Table 2. *Calculated and measured bond angles (°)*

| | Calculated | Measured |
|---|---|---|
| O1—C2—C3 | 110.63 | 110.9 (2) |
| O1—C2—C21 | 117.01 | 120.2 (2) |
| O1—C7a—C3a | 110.59 | 111.4 (2) |
| O1—C7a—C7 | 126.70 | 125.6 (3) |
| C2—O1—C7a | 106.26 | 105.4 (2) |
| C2—C3—C3a | 106.86 | 107.4 (2) |
| C2—C3—O3 | 125.45 | 129.5 (2) |
| C2—C21—O22 | 117.01 | 114.2 (2) |
| C2—C21—O21 | 119.40 | 121.6 (2) |
| C3—C2—C21 | 125.64 | 128.9 (2) |
| C3—C3a—C7a | 105.65 | 105.0 (2) |
| C3—C3a—C4 | 133.86 | 135.6 (3) |
| C3a—C3—O3 | 123.69 | 123.1 (2) |
| C3a—C7a—C7 | 122.74 | 122.9 (3) |
| C3a—C4—C5 | 117.75 | 118.2 (3) |
| C4—C3a—C7a | 120.49 | 119.4 (3) |
| C6—C7—C7a | 116.42 | 116.5 (3) |
| C4—C5—C6 | 120.83 | 121.0 (3) |
| C5—C6—C7 | 121.79 | 121.9 (3) |
| C21—O22—C23 | 120.43 | 117.1 (2) |
| O22—C21—O21 | 123.53 | 124.2 (2) |
| O22—C23—C24 | 106.57 | 107.4 (3) |

The equilibrium structures of the monomer and dimer were obtained by *ab initio* Hartree–Fock SCF methods using a double-$\zeta$ basis set of Gaussian functions (Huzinaga, 1965; Dunning, 1970). This method is known to give structures close to experiment for small molecules. All calculations were performed with the *GAMESS-UK* suite of programs (Dupuis *et al.*, 1980; Guest *et al.*, 1995). Diffraction data were collected to $2\theta_{max} = 120°$, the presence of a low-temperature device precluding collection to higher resolution.

Data collection: *DIF4* (Stoe & Cie, 1990*a*). Cell refinement: *DIF4*. Data reduction: *REDU4* (Stoe & Cie, 1990*b*). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *SHELXTL* (Sheldrick, 1995). Software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1279). Services for accessing these data are described at the back of the journal.

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# 4′-Methylaminoavarone from *Dysidea avara*†

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## Abstract

The title compound, 2-methylamino-5-[(1,2,3,4,4a,7,8,8a-octahydro-1,2,4a,5-tetramethyl-1-naphthyl)methyl]-2,5-cyclohexadiene-1,4-dione, $C_{22}H_{31}NO_2$, is a natural substance with a sesquiterpenoid-substituted quinone skeleton. As found in all structures of the avarol-avarone family, the quinone ring is almost perpendicular to the bicyclic sesquiterpene system. Some molecular parameters are outside the standard values because of bulky substituents crowding the bicyclic system. The crystal packing is characterized by rows of translated molecules interconnected through hydrogen bonds between the amino groups and O1 carbonyl atoms giving rise to alternate polar layers and van der Waals regions.

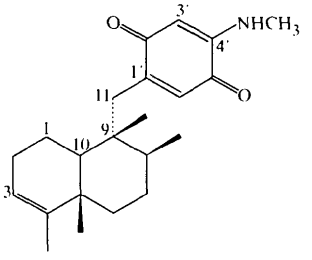

## Comment

Sponge *Dysidea avara* is a very rich source of secondary metabolites, such as the avarol-avarone pair and derivatives, with sesquiterpenoid-monosubstituted quinone (or hydroquinone) skeletons (Minale *et al.*, 1974; Cimino *et al.*, 1982; De Giulio *et al.*, 1990; Faulkner, 1997). These substances have been widely investigated because of their various biological properties, *e.g.* anti-inflammatory, antileukaemic, antimutagenic, cytotoxic

† Dedicated to the memory of Professor Luigi Minale.

‡ Associated to the National Institute for the Chemistry of Biological Systems (CNR).

(De Giulio *et al.*, 1991; Belisario *et al.*, 1996). These properties, together with low toxicity, make such substances potentially useful in the pharmacological field. The crystal structure of 4′-methylaminoavarone, (I), has been determined as part of a program studying the structures, biological activities and pharmacological implications of this type of molecule (Puliti *et al.*, 1995*a* and references therein; Belisario *et al.*, 1996).




