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A Simple Synthesis of Methyl Ethers of Tribromophenols from the Red Alga *Symphyocladia latiuscla*[1)]

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Bis(2,3,6-tibromo-4,5-dimethoxybenzyl) ether (IV), 2,3,6-tribromo-4,5-dimethoxybenzyl methyl ether (V), 2,3,6-tribromo-4,5-dimethoxybenzyl ethyl ether (VI) and 2,3,6-tribromo-4,5-dimethoxybenzyl alcohol (VIII) were prepared by simple procedures involving one-step bromination from 3,4-dimethoxybenzylacetate (IX).

Keywords——methyl ether of tribromophenol; *Symphyocladia latiuscla*; bromination; ^{13}C-NMR

Several bromophenols have been obtained from red marine algae, Rhodomelaceae.[2)] The antibiotic activity of the bromophenols has been investigated.[3)] During an investigation of the constituents of red marine algae,[4)] a new bromophenol, bis(2,3,6-tribromo-4,5-dihydroxybenzyl) ether (I), was obtained together with two other new bromophenols, 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether (II) and 2,3,6-tribromo-4,5-dihydroxybenzyl ethyl ether (III), from the red alga *Symphyocladia latiuscla*.[5)]

We wish to report here simple syntheses of bis (2,3,6-tribromo-4,5-dimethoxybenzyl) ether (IV), the tetramethyl ether of I, 2,3,6-tribromo-4,5-dimethoxybenzyl methyl ether (V), the dimethyl ether of II, and 2,3,6-tribromo-4,5-dimethoxybenzyl ethylether (VI), the dimethyl ether of III, together with 2,3,6-tribromo-4,5-dimethoxybenzyl alcohol (VII), the dimethyl

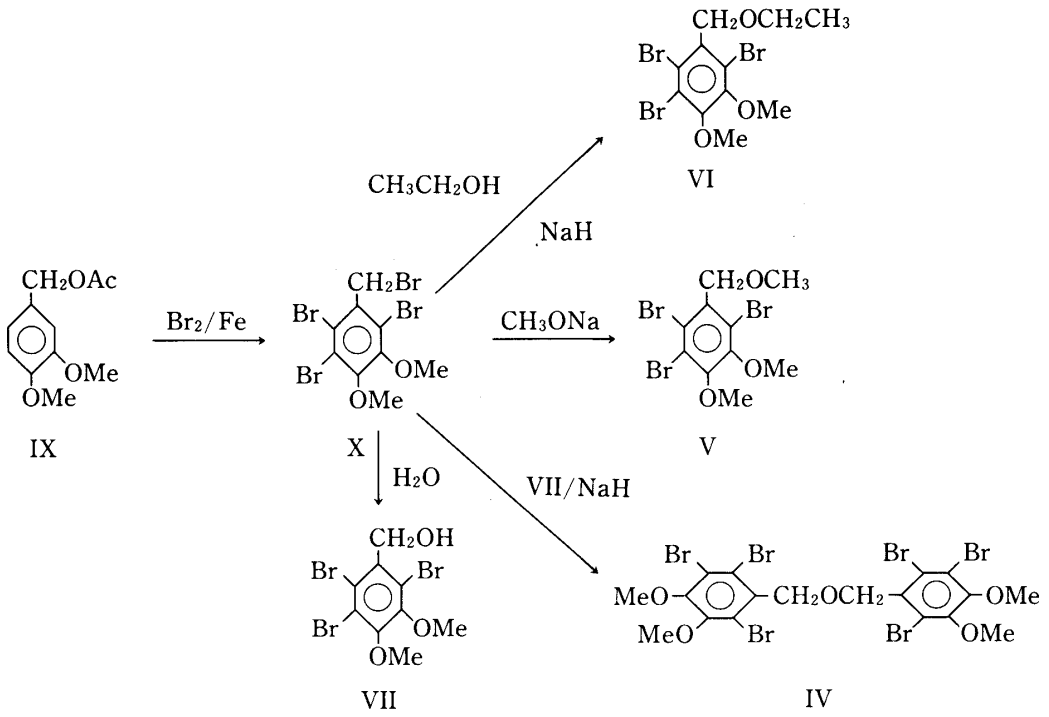

Chart 1

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ether of 2,3,6-tribromo-4,5-dihydroxybenzyl alcohol (VIII).[5a] The syntheses involve one-step bromination to obtain the methyl ethers of the tribromophenols (Chart 1).

