Tetrahedron. Vol. 34, pp. 1227 to 1229. Pergamon Press 1978. Printed in Great Britain

7-HYDROXY (AND ACETOXY)-α-MULLOLENE FROM THE SOFT-CORAL *HETEROXENIA FUSCESCENS*

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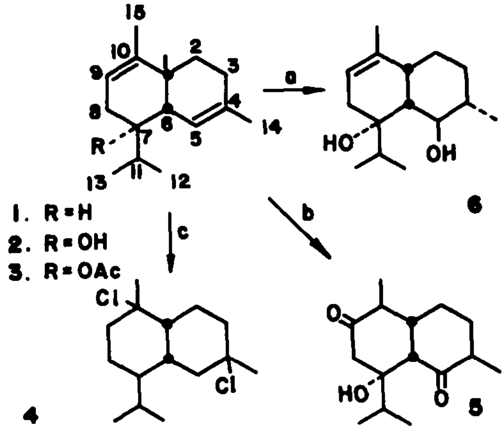
(*Received in UK* 18 *August* 1977; *Accepted for publication* 10 *October* 1977)

Abstract—The isolation and structural determination of three cadalane type sesquiterpenes from a soft coral is reported. The ^{13}C NMR of these compounds namely (+)-α-murrolene, 7-hydroxy, and 7-acetoxy-α-murrolene is discussed.

In continuation of our earlier studies[1] on the chemistry of soft-corals, we report on the isolation and structure determination of three interrelated sesquiterpenes of the cadalane type from *Heteroxenia fuscescens* (Octocorallia, Alcyonacea, Xeniidae).

Hexane extraction of freeze-dried *Heteroxenia fuscescens* (and of the aqueous emulsion collected during drying) followed by chromatographic separation resulted in the isolation of three compounds: an hydrocarbon (1) $C_{15}H_{24}$, an alcohol (2) $C_{15}H_{24}O$ and an acetate (3), $C_{17}H_{26}O_2$ in *ca.* 0.5, 0.8 and 2% dry weight respectively.

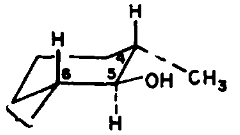
Compound 1, $[\alpha]_D = +58°$, M$^+$ 204 ($C_{15}H_{24}$, 35%), *m/e* 189 (M–CH$_3$, 10%) and 161 (M–iPr, 70%), is the major (>85% hydrocarbon content) hydrocarbon constituent. Its structure was confirmed to be (+)-α-murrolene by its NMR spectrum, δ 0.73d and 0.79d (J = 7 Hz, iPr-Me groups), 1.60 brs (two vinyl Me groups) and 5.35 m (2H); ^{13}C NMR (Table 1) and finally unequivocally by the preparation of its dihydrochloride (4).[2] (+)-α-Murrolene is one out of four possible isomers of the cadalane sesquiterpenes[3] and has already been reported to be found in marine gorgonarians.[4]



Scheme 1. a, B_6H_6, rt, 1 hr; b, B_2H_6, rt, 24 hr; c, HCl.

The second compound to be eluted was the acetate 3. Compound 3 can be converted into alcohol 2 by reduction with LAH. The ^{1}H NMR spectrum of 3 indicates the existence of two 3-substituted double bonds (–C(Me)C=CH–, δ 1.52 brs 6 H and δ 5.20 m(2 H)) an isopropyl (δ 0.85 and 0.91 d) and a t-acetoxy group (δ 1.95s). These functional groups can be further confirmed by the ^{13}C NMR spectrum (Table 1). Dihydroboration of the two double bonds of 3 followed directly by oxidation results in a diketone† (5), in which both carbonyls absorb at ν_{max} 1705–1710 cm^{-1}.[2] Based on this diketone and the above mentioned moieties compound 3 (and 2) is expected to be of the cadalane type.[3] Furthermore one of the two double bonds, of 3, must be at Δ^9 (Scheme 1) whereas for the second double bond either the Δ^3 or the Δ^4 position can be considered.

