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5,6-DIBROMOPROTOCATECHUALDEHYDE AND 2,3-DIBROMO-4,5-DIHYDROXYBENZYL METHYL ETHER

NEW DIBROMOPHENOLS FROM *RHODOMELA LARIX**

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Abstract—Two new dibromophenols have been isolated from a red alga *Rhodomela larix* and are shown to be 5,6-dibromoprotocatechualdehyde and 2,3-dibromo-4,5-dihydroxybenzyl methyl ether.

Only a few of bromophenols have been isolated from marine algae; namely, 5-bromoprotocatechualdehyde from *Polysiphonia morrowi*,[1] 2,3-dibromobenzyl alcohol 4,5-disulfate dipotassium salt from *P. lanosa*[2] and laurinterol from *Laurencia intermedia*.[3] In the present study we have obtained two new dibromophenols together with phenylacetic acid, *trans*-aconitic acid and palmitic acid, while neither neutral nor basic halogenated compounds have been isolated. In this paper it is shown that the new phenols are 5,6-dibromoprotocatechualdehyde and 2,3-dibromo-4,5-dihydroxybenzyl methyl ether.

One of the two new dibromophenols was isolated by chromatography of the acidic fraction obtained by extraction of the alga with ether, which was collected in March at Hakodate Bay, Hokkaido. The bromophenol (I) had m.p. 203–203·5° and was analyzed for $C_7H_4O_3Br_2$. It gave an intense green color with ferric chloride, and was readily soluble in aqueous sodium carbonate solution.[4] The phenol (I) also gave positive color tests with a Tollen's reagent and with 2,3,5-triphenyltetrazolium chloride, and decolorized a potassium permanganate solution on heating.[5] The IR spectrum of I showed the presence of OH groups at 3300 cm^{-1}, a benzene ring at 1595, 1574, 1503 and 878 cm^{-1}, and a CO group at 1645 cm^{-1}. These facts strongly suggested that compound I would be a dibromo and dihydroxy derivative of benzaldehyde. The presence of a formyl group was further supported by the behaviour of the UV spectra in neutral and acidic media; in methanol, I exhibited maxima at 239 (ε 12,200), 292 (ε 6,000) and 357 mμ (ε 11,700), whereas in a methanol solution containing one drop of sulfuric acid, the absorption at 357 mμ disappeared, although those near 239 and 292 mμ remained at almost the same wave-lengths but with

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* Part VI of *Constituents from Marine Plants*; Part V, E. Kurosawa, M. Izawa, K. Yamamoto, T. Masamune and T. Irie, *Bull. Chem. Soc. Japan* in press.

[1] T. Saito and Y. Ando, *J. Chem. Soc. Japan* (*Nippon Kwagaku Zasshi*) **76**, 478 (1955).

[2] [a] J. Augier and P. Mastagli, *C.R. Acad. Sci., Paris* **229**, 775 (1949); *Ibid.* **242**, 190 (1956); [b] J. H. Hodgkin, J. S. Craigie and A. G. McInnes, *Canad. J. Chem.* **44**, 74 (1966).

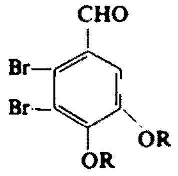
[3] T. Irie, M. Suzuki, E. Kurosawa and T. Masamune, *Tetrahedron Letters* 1837 (1966).

[4] Halogenated phenols are generally stronger acids than usual phenols; cf., S. Huneck, *Z. Naturforsch.* **20b**, 1119 (1931).

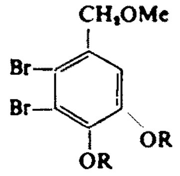
[5] An aromatic aldehyde having an OH group as a nuclear substituent often resists oxidation with $KMnO_4$ at room temp; cf., W. Pondorf, *Chem. Ber.* **64**, 1913 (1931).

reduced intensities. This behaviour was ascribed to an acetal formation of a formyl group with methanol as similar phenomena are observed for protocatachualdehyde and related aldehydes.[6] As the phenol I does not give a fluorescing ketazine with hydrazine,[7] no OH group is situated *ortho* to the formyl group. Therefore, since monobromoprotocatechualdehyde and its derivatives are isolated from the algae of the family *Rhodomelaceae*,[1,2] the phenol I is probably dibromoprotocatechualdehyde.

