Journal of Natural Products
Vol. 50, No. 4, pp. 735-737, Jul-Aug 1987

A NEW BROMINATED MONOTERPENOID QUINOL FROM *CYMOPOLIA BARBATA*

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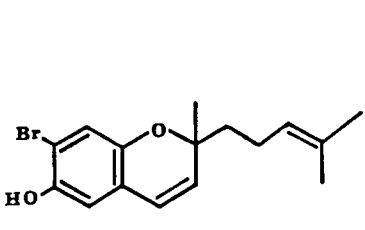
The Et_2O extracts from the green calcareous alga *Cymopolia barbata* (L.) Lamx. (Dasycladaceae) collected near Puerto Rico have been shown (1) to possess antibiotic and antifungal properties, although no specific compounds were isolated and characterized. Lipid extracts of this alga collected in Bermuda (2) and Florida (3) were shown to be a fertile source of prenylated bromohydroquinones, which exhibit additional biological activities such as antifeedant properties determined in bioassays employing common marine invertebrates (4).

In the course of studies on the chemical constituents of the Canary Islands *C. barbata* we became aware that the crude Me_2CO extract of this alga showed antimicrobial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* in a disc assay. After the crude Me_2CO extract was partitioned between Et_2O and H_2O, concentration of the Et_2O layer yielded a black oil. This oil was separated by passage through a Si gel column (hexane/EtOAc), and the active fractions were further purified by passage through a prepared Merck Size C Si gel 60 column (hexane/Et_2O) to give the compounds: 7-bromo-6-hydroxy-2-methyl-2 (4-methylpent-3-enyl)-2H-benzopyran [**1**] (0.02% dry weight), (4-bromo-2,5-dihydroxyphenyl)-*E*-(2,6-dimethylhepta-1,5-dienyl) ketone [**2**] (0.006%), the *cis* isomer (4-bromo-2,5-dihydroxyphenyl)-*Z*-(2,6-dimethylhepta-1,5-dienyl) ketone [**3**] (0.002%), and the triol (4-bromo-2,5-dihydroxyphenyl)-*E*-(2,6-dimethyl-6-hydroxyhept-2-enyl) ketone [**4**] (0.04%). The compounds **1-3** were respectively identified with the previously reported cymopochromenol (2,3), cymopolone (2,3), and isocymopolone (2) from spectral data that were identical with literature values.

The triol **4** is a yellow crystalline compound, and its molecular formula $C_{16}H_{21}BrO_4$ suggests that it is a hydrated form of cymopolone [**2**]. The uv spectrum, λ max 280 and 380 nm (log ϵ 4.35 and 3.90), is consistent with a 4-bromo-2,5-dihydroxyphenone chromophore (5) identical to that observed (2) in cymopolone [**2**]. The ir spectrum shows aromatic carbonyl absorption at 1630 cm^{-1} shifted to 1660 cm^{-1} in the diacetate **5**. The ^{1}H-nmr spectrum shows signals for three methyl groups at δ 1.19 (6H, s) and 2.12 (3H, d, J=1.5 Hz), one olefinic proton α to a carbonyl group as a broadened singlet at δ 6.62, and two *para*-aryl protons at δ 7.12 and 7.38 (s, 1H each). The spectral evidence is fully consistent with structure **4**, which was established by synthesis. This was



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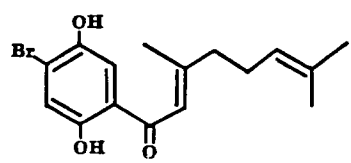

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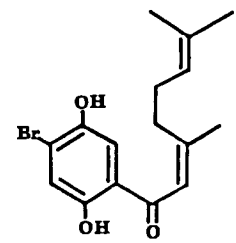

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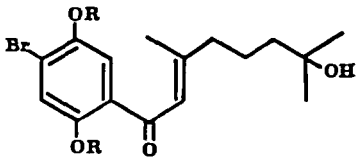
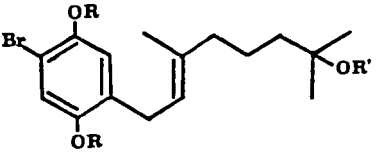


4 R=H
5 R=Ac



6 R=R'=H
7 R=Ac, R'=H
8 R=R'=Ac

achieved by alkylation of bromohydroquinone with (*E*)-1,7-dihydroxy-3,7-dimethyloct-2-ene (boron trifluoride-Et_2O as catalyst) to give **6**. Acetylation of **6** to give **7**, followed by oxidation with chromium troxide-dimethylpyrazole in CH_2N_2 at 0° gave a modest yield of the α,β-unsaturated ketone **5** which was shown to be identical with the acetylated natural compound.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were determined on a Kofler block. Ir spectra were recorded on Perkin-Elmer 237 and 681 spectrophotometers. Uv spectra were recorded on a Perkin-Elmer 402 spectrophotometer. Mass spectra were obtained from VG Micromass ZAB-2F. ^{1}H-nmr spectra were determined on Perkin-Elmer R-12 (60 MHz) and R-32 (90 MHz) spectrometers. Column and dry column chromatography were performed on Si gel G, all Merck products. Si gel GF_{254} (Type 60) was utilized for tlc, and the spots were visualized by staining with anisaldehyde-H_2SO_4 (6). All solvents used were either spectral grade or distilled from glass prior to use. Anhydrous Na_2SO_4 was used for drying solutions.

