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A New Bromophenol from the Red Alga *Polysiphonia urceolata*[1]

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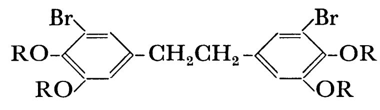
The investigation of the red alga *Polysiphonia urceolata* afforded a new bromophenol, 3,3′-dibromo-4,4′,5,5′-tetrahydroxybibenzyl. The structure was elucidated by a combination of spectroscopic methods and chemical transformations. Besides this compound, seven known bromophenols were isolated.

Many bromophenols have been previously obtained from the red marine algae, Rhodomelaceae,[1–18] with the *Polysiphonia*, *Rhodomela*, *Odonthalia*, and *Symphyocladia* species being especially rich in bromine-containing compounds. Bromophenols of *Polysiphonia* species have been extensively investigated.[1,3,4,8,9,15,17] In the course of the investigation of the constituents of the red marine algae, we obtained a new bromophenol, 3,3′-dibromo-4,4′5,5′-tetrahydroxybibenzyl (**1**), together with seven known bromophenols, from *Polysiphonia urceolata.* In this paper the isolation and structural elucidation of these compounds will be described.

An acidic fraction obtained from the dried alga collected at Matsumae Bay by extraction with methanol was chromatographed on silica gel. A benzene eluate gave 3,5-dibromo-4-hydroxybenzyl methyl ether (**2**)[8] and 3-bromo-4,5-dihydroxybenzyl methyl ether (**3**).[8,9,16] Their structures were deduced from the chemical and spectral properties, and confirmed by direct comparison with an authentic sample and by conversion to the dimethyl derivative (**3m**) respectively. Compounds **2** and **3** could be artifacts derived by the methylation of the corresponding alcohols or bromophenol precursors during the extraction procedure.[11] A benzene–ether (19:1) eluate gave 3-bromo-4,5-dihydroxybenzaldehyde (**4**)[3,9] as the main constituent and 3,3′-dibromo-4,4′,5,5′-tetrahydroxybibenzyl (**1**) as the minor constituent. Compound **1** was a colorless crystalline substance (mp 205—206 °C); elemental analysis established it to be $C_{14}H_{12}O_4Br_2$. It developed an intense green color with iron(III) chloride and precipitated easily on the addition of lead acetate. The mass spectrum showed the presence of 406, 404, and 402 (M^+). The UV spectrum in EtOH exhibited a maximum at 287 nm. The IR spectrum showed bands due to OH groups at 3550, 3470, and 3250 cm^{-1}, and benzene rings at 1595, 1520, and 845 cm^{-1}. The ^1H-NMR spectrum showed a signal of methylene protons at δ 2.58 (4H, s), signals of two aromatic protons at δ 6.54 (2H, d, J=2 Hz) and 6.73 (2H, d, J=2 Hz), and signals of phenolic protons at δ 8.72 (2H, bs), and 9.49 (2H, bs). Two finely split doublets at δ 6.54 and 6.73 in the ^1H-NMR spectrum indicated a 1,2,3,5-tetrasubstituted benzene ring. The oxidation of tetramethyl ether (**1m**) derived from **1** with potassium permanganate in acetone yielded 3-bromo-4,5-dimethoxybenzoic acid (**5**), which was confirmed by comparison with a synthetic sample of **5**. All of these results helped to elucidate the structure of Compound **1**.



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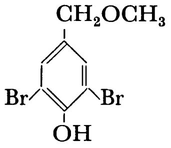
1m R=CH_3



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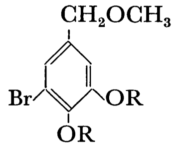

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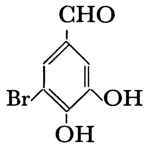

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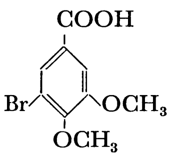

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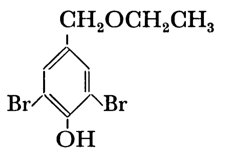

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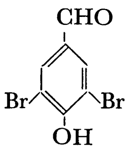

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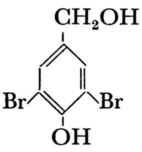

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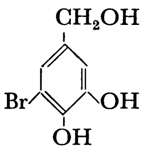

