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SIMPLE PRENYLATED HYDROQUINONE DERIVATIVES FROM THE MARINE UROCHORDATE APLIDIUM CALIFORNICUM. NATURAL ANTICANCER AND ANTIMUTAGENIC AGENTS.

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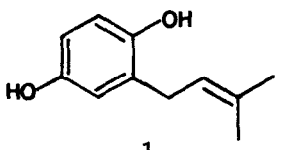
Summary: The structures and syntheses of prenylhydroquinone (1), 6-hydroxy-2,2-dimethylchromene (2), and prenylquinone (3), which are natural products isolated from the marine colonial tunicate Aplidium californicum, are described. Prenylhydroquinone shows in vivo activity against P388 lymphocytic leukemia (T/C=138). Both 1 and 2 significantly inhibit the mutagenic effects of benzo(a)pyrene, aflatoxin B_1 and ultraviolet light on Salmonella typhimurium, and may be cancer protective agents.

As part of our program to isolate, characterize and synthesize pharmacologically active substances of marine origin, we have focused our interests on the natural constituents of marine invertebrates from San Francisco Bay and local coastal regions. Based on the reported[1] high incidence of anticancer activity of the Subphylum Urochordata we have investigated the chemistry and pharmacological properties of the colonial tunicate Aplidium californicum (Polyclinidae, Urochordata).[2] Marine organisms of this genus have been previously reported to synthesize geranylhydroquinone[3] which has been shown to offer protection against leukemia and tumor development in test animals. Geranylhydroquinone, its chromenol, and a ten-membered ring ether derivative have also been isolated from the Australian tunicate Aplidium cavernosa.[4] Reported herein are the structures, syntheses and biological properties of three simple prenylated hydroquinone derivatives: prenylhydroquinone (1), 6-hydroxy-2,2-dimethylchromene (2), and prenylquinone (3). In addition, these compounds represent the first hemiterpene

derivatives to be isolated from a marine organism.



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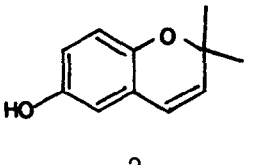

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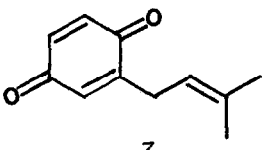

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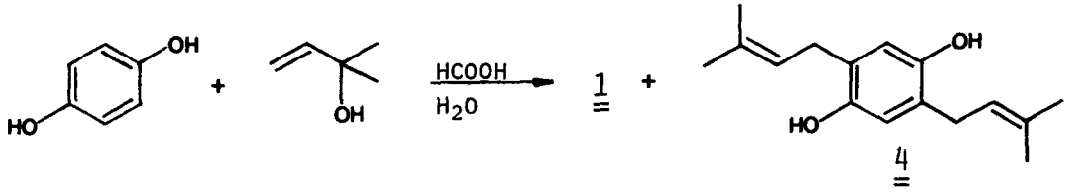
Aplidium californicum was collected near Montara Beach, California (10 miles south of the Golden Gate Bridge) from the intertidal zone. Silica gel chromatography of the chloroform-methanol (1:1) extract of the fresh organism gave prenylhydroquinone (1) (22% yield, crude extract, 30% diethyl ether-petroleum ether elution) as a crystalline solid, m.p. 100-101°. 6-Hydroxy-2,2-dimethylchromene (2) was isolated as a colorless oil in 2.9% yield (25% diethyl ether-petroleum ether elution), and prenylquinone (3) (1% yield, 2% diethyl ether-petroleum ether elution) was isolated as a yellow, low melting crystalline solid, m.p. 28-30°. Prenylhydroquinone (1) had the following NMR characteristics: ^{1}H NMR (100 MHz, d_6-benzene) δ 6.95 (1H, bs), 6.85 (2H, bs), 5.71 (1H, bt, J=8 Hz), 4.42 (1H, s, OH), 3.95 (1H, s, OH), 3.48 (2H, d, J=8 Hz), 1.69 (3H, s), and 1.63 (3H, s); ^{13}C NMR (25 MHz, d_6-acetone) 150.8, 148.3, 132.1, 129.3, 123.6, 116.9, 116.1, 113.5, 28.9, 25.8, 17.5. Analysis of these data revealed that 1 contained an isopropylidene unit and a trisubstituted benzene ring. Treatment of 1 with Jones' reagent gave the para-benzoquinone 3 (IR, 1675 cm^{-1}), ^{1}H NMR (100 MHz, $CDCl_3$) δ 6.70 (1H, s), 6.67 (1H, s), 6.47 (1H, bt), 5.50 (1H, bt, J=8), 3.09 (2H, d, J=8), 1.77 (3H, s), 1.68 (3H, s). To confirm these structure assignments prenylhydroquinone was synthesized. Condensation of hydroquinone with 2-methylbut-3-en-2-ol in aqueous formic acid gave prenylhydroquinone (1) as the major product, identical with the natural product and a low yield of the dialkylated product 4.[5,6]



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Both compounds 1 and 3 have been previously isolated from the terrestrial plant Phagnalon saxitale.[7] However, the chromenol 2 appears to be undescribed. ^{1}H and ^{13}C NMR data were of great utility in determining the structure of 2: ^{1}H NMR (100 MHz, CCl_4) δ 6.57 (1H, d, J=2), 6.50 (2H, bs), 6.12 (1H, d, J=10), 5.47 (1H, d, J=10), 1.33 (6H, s). ^{13}C NMR (acetate derivative) (25 MHz, $CDCl_3$) 169.5, 150.4, 144.1, 131.4, 121.7, 121.6, 121.5, 118.9, 116.6, 76.3, 27.9, 27.9, 20.9 ppm. Treatment of 2 with acetic anhydride/pyridine gave a monoacetate. Methylation of 2 with dimethyl sulfate/potassium carbonate gave a monomethyl ether which was shown to be isomeric with the antiallatotropin, precocene-I.[8] The structure of 6-hydroxy-2,2-dimethylchromene (2) was secured by synthesis. Treatment of prenylquinone (3) with sodium hydride in refluxing benzene gives 2 upon work-up with acetic acid.[9]

Based on the reported anticancer and cancer protective properties of isoprenylated hydroquinones, prenylhydroquinone was tested in vivo (mice) against P388 lymphocytic leukemia and resulted in a maximum T/C = 138 at 3.12 mg/kg. In an attempt to assess the potential cancer protective properties of these hydroquinone derivatives a modified Ames assay was performed for mutagenicity against Salmonella typhimurium.[10] The carcinogens benzo(a)pyrene and aflatoxin B_1 are potent mutagens in the Ames assay (S9 activation). However, when either prenylhydroquinone (1) or the chromenol (2) are added to assays with benzo(a)-pyrene or aflatoxin B_1, the mutagenic effects of these carcinogens are drastically reduced.[11] Similarly, the mutagenic effects of ultraviolet light, a potent mutagen and carcinogen, are dramatically reduced in the presence of prenylhydroquinone (1). Most cancer protective agents studied to date are also antioxidants.[12] Both compounds 1 and 2 are antioxidants and may be cancer protective agents. Further studies are being conducted on the anticancer and antimutagenic properties of natural hydroquinones of marine origin in our laboratories.

Acknowledgements

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References and Notes

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