

Synthesis of Some Bromophenols Present in Red Algae

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5,6-Dibromoprotocatechualdehyde (2), 2,3-dibromo-4,5-dihydroxybenzyl alcohol (lanosol, 5) and the new 3,4,3',4'-tetrabromo-5,5'-methylenedipyrocatechol (9) have been isolated from the red alga *Polysiphonia brodiaei* (Scheme 1), along with (\pm)-4-(2,3-dibromo-4,5-dihydroxyphenyl)-4-hydroxy-2-butanone (3) and 3,4-dibromo-5-(ethoxymethyl)pyrocatechol (6) revealed as artefacts. Syntheses of the above compounds are reported (Scheme 2).

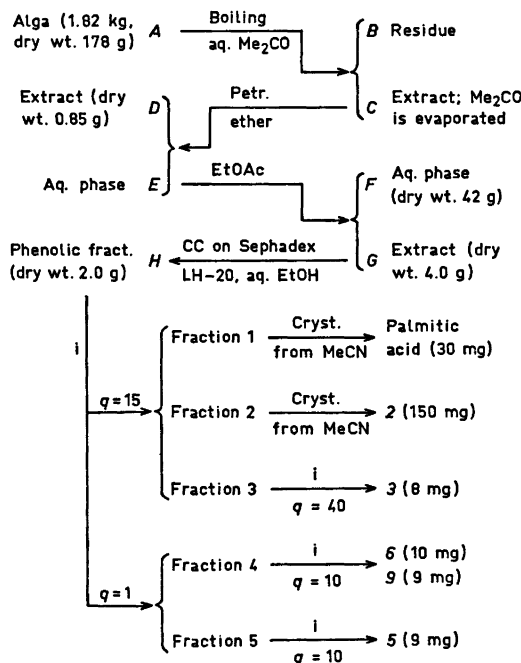
In recent years, many organic bromine compounds of marine origin have been described.¹ Red algae, notably *Rhodomelaceae* (*Rhodophycophyta*), often contain bromophenols.² These include 5,6-dibromoprotocatechualdehyde (2, Scheme 2),^{3,4} the corresponding alcohol (lanosol, 5)⁵⁻⁷ and a related diphenylmethane derivative.⁷ Similar diarylmethanes have been isolated from a marine annelid.⁸ This paper deals with the isolation of 2, 5 and a new, closely related diarylmethane (9) from the red alga *Polysiphonia brodiaei*, and with their synthesis. For the identification by chromatography and MS of these compounds in small amounts of algae it is important that authentic samples should be readily available. Thus, 9 was recently⁹ identified in two other red algae by comparison with our synthetic sample.

RESULTS AND DISCUSSION

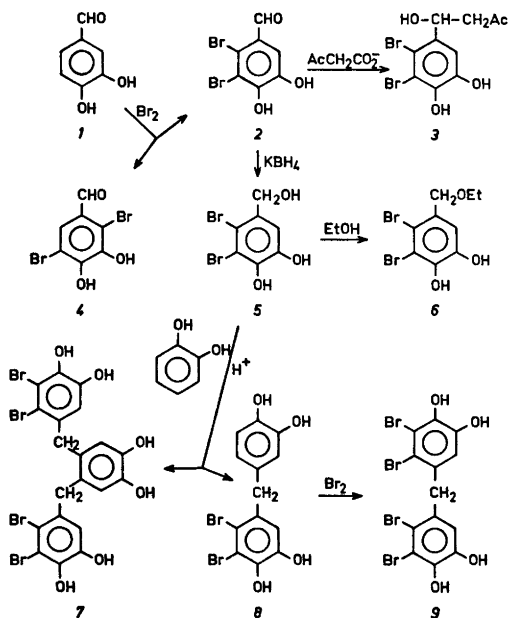
Bromophenols 2, 3, 5, 6 and 9 were isolated by treatment of the alga as outlined in Scheme 1. All steps were monitored by TLC; spraying of the plates with aqueous iron(III) chloride revealed the bromophenols as characteristic blue spots. The major bromophenols were 2 and 5. Their respective total yields were

320 and 130 mg (0.18 and 0.07 % of the dried alga), as estimated by GLC analysis of extract G.

