Journal of Natural Products
Vol. 51, No. 2, pp. 339-342, Mar-Apr 1988

SYNTHESIS OF 1,3-DIHYDROXY-5,6-DIMETHOXYXANTHONE, A CONFIRMATION OF STRUCTURE

S. GIL, M. PARRA, V. SANZ, and A. TORTAJADA*

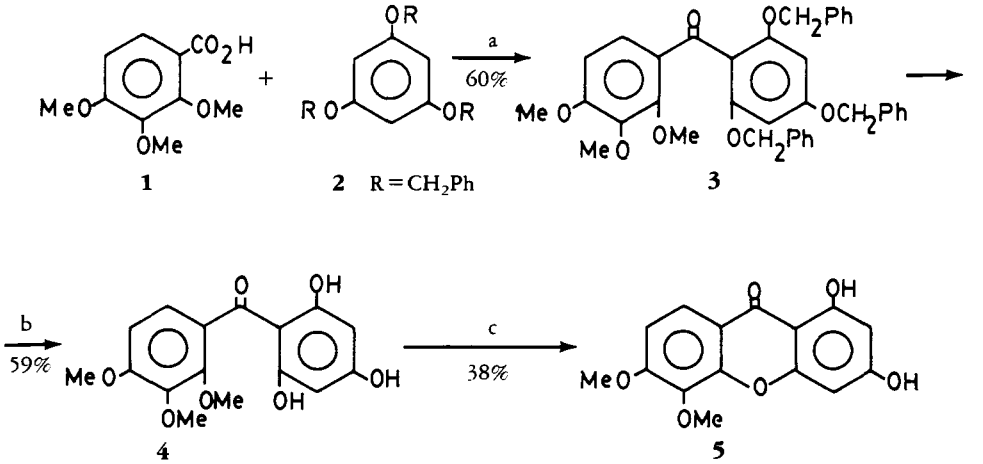
Department of Organic Chemistry, University of Valencia, Doctor Moliner 50, Burjassot 46100, Spain

A new xanthone was isolated from *Centaurium linarifolium* (Lamarck) G. Beck by Parra *et al.* (1) and was identified as 1,3-dihydroxy-5,6-dimethoxyxanthone [**5**]. The same structure was assigned by Nagem and da Silveira (2) to a xanthone isolated from *Haplocatha leiantha* (Benth.) Benth. The structural elucidation in both cases was mainly based on comparison of the data of the natural xanthone with those of the known compound 1,6-dihydroxy-3,5-dimethoxyxanthone (3) which is the alternative structure. However, the spectroscopic data given by Nagem and da Silveira (2) do not agree with ours, so an unambiguous synthesis of the assigned structure **5** was needed.

Good approaches to xanthone synthesis (4–6) are either cyclization of the appropriate benzophenones with elimination of H_2O or MeOH, or oxidative coupling. The benzophenones can be prepared by Friedel-Crafts acylation or trifluoracetic anhydride (TFAA) condensation (7) of suitably substituted benzene compounds, which can be synthesized by conventional methods.

The benzyloxy group has been shown to be adequate as a hydroxyl protecting group under the mild conditions used (4). Furthermore, its cleavage can be achieved in good yield, without disturbing the methoxy groups present in the molecule (8). This feature allows a distinction between hydroxy and methoxy groups placed at equivalent positions in the xanthone nucleus, as at positions 3 and 6 in 1,3-dihydroxy-5,6-dimethoxyxanthone [**5**].

In an attempt to devise an unambiguous synthesis of **5**, we prepared the benzophenone **3** from 2,3,4-trimethoxybenzoic acid [**1**] and 1,3,5-tribenzyloxybenzene [**2**] using TFAA as condensing agent (7) (Scheme 1). Hydrogenolysis of **3** with H_2/Pd-C (8) afforded 2,4,6-trihydroxy-2′,3′,4′-trimethoxybenzophenone [**4**]. When heated with tetramethylammonium hydroxide (5), **4** underwent cyclization to **5** (38%). This low yield may be due to the ionization of



SCHEME 1. a, TFAA/CH_2Cl_2 (room temperature); b, H_2(Pd-C)/EtOAc-HCl (room temperature); c, Me_4NOH/C_5H_5N-H_2O(Δ).

the hydroxyl groups under the basic conditions employed, which might promote several nucleophilic addition-elimination reactions (9) leading to unwanted products.

