

## Correction of a Reported Xanthone Synthesis: The Preparation of a Benzo[*c*]coumarin

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Reinvestigation of a reported synthesis of 5,8-dihydroxy-1,3-dimethoxyxanthone from the reaction of 3,5-dimethoxyphenol with 2-(methoxycarbonyl)-1,4-benzoquinone resulted in the identification of the product as the isomer of benzo[*c*]coumarin, *i.e.*, 7,10-dihydroxy-1,3-dimethoxy-6*H*-dibenzo[*b,d*]pyran-6-one, established by X-ray crystallography. This requires the revision of the structures of the derivatives that were reported.

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**Introduction.** – While searching the literature for <sup>1</sup>H- and <sup>13</sup>C-NMR data for 1,3,5,8-tetrahydroxyxanthone (= bellidin; **1**; *Scheme*) in order to compare them with those of a compound which we had isolated from a New Zealand gentian, *Gentianella antarctica* (HOOK.F.) T. N. HO and S. W. LIU, we noticed an account of a synthesis [1].

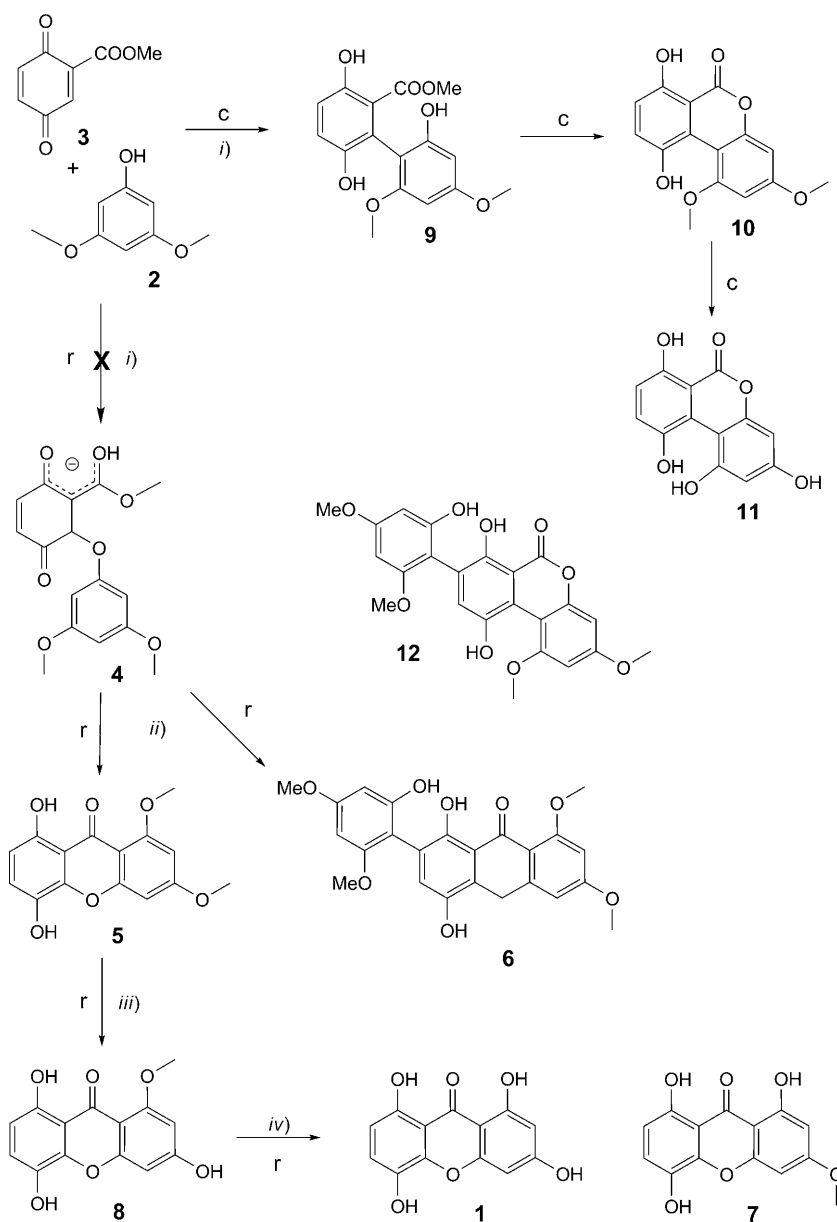
According to a literature procedure [2], 3,5-dimethoxyphenol (**2**) and 2-methoxypyridine were added to a solution of 2-(methoxycarbonyl)-1,4-benzoquinone (**3**) in benzene [1]. This was anticipated to yield a diphenyl ether, **4**, from which a xanthone could be produced *via* reductive methylation, hydrolysis of the ester, and cyclization with polyphosphoric acid [2]. Instead, two products were obtained, the major product being identified as the xanthone **5**, *i.e.*, **4** was thought to cyclize spontaneously under the reaction conditions to provide **5**. The minor product was ascribed the structure **6**.