Formulas 2, 3, 5, 6 and 9 (Scheme 2) were indicated by the well-known occurrence of 5 in red algae,⁵⁻⁷ the spectral data and the said blue colour, which is typical of pyrocatechol and its derivatives. The formulas were fully confirmed by synthesis according to Scheme 2, the isolated and the synthetic samples being identical (TLC, MS, IR and ¹H NMR).



Scheme 1. Isolation of bromophenols 2, 3, 5, 6 and 9 (Scheme 2) from *Polysiphonia brodiaei*. i=CC on silica gel with CHCl_3 -EtOH, q:1 (v/v), as eluent.



Scheme 2. Synthesis of lanosol (5) and related bromophenols.

The bromination of protocatechualdehyde (1) yielded 2 and its 2,5-dibromo isomer (4) in about equal amounts. The reaction of 2 with sodium acetoacetate was performed as for benzaldehyde¹⁰ but was slower, probably owing to lower solubility of 2. However, after two weeks, a small but sufficient amount of 3 had accumulated. A buffered medium was critical in the reduction of 2; a good yield of 5 was obtained at pH 8. The conversion 5 → 6 was nearly quantitative. The yield of compound 8 was only 25 %, calculated on 5, even though a large excess of pyrocatechol was used to reduce the formation of the by-product 7. The bromination of 8 resulted in an isomeric mixture, from which 9 was isolated in low yield. Compounds 3, 4 and 6–9 have apparently not been described previously.

As shown by appropriate control experiments, 3 was slowly formed from 2 and acetone during the extraction of the alga; and 6 was formed from 5 and ethanol during the CC separations. The latter mode of formation has already been suspected for 6^{7,11} and demonstrated for the corresponding methyl ether.^{4,11} The aldol condensation of 2 with acetone without concomitant dehydration is more

remarkable. In the absence of alga, 2 did not react with acetone until a little glycine and phosphate buffer of pH 5.2 (the pH of extract C) had been added, indicating that the reaction was catalysed by some constituent(s) of the alga.

On the other hand, our results did not support previous suggestions that 2 is an oxidation artefact of 5^{4,12} but indicated that 2, 5 and 9 are genuine constituents of the alga. These were isolated under milder conditions than in many previous investigations of algae and should therefore occur in the alga largely in free form. The release of some 2 and 5 on heating the aqueous phase *F* with 0.1 M hydrochloric acid indicated, however, that 2 and 5 are present to a small extent in the alga as readily hydrolysed conjugates. In *Polysiphonia lanosa*, 5 is known to occur as the dipotassium salt of its 4,α-disulfate,⁶ and other bromophenols may be present in algae as similar salts.⁴ Attempts to isolate 2 and 5 in sulfated form by paper electrophoresis or ion-exchange chromatography of *F* prior to hydrolysis were, however, unsuccessful.

EXPERIMENTAL

General

Nonaqueous extracts were dried with sodium sulfate before evaporation, which was performed at reduced pressure below 40°C. TLC was performed on silica gel (Merck, HF₂₅₄) with chloroform–acetic acid, 9:1 (v/v); toluene–butanone–acetic acid, 20:6:3 (v/v); or butanone, saturated with water, as eluent. After the plates had been inspected in UV light, ethanolic *p*-anisaldehyde–sulfuric acid, aqueous iron(III) chloride and aqueous sodium carbonate–diazotized sulfanilic acid were used as spray reagents. GLC was performed on a Packard 427 instrument equipped with a flame-ionization detector. The samples were treated with *N,O*-bis(trimethylsilyl)acetamide in pyridine 15 min before injection. Compounds 2 and 5 were analysed as their per(trimethylsilyl) ethers on a 25 m × 0.3 mm i.d. glass capillary column coated with OV-101. The helium flow rate was 0.9 ml/min and the temperature was programmed from 120 to 250°C at 6°C/min. Peak areas were measured with a Packard 427 Minigrator, *p*-terphenyl being used as internal standard. Unless otherwise stated, CC was carried out on silica gel (Merck 60, 230–400 mesh) with toluene–butanone–acetic acid, 6:2:1 (v/v), as eluent.

