Tetrahedron Vol. 35, pp. 609-612
© Pergamon Press Ltd., 1979. Printed in Great Britain

0040-4020/79/0301-0609/$02.00/0

ILIMAQUINONE, A SESQUITERPENOID QUINONE FROM A MARINE SPONGE[1]

RICHARD T. LUIBRAND,[2a] TIMOTHY R. ERDMAN,[2b] JOHN J. VOLLMER[2c]
and PAUL J. SCHEUER*
Department of Chemistry, University of Hawaii at Manoa, Honolulu, HI 96822, U.S.A.

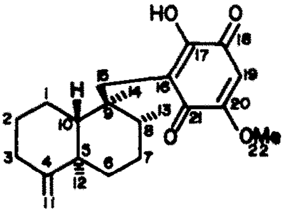
and

JANET FINER and JON CLARDY[2d]
Ames Laboratory-USERDA and Department of Chemistry, Iowa State University, Ames, IO 50011, U.S.A.

(*Received in USA* 6 *July* 1978)

Abstract—Ilimaquinone (1) is a new sponge metabolite of composition $C_{22}H_{30}O_4$. Its structure, which was determined by spectral correlations and X-ray crystallography, comprises a rearranged drimane sesquiterpene moiety linked to a 2-hydroxy-5-methoxybenzoquinone at C-3.

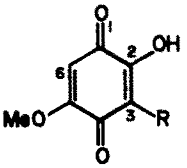
The rich harvest of terpenoids that has been plucked from marine sponges,[3] has included some sesquiterpenoids linked to a benzenoid moiety. We wish to report isolation and structural determination of such a compound, which we have named ilimaquinone (1).[4] The compound was isolated from a bristly yellow, orange, or brown sponge tentatively identified as *Hippiospongia metachromia*[5] that was initially collected off the island of Lanai and subsequently near the Blowhole on the southeast shore and at Sharks' Cove on the north shore of Oahu. The ethereal phase of an aqueous methanol–acetone extract showed mild anti-microbial activity against *Staphylococcus aureus*, *Candida albicans*, and *Mycobacterium smegmatis*. Preparative tlc on silica gel furnished ilimaquinone (1) as an amorphous orange solid in 4% yield.



1

Crystallization of ilimaquinone was eventually achieved after Sephadex chromatography; recrystallization from hexane yielded orange needles, m.p. 113–114°. Earlier attempts at crystallization involving methanol had always been fruitless and had led to products with the composition and spectral character of a partial methanol adduct.

Typical quinone behavior, as, e.g. color change in base from red to blue, loss of color in basic dithionite, and reoxidation in air, plus initial UV (287, 420 nm), IR (3340, 1660 sh, 1640, 1595 cm^{-1}) and ^{1}H NMR (δ 7.54 broad exchangeable one-proton singlet, δ 5.85 one-proton singlet, δ 3.85 three-proton singlet) spectral characteristics strongly suggested that we had in hand the chromophore of compound 2a, which is a constituent of the terrestrial plant *Ardisia japonica* (Myrsinaceae).[6] Suspected analogy of ilimaquinone (1 to 2a) was further strengthened by its composition of $C_{22}H_{30}O_4$ and a two-proton broadened singlet at δ 2.50 in the NMR spectrum, assigned to a benzylic methylene. Additional ^{1}H NMR signals at δ 1.04 (3 H s), and 0.84 (3 H s), and at 4.43 (2 H br s) ascribed to two Me's and a terminal methylene constituted evidence that the alkyl substituent of the benzoquinone was a sesquiterpene, although no tell-tale *gem*-dimethyl appeared to be present. A third, secondary, Me group at δ 1.00 (3 H d) was revealed in a 300 MHz spectrum[7] and was also resolved in the ^{1}H NMR spectrum of the leucotriacetate as a broad doublet at 0.74 ppm. These data pointed to a rearranged sesquiterpene, but failed to define an unambiguous skeleton.

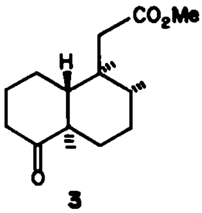


2a: R = n-$C_{15}H_{29}$
b: R = n-$C_{13}H_{27}$

The remaining uncertainty, placement of the OMe group at C-5 or C-6, could be removed by comparing the chemical shift of the sole benzenoid proton in the corresponding hydroquinone with values calculated as described by Ballantine and Pillinger.[8] Table 1 shows these data for the hydroquinone, the leucotriacetate, and the three possible leucodiacetates. Without exception, these data imply presence of chromophore 2.

