Acta Cryst. (1994). C**50**, 830–833

Avarol, a Sesquiterpenoid Hydroquinone from *Dysidea Avara*

RAFFAELLA PULITI AND SALVATORE DE ROSA

Istituto per la Chimica di Molecole di
Interesse Biologico CNR, Via Toiano 6,
80072 Arco Felice-Napoli, Italy

CARLO ANDREA MATTIA

Dipartimento di Chimica dell'Università "Federico II"
di Napoli, Via Mezzocannone 4, 80134 Napoli, Italy

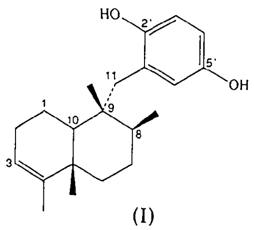
(*Received* 6 *May* 1993; *accepted* 18 *December* 1993)

Abstract

The X-ray analysis of avarol, 2-[(1,2,3,4,4a,7,8,8a-octahydro-1,2,4a,5-tetramethyl-1-naphthalenyl)methyl]-1,4-benzenediol, $C_{21}H_{30}O_2$, confirms the stereochemistry previously given on the basis of spectral measurements (De Rosa, Minale, Riccio & Sodano, 1976). In the *trans*-fused sesquiterpene system, the $\Delta^{3,4}$ cyclohexene ring has an approximate half-boat conformation and the cyclohexane has a nearly ideal chair form. The packing is governed by two intermolecular hydrogen bonds, which connect molecules in helical chains. In the crystal, the arrangement of avarol molecules forms a cylindrical channel around the 6_1 axis, which is delimited by hydroquinone residues and holds disordered water solvent molecules.

Comment

Avarol, (I), a sesquiterpene hydroquinone, and its quinone, avarone, are the main secondary metabolites of the marine sponge *Dysidea avara*. They were the first isolated natural sesquiterpenoids with a rearranged drimane skeleton (Minale, Riccio & Sodano, 1974). The current interest in the avarol–avarone pair, as well as their natural and synthetic derivatives, is stimulated by the wide variety of recently reported biological activities (*e.g.* antileukaemic, citotoxic, antimutagenic) (Müller, Sobel, Diehl-Seifert, Maidhof & Schröder, 1987; De Giulio, De Rosa, Di Vincenzo & Strazzullo, 1990). The crystal structure determination of (I) forms part of a program of studies (Puliti, Gavagnin, Cimino, Mattia & Mazzarella, 1992; Cimino, Crispino, Epifanio, Madaio, Mattia, Mazzarella, Puliti, Trivellone & Uriz, 1992; Puliti, Fontana, Cimino, Mattia & Mazzarella, 1993) of the structural features of unusual terpenoid metabolites, in connection with their biological activities and pharmacological implications.



(I)

A perspective view of the final X-ray model of avarol is shown in Fig. 1. The present structure is in total agreement with the previously reported structure and stereochemistry (De Rosa, Minale, Riccio & Sodano, 1976) established on the basis of circular dichroism and NMR data, including the S^* stereochemistry at C8, which has been questioned by Djura, Stierle, Sullivan, Faulkner, Arnold & Clardy (1980), and afterwards confirmed by means of stereocontrolled total synthesis of (±)-avarol (Sarma & Chattopadhyay, 1982) as well as by the crystal structure determination of avarol dimethyl ether (Giordano & Puliti, 1987).

The general trend of the molecular geometry reflects the presence of some 1–4 intramolecular short contacts deriving from the five bulky groups (four methyls and one methylene hydroquinone), which are linked to the *trans*-fused system. The atomic crowding induces significant distortions in the

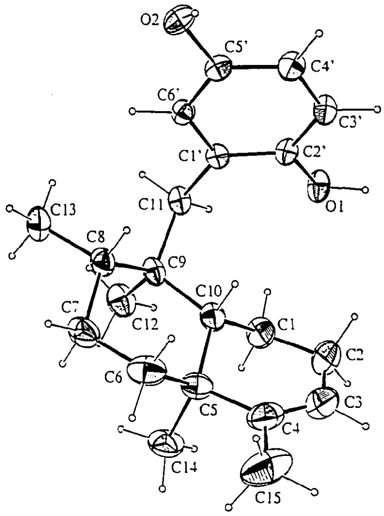


Fig. 1. Perspective view of the avarol molecule with the atomic numbering scheme for non-H atoms. Displacement ellipsoids are at the 30% probability level.