(I)

Compound (I) was isolated as a minor component from the ethanol extract of sponge *D. avara* and characterized by spectral data together with partial synthesis from avarol (Cimino *et al.*, 1982). Afterwards, the pharmacological properties were tested *in vitro* and compared with those of other naturally or synthetically related molecules (De Giulio *et al.*, 1991).

A perspective view of the molecule is shown in Fig. 1. The enantiomer was chosen according to the absolute configuration of avarol established on the basis of circular dichroism and NMR spectroscopy (De Rosa *et al.*, 1976).

The molecular geometry shows the effects of short intramolecular contacts, as found in other related structures (Giordano & Puliti, 1987; Puliti *et al.*, 1994, 1995*a*, 1995*b*). In particular, the bicyclic system presents rather long bond distances (> 1.55 Å) in the region of the C5, C10, C9 and C8 atoms and a few angles are remarkably distorted with respect to the normal tetrahedral values (see Table 1). The angle distortions and the long bonds partially relieve the short intramolecular interactions, especially the one between the axially isooriented methyl groups C12 and C14 [3.317 (5) Å]. Furthermore, the long bond distance C9—C11 [1.579 (4) Å] and the wide angle C9—C11—C1′ [117.4 (2)°] improve the intramolecular contacts between the $C_{15}$ sesquiterpene and the quinone residues.

The $\Delta^{3,4}$ cyclohexene ring adopts a distorted half-boat conformation with C10 0.712 (3) Å out of the best plane through the remaining ring atoms. Deviations from the ideal $C_s$(half-boat) and $C_2$(half-chair) symmetries can be measured by the asymmetry parameters $\Delta C_s$(C3) = 7.6 (5)° and $\Delta C_2$(C3—C4) = 15.3 (5)° (Duax *et al.*, 1976). The cyclohexane ring approximates to an ideal chair with puckering parameters (Cremer & Pople, 1975) $Q$ = 0.558 (3) Å, $\theta$ = 8.2 (3)° and $\varphi_2$ = 6 (2)° for the atomic sequence C6, C7–C10, C5. With respect to the ideal chair conformation, C9 is slightly flatter than C6, the distances from the best plane through the remaining atoms being 0.600 (3) and 0.698 (4) Å, respectively. The quinone ring is rather bent with an angle of 8.2 (5)° between the best planes through the C1′, C2′, C5′, C6′ and C2′, C3′, C4′, C5′ atoms. The least-squares planes through the sesquiterpene and quinone residues make an angle of 79.50 (7)° and the benzoquinone

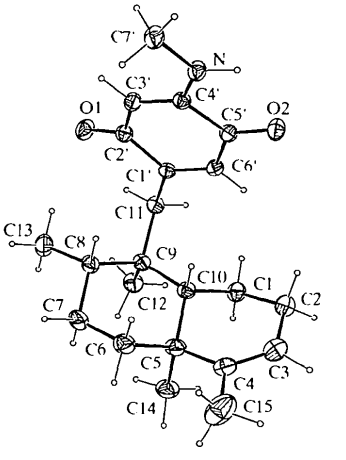



Fig. 1. Perspective view of 4′-methylaminoavarone. Labels of H atoms have been omitted for clarity. Displacement ellipsoids are plotted at the 30% probability level.

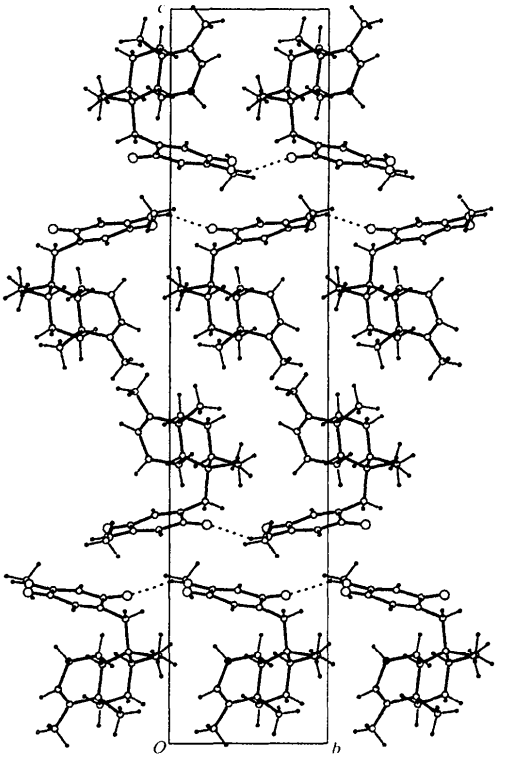



Fig. 2. Crystal packing along the *a* direction. Dashed lines indicate hydrogen bonds.

ring is oriented to optimize the intramolecular contacts [C13···O1 3.287 (5) and C10···C6′ 3.271 (4) Å]. The perpendicularity between the $C_{15}$ sesquiterpene and quinone (hydroquinone) systems is a constant characteristic of the structures in this family (Puliti *et al.*, 1995*a* and references therein) and the specific orientation of the moieties is determined in each structure by the different bulkiness and positions of the substituents. The perpendicularity is also kept in arenarol diacetate (Schmitz *et al.*, 1984), a hydroquinone-substituted sesquiterpenoid enantiomer of avarol.