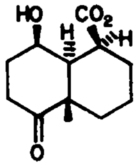
Our chief effort at chemical degradation was directed toward basic hydrogen peroxide oxidation of 1, which was expected to retain one carbon of the quinone as a carboxyl group. The reaction proceeded as expected but under a large variety of conditions led only to complex mixtures. The major product, $C_{14}H_{23}CH_2CO_2Me$ after esterification was separable by tlc and was ozonized to a 6-ring ketone (3, ν_{max} 1710 cm^{-1}), but attempted Baeyer–Villiger oxidation failed and furnished only starting material. Other unproductive degradations included ozonolysis of the *leuco*-triacetate, benzylic bromination of the *leuco*-diacetate and of its dihydro derivative.

Keto ester 3 exhibits a positive CD curve, $[\theta]_{298}$ =



3

+455, which by the octant rule requires the angular Me to have α-configuration; hence ketone 3 is antipodal at the ring fusion with the closely related degradation product (4) of a fungal metabolite.[9] Since the relative



4

configuration of all chiral centers was defined by X-ray diffraction, the absolute configuration of ilimaquinone is as shown in 1.

Preliminary X-ray photographs revealed no crystal symmetry and this, coupled with the known optical activity of the sample, indicated space group P_1. Accurate cell constants, obtained from least-squares fitting of 15 2θ values, were $a = 7.013(7)$, $b = 7.735(5)$, $c = 22.648(23)$ Å, $\alpha = 93.26(7)$, $\beta = 125.44(6)$ and $\gamma = 100.35(6)°$. A calculated density of 1.13 g/ml for $Z = 2$ indicated two molecules of $C_{22}H_{30}O_4$ in the asymmetric unit.

All unique diffraction maxima with $2\theta \leq 114.1°$ were measured using graphite monochromated CuK_α (1.54178 Å) radiation. A total of 2419 reflections were measured of which only 1313 (54%) were judged observed ($F_o \geq 3\sigma(F_o)$) after correction for Lorentz, polarization and background effects.

Intensity statistics ($\langle E^2 \rangle = 1.00$, $\langle E \rangle = 0.8513$, $\langle E^2 - 1 \rangle = 0.8685$) indicated that while the entire structure was noncentrosymmetric, large portions were related by a pseudocenter. Attempts to assign centro-symmetric phases to the larger E's were not successful, in spite of the fact that it was later shown that all of these normalized structure factors had centrosymmetric phases. Direct methods in space group P_1 combined with extensive recycling of plausible fragments through the tangent formula did finally succeed.[10] Full-matrix, least squares refinements[11] with anisotropic temperature factors for the nonhydrogen atoms and isotropic temperature factors for hydrogen have converged a standard crystallographic residual of 0.057. Both molecules in the asymmetric unit are identical within experimental error. Bond distances and angles generally agree well with anticipated values and additional crystallographic details may be found in the Supplemental Material.

A computer generated perspective drawing of the final X-ray model less hydrogens for one of the molecules is presented in Fig. 1. The two 6-membered rings are *trans*-fused. The quinone substituent at C(9) and the methyl group at C(8) have equatorial conformations. The pseudocenter is set up by hydrogen bonding between C(18)–O(23)···HO(22′)–C(17′) to join the two quinones by a center.

Ilimaquinone shares the rearranged drimane skeleton with other marine metabolites, e.g. avarol (5), which Minale *et al.*[12] isolated from the Mediterranean sponge *Disidea avara*, but with which ilimaquinone is enantiomeric. Another closely related compound, isospongiaquinone, (6) possessing avarol stereochemistry has been reported from the Australian sponge *Stelospongia conulata.*[13] A chroman, *ent*-chromazonarol (7), which the Italian workers[14] isolated from the sponge *D. pallescens*, possesses an unrearranged drimane skeleton and is related to avarol (5) by a common biogenetic precursor. Other unrearranged drimanes that are linked to a benzenoid moiety are known from the brown alga *Dictyopteris undulata.*[15,16] The algal metabolites possess ilimaquinone absolute stereochemistry and thus are enantiomeric with the Mediterranean sponge compounds.