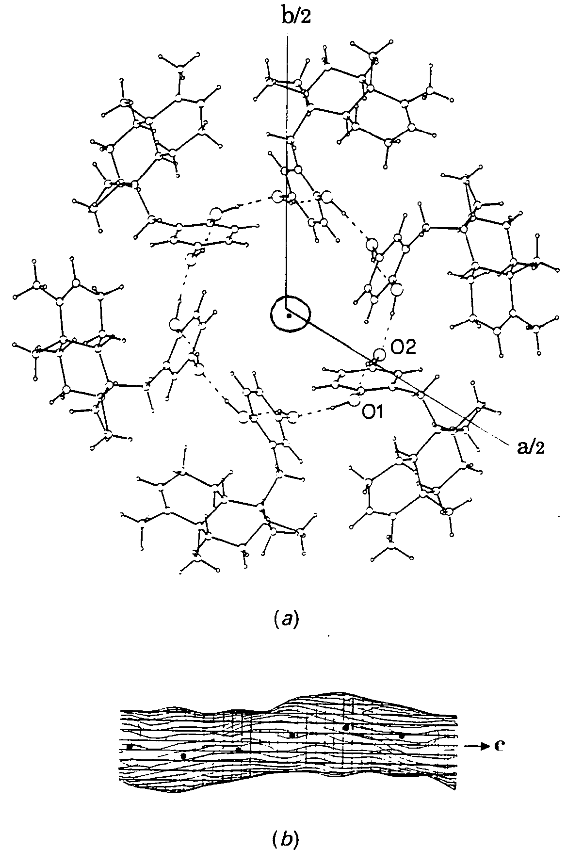
Acta Crystallographica Section C
ISSN 0108-2701 ©1994

bicyclic skeleton, with respect to normal tetrahedral values. In particular, the angles C5—C10—C9 [117.6 (3)°], C10—C5—C14 [115.7 (4)°] and C9—C8—C13 [113.7 (4)°] are increased. Likewise, the endocyclic bond distances, involving the atomic sequence C5, C10, C9 and C8, reach values longer than 1.550 Å and the C4—C5 (sp^2—sp^3) bond increases to 1.538 (6) Å. Furthermore; the large values of the angle C9—C11—C1′ and the distances at C11 partially release the steric strain between the sesquiterpene and hydroquinone fragments, which are connected through the equatorial C11 methylene bridge. The shortest contacts between these residues are O1···C1 3.152 (5) and C8···C6′ 3.243 (5) Å.

On the whole, the molecular geometry compares well to that of the avarol dimethyl derivative (Giordano & Puliti, 1987); the deviations from the expected values are consistent in the two structures. In both molecules, the hydroquinone ring is nearly perpendicular to the sesquiterpene residue [in avarol the angle between the average planes pertinent to the two moieties is 101.2 (1)°] and the torsion angles, around C9—C11 and C11—C1′, optimize the intramolecular interactions.

The conformation of the cyclohexene ring, which has the double bond in the 3,4 position, closely approximates a half-boat form with the apex at C10 and puckering parameters (Cremer & Pople, 1975) $Q = 0.539$ (4) Å, $\theta = 49.6$ (4), $\varphi = 5.7$ (5)°, for the atomic sequence C10, C1–C5. In this ring, C10 deviates by 0.679 (3) Å on one side and C1 by only 0.092 (4) Å on the other, with respect to the average plane through the remaining intracycle atoms. The cyclohexane exhibits an almost ideal chair form, with C5 and C8 displaced 0.634 (4) and 0.620 (3) Å, respectively, from the best plane defined by C6, C7, C9 and C10. The puckering parameters are $Q =$ 0.553 (3) Å, $q_2 = 0.087$ (3) Å, $\theta = 9.1$ (3), $\varphi = 30$ (2)°, for the atomic sequence C6, C7–C10, C5. The deviation from the ideal C_2 symmetry is essentially toward a twist form and can be quantified by ΔC_2 C6—C7 = 2.3 (6)° (Duax, Weeks & Rohrer, 1976). The hydroquinone ring is planar to within 0.025 (3) Å and the 2′,5′-hydroxyl O atoms are 0.139 (2) and 0.061 (2) Å, respectively, out of the best ring plane (on the same side).

