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AVAROL, A NOVEL SESQUITERPENOID HYDROQUINONE WITH A REARRANGED DRIMANE SKELETON FROM THE SPONGE DISIDEA AVARA

L. Minale*, R. Riccio and G. Sodano
Laboratorio per la Chimica delle molecole di interesse biologico del C.N.R.
via Toiano 2, Arco Felice, Napoli, Italy

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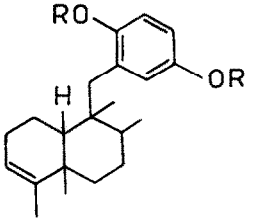
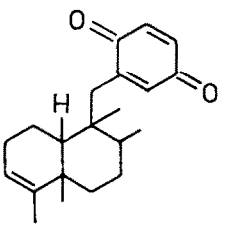
Marine sponges were previously shown to be sources of compounds of mixed biogenesis originating partly from mevalonate and partly from a benzenoid precursor. 2-Polyprenylbenzoquinones and the corresponding quinols were found in Ircinia sp.[1], while Halichondria panicea[2] yielded a group of C_{21} hydroquinones, the paniceins[2], including in their structures an aromatic sesquiterpenoid moiety.

We have now isolated from solvent extracts of the sponge Disidea avara a further C_{21} hydroquinone, avarol (1; 6% dry weigth), possessing a rearranged drimane skeleton, accompained by minor amounts of the corresponding quinone, avarone (2; 0.8%).



1, R=H
3, R=Ac
4, R=Me



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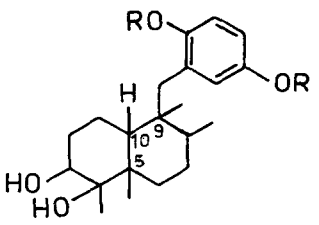
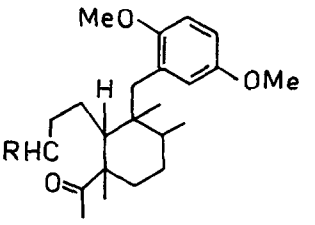
Avarol (1), m.p. 148-150° ($CHCl_3$), $[\alpha]_D$ +6.1°, M^+ 314.2243 (calcd. 314.2245), $C_{21}H_{30}O_2$, was recognized as a monosubstituted hydroquinone by u.v. (λ_{max} 298 nm, ϵ 3900), n.m.r. (three aromatic protons at δ 6.62 as a complex band) and its eventual conversion on Ag_2O oxidation to the corresponding quinone, oil, λ_{max} 246, 315 and 440 (ϵ 12300; 750; 30), ν_{max} 2920, 1660 and 1600 cm^{-1}, which was identical to

avarone (2). Avarol (1) contains two tertiary methyls (δ 0.84 and 1.02 p.p.m.), one secondary methyl (δ 1.00, J 6 Hz), one vinyl methyl (δ 1.50), a benzylic methylene linked to a quaternary carbon atom (AB quartet at δ 2.64, J 14 Hz) and an olefinic hydrogen (δ 5.09, m). It formed a diacetate (3), m.p. 91-93°, M^+398, a dimethyl ether (4; dimethylsulfate-NaOH), m.p. 80-81°, M^+ 342 and, on hydrogenation on Pd-C at room temp. and pressure, gave a dihydroderivative, m.p. 151-153°, M^+ 316. The diacetate 3 on hydroboration-oxidation gave a ketone, m.p. 201-213°, M^+ 414, whose i.r. at 1706 cm^{-1} placed the ketonic group in a six-membered ring.

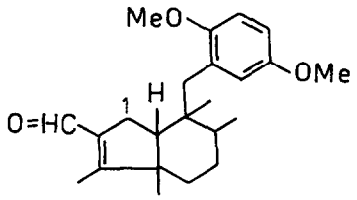
Osmilation of the dimethyl ether 4 and cleavage with lead tetraacetate of the diol 5 (possibly a single diastereoisomer, m.p. 138-140°, $[\alpha]_D$ -15.7°, M^+ 376) gave the ketoaldehyde 7, oil, $[\alpha]_D$ -54°, M^+ 374, ν_{max} 2710, 1725 and 1695 cm^{-1}, δ C<u>H</u>=O 9.66.



5, R=Me
6, R=Ac



7, R=O
8, R= 



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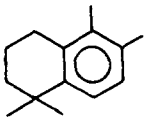

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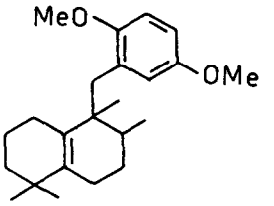