In order to improve the yield of **5**, a second route was attempted (Scheme 2). Thus, cleavage of the protecting groups was achieved in the last step, and the benzophenone precursor was prepared by Friedel-Crafts acylation of 1,3,5-tribenzyloxybenzene [**2**] (10) with 2,3,4-trimethoxybenzoyl chloride [**6**] generated in situ. This acylation yielded a mixture of 4,6-dibenzyloxy-2-hydroxy-2′,3′,4′-trimethoxybenzophenone [**7**] and 2′,4′,6′-tribenzyloxy-2-hydroxy-3,4-dimethoxybenzophenone [**8**], in 70 and 30% yield, respectively, as determined by ^{1}H-nmr spectroscopy.

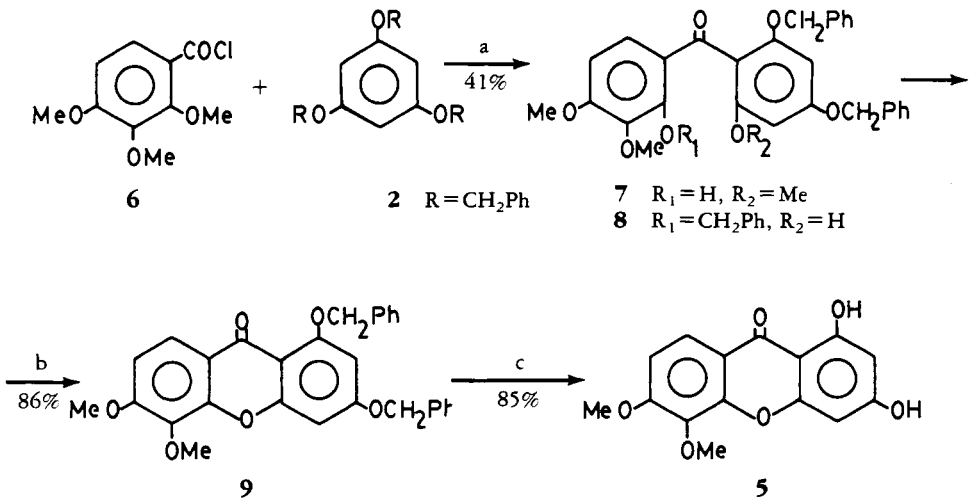
afforded 1,3-dihydroxy-5,6-dimethoxyxanthone [**5**], which was obtained as yellow needles with melting point 275–277°.

A mixed melting point with the natural xanthone isolated from *C. linarifolium* and crystallized from anhydrous Me_2CO showed no depression. Ir, ^{1}H-nmr, and uv data of both synthetic samples of xanthone **5** were identical to those of the xanthone isolated from *C. linarifolium*.

A sample of **5** was methylated with CH_2N_2, yielding 1-hydroxy-3,5,6-trimethoxyxanthone, whose physical and spectral data were in agreement with those found by Quillinan and Scheinmann (5).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—



SCHEME 2. a, $AlCl_3/Et_2O$ (room temperature); b, Me_4NOH/C_5H_5N-$H_2O(\Delta)$; c, H_2(Pd-C)/EtOAc-HCl (room temperature).

Cleavage of a benzyloxy group at position 2 under Friedel-Crafts conditions has been previously observed by us (4). In this particular case it facilitates cyclization to the xanthone **5** and improves yields. As benzophenones **7** and **8** both lead to the same xanthone on cyclization, the crude mixture was refluxed with tetramethylammonium hydroxide in pyridine (5) to afford 1,3-dibenzyloxy-5,6-dimethoxyxanthone [**9**], which on hydrogenolysis with Pd/C as catalyst,

All melting points were determined with a Reichert apparatus and are uncorrected. Uv spectra were determined with a Perkin-Elmer Lambda 9 spectrophotometer in MeOH solution. Ir spectra were determined with a Perkin-Elmer model 281 recording spectrophotometer for KBr or NaCl pellets. ^{1}H-nmr spectra were recorded in the stated solvents with a Bruker AC-200 (200 MHz) instrument; chemical shifts are reported as δ values with TMS as internal standard. Low and high resolution mass spectra were taken with a Varian-166 mass spectrometer. Si gel Merck 60 (0.06–0.20 mm) was used for cc and Si gel 60 $HF_{254+360}$ for tlc.

