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

by **Michael H. Benn**[a]), **Masood Parvez**[a]), **Nigel B. Perry**[b]), **Arvi Rauk**[a]), and **John W. van Klink***[b])

[a]) Chemistry Department University of Calgary, Calgary, Alberta, T2N1N4, Canada
[b]) Plant Extracts Research Unit, New Zealand Institute for Plant and Food Research Ltd, Chemistry Department, University of Otago, P. O. Box 56, Dunedin, New Zealand
(phone: +64-3-479-8966; e-mail: john.vanklink@plantandfood.co.nz)

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.

Introduction. – While searching the literature for ^{1}H- and ^{13}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].

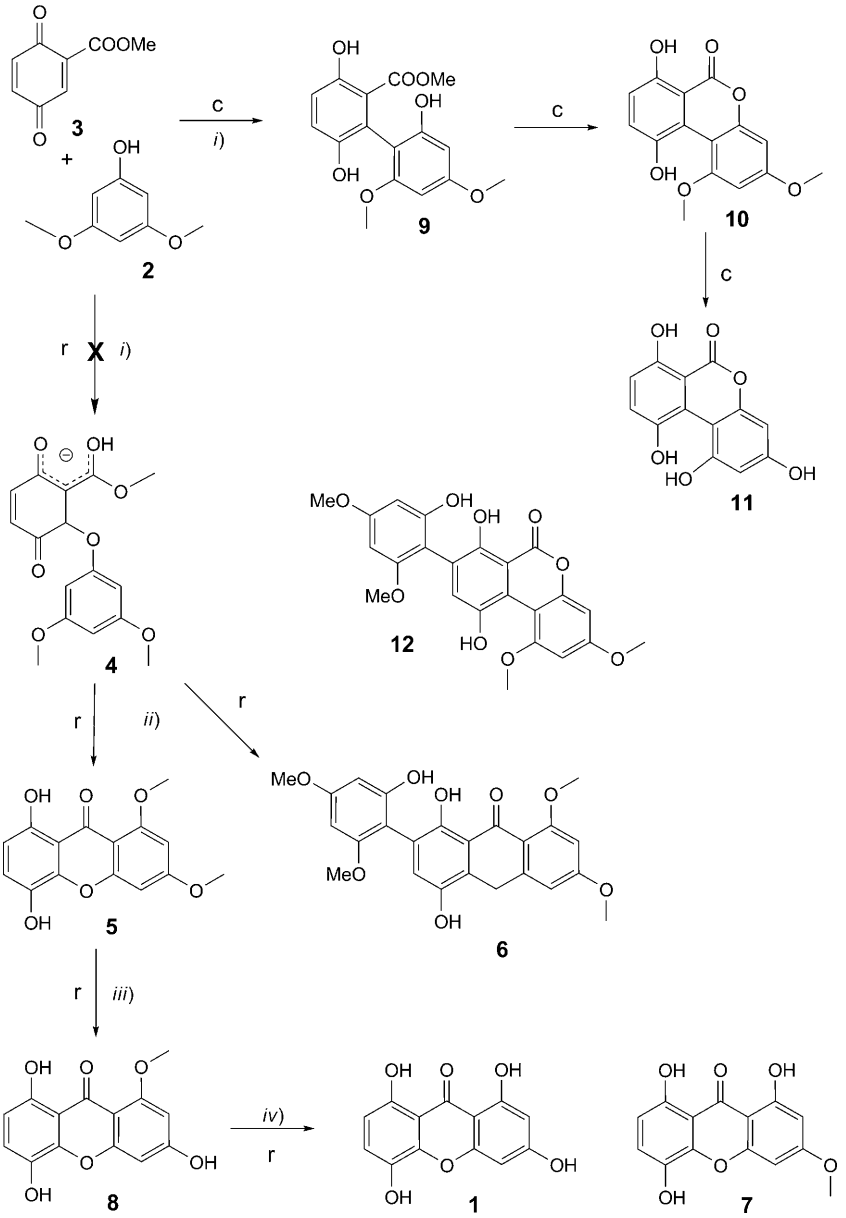
According to a literature procedure [2], 3,5-dimethoxyphenol (**2**) and 2-methoxypyridine were added to a solution of 2-(methoxycarbonyl)-1,4-benzoquinone (**3**) in benzene [1]. This was anticipated to yield a diphenyl ether, **4**, from which a xanthone could be produced *via* reductive methylation, 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 ^{1}H-NMR spectrum, and, as the ^{13}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) $MgSO_4$, 2-Methoxypyridine/25°. *ii*)–*iv*) See [1]: for monodemethylation: $AlCl_3$ in benzene/60°, or pyridinium hydrochloride/140°, or $ZnCl_2$ and $POCl_3$/60°, and for complete demethylation: HI/Ac_2O, or $AlCl_3$ in benzene/80°.

point and ^{1}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 $C_{15}H_{12}O_6$ composition for **5**. However, there were very peculiar discrepancies in the ^{13}C-NMR spectra (see *Table*): 14 of the 15 resonances were as reported, but absent was one at δ(C) 178.5 ppm attributed to the C=O group of a xanthone, and, instead, there was one for a fully substituted sp^2-C-atom at δ(C) 101.1 ppm. The lowest-field ^{13}C-NMR signal which we observed was at 164.8 ppm.