None of three possible isomers of dibromoprotocatechualdehyde have been prepared, but their dimethyl ether have been all synthesized.[8] The treatment of I with dimethyl sulfate afforded its dimethyl ether (II), m.p. 128–129°. In agreement with the supposed structure, the NMR spectrum of II displayed sharp singlets due to two non-equivalent MeO groups at τ 6·15 and 6·13, a singlet due to a single aromatic proton at τ 2·57, and a singlet due to an aldehyde proton at τ $-0{\cdot}23$. This dimethyl ether II has now been found to be 5,6-dibromoveratraldehyde, which was identical with an authentic specimen[8,9] in all respects.



I R = H, II R = Me



III R = H, IV R = Me—
V R = Ac—

The second bromophenol (III), isolated from the acidic fraction obtained by extraction of the alga with methanol, had m.p. 129–130° and analyzed for $C_8H_8O_3Br_2$. The compound (III) probably a phenol showed in the IR spectrum the presence of OH groups at 3480 cm^{-1} and a benzene ring at 1608, 1575 and 878 cm^{-1}. Since III had no CO function, the molecular formula and the biogenetic consideration suggested the phenol III to be formulated as a monomethyl ether of 2,3-dibromo-4,5-dihydroxybenzyl alcohol. In accordance with this formula, a dimethyl ether (IV), m.p. 71–72°, exhibited peaks due to MeO groups at τ 6·56, 6·23 and 6·17, a benzylic methoxymethylene group at τ 5·54[2b] and an aromatic proton at τ 2·54 in its NMR spectrum. The disposition of a MeO group at the side chain of IV was confirmed by examination of the spectra of a diacetate (V), m.p. 97–98°, which was obtained by acetylation with acetic anhydride in pyridine. The IR and NMR spectra of V displayed the absence of an aliphatic acetoxyl group and an aromatic MeO group; in the IR spectrum, absorption maximum appeared only at 1765 cm^{-1} at the CO region, and in the NMR spectrum of V no signal was observed near τ 8·0, while peaks due to Me groups of phenyl acetate type appeared at τ 7·74 and τ 7·67 as singlets. Therefore, the second dibromophenol was formulated as III, 2,3-dibromo-4,5-dihydroxybenzyl methyl ether.

During the structure determination of III, Matsumoto informed us that his group

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[6] E. P. Crowell, W. A. Powell and C. J. Varsel, *Analyt. Chem.* 35, 184 (1963).

[7] Feigl, *Spot Test in Organic Analysis* p. 234. Elsevier, London (1960).

[8] L. C. Raiford and R. P. Perry, *J. Org. Chem.* 7, 354 (1942); L. C. Raiford and F. B. Wittmer, *Ibid.* 10, 527 (1945).

[9] Although 5,6-dibromoveratraldehyde was reported to be yellow in the literatures (Footnote 8) both the aldehyde II and our authentic sample were obtained as colorless needles.

had isolated a bromophenol from *Odonthalia corymbifera* (*Rhodomelaceae*) and proved it to have the same formula as III on synthetic grounds, although they described a lower m.p.[10] of 117°. By the direct comparison, their synthetic specimen was shown to be identical with our sample III.[11]

EXPERIMENTAL

All m.ps are uncorrected. IR and UV spectra were measured in Nujol and in 99% EtOH unless otherwise noted. NMR spectra were taken in $CDCl_3$ at 60 Mc, using (TMS as internal standard. Chromatography was made with flowing method on "Mallinckrodt's Silica Gel, for Chromatography (A.R. 100 mesh)" containing celite powder (20%).