PREPARATION OF 2,4,6-TRIBENZYLOXY-2′,3′,4′-TRIMETHOXYBENZOPHENONE [**3**].—2,3,4-Trimethoxybenzoic acid [**1**] (420 mg, 1.98 mmol) and 1,3,5-tribenzyloxybenzene [**2**] (10) (782 mg, 1.97 mmol) were dissolved in anhydrous CH_2Cl_2 (16 ml), and the solution was kept in an ice bath under Ar atmosphere. TFAA (2.5 ml) was added (7), and the solution was stirred for 1 h at 0°. Afterwards, the solution was poured into ice H_2O and extracted with Et_2O. The organic layers were washed with aqueous $NaHCO_3$ and H_2O. After crystallization of the crude product from hexane/Et_2O, 636 mg (1.076 mmol, 60%) of 2,4,6-tribenzyloxy-2′,3′,4′-trimethoxybenzophenone [**3**] was obtained, mp 157–159°; ir ν max (KBr) cm^{-1} 2930, 1640 (C=O of benzophenone), 1605, 1585, 1460, 1430, 1410, 1385, 1290, 1235, 1215, 1175, 1120, 1105, 810, 705, 695; ^1H nmr ($CDCl_3$) δ 3.51, 3.78, 3.90 (9H, 3 s, 3 OMe), 4.97 (4H, s, 2 CH_2 of BzO), 5.02 (2H, s, CH_2 of BzO), 6.26 (2H, s, H-3, H-5), 6.63 (1H, d, J=8.9 Hz, H-5′), 7.2 (10H, m, aromatic protons of 2 BzO), 7.4 (6H, m, 5 aromatic protons of BzO+H-6′ overlapped); ^{13}C nmr ($CDCl_3$) δ 56.0, 60.9, 61.2, 70.2, 70.4, 93.4, 106.4, 115.2, 126.9, 127.5, 127.9, 128.1, 128.3, 128.6, 136.4, 136.6, 142.1, 154.3, 157.0, 157.8, 161.0, 192.3 (several signals are superimposed); hrms *m/z* (%) $[M]^+$ 590 (3) (found 590.228±0.009, calcd for $C_{37}H_{34}O_7$, 590.229), 469 (3), 423 (0.2), 379 (1.3), 195 (9), 91 (100).

PREPARATION OF 2,4,6-TRIHYDROXY-2′,3′,4′-TRIMETHOXYBENZOPHENONE [**4**].—2,4,6-Tribenzyloxy-2′,3′,4′-trimethoxybenzophenone [**3**] (590 mg, 1 mmol) was dissolved in EtOAc (90 ml). Concentrated HCl (0.25 ml) and 5% Pd/C (150 mg) were added, and the mixture was hydrogenated at room temperature for 2.5 h under 1 atm of pressure (8). The catalyst was filtered through Si gel, and the filtrate was washed with aqueous Na_2CO_3 and H_2O. Crystallization from CH_2Cl_2 yielded 189 mg (0.59 mmol, 59%) of yellow plates of 2,4,6-trihydroxy-2′,3′,4′-trimethoxybenzophenone [**4**], mp 109–111° (dec); ir ν max (KBr) cm^{-1} 3240, 2920, 1620 (C=O of benzophenone), 1585, 1480, 1450, 1410, 1320, 1290, 1270, 1230, 1170, 1090, 1070, 1000, 950, 825, 795, 725; ^1H nmr ($CDCl_3$) δ 3.88 and 3.92 (9H, 2s, 3 OMe), 5.80 (2H, m, H-5, H-3), 6.64 (1H, d, J=9 Hz, H-5′), 6.98 (1H, d, J=9 Hz, H-6′), 10.7 (1H, br s, OH-2); hrms *m/z* (%) $[M]^+$ 320 (1.08), 289 (100) (found 289.070±0.003, calcd for $[M-OMe]^+$, 289.071), 274 (4), 195 (4), 125 (4), 168 (24), 153 (27).