Melting points are corrected. Low and high resolution MS was performed at 70 eV on Varian MAT CH 7 and AEI MS 902 instruments, respectively, the latter located at the Institute of Medical Biochemistry, University of Gothenburg. The samples were inserted directly into the ion source. Data for the strongest peaks are listed below, disregarding ions containing ^{81}Br or no bromine. IR spectra were recorded on a Perkin-Elmer 337 instrument, using pressed potassium bromide plates. ^1H NMR spectra were recorded at 100.0 MHz and ca. 30 °C on a Varian HA-100 D instrument equipped with a Varian VFT-100 Fourier Transform System. Data for the strongly coupled protons in **3** and **8** were obtained by ABX analysis,¹⁸ checked by computer simulation and adjusted if necessary. A 620/i computer and a program (assembly No. 995128-00B) from Varian Data Machines were used.

All reagents were commercial samples of good grade. The solvents were freshly distilled before use. The light petroleum boiled at 40–60 °C. The alga *Polysiphonia brodiaei* was collected in September near Fiskebäckskil on the west coast of Sweden. It was rinsed, frozen, milled and processed according to Scheme 1, yielding bromophenols **2**, **3**, **5**, **6** and **9** as yellowish crystals.

Syntheses

5,6-Dibromoprotocatechualdehyde (2). Bromine (53 g, 320 mmol), dissolved in chloroform (50 ml), was added dropwise to a stirred and gently refluxing suspension of **1** (18 g, 130 mmol) in chloroform (300 ml). The stirring and heating were continued for 15 h. After chloroform (400 ml) had been added, the solid was collected and recrystallized from ethyl acetate, yielding **2** (9.8 g, 26 %), m.p. 204–206 °C (lit.³ 203–205 °C). MS, *m/e* (rel. int.): 294 (100, M), 293 (89), 157 (24), 186 (20), 185 (8), 265 (8). The IR spectral data agreed with those reported.³ ^1H NMR (CD_3OD): δ 7.34 (ArH, s), 10.11 (CHO, s).

Dimethyl ether. This was prepared from **2**.³ It melted at 130 °C (lit.³ 129–130 °C). The ^1H NMR spectral data agreed with those reported.³ Broadening of the corresponding signals revealed the expected¹⁴ weak coupling between the aromatic proton and those of the adjacent methoxyl group.

(±)-4-(2,3-Dibromo-4,5-dihydroxyphenyl)-4-hydroxy-2-butanone (3). Compound **2** (500 mg, 1.7 mmol) was treated with sodium acetoacetate as described for benzaldehyde¹⁹ but with stirring. CC of the evaporation residue from the ethereal extract yielded **3** (27 mg, 4.5 %), which was recrystallized from ethyl acetate–light petroleum. On heating, **3** decomposed at ca. 175 °C. Anal. $\text{C}_{10}\text{H}_{10}\text{Br}_2\text{O}_4$: C, H, Br. MS, *m/e* (rel. int.): 255 (100), 188 (81), 215 (38),

240 (23), 273 (21), 293 (18), ..., 352 (2, M). IR, $\tilde{\nu}_{\text{max}}$: 855 (m), 902 (w), 1098 (m), 1165 (m), 1275 (s), 1410 (s), 1600 (w), 1695 (s), 3360 (m, broad), 3520 (m) cm^{-1} . ^1H NMR (CD_3OD): δ 2.21 (Me, s), 2.63 (3-H, dd), 2.76 (3'-H, dd), 5.42 (4-H, dd), 7.08 (ArH, s); $|J|$ 2.5 (3',4), 9.9 (3,4), 15.8 (3,3') Hz.