It was reported that selective demethylation of the presumed **5** was surprisingly more difficult than expected for a 1-methoxyxanthone, and that, when one MeO was finally cleaved under forcing conditions, the product was not the known natural product bellidifolin (**7**). As only one chelated OH was revealed by the <sup>1</sup>H-NMR spectrum, and, as the <sup>13</sup>C-NMR spectrum lacked the resonances expected for a 1-hydroxyxanthone, it was concluded that this product was 3,5,8-trihydroxy-1-methoxyxanthone (**8**) [1]. Complete demethylation gave what was considered to be the 1,3,5,8-tetrahydroxyxanthone, bellidin (**1**) [1].

However, while the melting point of 318–320° of the synthetic product was in agreement with the literature values for bellidin (**1**; see [1]), the NMR data were significantly different from what we (unpublished data) and others [3] subsequently observed. This induced us to reexamine the synthesis.

**Results and Discussion.** – In our hands, repetition of the reaction of **2** and **3** afforded, after chromatographic purification, a major product with the same melting

Scheme. Reported (r) and Corrected (c) Reaction Pathways



*i*)  $\text{MgSO}_4$ , 2-Methoxypyridine/ $25^\circ$ . *ii*)–*iv*) See [1]: for monodemethylation:  $\text{AlCl}_3$  in benzene/ $60^\circ$ , or pyridinium hydrochloride/ $140^\circ$ , or  $\text{ZnCl}_2$  and  $\text{POCl}_3$ / $60^\circ$ , and for complete demethylation:  $\text{HI}/\text{Ac}_2\text{O}$ , or  $\text{AlCl}_3$  in benzene/ $80^\circ$ .

point and  $^1\text{H}$ -NMR spectrum as those reported in [1], and an EI-MS showing an apparent molecular-ion peak at  $m/z$  288 consistent with the required  $\text{C}_{15}\text{H}_{12}\text{O}_6$  composition for **5**. However, there were very peculiar discrepancies in the  $^{13}\text{C}$ -NMR spectra (see *Table*): 14 of the 15 resonances were as reported, but absent was one at  $\delta(\text{C})$  178.5 ppm attributed to the  $\text{C}=\text{O}$  group of a xanthone, and, instead, there was one for a fully substituted  $\text{sp}^2$ -C-atom at  $\delta(\text{C})$  101.1 ppm. The lowest-field  $^{13}\text{C}$ -NMR signal which we observed was at 164.8 ppm.

