Bromophenols from the Red Alga *Rhodomela larix*[1]

Minoru Suzuki, Nobuhiko Kowata, and Etsuro Kurosawa*
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060
(Received January 14, 1980)

Synopsis. Two new bromophenols, 3-bromo-4-hydroxybenzaldehyde and a brominated dibenzyl ether derivative, were isolated from the red alga *Rhodomela larix*, along with several known bromophenols which have previously been isolated from *R. larix* and other species.

In connection with our interest in the halogenated secondary metabolites of the marine red algae, especially Rhodomelaceae, we have investigated the neutral and acidic constituents of the red alga *Rhodomela larix* (Turner) C. Agardh, which was collected at Oshoro Bay, Hokkaido. Several bromophenols have previously been obtained from this algae, collected in different locations.[2-4] Our specimen displayed no halogenated compound in the neutral constituents, and instead yielded two new bromophenols, 3-bromo-4-hydroxybenzaldehyde (**6a**) and a brominated dibenzyl ether derivative (**8a**), along with known bromophenols, **1a**, **2a**, **3a**, **4a**, **5a**, and **7a**, from the acidic constituents. We wish to report herein the isolation and structures of these brominated phenols.

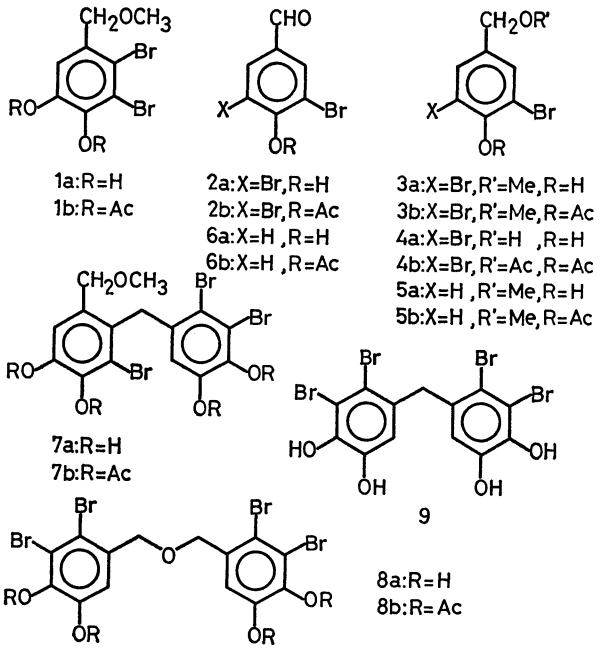
Half-dried algae were extracted with MeOH, and the neutral and acidic fractions were obtained from the MeOH extracts by the usual method. The neutral fraction gave no halogenated compound except for a sterol and a mixture of fatty acid esters. The acidic fraction was subjected to separation by a combination of column and thin-layer chromatography on silica gel to give several bromophenols. The isolation, purification, and identification of these bromophenols were carried out more conveniently *via* their acetates (**1b**—**8b**) (see Experimental section).

The major compound, **1b**, was identified as the acetate of 2,3-dibromo-4,5-dihydroxybenzyl methyl ether (**1a**)[2-4] by comparison of the spectral data with those of an authentic sample.[2] One of the minor compounds, **2b**, was found to be identical with the acetate of 3,5-dibromo-4-hydroxybenzaldehyde (**2a**), which has previously been isolated from the marine annelid *Thelepus setosus*[5] and recently from the red alga *Polysiphonia urceolata*.[6] Compounds **3b** and **4b** were found to be identical with the acetate of 3,5-dibromo-4-hydroxybenzyl methyl ether (**3a**) from *P. urceolata*[7] and *Odonthalia dentata*,[8] and the acetate of 3,5-dibromo-4-hydroxybenzyl alcohol (**4a**) from *O. dentata*,[8-10] *R. confervoides*,[8-10] *P. urceolata*,[6] and other species,[8,10] respectively. Furthermore, **5b** was identified as the acetate of 3-bromo-4-hydroxybenzyl methyl ether (**5a**) from *O. dentata*.[8] The structures of **2b**, **3b**, **4b**, and **5b** were confirmed by syntheses.

