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MARINE NATURAL PRODUCTS: FUSCOL, A NEW ELEMENE-TYPE DITERPENE ALCOHOL FROM THE GORGONIAN *EUNICEA FUSCA*.

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Diterpenes isolated from gorgonians (sea fans and sea whips) of the Caribbean and from alcyonaceans of the Pacific Ocean nearly all have a cembrane skeleton or one derivable from it by further cyclization.[1] The few non-cembranoid diterpenes isolated from these sources have been obtained from alcyonaceans. These include xenicin,[2] which has a monocyclic nine-membered ring skeleton, and the alcohols 1 and 2,[3] which possess the cyclization pattern characteristic of the eudesmane family of sesquiterpenes. We wish to report the isolation of the first non-cembranoid diterpene from a Caribbean gorgonian. The new compound, fuscol (3), is representative of a new class of diterpenes having a skeletal arrangement observed only among the elemene-type sesquiterpenes[4] until recently. Several related compounds have been obtained from alcyonaceans of the Pacific[5a] and various algae.[5b-d]

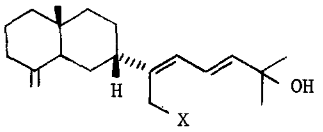
Fuscol (3) was isolated from Eunicea fusca, a gorgonian collected near South Caicos, W. I. The dichloromethane solubles from an isopropyl alcohol extract were partitioned between hexane and methanol-water (9:1), and the hexane fraction was chromatographed on tlc mesh silica gel. Selected fractions were rechromatographed rapidly over 5% silver nitrate-silica gel to give two clear oils, fuscol (3) and the ketone 4. Considerable losses of material were experienced during the chromatographies.

Fuscol (3), $[\alpha]_D$+16.3 ($C_{20}H_{32}O$, M^+, 288; M^+-18, 270), shows ir[6] (3380 cm^{-1}) and uv absorption (λ max 239 nm, ε 31,354; sh at 234, 246 nm, ε 29,682, 24,889) corresponding to hydroxyl and conjugated diene groups. The nmr spectrum[6] showed five singlet methyl signals indicative of a terpene skeleton and a dimethyl carbinol: 1.01 quaternary methyl; 1.36, 6H, geminal dimethyl group deshielded by oxygen; and 1.72, 1.80 ppm, vinyl methyl groups. The absence of signals in the 2.10-4.50 ppm region corroborated the tertiary alcohol assignment as did europium shift experiments, see below. Eight olefinic protons were revealed by low field nmr signals (see below) and these plus the two vinyl methyl groups accounted for four double bonds. This suggested that 3 must be monocyclic.

Several of the signals in the olefinic region were superimposed and a definitive interpretation was possible only after addition of shift reagent. However, irradiation of the peaks at 4.63 and 4.84 ppm in the routine spectrum[6] resulted in sharpening of the methyl resonance at 1.72 ppm, thus providing evidence for an isopropenyl group. In the presence of shift reagent (0.22 mole ratio Eu(fod)$_3$: 3), the geminal dimethyl group signal experienced the greatest shift, to 3.62 ppm, thus confirming the $-C(CH_3)_2$ -OH assignment. The 1.80 ppm vinyl methyl resonance moved downfield slightly, to 2.01 ppm, while the remaining vinyl methyl, quaternary methyl, and aliphatic proton signals were virtually unaffected. However, three of the olefinic proton multiplets were shifted downfield and became evident as distinct multiplets at 8.46 (dd, J = 16 11), 8.00 (d, J = 16) and 6.48 ppm (brd d J = 11). Decoupling confirmed the apparent interrelationship of these signals. The induced shifts and coupling of these signals suggested the partial structure $-C(CH_3)=CH-CH=CH-C(CH_3)_2-OH$ that is common to 1 and 2[3]. An E configuration can be assigned to the disubstituted double bond on the basis of the 16 Hz coupling of the sharp doublet at 8.00 ppm, but the geometry of the trisubstituted double bond cannot be specified.