Table.  $^{13}\text{C}$ -NMR Data for the Major Product ( $R_f$  0.6) of the Reaction of **2** with **3** (in  $(\text{D}_6)$ DMSO; ref.  $\delta(\text{C})$  39.5 ppm)

From [1] (20 MHz)	This work (100 MHz)
178.5 (s, CO)	–
164.8 (s, C(3))	164.8 (s)
161.0 (s, C(1))	161.0 (s)
155.9 (s, C(4a) or C(8))	155.9 (s)
155.1 (s, C(8) or C(4a))	155.0 (s)
151.5 (s, C(10a))	151.5 (s)
145.0 (s, C(5))	145.0 (s)
128.5 (d, C(6))	128.4 (d)
118.5 (s, C(8a))	118.5 (s)
116.8 (d, C(7))	116.7 (d)
105.2 (s, C(9a))	105.2 (s)
–	101.1 (s)
97.4 (d, C(2))	97.3 (d)
95.2 (d, C(4))	95.0 (d)
57.6 (q, MeO at C(1) or C(3))	57.4 (q)
56.0 (q, MeO at C(3) or C(1))	55.9 (q)

These data were compatible with the formation of a product isomeric with the xanthone, the benzo[*c*]coumarin, 6*H*-dibenzo[*b,d*]pyran-6-one **10**, which we visualized as formed *via Michael*-type addition of **2** to **3** yielding **9**, *i.e.*, initial *C*- rather than *O*-addition of the ambident **2** to **3**, with a subsequent base-catalyzed intramolecular lactonization transforming **9** to **10** (see *Scheme*). From a mechanistic viewpoint this seemed much more plausible than the original suggestion [1] that xanthone formation occurred *via* a spontaneous cyclization of the product of *O*-addition: while *O*-adducts had been obtained by the base-catalyzed addition of phenols to **2**, their conversion to xanthenes required acid catalysis [2]. Also, although the C,C coupling of **2** with phenols is normally associated with acid catalysis [4], it does occur with highly nucleophilic species such as enols [5] without such catalysis.

Consistent with our hypothesis,  $^{13}\text{C}=\text{O}$  signals around 165 ppm have been reported for a series of 7-hydroxy-6*H*-dibenzo[*b,d*]pyran-6-ones [6].

The matter was solved by X-ray crystallography which revealed our product to have the structure shown in the *Figure*: 7,10-dihydroxy-1,3-dimethoxy-6*H*-dibenzo[*b,d*]pyran-6-one (**10**). As shown, there were two intermolecularly H-bonded molecules per

unit cell, exhibiting the strong intramolecular H-bonds expected. Full crystallographic details have been deposited with the *Cambridge Crystallographic Data Centre*<sup>1)</sup>.

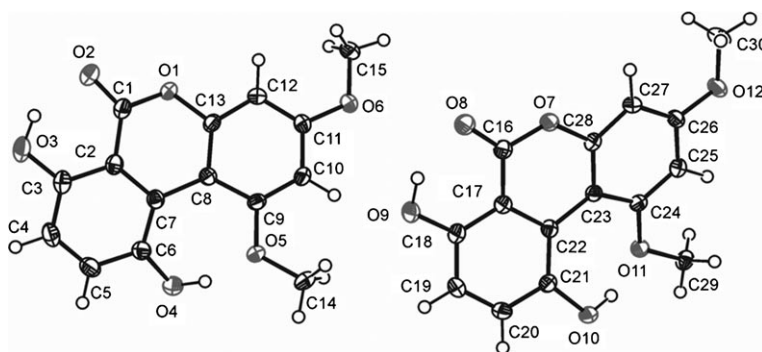


Figure. X-Ray crystal structures of the two crystallographically independent molecules **10**

In short, a crucial error in misidentifying the product of the condensation of 3,5-dimethoxyphenol (**2**) and 2-(methoxycarbonyl)-1,4-benzoquinone (**3**) as the xanthone **5**, rather than the benzocoumarin **9**, has resulted in the need to revise the structures of all of the derivatives of it described in the original publication [1]: 23 other compounds, the true structures of 7 of which can be deduced with reasonable certainty (the diacetate, dibenzoate, dimethyl, and dibenzyl derivatives of **10**; and the completely demethylated product, **11**, and its tetraacetate and tetrabenzoate). It also appears probable that the minor product assigned the structure **6** is actually **12**.