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Selective hydrogenation (CH_3CO_2H, 5% Pt-C, room temp. and pressure, 18 h) of the aldehyde group afforded the oily hydroxyketone 8, M^+ 376, ν_{max} 3600-3300 cm^{-1}, the base-catalyzed deuteration of which lead to the exchange of three protons, thus indicating the quaternary nature of the carbon attached to the methylketone grouping. The ketoaldehyde 7 was cyclized (dry benzene/CH_3CO_2H/piperidine, 60°, 1 h) to the cyclopentenaldehyde 9, oil, $[\alpha]_D$ -186.5°, λ_{max} 225, 256, 291 (ε 8760, 10340, 3670) nm, ν_{max} 2700, 1660 cm^{-1}, M^+ 356, in the n.m.r. spectrum of which an AB portion of an ABX system [double-doublet of one proton at δ 2.80 with J of 13 Hz and 6 Hz and a broadened triplet one proton at δ 2.18 with J of 13 Hz, converted into an AB quartet with J of 13 Hz on irradiation at δ 1.60] was assig-

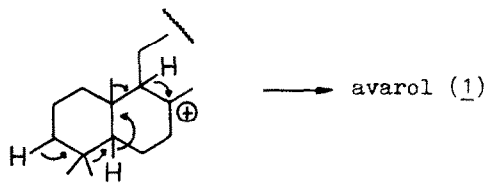
ned to protons in position 1 and confirmed that C-10 is tertiary and C-5 quaternary. A study of Eu(fod)$_3$induced shifts of the methyl resonances of the diol 6, m.p. 118-120°, M^+ 432, confirmed the presence at C-5 of a tertiary methyl. Addition of 0.1-0.4 moles of Eu(fod)$_3$ per mole of 6 caused downfield shifts, which were approximatively linear with respect to concentration of Eu(fod)$_3$. The largest shift was observed, of course, for the CH_3-C-OH protons; the next biggest shift is that of one tert-Me (C-5 Me); the Ar-CH_2 protons move about the same p.p.m. as the second tert-Me (C-9 Me), while the sec-Me is more slightly shifted. Dehydrogenation with 10% Pd-C (270°, 18 h) of avarol (1) afforded 1,2,5,6-tetramethylnaftalene and 1,2,5-trimethylnaftalene, isolated by g.l.c. and identified by comparison with authetics[3,4], along with major amounts of the tetralin 10, M^+ 188, λ_{max} 220, 266, 273 (ε 4550, 516, 446) nm, δ 6.98 (2H, ABq, J 8Hz, Ar-H) 2.62 (2H, t, J 6 Hz, Ar-CH_2), 2.20 (3H, s, Ar-CH_3), 2.09 (3H, s, Ar-CH_3), 1.70 (4H, m, CH_2), 1.24 (6H, s, tert-Me's) p.p.m.. The formation of the tetralin 10 on dehydrogenation of avarol (1) no doubt results from methyl group migration from C-5 to C-4 in view of the position of the double bond[5].

This results together with the evidence given above requires that avarol have the constitution 1. In confirmation, treatment of dimethylether 4 with acid (CH_3CO_2H-HCl conc., 4:1, room temp., 6 h), gave, in a quantitative yield, the tetrasubstituted olefin 11, m.p. 58-60°, M^+ 342, which showed three tert-Me's and one secondary at δ 1.00 (6H, s), 0.90 (3H, s) and δ 0.76 (3H, d, J 6Hz) and significantly no olefinic proton signals; the Ar-CH_2 protons resonate as ABq (J 14 Hz) at δ 2.62 and integration of the appropriate region (δ 2.2÷1.8) demonstrate that there are four allylic protons, thus confirming the quaternary nature of C-9 in avarol (1). In addition the doublet at δ 0.76 (sec-Me) was transformed into a singlet on irradiation at δ 1.60. Analogous acid-catalyzed rearrangements have been already encountered in friedel-3-ene[6]and in some diterpenoids[7].

Avarol (1) represent the first sesquiterpenoid with a rearranged drimane skeleton although a closely related structure has been proposed for Kamalone and Kamalol, sesquiterpenoid coumarins of Ferula penninervis, on appliyng the principles of the biogenetic theory[8].

Avarol (1) can be conceived as derivable from farnesylpyrophosfate by cyclization to an intermediate cation (12) involving drimane skeleton, followed by a 'friedo' rearrangment and finally deprotonation. Interestingly, two C-21 hydroquinones, zonarol (13) and isozonarol, with a drimane skeleton have been recently described from a brown seaweed[9].

The stereochemistry of avarol (1) is now under examination.



avarol (1)

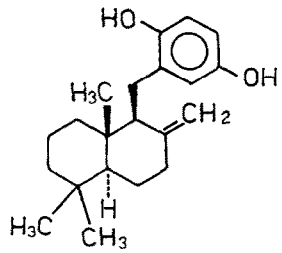


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TABLE 1.- N.m.r. data on the diol 6 before and after addition of the europium shift reagent Eu (fod-d_9)$_3$.

Signal identification	δ ($CDCl_3$)[a]	δ (Eu-$CDCl_3$)[b]	Δδ
CH_3-C-OH	1.09	7.38	6.29
CH_3 at C-5	0.95	3.60	2.65
$ArCH_2$	2.52	3.76	1.24
CH_3 at C-9	0.81	2.10	1.29
CH_3 at C-8	0.96	1.76	0.80

(a) relative to TMS in the absence of Eu (fod)$_3$.

(b) relative to TMS after the addition of 0.4 moles of Eu(fod)$_3$ per mole of 6.

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