The starting material, 3,4-dimethoxybenzyl acetate (IX), was prepared by the usual method from commercially available vanillin. Compound IX was bromination by the usual method, and purified on silica gel to give X. Treatment of X with sodium methoxide in THF afforded V. Compound X was reacted with absolute ethanol in the presence of sodium hydride to yield VI. Further, when X was refluxed in dioxane containing water, it was hydrolyzed to compound VII. Compound X was also reacted with VII in benzene in the presence of sodium hydride to give IV. The compounds thus prepared were identical with the samples prepared by methylation of the bromophenols obtained from the red alga.

Experimental

The mps are uncorrected. The infrared (IR) spectra were determined in KBr discs. Mass spectrum (MS) were measured with Shimadzu 9000B spectrometers. Proton nuclear magnetic resonance (^{1}H NMR) and carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were determined with a JEOL 100 spectrometer in the Fourier transform mode in chloroform-d_1 solution with Me_4Si as an internal standard, with multiplicity given for off-resonance proton decoupling, in 5-mm (o.d.) tubes. All values are reported in ppm downfield (δ) from the Me_4Si signal.

2,3,6-Tribromo-4,5-dimethoxybenzyl Bromide (X)——3,4-Dimethoxybenzyl acetate (IX) (6 g) was dissolved in acetic acid (50 ml). To this solution, iron powder (0.5 g) was added, then bromine (7 ml) was added dropwise. After being stirred for 5 h at 70—75°C, this reaction mixture was poured into water. The resultant precipitate was purified on a silica gel column. Elution with benzene–*n*-hexane (1: 1) yielded crystals (2.5 g, 18.7%), mp 148—150°C. *Anal.* Calcd for $C_9H_8Br_4O_2$: C, 23.08; H, 1.72; Br, 68.24. Found: C, 23.18; H, 1.68; Br, 68.22. MS *m/e*: 471, 469, 467, 465, 463 (M^+); UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 297 (4.10); IR ν_{max}^{KBr} cm^{-1}: 2950, 1450, 1370, 1280, 580, 520; ^{1}H NMR ($CDCl_3$, δ): 3.9 (6H, s, $-OCH_3$), 4.9 (2H, s, methylene of benzyl). ^{13}C NMR ($CDCl_3$, δ): 133.8 (s, C-1), 122.9 (s, C-2), 122.0 (s, C-3), 152.1 (s, C-4), 150.8 (s, C-5), 120.7 (s, C-6), 60.8 (q, C-4, 5 –OMe), 36.1 (t, methylene of benzyl).

2,3,6-Tribromo-4,5-dimethoxybenzyl Methyl Ether (V)——Compound X (450 mg) was dissolved in THF (20 ml). To this solution, sodium methylate (250 mg) dissolved in THF was added. After being stirred for 3 h at 40°C, this reaction mixture was poured into water. The ether extract of this solution yielded crystals (181 mg, 45%), mp 91—92°C. *Anal.* Calcd for $C_{10}H_{11}Br_3O_3$: C, 28.67; H, 2.64; Br, 57.22. Found: C, 27.58; H, 2.59; Br, 56.42. MS *m/e*: 422, 420, 418, 416 (M^+). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 283 (4.00) and 293 (3.94). IR ν_{max}^{KBr} cm^{-1}: 2900, 2820, 1580, 1550, 1080. ^{1}H NMR ($CDCl_3$, δ): 3.5 (3H, s, $-CH_2OC\underline{H}_3$), 3.9 (6H, s, $-OCH_3$), 4.88 (2H, s, methylene of benzyl). ^{13}C NMR ($CDCl_3$, δ): 134.0 (s, C-1), 123.8 (s, C-2), 121.7 (s, C-3), 151.9 (s, C-4), 150.5 (s, C-5), 121.6 (s, C-6), 60.7 (q, C-4, 5 –OMe), 75.3 (t, methylene of benzyl), 56.8 (q, $-CH_2O\underline{C}H_3$). The melting point showed no depresion on admixture of V with a sample prepared from 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether (II)[5a] by methylation with diazomethane, and the IR spectra of the two samples were identical.