COLLECTION, EXTRACTION AND CHROMATOGRAPHY.—The alga *C. barbata* was collected by hand using SCUBA (-6 m) at Playa de las Américas (Tenerife, Canary Islands) in August 1983, immediately frozen and then lyophilized. A voucher specimen is deposited at the Departamento de Biología Vegetal, Universidad de La Laguna, Tenerife, Spain. The alga was homogenized and repeatedly extracted with Me_2CO. The volume of the filtrate was reduced in vacuo and the residue was partitioned between Et_2O and H_2O. The Et_2O-soluble extract (12.5 g) obtained from 1.4 kg of dried fresh algae was judged to contain the majority of secondary metabolites. The black oil obtained was preabsorbed onto Si gel and applied to a column of Si gel (500 g) that was eluted with solvents of increasing polarity from hexane to EtOAc, yielding cymopochromenol [**1**] (280 mg, 0.02%), cymopolone [**2**] (84 mg, 0.006%), and isocymopolone [**3**] (28 mg, 0.002%) [identified by comparison of their physico-chemical properties (uv, ir, ^{1}H nmr, ms) with those reported in the literature (2)].

(4-BROMO-2,5-DIHYDROXYPHENYL)-*E*-(2,6-DIMETHYL-6-HYDROXYHEPT-2-ENYL) KETONE [**4**].—The more polar fractions (2.1 g) were rechromatographed on a pre-packed Merck Size-C Si gel 60 column in 25% EtOAc in hexane that allowed the isolation of a yellow solid that was recrystallized from hexane/CH_2Cl_2 to yield compound **4** (560 mg, 0.04%), mp 126-128° (Found: C, 53.5; H, 5.7; Br, 22.2; $C_{16}H_{21}BrO_4$ requires: C, 53.8; H, 5.9; Br, 22.4%); uv λ max (EtOH) 280 and 380 nm (log ε 4.35 and 3.90); ir ν max (KBr) 3590, 3520, 1630, 1580, 1480, 1460, 1125, 1120, 1090 cm^{-1}; ^{1}H nmr δ ($CDCl_3$) 1.19 (s, 6H), 1.50-1.70 (m, 4H), 2.12 (3H, d, J=1.5 Hz), 2.20 (m, 2H), 6.62 (brs, 1H), 7.12 and 7.38 (s, 1H each), and 11.79 (1H, s, chelated OH). Irradiation at δ 6.62 caused the doublet at δ 2.12 to collapse to a singlet; ms *m/z* 358 (2%), 356 (2), 343 (12), 341 (12), 325 (10), 323 (10), 297 (18), 295 (18), 269 (11), 267 (11), 257 (100), 255 (100), 217 (12), 215 (22). The diacetate formed an oil; uv λ max (EtOH) 265 nm (log ε 4.80); ir ν max (neat) 3450, 1765 and 1660 cm^{-1}; ^{1}H nmr δ ($CDCl_3$) 1.20 (s, 6H), 1.40-1.70 (m, 4H), 1.95 (m, 2H), 2.15 (3H, d, J=1 Hz), 2.28 and 2.34 (s, 3H each), 6.40 (br s, 1H), 7.40 and 7.45 (s, 1H each); ms *m/z* 442 (1%), 440 (1), 427 (5), 425 (5), 409 (3), 407 (3), 400 (54), 398 (54), 257 (100), 255 (100).

(*E*)-1,7-DIHYDROXY-3,7-DIMETHYLOCT-2-ENE.—This was prepared from freshly distilled geraniol acetate by the following sequence of reactions. *N*-Bromosuccinimide oxidation of the acetate in aqueous tetrahydrofuran (7) provided the geraniol acetate terminal bromohydrin which on treatment with K_2CO_3 in MeOH gave the geraniol epoxide. $LiAlH_4$ reduction of epoxygeraniol in dry Et_2O gave (*E*)-1,7-dihydroxy-3,7-dimethyloct-2-ene as an oil: ir ν max (neat) 3520, 3325, 1460, 1370, 1175, 1080 cm^{-1}; ^{1}H nmr δ ($CDCl_3$) 1.18 (6H, s), 1.63 (3H, s), 2.05 and 2.60 (br s, 1H each, D_2O-exchangeable), 4.15 (2H, d, J=7 Hz), 5.44 (1H, br t, J=7 Hz); ms *m/z* 154 (M^+-H_2O) (1.6%), 139 (15), 136 (34), 123 (14), 121 (37), 109 (11), 98 (41), 95 (24), 83 (100).