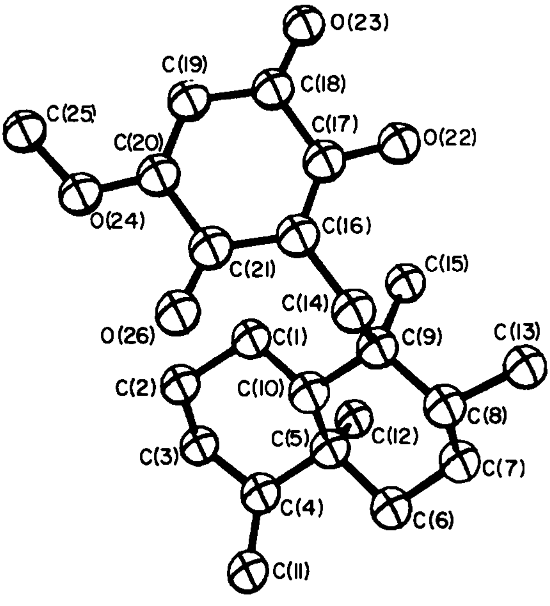
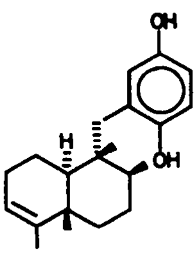
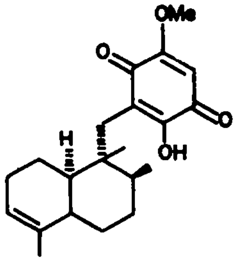


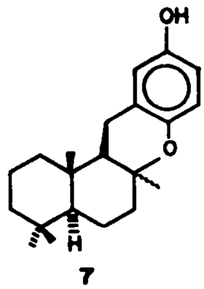
Fig. 1. A computer generated perspective drawing of one of the two identical molecules composing the asymmetric unit of ilimaquinone. Hydrogens are omitted for clarity and no absolute configuration is implied.



5

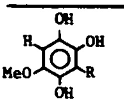
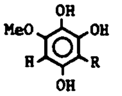
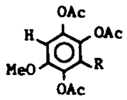
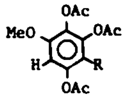
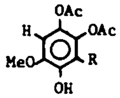
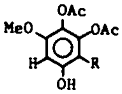
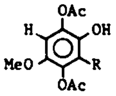
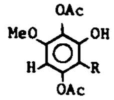
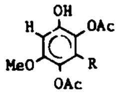
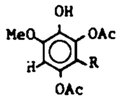


6



7

Table 1. Comparison of calculated and observed chemical shift values (δ) for trisubstituted hydroquinones and their acetates

Compound	Chemical Shift of Benzenoid H Calculated	Observed
	6.10	6.40
	5.80	
	6.75	6.72
	6.65	
	6.50	6.63
	6.20	
	6.35	6.63
	6.25	
	6.50	6.63
	6.20	

EXPERIMENTAL[17]

Isolation. The sponge (14 g dry wt) was cut into small pieces and extracted repeatedly with Me_2CO. Combined extracts were concentrated and the aq residue extracted with Et_2O yielding 1.42 g ether soluble material. Preparative tlc on silica gel with CH_2Cl_2 yielded an amorphous golden solid, m.p. 58–70°. Crystalline ilimaquinone, m.p. 113–114°, was obtained after Sephadex LH-20 chromatography ($CHCl_3$/MeOH, 4:3) and two recrystallizations from hexane.

