# Eunicin, An Oxa-bridged Cembranolide of Marine Origin

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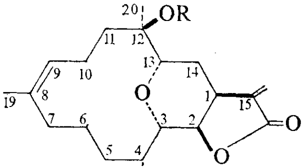
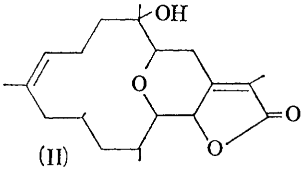
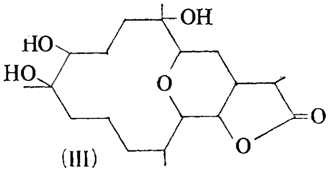
THE antibacterial marine diterpene eunicin (Ia),[1] $C_{20}H_{30}O_4$, m.p. 155°, $[\alpha]_D$ −89°, present to the extent of 1% of the dry weight of the gorgonian (octocoral) *Eunicea mammosa* Lamouroux and known[2] to occur at least in part within the unicellular algal symbionts (zooxanthellae) associated with the invertebrate host, is shown to be a cembrane derivative with the unusual feature of an ether bridge across the 14-membered carbocyclic ring. This assignment is fully substantiated by the *X*-ray crystallographic study reported in the Communication,[3] which follows.



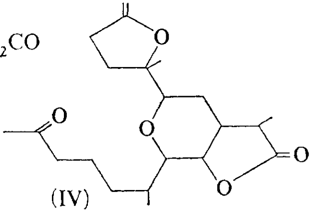
(Ia) R=H
(Ib) R=Ac
(Ic) R=$ICH_2CO$



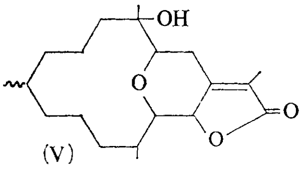
(II)



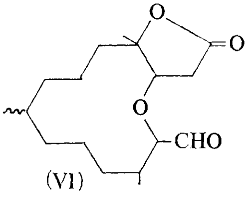
(III)



(IV)



(V)



(VI)

Eunicin (Ia) showed hydroxyl (3623 cm.$^{-1}$), αβ′-unsaturated lactone (1765 cm.$^{-1}$) and olefinic (1664 cm.$^{-1}$) absorptions in the infrared. Its two unsaturations were characterized as $-CMe{=}CH{\cdot}CH_2-$, based on the methyl singlet at δ 1·52† and the one proton triplet at δ 5·07 (*J* 7·5) (eunicin oxide, $C_{20}H_{30}O_5$, m.p. 188°), and as a conjugated *exo*-methylene, doublets at δ 5·70 (*J* 3·3) and 6·40 (*J* 3·5) (pyrazoline with $CH_2N_2$, $C_{21}H_{32}N_2O_4$, m.p. 122°) coupled (n.m.d.r.) to the β proton at C(1), a very broad signal at δ 3·40.

Acetylation of the oxidation resistant hydroxyl, $-C(Me)OH-$, shifted the methyl singlet at δ 1·15 to 1·45 in the acetate [(Ib), $C_{22}H_{32}O_5$, m.p. 157°,

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† The n.m.r. spectra were recorded in $CDCl_3$ and the coupling constants are in Hz.

no hydroxyl absorption]. The remaining methyl signal was a doublet at $\delta$ 0·85 (*J* 6·5).

The $\alpha\alpha'$-protons of a di-secondary ether appeared as a doublet, $\delta$ 2·85 (*J* 9·5) and a double doublet, $\delta$ 3·25 (*J* 11 and 2·5). The latter signal shifted to $\delta$ 3·80 and 3·93 in the *exo*- ($C_{20}H_{28}O_3$, m.p. 132°, 2H singlet at $\delta$ 4·92) and oily *endo*-forms‡ (1H, broad, at $\delta$ 5·70) of anhydro-(Ia) [formed by treatment of (Ia) with $SOCl_2$ in pyridine] on becoming allylic. The former ether signal was coupled (n.m.d.r.) with the lactone proton at C(2) appearing as a double doublet at $\delta$ 4·43 (*J* 9·5 and 7·8) in (I) and as a doublet at $\delta$ 4·52 (*J* 9·5) in isoeunicin [(II), $C_{20}H_{30}O_4$, m.p. 128°, $\nu_{max}$ 1745 cm.$^{-1}$) formed from (I) on pre-reduced platinum in a nitrogen atmosphere.

The triol [(III), $C_{20}H_{34}O_6$, m.p. 216°] resulting from permanganate hydroxylation of dihydroeunicin ($C_{20}H_{32}O_4$, m.p. 157°, $\nu_{max}$ 1770 cm$^{-1}$), obtained by sodium-butanol reduction of (I), was oxidized by Jones reagent to the keto-dilactone [(IV), $C_{20}H_{30}O_6$, m.p. 86°, $\nu_{max}$ 1712 and 1774 cm.$^{-1}$] in which the C(20) methyl singlet appeared at $\delta$ 1·40, as in (Ib). The simple methylene character of C(6) and C(7) was demonstrated by the triplet (2 H) at $\delta$ 4·08 (*J* 6) of the acetate ($C_{20}H_{30}O_7$, m.p. 133°, $\nu_{max}$ 1230, 1730, and 1775 cm.$^{-1}$) derived from (IV) with peroxytrifluoroacetic acid.

Catalytic hydrogenation of (I) led to a mixture of dihydroisoeunicins epimeric at C(8) [(V), $C_{20}H_{32}O_4$, m.p. 178—180°, $\nu_{max}$ 1740 cm.$^{-1}$], ozonolysis of which produced the aldehyde lactones [(VI), $C_{17}H_{28}O_4$, m.p. 93—100°, $\nu_{max}$ 1735 and 1780 cm.$^{-1}$] in which the C(20) methyl singlet was again shifted to $\delta$ 1·39.

The absence of further vicinal coupling of the C(3) ether proton absorption was compatible only with the location of the secondary methyl at C(4) in a stereochemical disposition permitting an approach to 90° for the value of the H–C(3)–C(4)–H dihedral angle.[4] The structure thus adduced for eunicin is shown in (Ia), which incorporates the stereochemical detail of the corroborating *X*-ray crystallographic results obtained[3] for eunicin iodoacetate (Ic). In the crystalline state, (Ic) displays the required 76° H–C(3)–C(4)–H dihedral angle.

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‡ This compound was susceptible to air oxidation, and was the only compound for which a satisfactory elemental analysis was not obtained.

[1] L. S. Ciereszko, D. H. Sifford, and A. J. Weinheimer, *Ann. New York Acad. Sci.*, 1960, **90**, 917.
[2] L. S. Ciereszko, unpublished observation.
[3] M. B. Hossain, A. F. Nicholas, and D. van der Helm, following Communication.
[4] S. Corsano, J. M. Mellor, and G. Ourisson, *Chem. Comm.*, 1965, 185.