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Xanthones from the cultured lichen mycobionts of *Pyrenula japonica* and *Pyrenula pseudobufonia*

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Abstract

Cultures of the spore-derived mycobionts of the Asian lichen *Pyrenula japonica* and the North American species *P. pseudobufonia* gave two xanthones, 1,5,8-trihydroxy-3-methylxanthone and 1,8-dihydroxy-5-methoxy-3-methylxanthone along with the known 1,7-dihydroxy-3-methylxanthone. Their structures were determined by spectroscopic methods. This is the first instance of the isolation of xanthones with a methyl group at C-3 from lichen mycobionts.

Keywords: *Pyrenula japonica*; *Pyrenula pseudobufonia*; Lichen; Isolated mycobiont; 1,5,8-Trihydroxy-3-methylxanthone; 1,8-Dihydroxy-5-methoxy-3-methylxanthone

1. Introduction

Lichens, a symbiotic association of mycobiont and phycobiont partners, produce a variety of characteristic secondary metabolites, some of which have been found to exhibit a wide range of potentially useful biological activities (Yamamoto, 1991). Recent studies demonstrated that cultures of spore-derived lichen mycobionts have the ability to produce certain lichen substances or novel metabolites in large amounts under osmotically stressed conditions (Hamada & Ueno, 1990; Miyagawa, Hamada, Sato & Ueno, 1994; Tanahashi, Kuroishi, Kuwahara, Nagakura & Hamada, 1997). It was pointed out that cultures of lichen mycobionts could be a new source of bioactive compounds. In the course of our studies on cultured lichen mycobionts, we cultivated the spore-derived mycobionts *Pyrenula japonica* Kurok. and *P. pseudobufonia* (Rehm) R.C. Harris and isolated from their cultures three xanthones, two of which are new compounds. In this paper, we report the isolation and structure determination of these compounds.

2. Results and discussion

The Me_2CO extracts of polyspore-derived mycobionts of *Pyrenula japonica* collected in Japan, cultured on conventional malt–yeast extract medium and separated by a combination of CC and preparative TLC, afforded three compounds, **1**, **2** and **3**.

Compound **1** was isolated as yellow needles. HR-EI mass spectrum of the compound exhibited a strong peak at m/z 242.0592 $[M]^+$, indicating a molecular formula of $C_{14}H_{10}O_4$. Its ^1H and ^{13}C NMR spectral data suggested **1** to be 1,7-dihydroxy-3-methylxanthone, which has previously been isolated from the roots of *Cassia occidentalis* Linn. (Wader & Kudav, 1987) and synthesized from orcinol and gentisic acid (Ginde, Hosangadi, Kudav, Nayak & Kulkarni, 1970;

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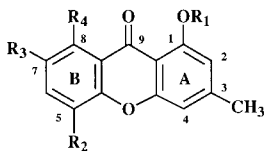
Munekata, 1953). Until now, 1,7-dihydroxy-3-methylxanthone (**1**) has never been isolated from lichens.

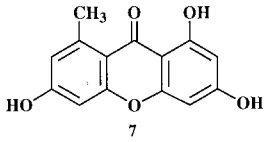
Compound **2** was also obtained as yellow needles. The HR-EIMS of **2** showed $[M]^+$ at m/z 258.0553, an increase of 16 mass units with respect to **1**. The ^1H NMR spectral features of **2** were similar to those of 1,7-dihydroxy-3-methylxanthone (**1**), the only significant difference in their spectra being that **2** showed a pair of *ortho*-coupled doublets at δ 6.64 and 7.24 (each 1H, d, J = 9.0 Hz) instead of an aromatic ABX system. Furthermore, its ^1H NMR spectrum in $CDCl_3$ demonstrated two low field singlets (δ 11.27 and 11.85), confirming the presence of two chelated hydroxyl groups. A comparison of the ^{13}C NMR spectral data suggested that **2** and **1** had the same substitution pattern of the A ring, but ring B in **2** possessed three oxygenated carbons rather than two. The substitution with hydroxyl groups at C-5 and C-8 was suggested by the fact that the chemical shifts of the carbon signals arising from the B ring in **2** were consistent with those of 1,5,8-trihydroxy-3-methoxyxanthone (Basnet, Kadota, Shimizu & Namba, 1994) rather than those of 1,7,8-trihydroxy-3-methoxyxanthone (Wolfender, Hamburger, Msonthi & Hostettmann, 1991). Detailed analysis of the HMBC spectrum supported the proposed structure of **2**. The chemical correlation with **3** further confirmed this suggestion.

