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THE ACID-CATALYZED REARRANGEMENT AND ABSOLUTE STEREOCHEMISTRY OF ISOSPONGIAQUINONE

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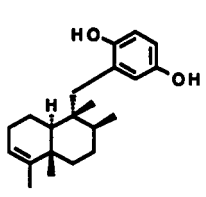
ABSTRACT.—Chemical correlation has confirmed the marine natural product isospongiaquinone [**3**] to be the endocyclic double bond isomer of ilimaquinone [**2**]. Acid-catalyzed cyclization of both **3** and **2** yielded a common product **4** formed via phenolic addition to an isolable tetrasubstituted olefinic intermediate **6**.

Secondary metabolites derived from mixed sesquiterpene and hydroquinone (quinone) biosynthesis represent a class of natural products common to marine brown algae (Phaeophyta) and sponges (Porifera). Of the several dozen known examples (1–3), particular attention has recently been directed towards the sponge metabolite avarol [**1**] due to its reported activity against HIV (4).

Although it is well documented that the absolute stereochemistry of potential drugs can be crucial to their mode of action in the "chiral environment" of living organisms, a degree of confusion exists in the assignment of such stereochemistries to sesquiterpene hydroquinones isolated from sponges. Historically this has arisen due to the fact that two of the earliest known examples, avarol [**1**] (5,6) and ilimaquinone [**2**] (7), were initially incorrectly assigned opposite absolute stereochemistries. Furthermore, the majority of "new" examples of this structure class were subsequently correlated (frequently with no chemical basis) (8) to ilimaquinone **2**. This was particularly unfortunate inasmuch as the absolute stereochemistry for ilimaquinone [**2**] was recently shown (8) to be misassigned and was revised to be the same as that for avarol [**1**]. This report extends these stereochemical investigations to include assignment of a complete absolute stereostructure to the marine natural product isospongiaquinone [**3**] (9). In doing so it also examines the acid-catalyzed rearrangement of sesquiterpene hydroquinones to give cyclic products.

Treatment of isospongiaquinone [**3**] under reflux for 2 h in MeOH-HOAc-HCl (1:1:1) followed by concentration under reduced pressure yielded two products, **4** and **5**. The more polar red product **5** proved to be the demethylated analogue of the yellow product **4**, and the two were readily interconverted by methylation of **5** with CH_2N_2. Products **4** and **5** had previously been reported by earlier workers, but their structures had not been rigorously established (9).

Milder treatment (80° for 2 h) of isospongiaquinone [**3**] with this same acid mixture, followed by methylation of the crude product with CH_2N_2 prior to chromatography, yielded the yellow cyclized product **4** together with a rearranged $\Delta^{5,10}$ analogue **6**. Spectroscopic analysis of **6** confirmed the absence of a



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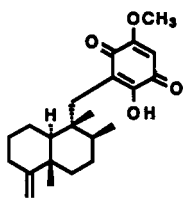

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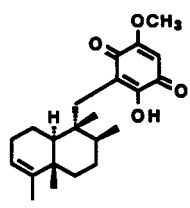

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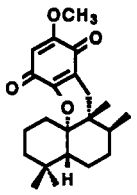

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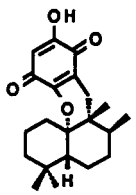

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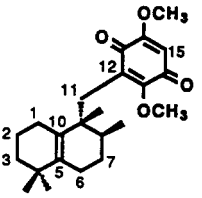

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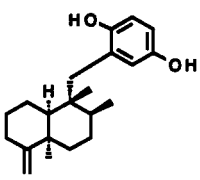
trisubstituted double bond complete with olefinic methyl and the appearance of a geminal dimethyl moiety together with a tetrasubstituted double bond. These features were consistent with migration of the C-5 methyl to C-4 and the incorporation of a $\Delta^{5,10}$ functionality. Such rearrangements are known to occur in systems of this type (5,6,8,10). Spectroscopic correlation with related compounds (8,10) supported the assigned structure. Speculation that the unmethylated precursor to **6** was an intermediate to the cyclized products was confirmed when prolonged treatment of **6** with the acid mixture described above was shown to return after methylation a quantitative yield of **4**. These conditions apparently first promote demethylation to return the unmethylated $\Delta^{5,10}$ intermediate, then facilitate the cyclization process. Given the intermediacy of a $\Delta^{5,10}$ analogue in the cyclization of **3** to give **4**, steric considerations would suggest that phenolic attack occurs only at C-10, not C-5. An nOe (10%) observed for the benzylic proton at δ 2.57 in **4**, on irradiation of the 8-Me, supports this proposal. Thus **4** and **5** must possess the cyclic structures as shown.

