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The Structure of Yahazunol, a New Sesquiterpene-substituted Hydroquinone from the Brown Seaweed *Dictyopteris undulata* Okamura

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Synopsis. The structure of yahazunol, an antimicrobial substance isolated from the brown seaweed *D. undulata* Okamura, was established on the basis of spectral and chemical evidence.

Fenical and coworkers have recently reported the isolation of five sesquiterpene-substituted phenols from *D. undulata* Okamura ("Shiwayahazu" in Japanese), and noted that the occurrence of these constituents was dependent upon the growth localities of the alga.[1-3] Our investigation of the phenolic components of the seaweed collected in the Bay of Tosa led to the isolation of a new sesquiterpene-substituted hydroquinone, designated as yahazunol, together with zonarol (**1**),[1] isozonarol (**2**),[1] and zonaroic acid (**3**).[3] These were all obtained in the crystalline state, contrary to previous descriptions. In this note, we will deal with the structure of this new compound. This compound was found to have a strong antimicrobial activity against some yeasts.[4]

Yahazunol (**4**), $C_{21}H_{32}O_3$, mp 127—129 °C, $[\alpha]_D^{27}$ $-12°$ (*c* 0.10, $CHCl_3$), was isolated in 0.008% yield from a methanol extract of the fresh alga by careful silica-gel column chromatography and fractional crystallization. **4** shows hydroxylic absorptions in the IR spectrum at 3400 and 3280 cm^{-1} and forms a diacetate (**5**), $C_{25}H_{36}O_5$, mp 95—96 °C, the IR spectrum of which still shows the presence of a hydroxyl group at 3560 cm^{-1}. The ^1H NMR spectrum of **5** shows signals due to three methyl groups attached to quaternary carbon atoms at δ 0.80, 0.87, and 0.89 (3H each, s), one methyl group on an oxygenated carbon atom at δ 1.25 (3H, s), two acetoxyl groups at δ 2.28 and 2.34 (3H each, s), one benzyl methylene group at δ 2.61 and 2.68 (1H each, dd, J=15 and 5 Hz), and one 1,2,4-trisubstituted benzene ring at δ 6.90 (1H, dd, J=9 and 2 Hz), 6.96 (1H, d, J=9 Hz), and 7.12 (1H, d, J=2 Hz). In addition, the ^{13}C NMR data of **4**, as summarized in Fig. 1, indicate the presence of five methylene groups, two methine groups, one oxygen-bearing tertiary carbon atom, and two quaternary carbon atoms.

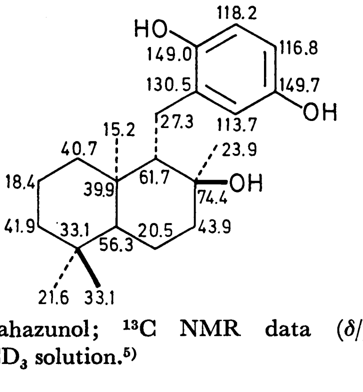
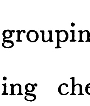
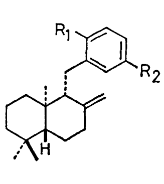


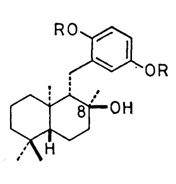
Fig. 1. Yahazunol; ^{13}C NMR data (δ/ppm) for CD_3COCD_3 solution.[5]

These facts suggest that **4** has a structure analogous to that of zonarol (**1**), in which the exocyclic methylene of **1** is displaced by a grouping  $>C(OH)CH_3$. This was confirmed by the following chemical correlation of **4** with **1**. The methylation of **1** with CH_3I-K_2CO_3 gave a dimethyl ether (**6**), $C_{23}H_{34}O_2$, mp 74—74.5 °C. The epoxidation of **6** with *m*-$ClC_6H_4CO_3H$ and the reduction of the resulting epoxide (**7**) with $LiAlH_4$ afforded a tertiary alcohol (**8**), which was found to be identical with the compound derived from **4** by the treatment with CH_3I-K_2CO_3.

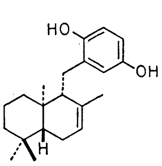
These correlation reactions also define the configuration at C-8 of **4**. The epoxidation of **6** should occur predominantly on the sterically less crowded β-side and, hence, the C-8 hydroxyl group of **4** is β-oriented. Therefore, yahazunol must be represented by the structure **4**.



1 $R_1 = R_2 = OH$
3 $R_1 = OH,\ R_2 = COOH$
6 $R_1 = R_2 = OCH_3$



4 R = H
5 R = Ac
8 $R = CH_3$



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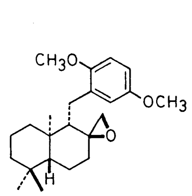

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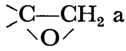
Experimental

All mp's are uncorrected. The IR spectra were recorded on a JASCO model IRA-1 spectrophotometer. The ^1H NMR spectra were determined using a JEOL PS-100 spectrometer in $CDCl_3$ solutions, with TMS as an internal standard. A Union Giken apparatus, model PM-101 was used for the measurement of the rotations.