The mass spectrum of compound **3** is in agreement with the molecular formula $C_{15}H_{12}O_5$. Its ^1H NMR spectrum showed the presence of two chelated hydroxyl groups (δ 11.33 and 11.73) and a methoxyl group at δ 3.94 (3H, s). The ^{13}C NMR data of **3** were nearly identical with those of **2** except for the presence of the methoxyl carbon signal resonating at δ 57.38 and the chemical shifts of C-5 and C-6. These values suggested that the hydroxyl group at C-5 of **2** was methylated in **3**. The position of the substituents on aromatic rings was further confirmed by its NOESY spectrum, which showed significant correlations between the methoxyl at δ 3.94 and a doublet at δ 7.23, between the hydroxyl at δ 11.33 and a doublet at δ 6.70 and between the hydroxyl at δ 11.73 and a broad singlet at δ 6.62, along with cross-peaks between the methyl and two broad singlets resonating at δ 6.62 and 6.84.

Finally, compound **3** was chemically correlated with **2** by methylation. Compound **2** was treated with CH_2N_2–Et_2O to yield a monomethyl, two dimethyl and a trimethyl derivative. The monomethyl ether was identified as **3** and the latter three products were also obtained by the methylation of **3**. All spectral data



1 $R_1 = R_2 = R_4 = H$, $R_3 = OH$
2 $R_1 = R_3 = H$, $R_2 = R_4 = OH$
3 $R_1 = R_3 = H$, $R_2 = OCH_3$, $R_4 = OH$
4 $R_1 = CH_3$, $R_2 = OCH_3$, $R_3 = H$, $R_4 = OH$
5 $R_1 = R_3 = H$, $R_2 = R_4 = OCH_3$
6 $R_1 = CH_3$, $R_2 = R_4 = OCH_3$, $R_3 = H$



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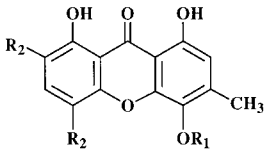

8 $R_1 = R_2 = H$
9 $R_1 = CH_3$, $R_2 = Cl$

including 2D-NMR studies, i.e. NOESY, HMQC and HMBC techniques, were fully consistent with the structures **4**–**6** for the methylated compounds. Consequently, compounds **2** and **3** were characterized as 1,5,8-trihydroxy-3-methylxanthone and 1,8-dihydroxy-5-methoxy-3-methylxanthone, respectively.

Mycobionts of *P. pseudobufonia* from Florida, USA, were cultivated in the same way as described for *P. japonica*. Purification of the metabolites yielded two xanthones, which were identical to **2** and **3**.

Lichens growing in natural habitats are known to produce a number of xanthones (Huneck & Yoshimura, 1996; Peres & Nagem, 1997). The large majority of lichen xanthones possess a methyl group at C-8 such as norlichexanthone (**7**), which is proposed to be biosynthesized by cyclization of a single, linear polyketide chain. By contrast, the occurrence of xanthones with a methyl group at C-3, as represented by thiomelin (**8**)[1], is relatively rare in lichens. Their biosynthesis was assumed to involve an anthrone or anthraquinone intermediate, with subsequent oxidative cleavage of the C–C bond of the intermediate by analogy to that of a fungal xanthone ravenelin (**9**) (Elix, Gaul, Sterns & Wahid bin Samsudin, 1987). In the present study, we isolated 1,7-dihydroxy-3-methylxanthone (**1**) and two new xanthones, **2** and **3**, all of which might possibly be derived from a common intermediate through oxidation, decarboxylation and recyclization steps in a manner similar to that assumed for ravenelin. This is the first instance of the isolation of xanthones with a methyl group at C-3 from lichen mycobionts.