Treatment of an authentic sample of ilimaquinone [**2**] under the same mild acid conditions as described above followed by methylation with CH_2N_2 resulted in an identical result. Compounds **4** and **6** prepared from **2** exhibited the same [α]D's as those prepared from **3**. Thus isospongiaquinone [**3**] must possess the same absolute stereochemistry as ilimaquinone [**2**].

To address the possibility that the acidic conditions may have affected other stereocenters in the transformation of **2** and **3** to **4** and **6**, the reaction of **3** was repeated in deuterated solvents (CD_3OD, acetic acid-d_4, DCl). The deuterated analogue of **4** prepared in this manner displayed a ^{13}C-nmr spectrum in which resonances for C-3, C-5, and C-15 were suppressed and the signal for the axial C-4 methyl substantially reduced in intensity. These observations are consistent with the incorporation of deuterium at these centers, as would be expected, but at no other sites. Similarly the deuterated analogue of **6** displayed a ^{13}C-nmr spectrum in which the C-3 and C-15 resonances were suppressed and the axial C-4 methyl was reduced in intensity. Thus the stereochemistry about C-8 and C-9 in **4** and **6** remains unaltered, while that at C-5 and C-10 in **4** is determined by the geometry of addition to the $\Delta^{5,10}$ in **6**.

Acid treatment (*p*-TsOH, C_6H_6, reflux) of the sesquiterpene hydroquinol arenarol [**7**], which occurs naturally with the hydroquinone arenarone [**8**]



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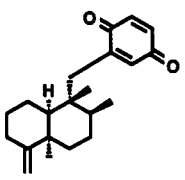

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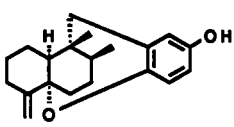

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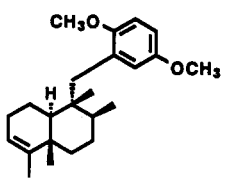
(11), has been reported (11) to yield a cyclic product that was tentatively identified as **9**. (Structures for arenarol [**7**], arenarone [**8**], the proposed acid-catalyzed cyclization product **9**, and the revised structure **14** are arbitrarily represented with an absolute stereochemistry consistent with those of avarol [**1**], ilimaquinone [**2**], isospongiaquinone [**3**], and aureol [**13**].) Although these workers did not identify a tetrasubstituted olefinic intermediate analogous to **6**, it is worth noting that mild acid treatment HOAc, HCl, room temperature) of avarol dimethyl ether [**10**] has been reported (3) to yield the rearrangement product **11**. Therefore, it is not unreasonable to assume that acid-catalyzed cyclization of arenarol [**7**] proceeds via the tetrasubstituted olefinic intermediate **12**. Compound **12** has previously been recorded (12) as a BF_3·etherate degradation product of aureol [**13**]. In light of these observations a more acceptable structure for the acid-catalyzed cyclization product of arenarol [**7**] would be **14**. Confirmation of the revised structure **14** has been independently secured by X-ray analysis.[1]

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H-nmr and ^{13}C-nmr spectra were recorded on a JEOL JNM GX-400 spectrometer in the solvent indicated and referenced to TMS (δ 0.0). Low and high resolution ei (70 eV) mass spectra were recorded on a Micromass 7070F instrument. Optical rotations were recorded on a Perkin Elmer 241 MC polarimeter.

ACID REARRANGEMENT OF **3** (First Procedure).—An authentic sample of isospongiaquinone [**3**] was provided by Dr. R.J. Wells, and this compound was also isolated in our laboratories from an unidentified sponge. Gentle reflux of a solution of isospongiaquinone [**3**] (20 mg) in MeOH-HOAc-HCl (1:1:1) (2 ml) for 2 h, followed by concentration under reduced pressure, resulted in quantitative conversion to **4** and **5** in a ratio of 1:1. Separation of the two components was achieved by normal phase hplc (elution with 20% EtOAc in hexane through an RCM-100 5 μm silica cartridge) to yield, in order of polarity, **4** and **5**.

