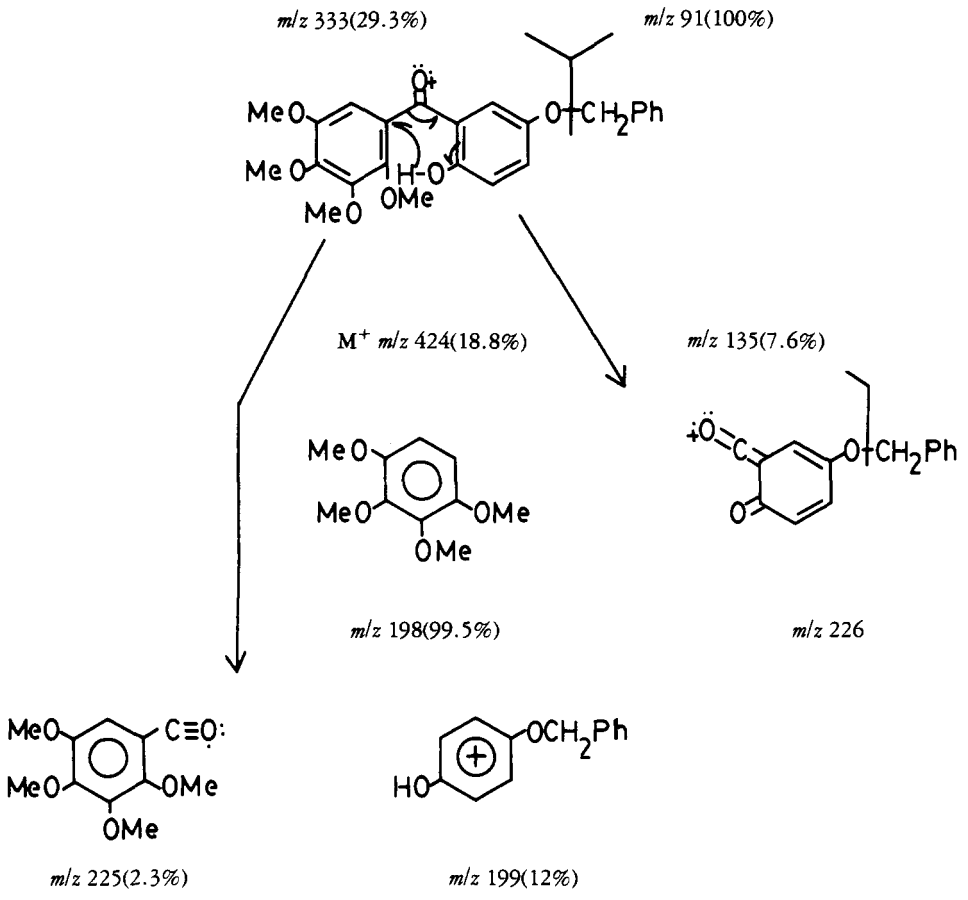
EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All melting points were taken in a Reichert apparatus and are uncorrected. Uv spectra were determined on a Perkin-Elmer Coleman 575 spectrophotometer in MeOH, and ir spectra were determined on a Perkin-Elmer model 281 recording spectrophotometer in KBr pellets and NaCl disks. ^{1}H-nmr spectra were recorded in the stated solvents on a Bruker AC-200 (200 MHz) instrument; chemical shifts are reported as δ values with TMS as internal standard. The following abbreviations are used: singlet, s: doublet, d: double doublet, dd: multiplet, m: shoulder, sh: broad, br. Low and high resolution mass spectra were taken with Varian-166 and Hewlett-Packard 5985-A mass spectrometers. Si gel Merck 60 (0.06-0.20 mm) was used for column chromatography and Si gel 60 $HF_{254+360}$ for tlc.