It is also noteworthy that the same xanthones were detected in the isolated mycobionts from North American as well as Japanese specimens. The species of the lichens used for the studies are different and the two collection sites, Florida in USA and Nara in Japan, are distant. Thus, although these compounds have not yet been found in lichenized condition, they appear to be commonly produced in mycobionts isolated from unrelated locations, suggesting a biological significance in the prelichenized condition.

[1] For convenience and in order to facilitate biogenetic discussion, the numbering chosen is not in accord with that reported for thiomelin.

3. Experimental

3.1. General

Melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. The UV spectra were recorded on a Shimadzu UV-240 spectrophotometer and the IR spectra on a Shimadzu FTIR-8200 infrared spectrophotometer. HR-EIMS were obtained with a Hitachi M-4100 mass spectrometer. The NMR experiments were performed with Varian VXR-500, Varian Gemini-300 and Varian Gemini-200 spectrometers, with tetramethylsilane as internal standard. HPLC was performed using a Waters system (600E multisolvent delivery system, 486 tunable absorbance detector). Thin-layer chromatography was performed on precoated Kieselgel $60F_{254}$ plates (Merck) and spots were visualized under UV light.

3.2. Plant material

Specimens of *P. japonica* Kurok. were collected from the bark of trees in Nara Prefecture, Japan (850 m alt.) in 1993. The voucher specimen (NH93975) was identified by Dr. H. Miyawaki, Saga University, Japan and was deposited at Osaka City Institute of Public Health and Environmental Sciences. Mycobionts of *P. japonica* were obtained from the spores discharged from apothecia of a thallus, and were cultivated in 58 test tubes containing modified MY10 medium (malt extract 10 g, yeast extract 4 g, sucrose 100 g, agar 15 g, H_2O 1l, pH 7) at 18° in the dark. Black compact colonies with yellow crystals which covered large areas of colonies and surrounding agar were found in each test tube. After cultivation for 10 months, the colonies and slants with crystals were harvested.

Specimens of *P. pseudobufonia* (Rehm) R.C. Harris were collected from the bark of trees in Florida, USA (0 m alt.) in 1995. The voucher specimen (NH9592552) was identified by Dr. Bruce Ryan, Arizona State University, USA and was deposited at Osaka City Institute of Public Health and Environmental Sciences. The mycobionts were cultivated for 10 months as described above.

3.3. Extraction and isolation of xanthones

3.3.1. Pyrenula japonica

The entire mycelia along with the cultured media (dry weight 32.5 g) were extracted with Me_2CO at room temperature four times for 6 h each, and the combined extracts were concentrated under red. pres. to give 2 g of residue. This was suspended in $CHCl_3$ and the $CHCl_3$-soluble material was chromatographed on silica gel column eluted with $CHCl_3$. The fractions, which contained yellow compounds, were combined (313.1 mg) and repeatedly subjected to preparative TLC on silica gel with $CHCl_3$–MeOH (9:1), toluene–Me_2CO (19:1) or toluene–HOAc (20:3), yielding **1** (25.2 mg), **2** (58.6 mg) and **3** (122.1 mg).