2,5-Dibromoprotocatechualdehyde (4). The chloroform and ethyl acetate mother liquors from the synthesis of **2** were combined and evaporated. The residue was crystallized, first from acetonitrile and then from aq. *p*-dioxane, yielding **4** (11.2 g, 29 %), m.p. 178–179 °C. Anal. $\text{C}_7\text{H}_4\text{Br}_2\text{O}_3$: C, H, Br, O. MS, *m/e* (rel. int.): 293 (100), 294 (80, M), 215 (11), 185 (10), 265 (9), 186 (9). IR, $\tilde{\nu}_{\text{max}}$: 826 (s), 1012 (s), 1243 (s, broad), 1280 (s), 1400 (s), 1430 (m), 1490 (s), 1560 (s), 1680 (s), 3340 (s, broad), 3450 (s) cm^{-1} . ^1H NMR (CD_3OD): δ 7.59 (ArH, s), 10.08 (CHO, s).

Dimethyl ether. This was prepared as the 5,6-dibromo isomer.³ It melted at 72–75 °C. ^1H NMR (CDCl_3): δ 3.92 (Me, s), 3.99 (Me, s), 7.92 (ArH, s), 10.25 (CHO, s). The equal line width of the methoxyl signals confirmed the substitution pattern.¹⁴

2,3-Dibromo-4,5-dihydroxybenzyl alcohol (5). Potassium borohydride (0.9 g, 17 mmol), dissolved in water (20 ml), was added to a suspension of **2** (5.2 g, 17 mmol) in 0.25 M phosphate buffer (pH 8.0, 50 ml). The mixture was stirred for 10 min and carefully acidified to pH 5.0. The solid was collected, washed with water, air-dried and recrystallized from benzene, yielding **5** (3.2 g, 61 %), m.p. 129–130 °C (lit. 137–138 °C,³ 123–125 °C,⁵ 128 °C⁶). MS, *m/e* (rel. int.): 296 (100, M), 188 (90), 217 (73), 279 (31), 143 (25), 295 (19). The IR³ and ^1H NMR^{2,5} spectral data agreed with those reported.

Triacetate. This was prepared from **5**.⁵ It melted at 105–106 °C (lit.⁵ 105–106 °C). The ^1H NMR spectral data agreed with those reported.^{5,6}

3,4-Dibromo-5-(ethoxymethyl)pyrocatechol (6). A solution of **5** (50 mg, 0.17 mmol) in 95 % ethanol (5 ml) was refluxed for 24 h and evaporated. The residue was recrystallized from carbon tetrachloride, yielding **6** (40 mg, 73 %), m.p. 92–93 °C. Anal. $\text{C}_9\text{H}_8\text{Br}_2\text{O}_3$: C, H, Br. MS, *m/e* (rel. int.): 201 (100), 279 (50), 217 (47), 188 (37), 324 (26, M), 280 (18). IR, $\tilde{\nu}_{\text{max}}$: 858 (m), 1020 (m), 1085 (s), 1170 (s), 1264 (s), 1470 (s), 1575 (m), 3200 (m, broad), 3490 (s) cm^{-1} . ^1H NMR (CD_3OD): δ 1.22 (Me, t), 3.57 (MeCH₂, q), 4.45 (ArCH₂, s), 6.97 (ArH, s); $|J|$ 7.1 Hz.

4,5-Bis-(2,3-dibromo-4,5-dihydroxybenzyl)pyrocatechol (7). Conc. sulfuric acid (4 drops) was added to a solution of **5** (1.0 g, 3.4 mmol) and pyrocatechol (1.1 g, 10 mmol) in hot water (20 ml). Heating on a steam-bath for 20 h and crystallization at 20 °C yielded **7** (140 mg, 6 %), m.p. 191–193 °C. IR, $\tilde{\nu}_{\text{max}}$: 756 (m), 855 (m), 1180 (s), 1272 (s), 1301 (s),

1400 (s), 1445 (m), 1475 (m), 1510 (m), 1600 (m), 3350 (s, broad) cm^{-1} . $^1\text{H NMR}$ (CD_3OD): δ 3.76 (2 CH_2 , s), 6.45 (2 ArH, s), 6.46 (2 ArH, s).