Extraction of the alga, Rhodomela larix. The freshly harvested and dried alga (8 kg) was extracted with several portions of ether in a Soxhlet apparatus and then digested with MeOH (30 l.) for a month. The ether extracts were concentrated to one l. and washed with 1N HCl to remove basic materials (140 mg). The extracts were then shaken with 3 portions of 500 ml 1N NaOH to be divided into neutral and acidic components, when an intractable emulsion resulted and separation of the two phases was made difficult. After standing for 24 hr after each operation, the separated organic phases were combined, dried and evaporated to a syrup, leaving neutral material (28 g) which contained no halogenated substances (Beilstein's test). The combined alkaline aqueous solns were acidified with 6N HCl and extracted with ether. Removal of the solvent left an acidic mixture (53 g) which was designated mixture A. When the MeOH extracts, described above, were concentrated to 4 l., tarry materials separated. After filtration, the filtrate was evaporated to dryness and the residue was treated twice with boiling ether (500 ml) to be divided into ether-soluble and insoluble parts. The ether-soluble part was further fractionated in a way similar to that used for the ether extracts of the alga; it was shaken with 1N NaOH. Regeneration from the aqueous alkaline soln with 6N HCl followed by extraction with ether gave the second acidic mixture (7 g) which contained halogen, and was designated mixture B. The ether-insoluble part was agitated with H_2O (60 ml) and then filtered. To the aqueous filtrate 4N H_2SO_4 (40 ml) was added, and the resulting acidic soln was extracted continuously with ether in a Soxhlet apparatus for 10 hr. The ether extracts thus obtained yielded an amorphous solid (600 mg) giving a negative Beilstein's test and being designated C.

Chromatography of the acidic mixtures

(a) The acidic mixture A (53 g) was chromatographed on silica gel (1·5 Kg). Elution with benzene gave a crystalline acid (25 g), m.p. 46–48°. Recrystallization from EtOH yielded colorless plates, m.p. 52–55°. Although the observed m.p. was slightly lower than the reported of palmitic acid, 63°. The IR spectrum of the acid was similar to that of an authentic specimen, showing five specific peaks over the region from 1570 to 1190 cm^{-1}. Hence the acid was identified as palmitic acid, but further characterization was not made.

Fractions eluted with benzene–ether (19:1) gave an acid (1·2 g), m.p. 113–115°. (Found: C, 70·87; H, 5·74. Calc. for $C_8H_8O_2$: C, 70·57; H, 5·92%.) This was shown to be phenylacetic acid by comparisons of the IR and UV spectra of authentic specimen. Final fractions eluted with benzene–ether (9:1) afforded a phenol (2·2 g).

(b) The acid mixture B (7 g) was alo subjected to chromatography on silica gel (200 g). Fractions eluted with benzene and benzene–ether (19:1) did not give any crystalline material besides a small amount of palmatic acid. Further elution with benzene–ether (9:1) gave a mixture of phenolic substances (TLC). One of which was confirmed (TLC) identical with the phenol obtained in "chromatography-a". The mixture was then re-chromatographed in silica gel (12 g), and elution with benzene–ether (99:1) afforded the second phenolic compound (400 mg) containing halogen.

trans-*Aconitic acid.* The amorphous powder C (600 mg) was dissolved in H_2O (10 ml), and the soln was treated with decolorizing charcoal and filtered. Removal of the solvent *in vacuo* left a crystalline acid, m.p. 160–170°. Recrystallization from AcOH afforded colorless prisms (300 mg),

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[10] T. Matsumoto and S. Kagawa, *Abstracts of the Annual Meeting of Chemical Society of Japan* 278 (1964).

[11] We wish to thank Professor T. Matsumoto for kind information and for supplying a synthetic specimen.

m.p. 188–189°. (Found: C, 41·25; H, 3·65. Calc. for $C_6H_6O_6$: C, 41·38; H, 3·45%.) The acid gave a characteristic color test for aconitic acid with Ac_2O[18]; pink color appeared and turned rapidly to deep red and then to magenta. On further heating it changed to bluish-green and finally to brown. Confirmative proof that the acid is *trans*-aconitic acid was accomplished by the direct comparison with an authentic specimen.