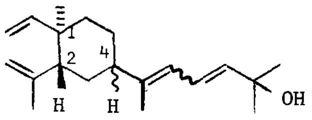
The remaining olefinic proton signals in the shifted spectrum could be attributed to an isopropenyl group (broad singlets at 4.62 4.84) and a vinyl group bonded to a quaternary center (ABX multiplet: 4.91, d, 18; 4.92, d, 10; 5.84 ppm, dd, 18, 10). The upfield members of the A and B signals were superimposed on one of the isopropenyl methylene hydrogens. Irradiation at 4.99 ppm collapsed the 5.84 ppm resonance to a broad singlet at 5.80 ppm.

The structural units identified thus far account for fourteen carbons, excluding the carbons to which these units are attached. Hence, the carbocyclic ring in fuscol must be six-membered or smaller. Arrangement of the defined structural units around a six-membered ring guided by biogenetic considerations leads to 3 as the most logical structure for fuscol. This structure contains the skeleton of the well-known sesquiterpene elemene,[4] extended by an additional isoprene unit in the alcohol bearing side chain. The data do not permit unambiguous assignment of configuration at C-4; the configurations at C-1 and -2 are discussed below.

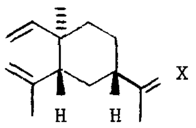


1 X = H

2 X = OH



3



4 X = =O

5 X = $<^{CH_3}_{OH}$

The second compound isolated from E. fusca was characterized as a ketone (ir 1712), M^+, 206, $C_{14}H_{22}O$. The nmr spectrum showed singlet signals for three methyl groups: 1.00, quaternary methyl; 1.72, vinyl methyl, and 2.16 ppm, CH_3-CO-. The olefinic region contained a four-line signal at 5.83 ppm (dd J = 18, 10) indicative of the X portion of an ABX signal arising from a vinyl group attached to a quaternary center. This was accompanied by signals at 4.60 (brd s) and 4.80, 5.00 ppm identical to those in fuscol which correspond to the AB portion of the vinyl group plus the methylene signals from an isopropenyl group. In view of the structure proposed for fuscol, these data suggested the structure 4 for the ketone.

Confirmation of proposed structure 4 was obtained by treating the ketone with methyl lithium in ether, whereupon the tertiary alcohol 5 was obtained (ir 3380 cm^{-1}; M^+, 222, M^+ -18, 204). The 270 MHz nmr spectrum of this alcohol exhibited four methyl signals (0.98, s; 1.20, s, 6H, and 1.72 ppm, s) and five clearly resolved olefinic signals: two broad singlets as expected for the isopropenyl methylene protons (4.57, 4.77 ppm) and three multiplets comprising an ABX pattern typical of an quaternary vinyl group (4.94, J = 18; 4.92, J = 10; 5.80, ppm, dd J = 18, 10.5 Hz). A one-proton doubled-doublet was observed at 1.97 ppm (J = 12, 2.9 Hz) corresponding to the allylic methine proton in 5 in an axial orientation. These data all indicate that the alcohol 5 is β-elemol. The optical rotation of 5 was found to be +5°, whereas that reported[7] for (-)-β-elemol is -5°. The rotation thus supports the structural assignment for 5, but reveals that this alcohol is antipodal to the (-)-β-elemol of plant origin. Since fuscol (3), displays a positive rotation, it seems likely that it has the same relative and absolute configuration as does 4. However, the data presented here do not permit unequivocal assignment of the stereochemistry at C-4 in fuscol.

In view of the observation[8] that a number of conventional sesquiterpenes, including elemene,[8a,b] isolated from marine sources are antipodal to the same hydrocarbons obtained from plants, it is interesting to note that fuscol has the same absolute configuration as (+)-β-elemene from marine sources. Since it has been observed in some other cases[8a,9] that elemene derivatives are artifacts arising from thermal izomerization of natural germacrene precursors, it is possible that fuscol also is a rearrangement product. The ketone 4 is likely an artifact derived from 3 or related compounds during chromatography, since there was no evidence by tlc for 4 in the mixture from which 3 and 4 were isolated. Efforts are underway to isolate the related compounds and resolve these questions.

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6. IR (film) 3380, 3085, 1645, 1375, 965, 885 cm^{-1}; NMR ($CDCl_3$) signals not discussed in text: 4.50-5.04 (4H, m), 5.62-6.00 (3H, m) and 6.50 ppm (1H, dd, J = 10, 16); m/e 288 (M^+), 273, 270, 255, 230, 216, 201, 189, 147, 133, 119, 109, 93, 81.

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