Short hydroboration (1 hr at rt) converts 3 (or 2) to diol 6 in which only one double bond is attacked. A one proton signal adjacent to the incoming OH group is observed in the NMR spectrum of 6 at δ 3.44 as a triplet with a coupling constant of 9 Hz (in addition to the remaining vinylic proton at δ 5.35). A triplet with a coupling constant of 9 Hz is best rationalized by coupling of the corresponding proton with two vicinal, to the OH, α, α'-axial protons. The best place for the OH group, which fulfills the above requirements, is at C-5 as shown by the following partial structure (a):



a

This means that the second double bond in 3 is at Δ^4 (placing the OH group at C-3, if Δ^3 would have been the location of this double bond, or at C-9, if the Δ^9 double bond would have been the first bond to be hydroborated, should both cause a different NMR pattern of CHOH).

The location of the acetoxy group of 3 (and hence of the OH at 2) has been assigned carbon-7 on the basis of the ^{1}H NMR spectrum recorded on a 270 MHz NMR instrument; the isopropyl proton signal appears in this spectrum as an heptet at δ 2.16 (J = 7.1 Hz) coupled by the two Me groups only. This finding is also in accordance with LIS experiments performed on 2 and 3 (Tables 1 and 2), as well as the suggested fragmentation pattern for the mass spectra of 2 and 5 (Scheme 2).

The ring fusion stereochemistry of 3 was established next. The ^{13}C NMR spectrum, which is known to distinguish between *cis* and *trans* dekalins, is equivocal in this specific case because of the unpredictable influence of the double bonds.† Attempts which have been under-

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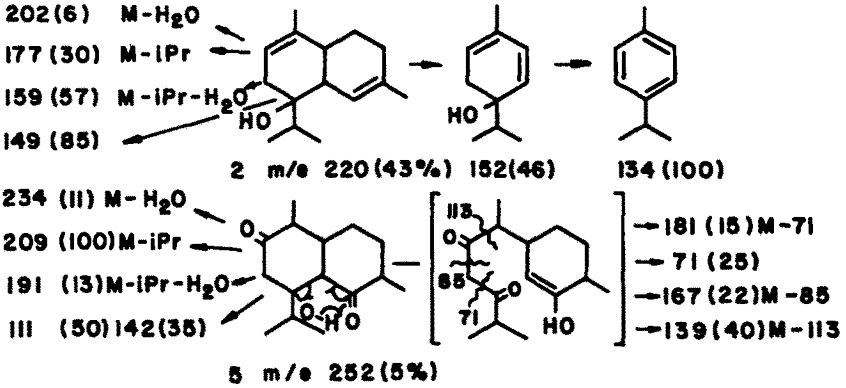
†It is well known[7] that upon introduction of a double bond into a 6-membered ring, the allylic carbons may be slightly shielded or deshielded, while the homoallylic carbons are either strongly shielded or, in some cases, little affected.



Scheme 2.

taken to hydrogenate 3 resulted in mixtures. The ring fusion mode could however be assigned upon the 270 MHz NMR spectrum; almost all of the methylene and methine molecule protons gave rise to separate resonance lines: 1.72 brd (J = 16.5 Hz, 2 H), 1.84 brd (J = 17 Hz, 1 H), 1.99 brd (J = 16.5 Hz, 1 H), 2.16 hep (J = 7.1 Hz, 1 H), 2.34 brd (J = 16.5 Hz, 1 H), 2.37 m ($\Delta W_{1/2}$ = 8 Hz, 1 H), 2.71 dd (J = 5.5 and 17 Hz, 1 H), 3.00 m ($\Delta W_{1/2}$ = 10 Hz, 1 H), and 5.27 m (2 H).

The two relatively narrow signals at δ 2.37 and 3.00 ($\Delta W_{1/2}$ = 8 Hz and $\Delta W_{1/2}$ = 10 Hz respectively) must belong to H-1 and H-6, the only methylene protons which are not part of a geminal pair ($J_{gem} \simeq$ 16–18 Hz).