The packing (Fig. 2) is characterized by rows of translated molecules interconnected along the *b* direction by hydrogen bonds between the amino groups and O1 carbonyl atoms, N(—H)···O1($x$, $y-1$, $z$) = 2.979 (3) Å. In the crystal, polar layers of pairs of screw-related quinone residues separate, along the *c* direction, wide regions of sesquiterpene residues with normal van der Waals contacts: the shortest contact is C3···C12($x$, $y-1$, $z$) = 3.607 (5) Å.

## Experimental

*Crystal data*

$C_{22}H_{31}NO_2$
$M_r$ = 341.50
Orthorhombic
$P2_12_12_1$
$a$ = 7.2040 (13) Å
$b$ = 7.6076 (11) Å
$c$ = 35.187 (9) Å
$V$ = 1928.5 (7) Å$^3$
$Z$ = 4
$D_x$ = 1.176 Mg m$^{-3}$
$D_m$ not measured
Cu $K\alpha$ radiation
$\lambda$ = 1.54056 Å
Cell parameters from 25 reflections
$\theta$ = 23–31°
$\mu$ = 0.544 mm$^{-1}$
$T$ = 293 K
Prism
0.38 × 0.33 × 0.29 mm
Translucent red

*Data collection*

Enraf–Nonius CAD-4 diffractometer
$\omega$–$\theta$ scans as suggested by peak-shape analysis
Absorption correction: none
2293 measured reflections
2293 independent reflections
2034 reflections with $I > 2.5\sigma(I)$
$\theta_{max}$ = 75°
$h$ = 0 → 9
$k$ = 0 → 9
$l$ = 0 → 44
4 standard reflections
frequency: 250 min
intensity decay: 2%

*Refinement*

Refinement on $F$
$R$ = 0.045
$wR$ = 0.044
$S$ = 0.927
2034 reflections
227 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o) + (0.01F_o)^2 + 0.5]$ (Killean & Lawrence, 1969)
Extinction correction: Stout & Jensen (1968)
Extinction coefficient: 1.56 (8) × 10$^{-6}$
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)
Absolute structure: assigned in agreement with the known stereochemistry of avarol
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.17 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.15 e Å$^{-3}$
Rogers parameter = 0.887 (5)

Table 1. *Selected geometric parameters (Å, °)*

| | | | |
|---|---|---|---|
| O1—C2′ | 1.235 (3) | C4—C5 | 1.523 (5) |
| O2—C5′ | 1.215 (3) | C5—C10 | 1.561 (4) |
| N—C4′ | 1.337 (4) | C8—C9 | 1.566 (4) |
| N—C7′ | 1.454 (4) | C9—C10 | 1.555 (4) |
| C2—C3 | 1.488 (5) | C9—C11 | 1.579 (4) |
| C3—C4 | 1.336 (5) | C11—C1′ | 1.497 (4) |
| C4′—N—C7′ | 122.2 (2) | C1—C10—C9 | 114.0 (2) |
| C2—C3—C4 | 125.0 (3) | C1—C10—C5 | 108.8 (2) |
| C3—C4—C5 | 121.2 (3) | C9—C11—C1′ | 117.4 (2) |
| C10—C5—C14 | 115.5 (2) | C11—C1′—C6′ | 123.3 (3) |
| C9—C8—C13 | 114.6 (3) | C11—C1′—C2′ | 119.1 (2) |
| C11—C9—C12 | 104.6 (2) | N—C4′—C3′ | 128.2 (3) |
| C10—C9—C12 | 113.3 (2) | N—C4′—C5′ | 113.3 (2) |
| C5—C10—C9 | 117.2 (2) | | |
| C7′—N—C4′—C3′ | 7.9 (4) | C12—C9—C11—C1′ | −179.8 (2) |
| C15—C4—C5—C10 | 151.5 (3) | C9—C11—C1′—C2′ | −100.2 (3) |
| C4—C5—C10—C9 | −171.9 (2) | N—C4′—C5′—O2 | −4.8 (4) |
| C8—C9—C11—C1′ | 62.2 (3) | | |

The Laue group, systematic absences and lack of centrosymmetry, as indicated by the intensity statistics, led to the unique assignment of the space group $P2_12_12_1$, confirmed also by successful refinement of the structure. The structure was solved using the *SIR*92 package (Altomare *et al.*, 1993). H atoms were placed on the basis of geometrical considerations and difference Fourier map suggestions for methyl groups. All H atoms were included in the final refinement as fixed atoms with $B_{iso}$ set equal to $B_{eq}$ of the parent atom. All calculations were performed using *SDP* software (Enraf–Nonius, 1985) on a MicroVAX 3100 computer.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1378). Services for accessing these data are described at the back of the journal.