Hexamethyl ether. This was prepared by treating 7 with ethereal diazomethane for 30 min and recrystallizing from aq. acetone. It melted at 150–152°C. Anal. $\text{C}_{26}\text{H}_{26}\text{Br}_2\text{O}_6$: C, H, Br. MS, m/e (rel. int.): 307 (100), 750 (27, M), 592 (25), 513 (22), 735 (11), 671 (2). $^1\text{H NMR}$ (CDCl_3): δ 3.65 (2 Me, s), 3.79 (2 Me, s), 3.81 (2 Me, s), 3.96 (2 CH_2 , s), 6.39 (2 ArH, s), 6.64 (2 ArH, s).

3,4-Dibromo-5,5'-methylenedipyrocatechol (8). The mother liquor from the synthesis of 7 was extracted with ethyl acetate and the extract evaporated. CC of the residue yielded 8 (325 mg, 25%), m.p. 161–164°C. Anal. $\text{C}_{15}\text{H}_{10}\text{Br}_2\text{O}_4$: C, H, Br. MS, m/e (rel. int.): 291 (100), 388 (57, M), 309 (47), 308 (23), 263 (16), 262 (13). IR, $\tilde{\nu}_{\text{max}}$: 799 (m), 822 (m), 853 (m), 881 (m), 954 (m), 1180 (s), 1270 (s), 1335 (s), 1460 (s), 1505 (s), 1570 (m), 1595 (m), 3350 (s, broad) cm^{-1} . $^1\text{H NMR}$ (CD_3OD): δ 3.88 (CH_2 , s), 6.49 (4'-H, dd), 6.58 (6'-H, d), 6.59 (6-H, s), 6.69 (3'-H, d); $|J| < 0.5$ (3',6'), 2.1 (4',6'), 8.0 (3',4') Hz.

3,4,3',4'-Tetrabromo-5,5'-methylenedipyrocatechol (9). A solution of 8 (210 mg, 0.54 mmol) and bromine (180 mg, 1.1 mmol) in chloroform (3 ml) was kept at 60°C in a sealed vial for 5 h and then evaporated. CC of the residue yielded 9 (20 mg, 7%), m.p. 196–199°C. MS, m/e (rel. int.): 386 (100), 307 (90), 278 (17), 306 (16), 279 (16), 544 (12, M); M, obs. 543.716, calc. for $\text{C}_{15}\text{H}_6\text{Br}_4\text{O}_4$ 543.716. IR, $\tilde{\nu}_{\text{max}}$: 830 (m), 859 (m), 869 (m), 1159 (m), 1285 (s), 1410 (s), 1420 (m), 1485 (w), 1580 (w), 1595 (w), 1610 (w), 3400 (s, broad), 3600 (w) cm^{-1} . $^1\text{H NMR}$ (CD_3OD): δ 4.02 (CH_2 , s), 6.48 (2 ArH, s).

Tetramethyl ether. This was prepared as the hexamethyl ether of 7. It melted at 150–151°C. Found: C 34.0; H 2.6; Br 51.7. Calc. for $\text{C}_{17}\text{H}_{16}\text{Br}_4\text{O}_4$: C 34.0; H 2.7; Br 52.7. MS, m/e (rel. int.): 442 (100), 305 (31), 363 (28), 427 (27), 600 (26, M), 348 (24). IR, $\tilde{\nu}_{\text{max}}$: 1003 (m), 1058 (m), 1365 (m), 1405 (s), 1455 (s), 1535 (w), 1565 (w) cm^{-1} . $^1\text{H NMR}$ (CCl_4): δ 3.72 (2 Me, s), 3.77 (2 Me, s), 4.19 (CH_2 , s), 6.54 (2 ArH, s).

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