Table 1
^{13}C-NMR data of compounds **1**–**6**

C	**1**[a]	**2**[a]	**3**[b]	**4**[b]	**5**[b]	**6**[b]
1	161.71	161.41	160.97	160.43	161.70	160.17
2	111.06	111.94	111.71	107.03	111.63	107.12
3	149.48	150.62	149.92	147.79	148.40	145.46
4	108.11	108.47	107.97	110.40	107.14	109.68
4a	157.08	156.84	156.03	157.94	155.14	156.84
4b	150.84	144.70	145.62	144.97	147.91	146.89
5	119.62	137.78	140.01	139.46	142.17	141.91
6	125.53	124.58	120.80	119.88	117.37	115.72
7	154.48	109.92	109.06	108.89	104.27	104.96
8	108.96	153.61	154.16	155.00	153.81	153.69
8a	121.64	108.63	108.29	109.93	111.96	114.91
9	182.50	186.47	185.63	182.23	182.47	176.00
9a	107.08	106.38	105.86	109.07	107.45	111.64
3-Me	22.58	22.69	22.63	22.57	22.47	22.28
1-OMe				56.46		56.70[c]
5-OMe			57.38	57.48	57.03[c]	56.95[c]
8-OMe					56.53[c]	56.25[c]

[a] Measured in $CDCl_3$–CD_3OD.
[b] Measured in $CDCl_3$.
[c] Assignments may be interchangeable.

3.3.2. P. pseudobufonia

The harvested colonies (28 test tubes, dry weight 7.55 g) and agar media were extracted with Et_2O. The extract (293 mg) was purified by preparative TLC with $CHCl_3$–MeOH (9:1) or toluene–Me_2CO (3:1), yielding **2** (3.3 mg) and **3** (14.7 mg).

3.3.3. 1,7-Dihydroxy-3-methylxanthone (*1*)

Yellow needles ($CHCl_3$), mp 259.5–260°. UV λ_{max}^{MeOH} nm (log ε): 235 (4.45), 261 (4.58), 290 (3.98), 384 (3.84). IR ν_{max}^{KBR} cm^{-1}: 3285, 1653, 1607, 1585, 1483. ^{1}H NMR ($CDCl_3$–CD_3OD): δ 2.42 (3H, s, 3-CH_3), 6.57 (1H, br s, H-2), 6.75 (1H, br s, H-4), 7.29 (1H, dd, J = 9.0, 2.5 Hz, H-6), 7.37 (1H, d, J = 9.0 Hz, H-5), 7.52 (1H, d, J = 2.5 Hz, H-8). ^{13}C NMR data: Table 1. HMBC correlations: H-2 → C-1/C-4/C-9a, 3-CH_3 → C-2/C-3/C-4, H-4 → C-2/C-4a/C-9a, H-5 → C-4b/C-7/C-8a, H-6 → C-4b/C-8, H-8 → C-4b/C-6/C-9. NOESY correlations: H-2 ↔ 3-CH_3, H-4 ↔ 3-CH_3. HR-EIMS Found: 242.0592 $[M]^+$; $C_{14}H_{10}O_4$ requires 242.0579. This compound was identified by comparison with the authentic sample prepared from orcinol and gentisic acid.

3.3.4. 1,5,8-Trihydroxy-3-methylxanthone (*2*)

Yellow needles (MeOH), mp 276.5–278°. UV λ_{max}^{MeOH} nm (log ε): 236 (4.32), 255 (4.47), 263 sh (4.40), 272 (4.31), 341 (4.01), 403 (3.54). IR ν_{max}^{KBr} cm^{-1}: 3461,