Ilimaquinone (1). Found: C, 73.63; H, 8.44. Calc. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44%. $[\alpha]_D^{23°}$ −23.2° (*c* 1.12, $CHCl_3$). UV ($CHCl_3$): 285 (4.21), 420 (2.76) nm; (MeOH) 214 (4.02), 286 (4.12), 435 (2.73) nm; ($Me\overset{\oplus}{O}H_2$) 204 (4.01), 212 sh (3.92), 285 (4.21), 425 (2.90) nm; (MeOH, $OH^{\ominus}$) 209 (4.12), 238 sh (3.97), 288 (4.11), 523 (3.20) nm. IR(KBr): 3340, 1660 sh, 1640, 1605, 1205 cm^{-1}. MS (70 eV): 360 (M + 2, variable), 358 (M^+, 34 rel%), 191(75), 170 (62), 168 (100), 135 (53), 121 (62), 109 (64), 95 (100), 93 (55), 81 (58), 79 (55), 69 (47), 67 (56), 55 (64), 41 (62). ^1H NMR ($CDCl_3$, δ): 7.50 (1 H s, exchangeable), 5.86 (1 H s), 4.44 (2 H br s), 3.87 (3 H s), 2.50 (2 H d), 1.03 (3 H s), 0.82 (3 H s), 2.40–0.67 (complex). ^{13}C NMR ($CDCl_3$, δ): 182.4 (C-18), 182.04 (C-21), 161.78 (C-20), 160.46 (C-17), 153.42 (C-4), 117.41 (C-16), 102.56 (C-11), 102.06 (C-19), 56.84 (C-22), 50.22 (C-10), 43.34, 40.47 (C-5, 9), 38.16 (C-8), 36.69 (C-3), 33.00, 28.65, 27.99, 23.21 (C-12, 6, 7), 32.44 (C-15), 20.56, 17.87, 17.32 (C-12, 13, 14).

Ilimaquinone monoacetate. Ilimaquinone (1, 17.2 mg) was treated with Ac_2O, pyridine at room temp. overnight to yield 14.4 mg monoacetate. ^1H NMR ($CDCl_3$, δ): 5.89 (1 H s), 4.45 (2 H br s), 3.83 (3 H s), 2.47 (2H AB q), 2.32 (3 H s), 1.04 (3 H s), 0.91 (3 H, br d), 0.84 (3 H s).

Leucodiacetate. Ilimaquinone (1) in Ac_2O containing substantial amounts of HOAc and a trace of Et_3N yielded leucodiacetate, $C_{26}H_{36}O_6$. (Found: C, 70.21, H, 7.92. Calcd. for $C_{26}H_{36}O_6$: C, 70.24, H, 8.16). MS (20 eV): *m/e* 444 (19), 402 (14), 360 (10), 254 (100), 212 (60), 191 (25), 177 (11), 95 (12%), IR (KBr) 3440, 3100, 1760 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.63 (1 H s), 4.46 (2 H br s), 3.83 (3 H s), 2.47 (2H AB q), 2.32 (3 H s), 1.04 (3 H s), (3 H s), 0.90 (3 H s).

Leucotriacetate. Ilimaquinone (1, 116 mg) in freshly distilled Ac_2O, Zn dust and a trace of Et_3N furnished after tlc 84 mg of triacetate, crystals from C_6H_6, m.p. 156–158.5°. ^1H NMR ($CDCl_3$, δ): 6.72 (1 H s), 4.48 (2 H br s), 3.77 (3 H s), 2.40 (2H AB q), 2.29, 2.26, 2.24 (3 H s each), 1.05 (3 H s), 0.87 (3 H s), 0.74 (3 H br d).

Hydrogen peroxide reaction of ilimaquinone. Ilimaquinone (1, 1.75 g) in 50 ml 5N KOH was treated with 25 ml 30% H_2O_2 in small portions. The mixture was stirred at 80–90° for 1 hr, when 10 ml KOH and 25 ml H_2O_2 was added. Stirring for 1 hr near the b pt was followed by acidification with conc HCl, heating, and stirring for 1 hr. Cooling and $CHCl_3$ extraction yielded 1.09 g oil which was treated with CH_2N_2 in Et_2O and separated by tlc on $AgNO_3$/silica gel into 4 major fractions. The major (277 mg) and most polar spot was isolated and characterized. IR (film) 3080, 2920, 2850, 1740, 1635, 885 cm^{-1}. MS (70 eV) *m/e* 278 (5), 263 (3), 191 (100), 163 (15), 135 (36), 121 (22), 109 (23), 95 (54), 81 (23%). ^1H NMR ($CDCl_3$) δ 4.48 (2 H, 2s), 3.63 (3 H s), complex signals near 2.10, 1.50, 1.04 (3 H s), 0.81 (3 H d, J = 6 Hz), 0.76 (3 H s).

Ketone 3. The methyl ester (160 mg) in 6 ml $CHCl_3$ at 0° was ozonized with reductive (Zn/HOAc) work-up to yield 142 mg of product, 71 mg of ketone 3, colorless oil, after tlc. IR (film): 1740, 1710 cm^{-1}. MS (20 eV) m/e 280 (10), 265 (27), 262 (42), 194 (32), 193 (28), 175 (100), 105 (10%). ^1H NMR ($CDCl_3$) δ 3.65 (3 H s), 1.14 (3 H s), 0.84 (3 H s). CD (EtOH) $[\theta]_{298}^{29°}$ + 455 (*c* 1.2×10^{-2} M).