Some 6*H*-dibenzo[*b,d*]pyran-6-ones have biological activities (see those noted in [6]) so it would be interesting to examine the activities of the derivatives synthesized by *Vermes et al.* [1].

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### Experimental Part

*General.* Anal. and prep. TLC: SiO<sub>2</sub> 60 (0.2 mm) on glass plates (5 × 20 and 20 × 20 cm, resp.) with EtOH/toluene 1 : 9 (v/v) as eluent, visualization under short- and long-wavelength UV light. UV Spectra: *Cary 300* spectrometer, absorptions reported as  $\lambda_{\max}$  in nm (log  $\epsilon$ ). Fluorescence spectrum: *Aminco Bowman Series 2* luminescence spectrometer. NMR Spectra: *Bruker Instruments DRX 400* spectrometer using CDCl<sub>3</sub> or (D<sub>6</sub>)DMSO (chemical shifts in ppm referred to solvent signals  $\delta$ (H) 7.25 or 2.51,  $\delta$ (C) 77.0 or 39.5, resp.), coupling constants *J* in Hz. EI-MS (70 eV): *Finnigan MAT* instrument; only ions with an abundance greater than 20% of the most abundant ion are reported; in *m/z*.

For the X-ray crystallographic study, a colorless plate crystal of the compound was coated with *Paratone 8277* oil (*Exxon*) and mounted on a glass fiber. All measurements were made on a *Bruker APEX2* CCD installed on a *Nonius Kappa Goniometer* diffractometer with graphite monochromated MoK $\alpha$  radiation. The data were collected [7] using  $\omega$  and  $\varphi$  scans. The data were corrected for *Lorentz*

<sup>1)</sup> CCDC-729937 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre*, via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

and polarization effects, and for absorption using multi-scan method [8]. The structure was solved by direct methods [9] and expanded using *Fourier* techniques [10]. The asymmetric unit contains two independent molecules. The non-H-atoms were refined anisotropically. All of the H-atoms were located from a difference *Fourier* map and were allowed to refine with isotropic thermal parameters. The final cycle of full-matrix least-squares refinement using SHELXL97 [11] converged with unweighted and weighted agreement factors,  $R = 0.0415$  and  $wR = 0.1071$  (all data), resp., and goodness-of-fit,  $S = 1.081$ . The weighting scheme was based on counting statistics, and the final difference *Fourier* map was essentially featureless. The figures were plotted with the aid of ORTEP-3 for Windows [12].