1661, 1633, 1606, 1591, 1497. ^{1}H NMR ($CDCl_3$–CD_3OD): δ 2.45 (3H, s, 3-CH_3), 6.62 (1H, m, H-2), 6.64 (1H, d, J = 9.0 Hz, H-7), 6.89 (1H, m, H-4), 7.24 (1H, d, J = 9.0 Hz, H-6). ($CDCl_3$): δ 2.44 (3H, s, 3-CH_3), 6.64 (1H, br s, H-2), 6.67 (1H, d, J = 9.0 Hz, H-7), 6.83 (1H, br s, H-4), 7.24 (1H, d, J = 9.0 Hz, H-6), 11.27 (1H, br s, H-8), 11.85 (1H, br s, H-1). ^{13}C NMR data: Table 1. HMBC correlations: H-2 → C-1/C-4/C-9a, 3-CH_3 → C-2/C-3/C-4, H-4 → C-9a, H-6 → C-4b/C-5/C-8, H-7 → C-5/C-8/C-8a. HR-EIMS Found: 258.0553 $[M]^+$; $C_{14}H_{10}O_5$ requires 258.0529.

*3.3.5. 1,8-Dihydroxy-5-methoxy-3-methylxanthone (**3**)*

Yellow needles ($CHCl_3$), mp. 214–215°. UV λ_{max}^{MeOH} nm (log ε): 235 (4.36), 254 (4.49), 272 (4.30), 339.5 (4.00), 392.5 (3.54). IR ν_{max}^{KBr} cm^{-1}: 3445, 1661, 1631, 1609, 1585, 1489. ^{1}H NMR ($CDCl_3$): δ 2.42 (3H, s, 3-CH_3), 3.94 (3H, s, 5-OCH_3), 6.62 (1H, br s, H-2), 6.70 (1H, d, J = 9.0 Hz, H-7), 6.84 (1H, br s, H-4), 7.23 (1H, d, J = 9.0 Hz, H-6), 11.33 (1H, br s, 8-OH), 11.73 (1H, br s, 1-OH). ^{13}C NMR data: Table 1. HMBC correlations: 1-OH → C-1, H-2 → C-1/3-CH_3/C-4/C-9a, 3-CH_3 → C-2/C-3/C-4, H-4 → C-2/3-CH_3/C-4a/C-9a, 5-OCH_3 → C-5, H-6 → C-4b/C-5/C-8, H-7 → C-5/C-8a, 8-OH → C-7/C-8. NOESY correlations: 1-OH ↔ H-2, H-2 ↔ 3-CH_3, 3-CH_3 ↔ H-4, 5-OCH_3 ↔ H-6, H-7 ↔ 8-OH. HR-EIMS Found: 272.0685 $[M]^+$; $C_{15}H_{12}O_5$ requires 272.0685.

*3.4. Methylation of **2** and **3***

Compound **2** (9.9 mg) in MeOH was treated with excess CH_2N_2–Et_2O for 20 h in an ice bath. After evapn of the solvent, the residue was subjected to prep. TLC with toluene–HOAc (20:3) to afford **6** (1.0 mg), **3** (1.1 mg) and a mixt. (8.0 mg) of dimethyl compounds. Prep. HPLC (μBondasphere 5 μC18–100 Å, H_2O–MeOH, 7:13) of this mixt. gave **4** (4.4 mg) and **5** (1.9 mg). In the same way, compound **3** was methylated yielding **4**, **5** and **6**.

*3.4.1. 8-Hydroxy-1,5-dimethoxy-3-methylxanthone (**4**)*

Yellow crystalline solid (MeOH), mp 188–189.5°. UV λ_{max}^{MeOH} nm (log ε): 240 (4.45), 245 sh (4.40), 263.5 (4.28), 325 (4.04), 381 (3.50). IR ν_{max}^{KBr} cm^{-1}: 3432, 1655, 1612, 1489. ^{1}H NMR ($CDCl_3$): δ 2.47 (3H, s, 3-CH_3), 3.95 (3H, s, 5-OCH_3), 4.03 (3H, s, 1-OCH_3), 6.63 (1H, m, H-2), 6.69 (1H, d, J = 9.0 Hz, H-7), 6.99 (1H, m, H-4), 7.20 (1H, d, J = 9.0 Hz, H-6). ^{13}C NMR data: Table 1. HMBC correlations: 1-OCH_3 → C-1, H-2 → C-1/3-CH_3/C-4/C-9a, 3-CH_3 → C-2/C-3/C-4, H-4 → C-2/3-CH_3/C-4a/C-9a, 5-OCH_3 → C-5, H-6 → C-4b/C-5/C-8, H-7 → C-5/C-6/C-8/C-8a. NOESY correlations: 1-OCH_3 ↔ H-2, H-2 ↔ 3-CH_3, 3-CH_3 ↔ H-4, 5-OCH_3 ↔ H-6. HR-EIMS Found: 286.0834 $[M]^+$; $C_{16}H_{14}O_5$ requires 286.0842.