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# *tert*-Butyl 3-[4-(2-Bromoethoxy)-3-chlorophenyl]-5-methylisoxazole-4-carboxylate

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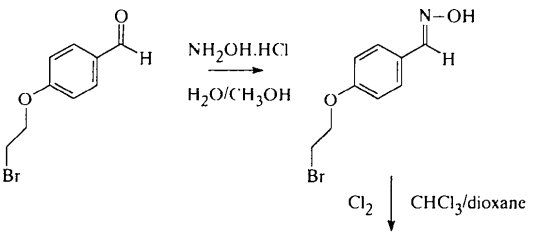
## Abstract

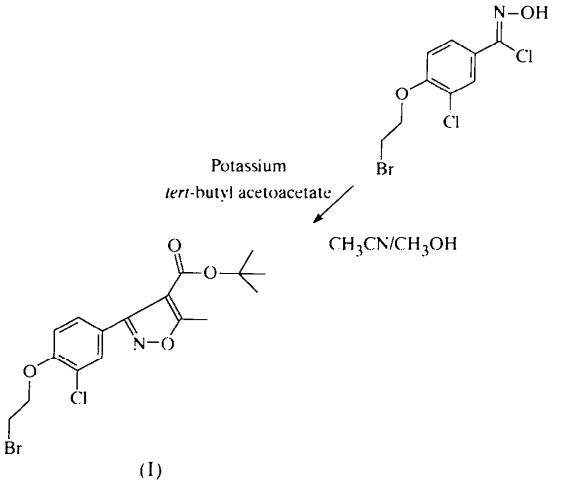
The title compound, $C_{17}H_{19}BrClNO_4$, has been prepared for the development of homogeneous immunoassays involving penicillins as tracers. An X-ray diffraction study has shown that the Cl atom is located *ortho* to the bromoethoxy group on the aromatic ring.

## Comment

For the development of homogeneous immunoassays involving penicillins as tracers, carbenicillin, cefuroxime, cefotaxime and oxacillin conjugates to low molecular weight compounds (haptens) have been prepared (Kohl *et al.*, 1997). By a competition pathway, these conjugates are able to diminish the hydrolysis rate of nitrocephin, which is a coloured revelator of a specific enzyme and a class C $\beta$-lactamase. This interference is suppressed by antibody addition and restored when a free hapten is introduced into the medium (Kohl *et al.*, 1996).

A modulation of colour production by the hapten results in its determination. These reactions are only possible if the conjugate affinity for the specific enzyme (represented by the Michaelis enzymatic constant, $K_m$) is high (low $K_m$ values) and their own hydrolysis rate (represented by the catalytic constant $k_{cat}$) is slow (Galleni & Frère, 1988). Oxacillin is the best $\beta$-lactamic antibiotic from this point of view. Unfortunately, oxacillins have no functional groups available for coupling and therefore cannot be conjugated if they are not functionalized.




(I)

It is for this purpose that the preparation of the title compound, (I), has been investigated. The following procedure has been carried out in three steps: (1) starting from 4-(2-bromoethoxy)benzaldehyde, preparation of the corresponding oxime by reaction with hydroxylamine in hydromethanolic medium buffered at pH 5; (2) oxime chlorination using gaseous chlorine in chloroform for the preparation of the chloroxime; (3) reaction of the chloroxime with one equivalent amount of *tert*-butyl acetoacetate potassium salt in the presence of acetonitrile/methanol. During the second step of this synthesis, the aromatic ring has been substituted by a Cl atom. This phenomenon has been confirmed by elemental analysis, by mass spectrometry and by proton nuclear magnetic resonance. However, with these techniques the position of the Cl atom on the aromatic ring cannot be located exactly. Consequently, it was decided to establish the position of the substitution by X-ray diffraction. The crystal structure determination has shown that the electrophilic substitution is in the position *ortho* to the bromoethoxy group. The achiral compound crystallizes in a polar space group and the absolute direction of the polar axis has been determined. The bond lengths and angles are within expected values. Steric interactions between the rings and the carboxylate group in