**7,10-Dihydroxy-1,3-dimethoxy-6H-dibenzo[b,d]pyran-6-one (10).** According to the procedure described in [1], a soln. of 2-(methoxycarbonyl)-1,4-benzoquinone (**3**) in anh. benzene (17 ml) was prepared *in situ* by the oxidation of methyl 2,5-dihydroxybenzoate (1.68 g) with a suspension of  $\text{Ag}_2\text{O}$  (5.1 g) and anh.  $\text{K}_2\text{CO}_3$  (850 mg) at  $50^\circ$ . After filtration,  $\text{MgSO}_4$  (1.7 g) was added, and the suspension was stirred, while a soln. of 3,5-dimethoxyphenol (1.07 g) and 2-methoxypyridine (2.28 g) in dry benzene (10 ml) was added dropwise over the course of 10 min. After having been stirred for a further 2 h at r.t., the mixture was filtered, and the filter cake was washed with a little dry benzene. The combined filtrate and washings were evaporated under reduced pressure (17 mm, rotovap,  $65^\circ$ ) to yield a dark red-brown oil. This was dissolved in MeOH (50 ml) and stored at  $0^\circ$  overnight. The bronze-colored solid which separated was collected by filtration, washed with a little ice-cold MeOH, and air-dried to yield a copper-colored solid (540 mg, ca. 19%). TLC (toluene/EtOH 9:1 (v/v)) revealed two components as yellow spots with  $R_f$  0.6 and 0.42. A portion of this mixture (15 mg) was separated by prep. TLC in the same solvent system, and the material with  $R_f$  0.6 was recrystallized from EtOH to afford **10** (8 mg, 0.4%). Pale yellow laths. M.p. 168–169 ([1]: 167–168°). UV and fluorescence spectra (in 95% EtOH): 213 (4.57), 246 (4.48), 276 (4.02), 379 (4.16);  $\lambda_{\text{ex}}$  379,  $\lambda_{\text{em}}$  464.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 11.21 (s, 1 H); 8.77 (s, 1 H); 7.33 (d,  $J = 9.0$ , 1 H); 7.01 (d,  $J = 9.0$ , 1 H); 6.62 (d,  $J = 2.5$ , 1 H); 6.53 (d,  $J = 2.5$ , 1 H); 4.06 (s, 3 H); 3.88 (s, 3 H).  $^1\text{H-NMR}$  from [1] (100 MHz): 11.22 (s, 1 H); 8.77 (s, 1 H); 7.31 (d,  $J = 9$ , 1 H); 7.00 (d,  $J = 9$ , 1 H); 6.57 (d,  $J = 2.5$ , 1 H); 6.49 (d,  $J = 2.5$ , 1 H); 4.05 (s, 3 H); 3.86 (s, 3 H).  $^{13}\text{C-NMR}$ : see Table. EI-MS: 288 (100), 273 (92), 245 (33), 213 (47).

The minor product, **7,10-dihydroxy-8-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dimethoxy-6H-dibenzo[b,d]pyran-6-one (12)** with  $R_f$  0.42 was similarly obtained as bronze prisms (2 mg, 0.06%). M.p. 259–262° ([1]: 259–262°).  $^1\text{H-NMR}$  ( $(\text{D}_6)\text{DMSO}$ ): 11.11 (s, 1 H); 9.26 (s, 1 H); 8.80 (s, 1 H); 7.08 (s, 1 H); 6.77 (d,  $J = 2.5$ , 1 H); 6.74 (d,  $J = 2.5$ , 1 H); 6.15 (s, 2 H); 4.05 (s, 3 H); 3.87 (s, 3 H); 3.75 (s, 3 H); 3.63 (s, 3 H).  $^1\text{H-NMR}$  from [1] (100 MHz): 11.11 (s, 1 H); 9.25 (s, 1 H); 8.80 (s, 1 H); 7.10 (s, 1 H); 6.77 (2 arom. H); 6.2 (s, 2 H); 4.10 (s, 3 H); 3.90 (s, 3 H); 3.77 (s, 3 H); 3.65 (s, 3 H).  $^{13}\text{C-NMR}$  ( $(\text{D}_6)\text{DMSO}$ ): 165.6 (s); 160.8 (s); 160.4 (s); 158.6 (s); 156.3 (s); 155.9 (s); 154.2 (s); 151.4 (s); 144.0 (s); 131.5 (d); 123.9 (s); 117.0 (s); 104.8 (s); 104.6 (s); 101.3 (s); 97.3 (d); 95.3 (d); 94.1 (d); 90.1 (d); 57.6 (q); 56.0 (q); 55.6 (q); 55.1 (q).  $^{13}\text{C-NMR}$  from [1] (20.15 MHz; only 22 resonances listed): 165.7 (s); 160.9 (s); 160.6 (s); 158.7 (s); 156.4 (s); 155.8 (s); 154.5 (s); 151.5 (s); 144.0 (s); 131.7 (d); 124.1 (s); 117.1 (s); 105.2 (s); 104.7 (s); 97.5 (d); 95.3 (d); 94.1 (d); 90.1 (d); 57.6 (q); 56.0 (q); 55.6 (q); 55.1 (q). EI-MS: 440 (100), 422 (30), 407 (22).

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