PREPARATION OF 1,3-DIHYDROXY-5,6-DIMETHOXYXANTHONE [**5**] (SCHEME 1).—To 2,4,6-trihydroxy-2′,3′,4′-trimethoxybenzophenone [**4**] (79.5 mg, 0.248 mmol) in pyridine (1.1 ml), H_2O (0.6 ml) and aqueous 10% tetramethylammonium hydroxide (0.4 ml) were added, and the solution was refluxed 17 h (5), poured onto ice, acidified with HCl, and extracted with Et_2O, yielding a solid which after crystallization from anhydrous Me_2CO yielded 26.8 mg (0.093 mmol, 38%) of yellow needles, mp 275–277°, of 1,3-dihydroxy-5,6-dimethoxyxanthone [**5**]; ir ν max (KBr) cm^{-1} 3650–3300, 2940, 2655, 1655 (C=O of xanthone), 1605, 1585, 1570, 1505, 1470, 1450, 1435, 1330, 1295, 1225, 1195, 1175, 1120, 1090, 1040, 980, 870, 800, 780, 710, 640; ^1H nmr (DMSO-d_6) δ 3.88 (3H, s, -OMe), 3.96 (3H, s, -OMe), 6.19 (1H, d, J=2 Hz, H-2), 6.40 (1H, d, J=2 Hz, H-4), 7.23 (1H, d, J=9 Hz, H-7), 7.86 (1H, d, J=9 Hz, H-8), 12.91 (s, 1H, -OH); OH at 3 appears as a broad signal at 9.85 δ (Me_2CO-d_6); ^{13}C nmr (DMSO-d_6) δ 56.5, 60.9, 94.2, 98.1, 101.5, 109.6, 114.3, 120.9, 135.7, 149.2, 157.3, 157.7, 162.9, 165.6, 179.3; uv λ max (MeOH) nm (log ϵ) 243 (3.78), 280 (3.37), 317 (3.48); λ max (MeOH+NaOMe) 241, 268, 355; λ max (MeOH+NaOAc) 241, 269, 353; λ max (MeOH+$AlCl_3$) 248, 262 (sh), 284, 344, 390; λ max (MeOH+$AlCl_3$+HCl) 245, 262 (sh), 283, 339, 390; hrms *m/z* (%) $[M]^+$ 288 (100) (found 288.061±0.003, calcd. for $C_{15}H_{12}O_6$ 288.063), 290 (6), 289 (25), 273 (18), 259 (20), 245 (52), 244 (11), 217 (23). Its tlc, uv, ir, and ^1H nmr are identical with those of naturally occurring 1,3-dihydroxy-5,6-dimethoxyxanthone [**5**] isolated from *C. linarifolium* (1).

PREPARATION OF 4,6-DIBENZYLOXY-2-HYDROXY-2′,3′,4′-TRIMETHOXYBENZOPHENONE [**7**] AND 2′,4′,6′-TRIBENZYLOXY-2-HYDROXY-3,4-DIMETHOXYBENZOPHENONE [**8**].—2,3,4-Trimethoxybenzoic acid (260 mg, 1.23 mmol) in dry C_6H_6 (4 ml) was treated under Ar atmosphere and thorough stirring at room temperature with 0.4 ml of oxalyl chloride (5). After 1 h the solvent and the excess of reagent were removed under reduced pressure. The residuum **6** was dissolved in anhydrous Et_2O (9 ml), and 1,3,5-tribenzyloxybenzene [**2**] (485 mg, 1.22 mmol) and $AlCl_3$ (500 mg) were added (5). After stirring 2.5 h at room temperature, the mixture was hydrolyzed with ice H_2O (50 ml) containing concentrated HCl (5 ml), and extracted with Et_2O to give a crude product that was purified on cc (hexane-Et_2O, 7:3) to yield an oil (280 mg, 41%); ir ν max cm^{-1} 1600–1625 (br, C=O of benzophenone); ^1H nmr ($CDCl_3$) δ 3.57, 3.67, 3.80 (9H, 3s, 3 OMe of **7**), 3.60, 3.65 (6H, 2s, 2 OMe of **8**), 4.71 (2H, s, CH_2 of BzO of **8**), 4.75 (2H, s, CH_2 of BzO of **7**), 5.09 (6H, s, 1 CH_2 of BzO of **7** and 2 CH_2 of BzO of **8**), 6.03 (2H, s, H-3′+H-5′ of **8**), 6.06 (1H, d, J=2.2 Hz, H-5 of **7**), 6.23 (1H, d, J=2.2 Hz, H-3 of **7**), 6.51 (1H, d, J=8.5 Hz, H-5 of **8**), 6.52 (1H, d, J=8.6 Hz, H-5′ of **7**), 6.95 (1H, d, J=8.5 Hz,