PREPARATION OF BENZYL-2,5-DIBENZYLOXYBENZOATE.—2,5-Dihydroxybenzoic acid (1.50 g, 10 mmol) in dry Me_2CO (30 ml) and K_2CO_3 (9 g) was treated at room temperature with benzyl bromide (7 g, 36 mmol) which was added slowly in an Ar atmosphere (13). After 72 h, the reaction mixture was filtered, concentrated, poured into H_2O and extracted with CH_2Cl_2 to yield an oil that crystallized from EtOH to give 2.96 g (72%) of benzyl 2,5-dibenzyloxybenzoate as colorless needles, mp 88-90°; ir ν max (KBr) cm^{-1} 1730 and no OH bands; ^{1}H nmr ($CDCl_3$) δ 5.03 and 5.10 (4H, 2s, 2 CH_2 of BzO), 5.34 (2H, s, CH_2 of BzOCO), 6.94 (1H, d, J=9 Hz, H-3), 7.06 (1H, dd, J_1=9Hz; J_2=3 Hz, H-4), 7.30 (15H, m, aromatic protons), 7.47 (1H, d, J=3Hz, H-6).

PREPARATION OF 2,5-DIBENZYLOXYBENZOIC ACID.—Benzyl 2,5-dibenzyloxybenzoate, (1.70g, 4.07 mmol) was hydrolyzed by refluxing it with 10% KOH in EtOH for 2 h. The reaction mixture was poured into ice-H_2O (200 ml), acidified with HCl, and the precipitate collected and dried to give 1.15 g (86%) of 2,5-dibenzyloxybenzoic acid as colorless needles (EtOH), mp 108-109° [lit. 109-110° (14)]; ir ν max (KBr) cm^{-1} 3500-2400 (OH) and 1695, 1670, two bands from $PhCO_2R$; ^{1}H nmr ($CDCl_3$) δ 5.07 and 5.25 (4H, 2s, $2CH_2$ of BzO), 7.07 (1H, d, J=9Hz, H-3), 7.17 (1H, dd, J_1=9 Hz; J_2=3 Hz, H-4), 7.40 (10H, m, aromatic protons), 7.81 (1H, d, J=3 Hz, H-6).

2,5-DIBENZYLOXYBENZOYL CHLORIDE [7].—2,5-dibenzyloxybenzoic acid (180 mg, 0.53 mmol) in dry C_6H_6 (2 ml) was treated under an Ar atmosphere with good stirring with oxalyl chloride (0.4 ml, 4.6 mmol) (10). After 20 min the solvent and excess of reagent were removed under reduced pressure, and the 2,5-diben-



SCHEME 3

zyloxybenzoyl chloride was employed in the next step without further purification.

5-BENZYLOXY-2-HYDROXY-2′,3′,4′,5′-TETRAMETHOXYBENZOPHENONE [**8**].—To the flask containing the 2,5-dibenzyloxybenzoyl chloride [**7**] (0.53 mmol) were added tetramethoxybenzene [**6**] (9) (0.10 g, 0.51 mmol), dry Et_2O (12 ml) and anhydrous $AlCl_3$ (0.35 g, 2.6 mmol) (8). After 1.5 h at room temperature the reaction was hydrolyzed with ice-H_2O (50 ml) containing HCl (5 ml) and extracted with CH_2Cl_2 (3×25 ml); the organic layer was washed with saturated $NaHCO_3$ aqueous (4×10 ml) and H_2O (4×10 ml) to give a crude product (0.25 g) that was purified by column chromatography (20% CH_2Cl_2 in C_6H_6) and preparative tlc [*n*-hexane-Et_2O(2:1)] to yield **8** as a yellow oil (0.035 g, 16%); ir ν max (NaCl) cm^{-1} 3060, 2940, 2845, 2830, 1635 (C=O of benzophenone), 1620, 1470, 1430, 1320, 1290, 1210, 1085, 1045, 740, 700, there are no OH bands by chelation (15); uv λ max (MeOH) nm 264, 367; λ max (MeOH+NaOMe) nm 270, 410; λ max (MeOH+$AlCl_3$) nm 282, 440; ^{1}H nmr ($CDCl_3$) δ 3.72, 3.80, 3.96, and 3.98 (12H, 4s, 4 OCH_3), 4.91 (2H, s, CH_2 of BzO), 6.50 (1H, s, H-6′), 6.92 (1H, d, J=3 Hz, H-6), 6.98 (1H, d, J=9 Hz, H-3), 7.20 (1H, dd, J_1=3 Hz; J_2=9 Hz, H-4), 7.31 (5H, m, aromatic protons), 11.71 (1H, s, OH-2); ms M^+ *m/z* 429 (19%) (measured 424.148±0.005, calcd. 424.151 for $C_{24}H_{24}O_7$), 394 (11%), 393 (44%), 333 (29%), 225 (2%), 199 (12%), 198 (100%), 183 (30%), 135 (8%), 91 (100%).