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An ethanol extract of the dried alga collected at Hakodate Bay was chromatographed on silica gel. The TLC separation of a benzene eluate gave 3,5-dibromo-4-hydroxybenzyl ethyl ether (**6**)[8] and the corresponding benzaldehyde (**7**), which has also been obtained from other marine sources. Compound **4** was also isolated from the benzene–ether (19:1) eluate. Compounds **6** and **7** were identified by comparison with the respective authentic samples. The presence of the benzyl methyl ethers (**2** and **3**) and ethyl ether (**6**) in the methanol and ethanol extracts respectively suggested the existence of a bromophenol precursor similar to lanosol sulfate in *P. lanosa* and *R. larix.* Therefore, we extracted the frozen alga collected at Hakodate Bay with 80% acetone. An acetone-soluble fraction was chromatographed on silica gel. Early-eluted fractions of the benzene–ether (19:1) eluate gave 3,5-dibromo-4-hydroxybenzyl alcohol (**8**),[8,9,15] which was confirmed by comparison with an authentic sample, whereas later-eluted fractions gave **4** and 3-bromo-4,5-dihydroxybenzyl alcohol (**9**).[8,9,16] Compound **9** was identified by comparison with a synthetic sample. The dried and frozen alga from Hakodate Bay was lacking in Compound **1**, which is present in the dried alga from Matsumae Bay.

Experimental

All the melting points were determined on a micro hot stage and are uncorrected. The IR spectra were taken on a Hitachi EPI-G2 spectrophotometer, and the UV spectra, on a Hitachi 124 spectrophotometer. The mass spectra were measured on a Hitachi RMO-4E spectrometer, and the ^{1}H-NMR spectra, on a JEOL PMX-60 or Hitachi R-20B spectrometer, using TMS as the internal standard. The column chromatography was carried out over silica gel (Wakogel C-100 or C-200). The TLC was performed on silica gel (Merck silica gel 60 F_{254}) and polyamide (Carl Chleicher & Chüll), with benzene–methanol–acetic acid (45:8:4 v/v) as the eluent.

Extraction and Isolation.   *Methanol Extraction*: *P. urceolata* was collected at Matsumae Bay in May, 1974. A methanol extract of the air-dried alga (2.5 kg) gave a syrup, which was then treated with ether. The ether solution was treated with 5% aqueous KOH. The alkaline aqueous solution was acidified with hydrochloric acid and extracted with ether. The acidic fraction (75 g) from the ether extract was chromatographed on a silica-gel column. The column was then eluted, yielding 17 fractions, 4 l each; Fractions 1—13 with benzene and Fractions 14—17 with benzene–ether (19:1). Fractions 1—2 and 7—12 afforded Compounds **2** (650 mg) and **3** (460 mg) respectively. The recrystallization of a solid residue of Fractions 15—17 from benzene–methanol gave Compound **4** (2 g), while Compound **1** (400 mg) was obtained on the recrystallization of the mother liquor.

Ethanol Extraction: The dried alga (2.0 kg) collected at Hakodate Bay in May, 1976, was immersed in ethanol. The subsequent removal of the solvent from the ethanol solution gave an ethanol extract, which was treated with ether. The ether extract (3.2 g) was subjected to chromatography on a silica-gel column. The column was eluted with benzene as has been described above. On separation by TLC (polyamide), the eluate gave Compounds **7** (43 mg; R_f 0.69) and **6** (25 mg; R_f 0.94). The further elution of the column with benzene–ether (19:1) afforded Compound **4** (78 mg).

80% Acetone Extraction: The alga (14 kg) collected at Hakodate Bay in May, 1978, was immersed in 80% acetone. The acetone solution was then evaporated to dryness and treated with dry acetone. The acetone extract (70 g) was chromatographed on a silica-gel column. The column was then eluted with the series of solvents mentioned above. Early-eluted fractions of a benzene–ether (19:1) eluate afforded Compound **8** (1.8 g). Later-eluted fractions contained two components which gave spots with R_f 0.65 and 0.16 on TLC (silica gel). A mixture (3.1 g) of these components was rechromatographed on a silica gel column with benzene–ether (19:1) to give Compounds **4** (670 mg) and **9** (190 mg).