Isolation. Fresh alga (4.3 kg), collected in the Bay of Tosa in May 1977, was chopped up and extracted with 13 liter of methanol for 10 days. The aqueous methanol solution was washed with petroleum ether, concentrated up to about 1.5 liter and extracted with dichloromethane. The dichloromethane layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue (27.9 g) was subjected to repeated chromatography over silicic acid. The fractions eluted with benzene–ether (19: 1) gave zonarol (**1**)[6] (1.49 g), needles (from ether–petroleum ether), mp 173.5—174.5 °C, $[\alpha]_D^{27}$ $+18°$ (c 0.10, $CHCl_3$), isozonarol (**2**)[6] (322 mg), spherulites (from benzene), mp 116—117 °C, $[\alpha]_D^{27}$ $+30°$ (c 0.10, $CHCl_3$), and zonaroic acid (**3**)[6] (1.28 g), needles (from aqueous methanol), mp 108—109 °C, $[\alpha]_D^{27}$ $+32°$ (c 0.10, $CHCl_3$). The fractions eluted with benzene–ether (9: 1) yielded yahazunol (**4**) (343 mg), needles (from acetone–ether), mp 127—129 °C, $[\alpha]_D^{27}$ $-12°$ (c 0.10, $CHCl_3$); IR (KBr) 3400, 3280, 1625, 1507, and 1240 cm^{-1}. Found: C, 76.07; H, 9.82%. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70%.

Acetylation of ***4***. A solution of **4** (50 mg) in acetic anhydride (0.5 ml) and pyridine (0.5 ml) was allowed to stand at room temperature overnight and then worked up in the usual way to give a diacetate (**5**) (39 mg), needles (from ether–petroleum ether), mp 95—96 °C; IR (Nujol) 3560, 1760, 1745, and 1250 cm^{-1}. Found: C, 72.27; H, 8.94%. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71%.

Methylation of ***1***. To a solution of **1** (1 g) in dry acetone (10 ml) were added methyl iodide (5 ml) and anhydrous K_2CO_3 (5 g). The mixture was refluxed for 8 h, diluted with water, and extracted with ether. The ether layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. The resulting gum was subjected to chromatography over silicic acid with benzene as solvent to give a dimethyl ether (**6**) (415 mg), needles (from methanol), mp 74—74.5 °C; IR (Nujol) 3080, 1645, and 890 cm^{-1}; ^1H NMR δ 3.74 and 3.80 (3H each, s). Found: C, 80.64; H, 10.01%. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01%.

Conversion of ***6*** *into* ***8***. A mixture of **6** (200 mg) and m-$ClC_6H_4CO_3H$ (138 mg) in dichloromethane (5 ml) was stirred at room temperature for 4 h under nitrogen atmosphere. The reaction mixture was worked up in the usual way and the resulting product was chromatographed over silicic acid with petroleum ether as solvent to give an epoxide (**7**) (110 mg). The ^1H NMR spectrum of this compound no longer showed the presence of the exocyclic methylene but the presence of a grouping  $\underset{\diagdown O \diagup}{>C—CH_2}$ at δ 2.51 and 2.62 (1H each, d, $J=6$ Hz).

To a solution of **7** (90 mg) in dry ether (4 ml) was added $LiAlH_4$ (180 mg) dissolved in dry ether (9 ml). The mixture was stirred for 2 h at room temperature, refluxed for 1 h, and then poured into ether floated on water. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was subjected to chromatography over silicic acid and subsequent elution with benzene–ether (49: 1) gave a tertiary alcohol (**8**) (42 mg), oil, $[\alpha]_D^{14}$$+4°$ (c 0.42, $CHCl_3$); IR (neat) 3480 cm^{-1}; ^1H NMR δ 1.28 (3H, s, $>C(CH_3)OH$, which was also obtained by the tratment of **4** with CH_3I–K_2CO_3 in a similar manner to that described.

We are grateful to Professor W. Fenical, University of California, for the extract of *D. undulata* and for the IR and ^1H NMR spectra of zonarol, isozonarol, and related compounds, and to Dr. S. de Stefano, Consiglio Nazionale Delle Ricerche, Italy, for a sample of zonaroic acid. We also thank Dr. M. Taniguchi, Osaka City University, for carrying out the antimicrobial activity test.

References

1) W. Fenical, J. J. Sims, D. Squatrito, R. M. Wing, and P. Radlick, *J. Org. Chem.*, **38**, 2383 (1973).

2) W. Fenical and O. McConnell, *Experientia*, **31**, 1004 (1975).

3) G. Cimino, S. de Stefano, W. Fenical, L. Minale, and J. J. Sims, *Experientia*, **31**, 1250 (1975).

4) The results of antimicrobial activity test will be givn in detail elsewhere.

5) The ^{13}C NMR spectrum was recorded at the UCSD NMR Facility, supported by the National Institutes of Health (RR-0708). Assignments are attributed to Dr. D. J. Faulkner, University of California, to whom we are grateful.

6) These compounds are described as noncrystalline gums in the literature. See Refs. 1 and 3.