Marine Natural Products: Nephthenol and Epoxynephthenol Acetate, Cembrene Derivatives from a Soft Coral

By Francis J. Schmitz,* David J. Vanderah, and L. S. Ciereszko

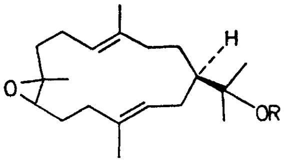
(*Department of Chemistry, University of Oklahoma, Norman, Oklahoma* 73069)

Summary Two new cembrene derivatives (**1**) and (**5**) have been isolated from a Pacific soft coral and their structures have been established by spectroscopic analyses and chemical degradations.

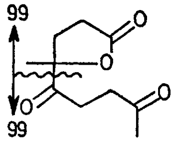
A variety of interesting natural products have been isolated from gorgonians which are common to reefs in the Caribbean.[1] In contrast there appears to be very little known[2] regarding the compounds produced by a related group of coelenterates, the soft corals or alcyonaceans (class Anthozoa, subclass Octocorallia, order Alcyonacea) which are prominent members of the reef fauna in the Indo-Pacific. We report herein the isolation of two new cembrene derivatives from our preliminary investigation of a soft coral (*Nephthea sp.*) from Eniwetok, Marshall Islands.

The two new compounds were isolated by silica gel chromatography of the hexane extract of air-dried specimens. The more abundant substance (0·75% of dry animal wt.), epoxynephthenol acetate (**1**), was obtained as an oil, b.p. *ca.* 96° at 0·03 mmHg, $[\alpha]_D$ −20·7°, $C_{22}H_{36}O_3$,† i.r.: 3100, 1658 (double bond), 1730 and 1255 cm^{-1} (acetate); only end absorption was noted in the u.v. spectrum. A positive reaction of (**1**) with acidic silver periodate indicated the presence of an epoxide linkage.

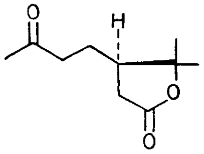
The n.m.r. spectrum ($CDCl_3$; 60 and 100 MHz) of (1) showed six methyl signals: δ 1·30 (3H, s, O·CH·C*Me*), 1·48 (6H, s, C*Me*$_2$OAc), 1·55 and 1·67 (each 3H, br s, 2 × HC=C*Me*), and 1·97 (3H, s, OAc), and other signals at δ 2·84 (1H, t, *J ca.* 5 Hz, O·C*H*·CMe) and 5·18 (2 overlapping olefinic H). Irradiation at δ 1·90 collapses the triplet at δ 2·84, but does not alter the olefinic absorption pattern, while irradiation at δ 2·13 (allylic region) does convert the olefinic absorption into two nearly separated, broad singlets but does not perturb the triplet at δ 2·84. Thus at least one methylene unit must be interposed between any allylic carbon atoms and the monosubstituted side of the epoxide unit. The foregoing evidence for one acetate group, two double bonds and an epoxide accounts for only 4 of the 5 degrees of unsaturation required by the formula of (**1**) and indicates that the natural product contains one carbocyclic ring.



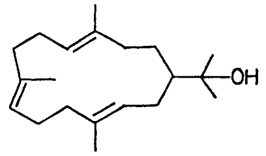
(1) R = Ac
(2) R = H



(3)



(4)



(5)

Mild reduction ($LiAlH_4$) of (**1**) gave epoxynephthenol (**2**), m.p. 58·7—61·8°, M^+ 306. Stepwise oxidation of (**2**) with OsO_4–$NaIO_4$ and then Jones reagent produced two lactones, (**3**) and (**4**). The structure of the lactone (**3**) was ascertained

---

† Satisfactory elemental analyses and/or mass spectra were obtained for all new compounds.