2-BENZYLOXY-5,6,7-TRIMETHOXYXANTHONE [**9**].—The benzophenone **8** (27 mg, 0.06 mmol), pyridine (0.5 ml), and tetramethylammonium hydroxide (10% aqueous solution 0.18 ml) were refluxed for 16 h (8,12). The crude reaction mixture was poured into ice-H_2O, acidified with HCl, and the precipitate that formed was collected and purified by preparative tlc (20% CH_2Cl_2 in C_6H_6) to afford **9** (20 mg, 78%) which after recrystallization from CH_2Cl_2/hexane yield pale yellow needles, mp 118°; ν max (KBr) cm^{-1} 2940, 2860, 2840, 1645 (C=O of xanthone) 1620, 1480, 1450, 1430, 1265, 1210, 1055, 1040, 740, 700; uv λ max (MeOH) nm 240,

262, 285(sh), 320, 380; ^{1}H nmr ($CDCl_3$) δ 3.99 and 4.08 (9H, 2s, 3-OCH_3), 5.19 (2H, s, CH_2 of BzO), 7.5 (8H, m, aromatic protons), 7.81 (1H, d, J=3 Hz, H-8); ms M^+ *m/z* 392 (8%) (measured 392.127±0.002, calcd 392.126 for $C_{23}H_{20}O_6$) 301 (5%), 273 (9%), 257 (5%), 91 (100%).

2-HYDROXY-5,6,7-TRIMETHOXYXANTHONE [**10**].—2-Benzyloxy-5,6,7-trimethoxyxanthone [**9**] (15 mg, 0.038 mmol) was dissolved in absolute EtOH (3 ml), 5% Pd/C (5 mg) was added, and the mixture was hydrogenated at 55° for 1 h under 1 atm of pressure (11,13). After filtration through Si gel to remove the catalyst, the solvent was removed under vacuum. Crystallization of the crude product from EtOH yielded the pure xanthone **10** (10 mg, 87%) as yellow crystals; mp 205-206°; ir ν max (KBr) cm^{-1} 3200br, 2940, 2830, 1635 (C=O of xanthone), 1610, 1590, 1460, 1380, 1240, 1200, 1045; uv λ max (MeOH) nm 240, 261, 285sh, 322, 373; λ max (MeOH+NaOMe) nm 255, 280sh, 338, 410; ^{1}H nmr (DMSO-d_6) δ 3.89, 3.93, and 3.98 (9H, 3s, 3-OCH_3), 7.25 (1H, dd, J_1=3 Hz; J_2=9 Hz, H-3), 7.34 (1H, s, H-8), 7.42 (1H, d, J=3 Hz, H-1), 7.56 (d, J=8.6 Hz, H-4), 9.98 (1H,br,OH); ms M^+ *m/z* 302 (100%) (measured 302.081±0.004, calcd. 302.079 for $C_{16}H_{14}O_6$).

The tlc, uv, ir, and ^{1}H nmr of this product were identical with those of naturally occurring 2-hydroxy-5,6,7-trimethoxyxanthone [**10**] isolated from *H. ericoides* (4). A mixed melting point of this product with authentic **10** also showed no depression.

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