*3,3′-Dibromo-4,4′5,5′-tetrahydroxybibenzyl (**1**).*   Compound **1** was recrystallized from benzene–methanol to yield colorless needles (120 mg); mp 205—206 °C; λ_{max} (EtOH) 287 nm; IR(KBr) ν 3550, 3470, 3250, 2930, 2860, 1630, 1610, 1595, 1520, 1430, 1340, 1295, 1190, 1000, 905, and 845 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.58 (4H, s, methylene protons), 6.54 (2H, d, $J=2$ Hz, aromatic protons), 6.73 (2H, d, $J=2$ Hz, aromatic protons), 8.72 (2H, bs, phenolic protons), and 9.49 (2H, bs, phenolic protons); MS *m/e* 406, 404, 402 (M^+), 203, 201 ($M^+-C_7H_6O_2Br$), and 185, 183 ($M^+-C_7H_6O_2Br-H_2O$). Compound **1** gave an intense green color with iron(III) chloride and was precipitated easily on the addition of lead acetate.

Found: C, 41.38; H, 2.92%. Calcd for $C_{14}H_{12}O_4Br_2$: C, 41.62; H, 2.99%.

*Identification of **1**.*   *a*): The phenol **1** (20 mg), dissolved in ether, was treated with diazomethane, thus yielding a tetramethyl derivative (**1m**) (13 mg) as colorless needles; mp 92—95 °C; IR(KBr) ν 2900, 1600, 1455, 1410, 1365, 1210, 1085, 975, 835, and 770 cm^{-1}.

b): A solution of **1m** (10 mg) in acetone (3 ml) was added to a solution of potassium permanganate (30 mg) in acetone (10 ml). The mixture was refluxed. The resulting precipitates were filtered and extracted with water. The water solution, after acidification with dilute hydrochloric acid, was extracted with ether. The subsequent removal of the solvent from the ether extract gave crystals, which were recrystallized from hexane–ethanol to yield 3-bromo-4,5-dimethoxybenzoic acid (**5**) (2.8 mg); mp 195—198 °C; IR(KBr) ν 2950, 1690, 1595, 1575, 1410, 1290, 1115, 1045, and 990 cm^{-1}. Compound **5** was shown to be identical with a synthetic sample by a comparison of the IR spectrum and TLC.

*Synthesis of **5**.*   3-Bromo-4,5-dimethoxybenzaldehyde was oxidized by the procedure described for the oxidation of **1m**. The recrystallization of the oxidation product from hexane–ethanol furnished **5** as colorless needles; mp 197—198 °C.

Found: C, 41.55; H, 3.28; Br, 30.28%.

*3,5-Dibromo-4-hydroxybenzyl Methyl Ether (**2**).*   Compound **2** was recrystallized from hexane to yield colorless crystals; mp and mixed mp 70—71 °C; λ_{max} (EtOH) 290 nm (log ε 3.46); IR(KBr) ν 3240, 2990, 2920, 2810, 1590, 1550, 1475, 1280, 1140, 1080, and 860 cm^{-1}; ^{1}H-NMR(CDCl$_3$) δ 3.31 (3H, s, $-CH_2O\underline{CH_3}$), 4.28 (2H, s, $-\underline{CH_2}OCH_3$), 5.93 (1H, bs, phenolic proton), and 7.38 (2H, s, aromatic protons); MS *m/e* 298, 296, 294 (M^+), 267, 265, 263 (M^+-OCH_3), 217, 215 (M^+-Br).

*3-Bromo-4,5-dihydroxybenzyl Methyl Ether (**3**).*   Compound **3** was recrystallized from benzene–methanol to afford colorless needles; mp 98—99 °C; λ_{max} (EtOH) 287 nm; IR(KBr) ν 3450, 3075, 3050, 2950, 2925, 2860, 2830, 1610, 1590, 1525, 1425, 1065, 855, and 840 cm^{-1}; ^{1}H-NMR(CDCl$_3$) δ 3.37 (3H, s, $-CH_2O\underline{CH_3}$), 4.33 (2H, s, $-\underline{CH_2}OCH_3$), 5.98 (2H, bs, phenolic protons), 6.79 (1H, d, $J=2$ Hz, aromatic proton), and 6.98 (1H, d, $J=2$ Hz, aromatic proton); MS *m/e* 234, 232 (M^+), 203, 201 (M^+-OCH_3), and 153 (M^+-Br).