Table 1. ^{13}C Chemical shifts[a] of compounds 1–3

C atom	multiplicity	1	2	3[d]	LIS of 2[e]
C-12,13	q	15.9	15.9	17.5	1.9
		21.3	17.5	18.5	1.5
C-15	q	21.5	21.1	20.3	0.7
C-14	q	23.7	24.1	24.0	0.3
C-2[b]	t	(24.5)	24.3	24.7	1.1
C-8[b]	t	(24.6)	28.6	26.7	0.8
C-3[b]	t	30.4	31.0	31.0	2.9
C-1[c]	d	39.0	37.9	36.7	1.5
C-6[c]	d	26.5	33.3	31.7	2.5
C-11[c]	d	36.6	39.7	40.4	2.2
C-7		41.0d	74.8s	89.2s	6.7
C-5,9	d	121.1	119.2	120.0	1.7
		123.8	119.2	121.0	2.2
C-4,10	s	134.0	134.7	133.3	1.7
		135.8	137.2	135.5	1.7

[a] In ppm from internal TMS in CDCl$_3$. Parentheses indicate that assignments are not unambiguous.

[b] Tentative assignment based on model monoterpene compounds,[5] substitution effects[6] (e.g. C-2 should be upfield shifted by a Me$_{15}$ γ-effect) and the assumption that C-2 and C-3 should be less influenced by the C-7 substitution. Possible conformational mobility complicates the identification.

[c] Assignments may be changed—see note b.

[d] COCH$_3$, 169.9 and 22.3.

[e] Δδ values for Eu(fod)$_3$/2 ratio of 0.4.

If a *trans*-dekalin skeleton would be incorporated in compound 3 a dihedral angle of *ca.* 180° between H-1 and H-6 should result and consequently, a mutual coupling constant of 8–10 Hz should be measurable. At least H-1 is expected to be further split by the C-2 protons in the order of $J_{H-1/H-2(ax)} \simeq$ 7–10 Hz and $J_{H-1/H-2(eq)} \simeq$ 2–4 Hz causing a significant broadening of the H-1 signal up to $\Delta W_{1/2} \simeq$ 17–24 Hz—which is not the case. The *cis*-fusion, however, does agree with the finding as the $J_{H-1/H-6}$ in this case is expected to be in the order of *ca.* 4–6 Hz only (the corresponding dihedral angle being about 60°).

The last structural feature which has to be accounted for is the stereochemistry at C-7. Each one of the two C-7 isomers (7α-OR and 7β-OR, R=H or Ac) can exist in two conformers: A—the conformer in which H-1 is axial towards the more substituted ring and B in which H-1 is equatorial towards this ring—as is known for *cis*-dekalin. Differentiation between the isomers is achieved by ^{13}C NMR and ^{1}H NMR LIS-measurements (Tables 1 and 2). This leaves us with structures 7α-OR (A) and 7β-OR (B) the NMR spectra of which agree with the above results. However, inspection of Dreiding and CPK models of the isomers reveals that 7β-OR (B) is of low probability because of severe interactions of the axial iPr-group with the less substituted ring. Thus the 7α-OR seems to have the right configuration, namely, compound 3 should be 7-acetoxy-α-murrolene (experiments conducted to convert either 2 or 3 into 1 have so far failed).

At last, it is worthwhile to mention the total high percentage of organic material in the *Heteroxenia fuscescens* (8–10% dry weight) which contains mainly a mixture of glycerides and sterols. In contrast to the diversity in terpenoid composition reported for other soft-corals, no significant changes of the organic components with place, depth, and time of collection, could be observed.

Table 2. LIS measurements of compounds 2–3[a]

Proton Comp.	H$_5$	H$_6$	H$_8$	H$_9$	H$_{11}$	Me$_{12}$	Me$_{13}$	Me$_{14}$	Me$_{15}$	OAc	Eu(fod)$_3$/sub
2	1.03	1.2	1.6[b]	0.47	0.8[b]	0.53	0.68	0.24	0.03		0.18
3	1.1	0.9	1.7	0.40	0.9	0.60	0.90	0.15	0.15	1.7	0.20

[a] All other protons are less shifted and/or unresolved.