The avarol molecules assemble in the crystal (Fig. 2*a*) leaving a cylindrically shaped hole of diameter *ca* 7 Å around the 6_1 axis, delimited by the hydroquinone residues, which holds disordered solvent in a central twisted channel (Fig. 2*b* and experimental details). Each OH group is engaged, as donor and acceptor, in two intermolecular hydrogen bonds: O1—H···O2′ = 2.751 (3), O2—H···O1$^{\text{ii}}$ = 2.720 (3) Å, O1—H···O2 = 169 and O2—H···O1 = 150°; symmetry code: (i) $y, y - x, \frac{5}{6} + z$; (ii) $x, y, z - 1$. Thus, the crystal packing is governed by a hydrogen-bonding network which links the molecules in helical chains along the *c* direction, while in the *ab* plane, only weak van der Waals interactions (≥ 3.76 Å) occur between the sesquiterpene residues.



(*a*)

(*b*)

Fig. 2. (*a*) Crystal packing projected in the *ab* plane; dashed lines indicate hydrogen bonds. A section of residual electron density, contoured at 0.45 e Å^{-3} (shaded area), is also represented. (*b*) View in the perpendicular direction of the residual solvent density at the same contour level. In both (*a*) and (*b*), filled circles indicate the 'ordered' solvent atoms.

Experimental

Crystal data

$C_{21}H_{30}O_2$
$M_r = 314.47$
Hexagonal
$P6_1$
$a = 21.938$ (4) Å
$c = 6.870$ (1) Å
$V = 2864$ (1) Å^3
$Z = 6$
$D_x = 1.094$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 24 reflections
$\theta = 20$-$25°$
$\mu = 0.497$ mm^{-1}
$T = 293$ K
Prisms
0.32 × 0.14 × 0.12 mm
Colourless
Crystal source: slow evaporation from chloroform

Data collection

Enraf-Nonius CAD-4F diffractometer
ω-2θ scans
Absorption correction: none
2139 measured reflections
2139 independent reflections
1730 observed reflections $[I \geq 2.5\sigma(I)]$
$\theta_{\max} = 75°$
$h = 0 \rightarrow 27$
$k = 0 \rightarrow 27$
$l = 0 \rightarrow 8$
3 standard reflections frequency: 240 min intensity variation: 4%

Refinement

Refinement on F
$R = 0.044$
$wR = 0.043$
$S = 0.79$
1730 reflections
208 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o) + (0.01F_o)^2 + 0.3]$
$(\Delta/\sigma)_{\max} = 0.01$
$\Delta\rho_{\max} = 0.15$ e Å^{-3}
$\Delta\rho_{\min} = -0.14$ e Å^{-3}
Extinction correction: Stout & Jensen (1968)
Extinction coefficient: $1.69(8) \times 10^{-6}$
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$$B_{eq} = (1/3)\Sigma_i\Sigma_j B_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}
O1	0.1548 (1)	−0.0913 (1)	0.000	4.38 (5)
O2	0.2096 (1)	0.0184 (1)	−0.7454 (3)	4.42 (5)
C1	0.2537 (2)	−0.1537 (2)	0.0887 (6)	5.98 (9)
C2	0.1870 (2)	−0.2259 (2)	0.0842 (8)	8.6 (1)
C3	0.1900 (2)	−0.2758 (2)	−0.0572 (9)	8.7 (1)
C4	0.2409 (2)	−0.2601 (2)	−0.1839 (8)	6.8 (1)
C5	0.3065 (2)	−0.1862 (2)	−0.1894 (6)	5.15 (8)
C6	0.3342 (2)	−0.1671 (2)	−0.3985 (6)	6.15 (9)
C7	0.3933 (2)	−0.0916 (2)	−0.4118 (6)	5.80 (8)
C8	0.3689 (1)	−0.0403 (1)	−0.3555 (5)	4.23 (7)
C9	0.3380 (1)	−0.0530 (1)	−0.1453 (5)	3.76 (6)
C10	0.2843 (1)	−0.1330 (1)	−0.1184 (5)	4.24 (7)
C11	0.2995 (1)	−0.0098 (1)	−0.1164 (5)	3.81 (7)
C12	0.3969 (2)	−0.0246 (2)	0.0096 (6)	5.94 (9)
C13	0.4281 (2)	0.0356 (2)	−0.3920 (7)	6.1 (1)
C14	0.3629 (2)	−0.1908 (2)	−0.0632 (7)	7.0 (1)
C15	0.2371 (3)	−0.3155 (2)	−0.3225 (9)	11.1 (2)
C1′	0.2380 (1)	−0.0263 (1)	−0.2490 (5)	3.21 (6)
C2′	0.1687 (1)	−0.0680 (1)	−0.1926 (4)	3.40 (6)
C3′	0.1129 (1)	−0.0847 (1)	−0.3182 (5)	3.97 (7)
C4′	0.1264 (1)	−0.0571 (1)	−0.5060 (5)	4.11 (7)
C5′	0.1949 (1)	−0.0131 (1)	−0.5612 (4)	3.46 (6)
C6′	0.2497 (1)	0.0029 (1)	−0.4361 (5)	3.35 (6)
HO1	0.1072	−0.1289	0.0149	4.4
HO2	0.1838	−0.0106	−0.8518	4.4