*3.4.2. 1-Hydroxy-5,8-dimethoxy-3-methylxanthone (**5**)*

Yellow crystalline solid (MeOH), mp 195–197°. UV λ_{max}^{MeOH} nm (log ε): 235 sh (4.36), 252.5 (4.47), 271 sh (4.08), 332 (3.94), 376 (3.59). IR ν_{max}^{Kbr} cm^{-1}: 1653, 1616, 1591, 1493. ^{1}H NMR ($CDCl_3$): δ 2.41 (3H, s, 3-CH_3), 3.97, 3.99 (each 3H, s, 5-, 8-OCH_3), 6.61 (1H, m, H-2), 6.72 (1H, d, J = 9.0 Hz, H-7), 6.82 (1H, m, H-4), 7.21 (1H, d, J = 9.0 Hz, H-6), 12.90 (1H, s, 1-OH). ^{13}C NMR data: Table 1. HMBC correlations: 1-OH → C-1/C-2/C-9a, H-2 → C-1/3-CH_3/C-4, 3-CH_3 → C-2/C-4, H-4 → C-2/3-CH_3/C-4a/C-9a, 5-OCH_3 → C-5, H-6 → C-4b/C-5/C-8, H-7 → C-5/C-8/C-8a, 8-OCH_3 → C-8. NOESY correlations: 1-OH ↔ H-2, H-2 ↔ 3-CH_3, 3-CH_3 ↔ H-4, 5-OCH_3 ↔ H-6, H-7 ↔ 8-OCH_3. HR-EIMS Found: 286.0857 $[M]^+$; $C_{16}H_{14}O_5$ requires 286.0842.

*3.4.3. 1,5,8-Trimethoxy-3-methylxanthone (**6**)*

Yellow needles (MeOH), mp 228–229°. UV λ_{max}^{MeOH} nm (log ε): 238 (4.53), 314 (4.08), 355 (3.65). IR ν_{max}^{Kbr} cm^{-1}: 1663, 1609, 1489. ^{1}H NMR ($CDCl_3$): δ 2.43 (3H, s, 3-CH_3), 3.92 (3H, s, 8-OCH_3), 3.95 (3H, s, 1-OCH_3), 3.96 (3H, s, 5-OCH_3), 6.58 (1H, br s, H-2), 6.67 (1H, d, J = 9.0 Hz, H-7), 6.92 (1H, br s, H-4), 7.10 (1H, d, J = 9.0 Hz, H-6). ^{13}C NMR data: Table 1. HMBC correlations: 1-OCH_3 → C-1, H-2 → C-1/C-3/3-CH_3/C-4/C-9a, 3-CH_3 → C-2/C-3/C-4, H-4 → C-2/3-CH_3/C-4a/C-9a, 5-OCH_3 → C-5, H-6 → C-4b/C-5/C-8, H-7 → C-5/C-8/C-8a, 8-OCH_3 → C-8. NOESY correlations: 1-OCH_3 ↔ H-2, H-2 ↔ 3-CH_3, 3-CH_3 ↔ H-4, 5-OCH_3 ↔ H-6, H-7 ↔ 8-OCH_3. HR-EIMS Found: 300.1015 $[M]^+$; $C_{17}H_{16}O_5$ requires 300.0998.

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