Table. *^{13}C-NMR Data for the Major Product* (R_f 0.6) *of the Reaction of* **2** *with* **3** (in (D_6)DMSO; ref. δ(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 xanthones 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}C=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*[1]).

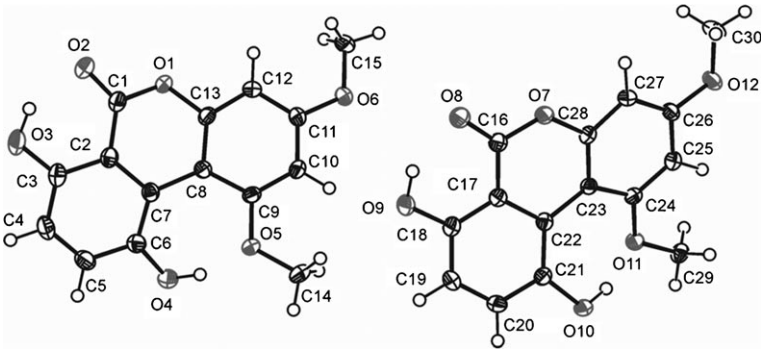


Figure. *X-Ray crystal structures of the two crystallographically independent molecules* **10**

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].

We thank *Dorothy Fox*, *Johnson Li*, *Loeke Janzen*, *Qiao Wu*, and *Ragav Yamdagni* for assistance in collecting the spectrometric data. Financial support was provided from funds provided by *Sigma Aldrich* (to *M. H. B.*).

Experimental Part

General. Anal. and prep. TLC: SiO_2 *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 λ_{max} in nm (log ε). Fluorescence spectrum: *Aminco Bowman Series 2* luminescence spectrometer. NMR Spectra: *Bruker Instruments DRX 400* spectrometer using $CDCl_3$ or (D_6)DMSO (chemical shifts in ppm referred to solvent signals δ(H) 7.25 or 2.51, δ(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_α radiation. The data were collected [7] using ω and φ scans. The data were corrected for *Lorentz*

[1]) 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.

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-6*H-*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 Ag_2O (5.1 g) and anh. K_2CO_3 (850 mg) at 50°. After filtration, $MgSO_4$ (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°) to yield a dark red-brown oil. This was dissolved in MeOH (50 ml) and stored at 0° 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); λ_{ex} 379, λ_{em} 464. ^{1}H-NMR ($CDCl_3$): 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}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}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-6*H-*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}H-NMR ((D_6)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}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}C-NMR ((D_6)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*). ^{1}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).

REFERENCES

[1] B. Vermes, O. Seligmann, H. Wagner, *Helv. Chim. Acta* **1985**, *92*, 375.
[2] P. Müller, T. Venakis, C. H. Eugster, *Helv. Chim. Acta* **1979**, *62*, 2350.
[3] a) H. Kanamori, I. Sakumoto, M. Mizuta, K. Hashimoto, O. Tanaka, *Chem. Pharm. Bull.* **1984**, *32*, 2290; b) H.-M. Zhou, Y.-L. Liu, G. Blasko, G. A. Cordell, *Phytochemistry* **1989**, *28*, 3569.
[4] P. Müller, T. Venakis, C. H. Eugster, *Helv. Chim. Acta* **1979**, *62*, 2833.
[5] S. E. Fumagalli, C. H. Eugster, *Helv. Chim. Acta* **1971**, *54*, 959.
[6] B. Appel, N. N. R. Saleh, P. Langer, *Chem. – Eur. J.* **2006**, *12*, 1221.
[7] Z. Otwinowski, W. Minor, *Methods Enzymol*. **1997**, *276*, 307.
[8] R. Hooft, COLLECT, *Nonius BV*, Delft, The Netherlands, 1998.
[9] A. Altomare, M. Cascarano, C. Giacovazzo, A. Guagliardi, *J. Appl. Crystallogr.* **1993**, *26*, 343.

[10] P. T. Beurskens, G. Admiraal, G. Beurskens, W. P. Bosman, R. de Gelder, R. Israel, J. M. N. Smits, The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands, 1994.
[11] G. M. Sheldrick, *Acta Crystallogr., Ser. A* **2008**, *A64,* 112.
[12] L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565.

Received August 4, 2009