Acknowledgements—We are grateful to Dr. J. N. Shoolery for the 300 MHz NMR spectra, to Dr. M. Volini for use of her CD facility, Dr. R. J. Wells for a preprint of Ref. 13, and to the National Science Foundation for financial support.

REFERENCES

[1] A preliminary account was presented at the 1976 *Pacific Conference on Chemistry and Spectroscopy*, Phoenix, Arizona (November 1976).

[2a] Permanent address: California State University, Hayward, CA 94542; [2b] NIH Postdoctoral Fellow (1971–73); [2c] permanent address: Mills College, Oakland, CA 94613; [2d] present address: Department of Chemistry, Cornell University, Ithaca, NY 14853, U.S.A.; Camille and Henry Dreyfus Foundation Teacher Scholar Grant Awardee 1972–77.

[3a] L. Minale, G. Cimino, S. De Stefano and G. Sodano, *Fortschr. Chem. Org. Naturstoffe* 33, 1 (1976); [3b] L. Minale in *Marine Natural Products: Chemical and Biological Perspectives* (Edited by P. J. Scheuer), Vol. 1, pp. 175–240. Academic Press, New York (1978).

[4] Crystalline ilimaquinone has the rich golden yellow color of *ilima* (*Sida fallax*, Malvaceae), the flower of Oahu, highly prized for leis, and said to be one of the forms that Laka, the goddess of the hula, can take.

[5] We thank Dr. Ole Tendal, Zoological Museum, University of Copenhagen, for identification.

[6] H. Ogawa and S. Natori, *Chem. Pharm. Bull.* 16, 1709 (1968).

[7] We are indebted to Dr. James Shoolery, Varian Associates, for these data.

[8] J. A. Ballantine and C. T. Pillinger, *Tetrahedron* 23, 1691 (1967).

[9] G. A. Ellestad, R. H. Evans, Jr., M. P. Kunstmann, J. E. Lancaster and G. O. Morton, *J. Am. Chem. Soc.* 92, 5483 (1970).

[10] G. Germain, P. Main and M. M. Woolfson, *Acta Crystallogr. Sect. B*, 24, 274 (1970).

[11] The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, *The Fast Fourier Algorithm and the ALFF, ALFFDP, ALFFT and FRIEDEL*, USAEC Rep. IS-2625, IOWA State University-Institute for Atomic Research, Ames, Iowa (1971); W. R. Busing, K. O. Martin and H. A. Levy, *A Fortran Crystallographic Least Squares Program*. USAEC Rep. ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn. (1965); C. Johnson, *ORTEP, A Fortran Thermal-Ellipsoid Plot Program*. U.S. Atomic Energy Commission Rep. ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn. (1965).

[12] L. Minale, R. Riccio and G. Sodano, *Tetrahedron Letters* 3401 (1974); S. DeRosa, L. Minale, R. Riccio and G. Sodano; *J. Chem. Soc.* Perkin Trans 1 1408 (1976).

[13] R. Kazlauskas, P. T. Murphy, R. G. Warren, R. J. Wells and J. F. Blount, *Aust. J. Chem.* In press.

[14] G. Cimino, S. De Stefano and L. Minale, *Experientia* 31, 1117 (1975).

[15] W. Fenical and O. McConnell, *Ibid* 31, 1001 (1971).

[16] L. Minale, *Marine Natural Products*: *Chemical and Biological Perspectives* (Edited by P. J. Scheuer), Vol. 1, pp. 227–229. Academic Press, New York (1978).

[17] M.p's on a Fisher–Johns apparatus and uncorrected. Rotation on a Bendix-Ericsson ETL-NPL polarimeter, type 143A. CD curve on a Cary 61 instrument. UV spectra on a Cary 14 instrument. IR spectra on a Perkin–Elmer 467 spectrometer. Mass spectra on a Varian-MAT 311 spectrometer. ^{1}H NMR spectra on Varian HA-100 on XL-100 spectrometers. ^{13}C NMR spectrum on a Varian CFT-20 instrument. Combustion analyses by Chemical Analytical Services, University of CA, Berkeley.