Compound **6b**, $C_9H_7O_3Br$, mp 60—62 °C, showed in its NMR spectrum the presence of an aryl acetate group at 2.34 (3H, s), a 1,3,4-trisubstituted aromatic ring at δ 7.26 (1H, d, J=8 Hz), 7.78 (1H, dd, J=8, 2 Hz), and 8.05 (1H, d, J=2 Hz), and an aldehyde group at 9.85 (1H, s). The spectral data of **6b** suggested that **6b** would be the acetate of 3-bromo-4-hydroxybenzaldehyde (**6a**), the structure of which was confirmed by comparison of the physical properties with those of the synthetic sample. To our knowledge, the isolation of 3-bromo-4-hydroxybenzaldehyde (**6a**) is the first example of the natural product.

One of the two other compounds, **7b**, was identified as the acetate of the brominated diphenylmethane derivative (**7a**), which has previously been isolated from *R. larix* together with **9**,[4] by comparison of the spectral data. The other compound, **8b**, $C_{22}H_{18}O_9Br_4$, mp 176—177 °C, revealed in its IR spectrum the absence of hydroxyl and carbonyl groups except for the acetoxyl groups at ν_{max} 1781 cm^{-1}. The NMR spectrum of **8b** showed four signals (each singlet) at δ 2.30 (6H) and 2.36 (6H) due to four acetoxyl groups, 4.70 (4H) due to two Ar–CH_2–(O) moieties, and 7.39 (2H) due to two aromatic protons. Hence, one of nine oxygen atoms in **8b** must form a straight chain ether linkage. The NMR spectrum of **8b** was very similar to that of **1b**, except for the signal of the methoxyl group in **1b**. Therefore, the structure of **8b** would be represented by formula **8b**, which will also be explicable well from the standpoint of biogenesis.

2,3-Dibromo-4,5-dihydroxybenzaldehyde has previously been isolated from *R. larix*.[2-4] However, we could not detect this aldehyde during our examination.[11] The result of our present study seems to be different from those of the previous studies[2-4] on account of the differences of the locations and seasons of the algal collections and/or the extraction procedures.



Experimental

All the mps were uncorrected. The IR spectra were measured on a Nihon-Bunko A-102 spectrometer. The NMR spectra were recorded on a JEOL JNM-PS-100 spectrophotometer, TMS being used as the internal reference. Coupling constants are given in Hz. Silica gel (Merck, Kieselgel 60, 70—230 mesh) was used for the column chromatography, and silica gel (Merck, Kieselgel GF_{254} (Type 60)) was used for the preparative thin-layer chromatography (PTLC).

Isolation. *Rhodomela larix* was collected in September 22, 1978, at Oshoro Bay, Hokkaido. The half-dried algae (1.3 kg) were extracted with MeOH, and the MeOH soln was concentrated under reduced pressure. The residue was percolated with ether, and the ether soln was shaken with 1 M KOH. The ether layer was washed with water, dried over Na_2SO_4, and then evaporated to give a neutral fraction (8 g). The KOH layer was cautiously acidified with dilute HCl and extracted with ether. The ether soln was washed with water, dried over Na_2SO_4, and then evaporated to give an acidic fraction (8 g). Repeated column chromatography of the neutral fraction gave only a sterol (probably cholesterol) and a mixture of fatty acid esters. The acidic fraction was fractionated by column chromatography as follows.

A Benzene-eluted Fraction: This fraction consisted of a mixture of **2a** and **3a**, which was subjected to repeated column chromatography and PTLC to yield **2a** (0.1% of the acidic constituents) and **3a** (0.8%). Acetylation of **2a** and **3a** was carried out with acetic anhydride in pyridine at room temp in the usual manner to yield **2b** and **3b**, respectively.

A Benzene/ether (10:1)-eluted Fraction: This fraction was further chromatographed on PTLC to yield **4a** (0.3%), **5a** (0.6%), **6a** (0.2%), and **1a** (6%). These phenols were acetylated by the usual method to yield **4b**, **5b**, **6b**, and **1b**.

A Benzene/ether (1:1)-eluted Fraction: This fraction consisted of a mixture of **7a** (1%) and **8a** (0.2%), which, following acetylation, was purified by PTLC to yield **7b** and **8b**.