5,6-*Dibromoprotocatechualdehyde* (I). The first phenolic compound (2·2 g), obtained from "chromatography-a", was crystallized from AcOEt–benzene as brownish crystals, m.p. 195–202°. The crude phenol was purified by repeated recrystallizations from AcOET to yield pale yellow needles which were pure on TLC. The purification was effected by sublimation (150°, 15 mm), and yielded a colorless sample (1·2 g) of I, m.p. 203–205°, λ_{max} 332 (ε 6,400), 294 (ε 8,400), 240 mμ (ε 26,800), λ_{max} (0·1N NaOH–EtOH) 404 (ε 14,400), 274 mμ (ε 10,800), ν_{max} 3300 (OH), 1645 (CO), 1595, 1574, 1503, 876 cm^{-1} (aromatic ring). (Found: C, 28·64; H, 1·37; Br, 53·87. $C_7H_4O_3Br_2$ requires: C, 28·76; H, 1·41; Br, 54·05%.) The phenol was readily soluble in EtOH, acetone and ether, but sparingly in chf and benzene. It was soluble in 10% Na_2CO_3aq and exhibited a deep green color with $FeCl_3$ in EtOH. I also gave positive color test with Tollen's reagent, 2,3,5-triphenyltetrazolium-chloride and $KMnO_4$.

Identification of I. The phenol I (80 mg) was dissolved in anhyd acetone (20 ml) containing anhyd K_2CO_3 (800 mg). To this mixture was added Me_2SO_4 (0·4 ml) in small portions over 5 min under refluxing. The resulting pale yellow mixture was decolorized after 30 min, and then refluxed for additional 30 min. After cooling the reaction mixture was filtered to remove K_2CO_3 and the filtrate was evaporated to dryness. The residue was crystallized from acetone–H_2O to yield 5,6-dibromoveratraldehyde (60 mg), m.p. 128–129°. (Found: C, 33·48; H, 2·50. Calc. for $C_9H_8O_3Br_2$: C, 33·33; H, 2·47%.) NMR τ 6·15 (3H), τ 2·57 (1H), τ −0·23 (1H). This compound was shown to be identical with synthetic 5,6-dibromoveratraldehyde by a comparison of the NMR spectra and mixed m.p.; our sample (lit.[9] yellow needles), prepared according to the procedure of Rayford and Wittmer, was obtained as colorless needles, m.p. 129–130°.

2,3-*Dibromo*-4,5-*dihydroxybenzyl methyl ether* (III). The second phenolic compound (400 mg), obtained from MeOH extracts, was recrystallized from benzene to yield III, colorless prisms, m.p. 129–130°. (Found: C, 31·26; H, 2·64. $C_8H_8O_3Br_2$ requires: C, 30·77; H, 2·56%), λ_{max} 230 (ε 12,000), 292 mμ (ε 3,500), λ_{max} (0·1N NaOH–EtOH) 269 (ε 10,300), 303 mμ (ε 7,300). The IR spectrum was identical with that of the phenol which had been isolated by Matsumoto and Kagawa[10]; ν_{max} 3485, 1608, 1575, 1428, 1167, 920, 878 cm^{-1}.

Dimethyl derivative (IV) *of* III. The phenol III (94 mg) in acetone (28 ml) containing anhyd K_2CO_3 (940 mg) was treated with Me_2SO_4 (0·6 ml) as for the methylation of I, yielding a crude ether. By chromatography on silica gel (3 g) with benzene, a pure sample of dimethyl deriv was isolated as colorless needles, m.p. 71–72°, NMR τ 6·56 (3H), τ 6·23 (3H), τ 6·17 (3H), τ 5·57 (2H), τ 2·97 (1H). (Found: C, 35·39; H, 3·70. $C_{10}H_{12}O_3Br_2$ requires: C, 35·29; H, 3·53%). This compound was identical with synthetic 2,3-dibromo-4,5-dimethoxybenzyl methyl ether.[11]

Diacetate (V) *of* III. The phenol III (140 mg) produced a diacetyl deriv when allowed to stand for 15 hr at room temp with excess Ac_2O in pyridine. This deriv crystallized from n-hexane–EtOH as colorless needles, m.p. 97–98°, ν_{max} 1765 cm^{-1}, NMR τ 7·74 (3H, s), τ 7·67 (3H s) τ 6·54 (3H, s), τ 5·54 (2H, d, $J \simeq 0·4$ c/s), τ 2·54 (1H, tr, $J \simeq 0·4$ c/s). (Found: C, 36·16; H, 3·54. $C_{12}H_{12}O_5Br_2$ requires: C, 36·36; H, 3·64%.)

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[18] C. S. Taylor, *J. Chem. Soc.* **115**, 887 (1919).