2-BROMO-5 (7-HYDROXY-3,7-DIMETHYLOCT-2-ENYL) HYDROQUINONE [**6**].—To a solution

of bromohydroquinone (2.19 g, 11.0 mmol) and boron trifluoride-Et_2O complex (2.0 ml) in freshly distilled dioxane (30 ml) was added dropwise, with stirring at room temperature and under N_2, a solution of the previously synthesized diol (1.89 g, 11.0 mmol) in dry dioxane (30 ml). After the addition was complete, stirring at room temperature was continued overnight. The mixture was poured onto crushed ice and extracted 3 times with 100 ml portions of Et_2O. The Et_2O solution was washed with H_2O (2×50 ml), 5% $NaHCO_3$ solution (2×50 ml), and H_2O (2×50 ml), and dried over Na_2SO_4. After removing the solvent, the oily residue (2.2 g) was chromatographed on Si gel (300 g). The hexane-EtOAc (9:1) fractions (720 mg) were carefully rechromatographed to yield 2-bromo-5 (7-hydroxy-3,7-dimethyloct-2-enyl) hydroquinone [**6**] (418 mg) as an oil. (Found: C, 56.0; H, 6.5; Br, 23.8; $C_{16}H_{23}BrO_3$ requires, C, 56.0; H, 6.7; Br, 23.3%); uv λ max (EtOH) 299 nm (log ε 3.90); ir ν max (neat) 3300, 1540, 1480, 1180, 1020, 960 cm^{-1}; ^1H nmr δ ($CDCl_3$) 1.20 (6H, s), 1.45 (3H, s), 3.35 (2H, d, J=7.5 Hz), 5.15 (1H, t, J=7.5 Hz), 6.81 and 7.04 (s, 1H each); ms *m/z* 344 (45%), 342 (45), 326 (24), 324 (24), 266 (31), 254 (18), 241 (12), 231 (22), 203 (14), 189 (84), 187 (84). The diacetate [**7**] formed an oil: ir ν max (neat) 3500, 1760, 1600, 1570, 1480, 1360, 1190, 1020 cm^{-1}; ^1H nmr δ ($CDCl_3$) 1.20 (6H, s), 1.68 (3H, br s), 2.30 and 2.32 (s, 3H each), 3.20 (2H, d, J=7.5 Hz), 5.22 (1H, t, J=7.5 Hz), 7.03 and 7.33 (s, 1H each); ms *m/z* 428 (3%), 426 (3), 410 (6), 408 (6), 367 (26), 365 (26), 351 (14), 325 (32), 321 (32), 311 (23), 291 (18), 269 (11), 267 (11), 240 (47), 238 (47), 202 (19), 123 (80), 120 (80). The triacetate **8** formed an oil: ^1H nmr δ ($CDCl_3$) 1.45 (6H, s), 1.62, 1.94, 2.25, and 2.30 (s, 3H each), 3.20 (2H, d, J=7.5 Hz), 5.11 (1H, t, J=7.5 Hz), 7.03 and 7.33 (s, 1H each).

(4-BROMO-2,5-DIACETOXYPHENYL)-*E*-(2,6-DIMETHYL-6-HYDROXYHEPT-2-ENYL) KETONE [**5**].—3,5-Dimethylpyrazole (346 mg, 3.6 mmol) was added to a suspension of chromium trioxide (360 mg, 3.6 mmol) in dry CH_2Cl_2 (25 ml) at −20°, and the reagent mixture was stirred for 15 min. A solution of the diacetate **7** (68.4 mg, 0.16 mmol) in CH_2Cl_2 (15 ml) was added dropwise, and the reaction mixture was stirred for 3 h at −15 to −20°. NaOH solution (5N, 10 ml) was added, and the reaction mixture was stirred for 1 h at 0°. The organic material was extracted with Et_2O (3×50 ml), and the combined Et_2O extracts were washed with 5% HCl (3×50 ml), brine (2×25 ml), and H_2O (2×25 ml). The extract was dried over Na_2SO_4 and the solvent evaporated under vacuum to yield the crude product (44 mg) that was chromatographed on Si gel using 5% Et_2O in hexane as eluent, to obtain the α,β-unsaturated ketone **5** (25 mg, 35%), which was shown to be identical in all respects (ir, ^1H nmr, ms) with the diacetate obtained by acetylation of the natural compound **4**.

ACKNOWLEDGMENTS

This investigation was supported by Grant 3481/83, awarded by the Spanish CAICYT.

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Received 16 September 1986