1b: The mp and the spectral data were consistent with those of an authentic specimen.[2)]

2b: Mp 110—111 °C (EtOH): IR, ν_{max} ($CHCl_3$): 1790, 1775, 1710, 1565, 1370, 1245, 1190, 1175, 1010, 925, and 890 cm^{-1}; NMR, δ (CCl_4): 2.39 (3H, s), 7.99 (2H, s), and 9.81 (1H, s); MS, *m/e* 324, 322, 320 (M^+). Found: C, 33.50; H, 1.86%. Calcd for $C_9H_6O_3Br_2$: C, 33.57; H, 1.88%.

3b: Colorless oil; IR, ν_{max} (film): 1785, 1775, 1595, 1560, 1405, 1370, 1245, 1205, 1180, 1110, 1010, 890, 805, and 740 cm^{-1}; NMR, δ ($CDCl_3$): 2.40 (3H, s), 3.40 (3H, s), 4.41 (2H, s), and 7.53 (2H, s); MS, *m/e* 340, 338, 336 (M^+).

4b: The mp and the NMR spectrum were consistent with those reported.[9)]

5b: Colorless oil; IR, ν_{max} (film): 1770, 1600, 1490, 1370, 1205, 1190, 1105, 1045, 1010, 910, 870, and 825 cm^{-1}; NMR, δ ($CDCl_3$): 2.35 (3H, s), 3.39 (3H, s), 4.43 (2H, s), 7.11 (1H, d, J=8), 7.30 (1H, dd, J=8, 2), and 7.58 (1H, d, J=2); MS, *m/e* 260, 258 (M^+).

6b: Mp 60—62 °C (EtOH–hexane); IR, ν_{max} ($CHCl_3$): 1775, 1705, 1597, 1485, 1375, 1185, 1045, 1010, 915, 890, and 835 cm^{-1}; NMR, δ (CCl_4): 2.34 (3H, s), 7.26 (1H, d, J=8), 7.78 (1H, dd, J=8, 2), 8.05 (1H, d, J=2), and 9.85 (1H, s); MS, *m/e* 244, 242 (M^+). Found: C, 44.44; H, 2.98%. Calcd for $C_9H_7O_3Br$: C, 44.47; H, 2.90%.

7b: Mp 175—177 °C (C_6H_6); IR, ν_{max} ($CHCl_3$): 1777, 1371, 1193, 1141, 1011, 916, and 889 cm^{-1}; NMR, δ ($CDCl_3$): 2.20, 2.30, 2.32, 2.34, 3.31 (each 3H, s), 4.28 (4H, br s), 6.38 (1H, s), and 7.31 (1H, s).

8b: Mp 176—177 °C (chloroform–ether); IR, ν_{max} ($CHCl_3$): 1781, 1372, 1196, 1181, 1141, 1011, 917, and 898 cm^{-1}; NMR, δ ($CDCl_3$): 2.30 (6H, s), 2.36 (6H, s), 4.70 (4H, s), and 7.39 (2H, s); MS, *m/e* 708, 706, 704, 702, 700 ($M^+ - CH_2{=}C{=}O$). Found: C, 35.28; H, 2.37%. Calcd for $C_{22}H_{18}O_9Br_4$: C, 35.42; H, 2.43%.

Syntheses of 2b—6b. Bromination of *p*-hydroxybenzaldehyde with Br_2 (1 eq) in AcOH gave a mixture of **2a** and **6a** (1:3), which, following acetylation, was purified by PTLC to give **2b** and **6b**. Treatment of the acetates, **2b** and **6b**, with $NaBH_4$ in EtOH afforded dibromo-*p*-acetoxybenzyl alcohol, and monobromo-*p*-acetoxybenzyl alcohol, respectively. The latter benzyl alcohol was refluxed with MeOH and H_2SO_4 to yield **5a**, which was converted to **5b** by acetylation. The former benzyl alcohol gave **3b** in the same way as has been described above. Moreover, acetylation of the dibromobenzyl alcohol yielded **4b**. These synthetic compounds were identical with the natural bromophenols and their acetates in all respects.

The authors are grateful to Dr. Kazuya Kurata, Department of Industrial Chemistry, Hakodate Technical College, for valuable discussions and for providing the IR and NMR spectra of the acetates of several bromophenols.

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