Compound **4**.—A pale yellow solid: $[\alpha]_D$ −75.6° (c = 0.16, $CHCl_3$); ^{1}H nmr ($CDCl_3$) 0.77 (d, J = 6 Hz, 8-Me), 0.94, 0.96, 1.17 (3s, 4-, 4-, 9-Me), 2.00 (½ ABq, J = 20 Hz, H-11), 2.57 (½ ABq, J = 20 Hz, H-11), 3.81 (s, OMe), 5.74 (s, H-15); ^{13}C nmr ($CDCl_3$) 16.4 (q), 16.9 (q), 17.8 (t), 21.9 (t), 22.2 (q), 26.7 (t), 29.4 (t), 30.3 (t), 32.4 (d), 32.5 (q), 33.5 (s), 37.2 (s), 41.7 (t), 45.6 (d), 56.4 (q), 86.4 (s), 104.9 (d), 115.2 (s), 152.7 (s), 159.5 (s), 181.4 (s), 181.5 (s); ms m/z $[M]^+$ 358.2141 (12%) ($C_{22}H_{30}O_4$ requires 358.2144), 330 (27), 191 (100), 177 (83), 175 (23), 170 (53).



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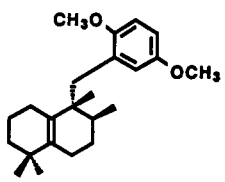

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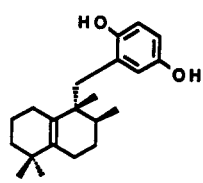

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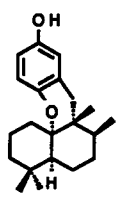

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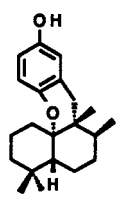

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[1]Personal communication from Prof. F.J. Schmitz.

Compound **5**.—A red oil: $[\alpha]_D$ −64.3° (c = 0.7, $CHCl_3$); ^1H nmr as for **4** except for the absence of the OMe resonance at δ 3.81 and a shift of the H-15 from δ 5.74 to 5.90. Treatment with an ethereal solution of CH_2N_2 resulted in the quantitative conversion of **5** to **4**.

ACID REARRANGEMENT OF **3** (Second Procedure).—Treatment of a sample of isospongiaquinone **3** (20 mg) in MeOH-HOAc-HCl (1:1:1) (2 ml) at 80° for 2 h, followed by concentration under reduced pressure and methylation with an ethereal solution of CH_2N_2, resulted in a quantitative yield of **4** together with the $\Delta^{5,10}$ analogue **6**. The 1:2 mixture of **4** and **6** was resolved by normal phase hplc (elution with 10% EtOAc in hexane through an RCM-100 5 μm silica cartridge, compound **6** eluting before **4**).

Compound **6**.—A bright yellow oil: $[\alpha]_D$ +2.4° (c = 0.9, $CHCl_3$); ^1H nmr ($CDCl_3$) 0.77 (d, J = 6 Hz, 8-Me), 0.79, 0.96, 1.01 (3 s, 4-, 4-, 9-Me), 2.55 (½ ABq, J = 10 Hz, H-11), 2.72 (½ ABq, J = 10 Hz, H-11), 3.80 (b s, OMe), 4.04 (b s, OMe), 5.74 (s, H-15); ^{13}C nmr ($CDCl_3$) 15.4 (q), 20.0 (t), 20.7 (t), 22.0 (q), 25.7 (t), 26.5 (t), 28.0 (q), 29.0 (q), 32.2 (t), 34.3 (d), 34.3 (s), 39.9 (t), 42.6 (s), 56.4 (q), 61.0 (q), 105.3 (d), 129.1 (s), 131.3 (s), 135.0 (s), 157.1 (s), 159.0 (s), 182.9 (s), 183.5 (s); ms *m/z* $[M]^+$ 372.2300 (<1%) ($C_{23}H_{32}O_4$ requires 372.2300), 356 (1), 340 (1), 325 (1), 311 (1), 191 (100).

ACID REARRANGEMENT OF **2** (Second Procedure).—Treatment of an authentic sample of ilimaquinone **2** (10 mg) in the manner described above for **3** gave an identical result.

ACKNOWLEDGMENTS

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