Table 2. *Selected geometric parameters* (Å, °)

O1—C2′	1.396 (4)	C8—C9	1.560 (5)
O2—C5′	1.400 (4)	C8—C13	1.535 (5)
C1—C2	1.528 (7)	C9—C10	1.559 (5)
C1—C10	1.541 (6)	C9—C11	1.568 (5)
C2—C3	1.490 (9)	C9—C12	1.544 (5)
C3—C4	1.318 (8)	C11—C1′	1.513 (5)
C4—C5	1.538 (6)	C1′—C2′	1.381 (4)
C4—C15	1.514 (8)	C1′—C6′	1.401 (5)
C5—C6	1.535 (7)	C2′—C3′	1.389 (5)
C5—C10	1.553 (6)	C3′—C4′	1.393 (6)
C5—C14	1.553 (6)	C4′—C5′	1.372 (5)
C6—C7	1.511 (7)	C5′—C6′	1.373 (5)
C7—C8	1.521 (5)		
C2—C1—C10	109.7 (4)	C10—C9—C11	109.4 (3)
C1—C2—C3	113.8 (5)	C10—C9—C12	112.5 (3)
C2—C3—C4	125.6 (5)	C11—C9—C12	105.3 (3)
C3—C4—C5	121.1 (5)	C1—C10—C5	108.7 (4)
C3—C4—C15	120.4 (6)	C1—C10—C9	114.5 (4)
C5—C4—C15	118.5 (6)	C5—C10—C9	117.6 (3)
C4—C5—C6	110.2 (4)	C9—C11—C1′	117.7 (3)
C4—C5—C10	107.7 (4)	C11—C1′—C2′	122.9 (3)
C4—C5—C14	105.9 (4)	C11—C1′—C6′	120.4 (3)
C6—C5—C10	108.5 (3)	C2′—C1′—C6′	116.7 (3)
C6—C5—C14	108.7 (4)	O1—C2′—C1′	118.4 (3)
C10—C5—C14	115.7 (4)	O1—C2′—C3′	119.3 (3)
C5—C6—C7	111.2 (4)	C1′—C2′—C3′	122.3 (3)
C6—C7—C8	111.6 (3)	C2′—C3′—C4′	119.6 (3)
C7—C8—C9	112.6 (3)	C3′—C4′—C5′	118.8 (3)
C7—C8—C13	109.9 (3)	O2—C5′—C4′	119.9 (3)
C9—C8—C13	113.7 (4)	O2—C5′—C6′	118.8 (3)
C8—C9—C10	109.1 (3)	C4′—C5′—C6′	121.2 (3)
C8—C9—C11	109.0 (3)	C1′—C6′—C5′	121.4 (3)
C8—C9—C12	111.5 (3)		
C2—C3—C4—C5	3.4 (8)	C8—C9—C11—C1′	60.6 (3)
C4—C5—C10—C9	−169.3 (3)	C9—C11—C1′—C2′	100.1 (3)
C14—C5—C10—C9	72.5 (4)	C6′—C1′—C2′—O1	−172.6 (2)
C13—C8—C9—C12	−49.2 (4)	C3′—C4′—C5′—O2	−176.5 (2)