*3-Bromo-4,5-dimethoxybenzyl Methyl Ether (**3m**).*
Compound **3** (100 mg), dissolved in ether, was treated with diazomethane, yielding a dimethyl ether (80 mg) as a colorless oil; bp 262 °C; $n_D^{20}=1.5474$; IR (neat) ν 2930, 2825, 1595, 1570, 1490, 1410, 1100, 1045, 1005, 845, and 815 cm^{-1}; ^{1}H-NMR(CDCl$_3$) δ 3.47 (3H, s, $-CH_2O\underline{CH_3}$), 3.95 (6H, s, ϕ-O$\underline{CH_3}$), 4.44 (2H, s, $-\underline{CH_2}OCH_3$), 6.93 (1H, d, $J=2$ Hz, aromatic proton), and 7.16 (1H, d, $J=2$ Hz, aromatic proton). This compound was identified with the synthetic **3m** by a comparison of their IR and ^{1}H-NMR spectra.

*3-Bromo-4,5-dihydroxybenzaldehyde (**4**).*   Compound **4** was recrystallized from benzene–methanol to yield colorless needles; mp and mixed mp 230 °C; λ_{max} (EtOH) 288 nm; IR (KBr) ν 3425, 1650, 1580, 1440, 1310, 1185, 860, and 845 cm^{-1}; ^{1}H-NMR(DMSO-d_6) δ 7.24 (1H, d, $J=2$ Hz, aromatic proton), 7.53 (1H, d, $J=2$ Hz, aromatic proton), 9.68 (1H, s, formyl proton), and 10.29 (2H, bs, phenolic protons); MS *m/e* 218, 216 (M^+), 217, 215 (M^+-1), 189, 187 (M^+-CHO), and 137 (M^+-Br).

*3,5-Dibromo-4-hydroxybenzyl Ethyl Ether (**6**).*   Compound **6** was recrystallized from hexane to yield colorless needles; mp and mixed mp 93—94 °C; λ_{max} (EtOH) 290 nm; IR (KBr) ν 3210, 2970, 2860, 1595, 1555, 1478, 1403, 1305, 1265, 1145, 1075, 1010, 875, and 730 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.24 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$), 3.53 (2H, q, J=7 Hz, $-\underline{CH_2}CH_3$), 5.94 (1H, bs, phenolic proton), and 7.42 (2H, s, aromatic protons).

3,5-Dibromo-4-hydroxybenzaldehyde (7). Compound **7** was recyrstallized from hexane, yielding colorless needles; mp and mixed mp 189—190 °C; λ_{max} (EtOH) 277 and 346 nm; IR(KBr) ν 3180, 2860, 1670, 1580, 1550, 1480, 1415, 1305, 1245, 1205, 1055, 875, 740, and 660 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 7.87 (1H, bs, phenolic proton), 8.10 (2H, s, aromatic protons), and 9.87 (1H, s, formyl proton).

3,5-Dibromo-4-hydroxybenzyl Alcohol (8). Compound **8** was recrystallized from benzene, yielding colorless crystals; mp and mixed mp 119—120 °C; λ_{max} (EtOH) 291 nm; ^{1}H-NMR (CDCl$_3$+DMSO-d_6) δ 4.12 (1H, t, J=4 Hz, $-CH_2O\underline{H}$), 4.60 (2H, d, J=4 Hz, $-\underline{CH_2}OH$), 7.50 (2H, s, aromatic protons), and 7.65 (1H, bs, phenolic proton). The ^{1}H-NMR spectrum of this compound has partially been reported previously.[19]

3-Bromo-4,5-dihydroxybenzyl Alcohol (9). Compound **9** was recrystallized from benzene–acetone yielding colorless needles; mp and mixed mp 104—105 °C; λ_{max} (EtOH) 287 nm; IR (KBr) ν 3410, 2960, 1595, 1425, 1340, 1290, 1185, 1120, 960, 860, and 840 cm^{-1}; ^{1}H-NMR (acetone-d_6) δ 4.48 (2H, s, $-\underline{CH_2}OH$), 4.3—4.7 (1H, bs, $-CH_2O\underline{H}$), 6.85 (1H, d, J=2 Hz, aromatic proton), 6.97 (1H, d, J=2 Hz, aromatic proton), and 8.02 (2H, bs, phenolic protons); MS *m/e* 220, 218 (M^+), 219, 217 (M^+-1), 203, 201 (M^+-H_2O+1), 202, 200 (M^+-H_2O), and 139 (M^+-Br).

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