H-6 of **8**), 6.98 (1H, d, J=8.6 Hz, H-6′ of **7**), 7.15–7.43 (25H, m, aromatic protons), 13.09 (2H, s, 2 OH of **7** and **8**). Integration of the signals gave the molar ratios [**7**]=0.7 and [**8**]=0.3.

PREPARATION OF 1,3-DIBENZYLOXY-5,6-DIMETHOXYXANTHONE [**9**].—The previous oil (280 mg) was treated with pyridine (5.2 ml), H_2O (2.6 ml), and aqueous 10% tetramethylammonium hydroxide (1.9 ml). The mixture was refluxed 15 h (5), poured into ice, acidified with HCl, and extracted with Et_2O, yielding an oil which, after purification by cc (CH_2Cl_2-Me_2CO, 9:1) and crystallization from CH_2Cl_2/hexane yielded white plates, 227 mg (0.49 mmol, 86%), mp 182–183°; ir ν max (KBr) cm^{-1} 2930, 1665 (C=O of xanthone), 1625, 1605, 1570, 1500, 1490, 1435, 1400, 1380, 1295, 1220, 1180, 1175, 1130, 1090, 985, 920, 825, 800, 790, 740, 700; ^1H nmr ($CDCl_3$) δ 3.97 (3H, s, -OMe), 4.00 (3H, s, -OMe), 5.12 (2H, s, $-CH_2$ of BzO), 5.22 (2H, s, $-CH_2$ of BzO), 6.48 (1H, d, J=1.9 Hz, H-2), 6.68 (1H, d, J=1.9 Hz, H-4), 6.9 (1H, d, J=9 Hz, H-7), 7.40 (10 H, m, aromatic protons of 2 BzO), 8.04 (1H, d, J=9 Hz, H-8); ^{13}C nmr ($CDCl_3$) δ 56.3, 61.5, 70.5, 70.7, 94.4, 97.3, 107.4, 108.3, 118.0, 122.2, 126.6, 127.6, 128.4, 128.6, 128.7, 135.7, 136.3, 156.6, 159.7, 160.7, 163.6, 174.7; uv λ max (EtOH) nm (log ϵ) 210 (4.63), 246 (4.72), 287 (sh), 406 (4.37), uv spectra showed no variation when NaOMe was added; hrms *m/z* (%) $[M]^+$ 468 (19) (found 468.152±0.005, calcd for $C_{29}H_{24}O_6$, 468.1566), $[M+2]^+$ 470 (1.3), $[M+1]^+$ 469 (6.1), $[M-CH_2C_6H_5]^+$ 377 (3.1), $[M-C_6H_5CH_2OH]^+$ 362 (2.8), $[M-CH_2C_6H_5-CO]^+$ 349 (2.8), $[CH_2C_6H_5]^+$ 91 (100).

PREPARATION OF 1,3-DIHYDROXY-5,6-DIMETHOXYXANTHONE [**5**].—Compound **9** (14 mg, 0.03 mmol) was dissolved in 2 ml of EtOAc, 10 mg of 5% Pd/C and 0.05 ml of concentrated HCl were added, and the mixture was hydrogenated at room temperature (8) for 4 h. After filtration of the catalyst and crystallization from CH_2Cl_2, 7.3 mg (0.025 mmol, 85%) of **5** was obtained, (Scheme 2). Recrystallization from anhydrous Me_2CO yielded pale yellow needles, mp 275–277°. Its properties are identical with those of the product synthesized by Scheme 1.

PREPARATION OF 1-HYDROXY-3,5,6-TRIMETHOXYXANTHONE.—Compound **5** (5 mg, 0.017 mmol) was treated overnight with ethereal solution of CH_2N_2, yielding, after crystallization from MeOH, 4 mg (0.013 mmol, 78%) of 1-hydroxy-3,5,6-trimethoxyxanthone which was identified by comparison of its data with those of Quillinan and Scheinmann (5).

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Received 12 August 1987