The structure was solved using the *MULTAN*82 package (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982). H atoms were located on the basis of geometrical considerations and difference Fourier map suggestions (for hydroxyl and methyl groups). All H atoms were included as fixed atoms in the final refinement, with isotropic displacement parameters set equal to B_{eq} of the parent atoms.

The avarol model refined to a rather high R factor (0.064) and with large e.s.d.'s for the positional parameters. A comparison between the observed and calculated factors showed remarkable differences for a few reflections with small indices. Moreover, the difference Fourier map revealed, around the 6_1 axis, a cylindrical channel of nearly continuous electron density (approximately 0.9 e Å^{-3}). This residual electron density is confined in a narrow area (within 0.6 Å of the radius value, dropping to 50%) and was ascribed to the presence of disordered solvent. In some cases, the contribution of disordered solvent to the total diffraction pattern, if properly calculated, can be as much as an 'ordered' contribution, without resorting to special procedures. In this structure, only one O atom, positioned at the centre of any channel section, is sufficient to describe satisfactorily the solvent region. The O atom was introduced in the last cycle of the refinement as a fixed atom ($x = 0.011$, $y = -0.009$, $z = -0.014$), with a low occupancy factor (0.4) and a large displacement parameter (24 Å^2). This minimum-parameter procedure yielded a considerable improvement in the final R (0.044) and local levelling in the difference Fourier map ($-0.11 \leq \rho \leq 0.13$ e Å^{-3}).

All calculations were performed using Enraf-Nonius *SDP* software (B. A. Frenz & Associates, Inc., 1985) on a MicroVAX 3100 computer.

Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71762 (13 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: NA1051]

References

B. A. Frenz & Associates, Inc. (1985). *SDP Structure Determination Package*. College Station, Texas, USA, and Enraf–Nonius, Delft, The Netherlands.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1361.

Cimino, G., Crispino, A., Epifanio, R. de A., Madaio, A., Mattia, C. A., Mazzarella, L., Puliti, R., Trivellone, E. & Uriz, M. (1992). *Tetrahedron*, **48**, 9013–9022.

De Giulio, A., De Rosa, S., Di Vincenzo, G. & Strazzullo, G. (1990). *Tetrahedron*, **46**, 7971–7976, and references therein.

De Rosa, S., Minale, L., Riccio, R. & Sodano, G. (1976). *J. Chem. Soc. Perkin Trans.* 1, pp. 1408–1414.

Djura, P., Stierle, D. B., Sullivan, B., Faulkner, D. J., Arnold, E. & Clardy, J. (1980). *J. Org. Chem.* **45**, 1435–1441.

Duax, W. L., Weeks, C. M. & Rohrer, D. C. (1976). *Top. Stereochem.* **9**, 271–383.

Giordano, F. & Puliti, R. (1987). *Acta Cryst.* C**43**, 985–988.

Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1982). *MULTAN*11/82. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

Minale, L., Riccio, R. & Sodano, G. (1974). *Tetrahedron Lett.* **38**, 3401–3404.

Müller, W. E. G., Sobel, C., Diehl-Seifert, B., Maidhof, A. & Schröder, H. C. (1987). *Biochem. Pharmacol.* **36**, 1489–1494, and references therein.

Puliti, R., Fontana, A., Cimino, G., Mattia, C. A. & Mazzarella, L. (1993). *Acta Cryst.* C**49**, 1373–1376.

Puliti, R., Gavagnin, M., Cimino, G., Mattia, C. A. & Mazzarella, L. (1992). *Acta Cryst.* C**48**, 2145–2147, and references therein.

Sarma, A. S. & Chattopadhyay, P. (1982). *J. Org. Chem.* **47**, 1727–1731.

Stout, G. H. & Jensen, L. H. (1968). In *X-ray Structure Determination*. New York: Macmillan.