2,3,6-Tribromo-4,5-dimethoxybenzyl Ethyl Ether (VI)——Compound X (200 mg) was dissolved in THF. To this solution, NaH (0.5 g) was added, then absolute ethanol (20 ml) was added dropwise. The mixture was stirred for 3 h, then NaH was decomposed by adding ethanol. The reaction mixture was extracted with benzene. The extract was applied to a column of silica gel. Elution with chloroform yielded crystals (85 mg, 43.7%), mp 52—53°C. *Anal.* Calcd for $C_{11}H_{13}Br_3O_3$: C, 30.51; H, 2.97; Br, 54.48. Found: C, 30.85; H, 3.06; Br, 54.51. MS *m/e*: 436, 434, 432, 430 (M^+). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 287 (3.57) and 293 (3.51). IR ν_{max}^{KBr} cm^{-1}: 2820, 1550, 1470, 1440, 1100, 880, 560. ^{1}H NMR ($CDCl_3$, δ): 1.25 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 3.67 (2H, q, J=7 Hz, $-C\underline{H}_2CH_3$), 3.88 (6H, s, $-OCH_3$), 4.88 (2H, s, methylene of benzyl). ^{13}C NMR ($CDCl_3$, δ): 134.7 (s, C-1), 124.0 (s, C-2), 122.2 (s, C-3), 152.2 (s, C-4), 150.9 (s, C-5), 121. 9 (s, C-6), 60.9 (q, C-4, 5 –OMe), 73.9 (t, methylene of benzyl), 66.5 (t, $-C\underline{H}_2CH_3$), 15.3 (q, $-CH_2\underline{C}H_3$). The melting point showed no depression on admixture of VI with a sample prepared from 2,3,6-tribromo-4,5-dihydroxybenzyl ethyl ether (III)[5a] by methylation with diazomethane, and the IR spectra of two samples were identical.

2,3,6-Tribromo-4,5-dimethoxybenzyl Alcohol (VII)——A solution of compound X (300 mg) dissolved in dioxane–water was refluxed for 72 h, then water was added. The resultant precipitate gave crystals (232 mg, 89.6%) after recrystallization from dioxane–water. *Anal.* Calcd for $C_9H_9Br_3O_3$: C, 26.69; H, 2.24; Br, 59.20. Found: C, 26.91; H, 2.36; Br, 59.12. MS *m/e*: 408, 406, 404, 402 (M^+). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 283 (3.97) and 293 (3.87). IR ν_{max}^{KBr} cm^{-1}: 3300, 2950, 1440, 1360, 1285. ^{13}C NMR ($CDCl_3$, δ): 136.3 (s, C-1), 122.8 (s, C-2), 121.8 (s, C-3), 151.9 (s, C-4), 150.7 (s, C-5), 120.8 (s, C-6), 60.8 (q, C-4 5 –OMe), 67.1 (t, methylene of benzyl). The melting point showed no depression on admixture of VIII with an authentic sample,[5a] mp 122—123°C, and the IR spectra of the two samples were identical.

Bis(2,3,6-tribromo-4,5-dimethoxybenzyl) Ether (IV)——NaH (500 mg) was added to a solution of X

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(100 mg) and VII (100 mg) in benzene (15 ml), and the mixture was refluxed for 3 h then stirred to decompose excess NaH. The benzene layer was separated, dried with $CaCl_2$ and concentrated. The residue was purified by thin layer chromatography (TLC) (silica gel) (benzene: *n*-hexane=2: 1) to afford crystals (56 mg, 33.4%). The melting point showed no depression on admixture of IV with an authentic sample,[5b] mp 137—138°C, and the IR spectra of the two samples were identical.

References and Notes

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