from spectral data: M^+ 198, base peak m/e 99, derivable from either half of the molecule as shown in (**3**); ν_{max} 1775 and 1720; δ ($CDCl_3$; 100 MHz) 2·20 (3H, s), 2·82 (4H, s), 1·57 (3H, s), 2·64 (3H, m), and 2·15 (1H, m). The lactone (**4**) was identified as (−)-homoterpenyl methyl ketone from its physical constants, m.p. 46·8—47·2°, $[\alpha]_D$ −41° (lit.,[3] $[\alpha]_D$ −59°), and identity of its i.r. and n.m.r. spectra with those of a sample of (±)-homoterpenyl methyl ketone prepared by oxidation of (±)-α-terpineol. Combination of the elements of the lactones (**3**) and (**4**) yields the structure (**1**) for epoxynephthenol acetate, the epoxide fragment having undergone ring opening and oxidation of the resulting secondary alcohol to give the α-hydroxy-keto-segment of (**3**). *trans*-Double bonds and epoxide functions are indicated by the failure to obtain any nuclear Overhauser effects[4] for the olefinic or epoxide methine proton signals upon irradiation at the position of the vinyl methyl and epoxide methyl group signals.‡ The (*R*) configuration at the carbon bearing the acetoxyisopropyl side chain follows from the known[3,5] (*R*) configuration of (−)-homoterpenyl methyl ketone. Epoxynephthenol acetate (**1**) thus has the same configuration at this centre as does cembrene-A[6] and cembrene.[7]

The minor component, nephthenol, (**5**), 0·05% of animal dry wt., was also obtained as an oil, b.p. *ca.* 96° at 0·03 mm-Hg; M^+ 290 ($C_{20}H_{34}O$); ν_{max} 3450br and 1655 cm^{-1}; δ 1·20 (6H, s, CMe_2OH), 1·60, [9H, s, 3 × $CH{=}C(Me)$–], 5·9 [3H, m, 3 × $CH{=}C(Me)$–], and 1·9—2·3 (12H, m, allylic-H). Oxidation of nephthenol ($KMnO_4$–KIO_4) gave levulinic acid and the lactone (**4**).§ On the basis of these data formula (**5**) is proposed for nephthenol. The double-bond geometry implied in formula (**5**) is only tentatively assigned by analogy with the stereochemistry assigned to (**1**); the configuration at the carbon bearing the hydroxyisopropyl unit in (**5**) has not yet been determined. Nephthenol is isomeric with mukulol.[6]

It is interesting to note that several cembranolides have been isolated from gorgonians.[1]

We gratefully acknowledge the use of the Eniwetok Marine Biological Laboratory, and thank the National Institutes of Health and the Commerce Department (N.O.A.A.) for support, Mr. Larry Wilson for 100 MHz n.m.r. spectra, Dr. K. Biemann's laboratory, MIT, for certain mass spectra, and the Phillips Petroleum Company, Bartlesville, for a grant towards the purchase of n.m.r. spectrometers.

(*Received*, 30*th January* 1974; *Com.* 139.)

---

‡ A 9 ± 3% signal intensity enhancement was observed for the olefinic protons upon irradiation in the allylic proton region, δ 2·04.

§ Identified by g.l.c. only, *i.e.* retention time and peak enhancement with authentic sample; no rotational data available.

[1] L. S. Ciereszko and T. K. B. Karns, in 'Biology and Geology of Coral Reefs,' ed. O. A. Jones and R. Endean, Vol. II, Academic Press, New York, 1973, ch. 6; P. J. Scheuer, 'Chemistry of Marine Natural Products,' Academic Press, New York, 1973.
[2] For sterols from a soft coral see: J. P. Engelbrecht, B. Tursch, and C. Djerassi, *Steroids*, 1972, **20**, 121.
[3] Y. R. Naves, *Bull. Soc. chim. France*, 1958, 1372.
[4] R. Kaiser, *J. Chem. Phys.*, 1965, **42**, 1838; F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, 1965, **87**, 5250.
[5] A. J. Birch, *Annual Reports*, 1950, **47**, 191.
[6] V. C. Patil, U. R. Nayak, and Sukh Dev. *Tetrahedron*, 1973, **29**, 341.
[7] W. G. Dauben, W. E. Thiessen, and P. R. Resnick, *J. Amer. Chem. Soc.*, 1962, **84**, 2015; M. G. B. Drew, D. H. Templeton, and A. Zalkin, *Acta Cryst.*, 1969, **B25**, 261, (the *R*-stereoisomer is depicted in this latter paper rather than the *S*-isomer specified by Dauben, Thiessen and Resnick on the basis of chemical degradations); H. Kobayashi and S. Akiyoshi, *Bull. Chem. Soc. Japan*, 1963, **35**, 1044; 1963, **36**, 823.