[b] Estimated.

EXPERIMENTAL

M.ps were taken on a Thomas Hoover capillary m.p. apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Infracord model 257. NMR were taken on Jeol JNM-C-60HL, Bruker WH-90 and Bruker HX-270 spectrometers using 5–10% soln in $CDCl_3$ with TMS as an internal standard. Mass spectra were recorded with a DuPont 21-491B instrument. $[\alpha]_D$ were taken on a Bellingham and Stanley polarimeter in $CHCl_3$ solns.

Isolation procedure of compounds 1, 2 *and* 3. Freeze-dried *Heteroxenia fuscescens* (60 g) was extracted during 48 hr with petrol-ether in a soxhlet to give 7 g crude extract. This extract was combined with the ether-extract of the aqueous freeze-dried emulsion (1 g) and then chromatographed on a silica gel (Merck 7734) column. Elution with hexane gave 1 (200 mg); further elution with hexane–chloroform 1:1 gave first mainly acetate-3 (1.5 g) and then alcohol 2 (2.5 g). Compounds 2 and 3 were both purified from glycerides by distillation at 0.1–0.01 mm Hg. The homogeneity of compounds 2 and 3 was confirmed by: (a) TLC on Silicagel (Merck 5735) as well as aluminum oxide (Merck 5550) plates (PhH-EtOAc, petrol ether—$CHCl_3$ and hexane-acetone), and (b) VPC which was carried out on a 5% SE-30 on GCQ column (6 ft, 1/8 in) at 160° (RT being 19 min and 8.5 min for compounds 2 and 3, respectively) and on a 10% OV-17 on GCQ column under the same conditions. Compound 1, b.p. 40°–50°/0.1 mm Hg; Found: M^+ 204 (35%), $C_{15}H_{24}$ requires: 204; $[\alpha]_D = +58°$ ($[\alpha]_D$ of (−)-α-murrolene −53°,[2a] and $[\alpha]_D$ for (+)-α-murrolene +67°);[4] ν_{max} 830, 803 cm^{-1}; dihydrochloride (4), m.p. 85° (EtOH),[2a] $[\alpha]_D = +14°$. Compound 2, b.p. 70°/0.03 mm Hg, m.p. 65°–70° (hexane), $[\alpha]_D = -20°$ (Found: C, 81.85; H, =10.85, $C_{15}H_{24}O$ requires: C, 81.76; H, 10.98%): mass spectrum see Scheme 2, NMR: δ 0.90 d (J = 7, Me_{12} and Me_{13}), 1.70 s and 1.72 s (two vinyl Me groups), 5.32 m and 5.55 m (two vinyl protons). ν_{max}^{neat} 3450, 1450, 1380, 1160, 1130, 1070 cm^{-1}. Compound 3, b.p. 110°–120°/0.1 mm Hg, *m/e* (%) 220 (0.7, M–CH_2=C=O), 202 (12, M–CH_3CO_2H), 187 (6); ν_{max}^{neat} 1740, 1440, 1370, 1250, 1200, 1115, 1020 cm^{-1}.

Hydroboration of 2 (*or* 3) *to diketone* 5 *and diol* 6. To a soln of 2 (100 mg) (or 3, 100 mg) in THF (10 ml) a soln of diborane in THF (Aldrich, 1.5 ml) was added. After stirring at rt for 1 hr, H_2O_2 (30%, 0.5 ml) and 3 N NaOH (1 ml) were added and the soln was heated to 40°–50° for 1 hr. Chloroform (25 ml) was then added and the organic layer washed with water several times, dried and evaporated to give 6 which was purified by chromatography to give low melting oily crystals; *m/e* (%) 238 (0.1), 220 (25), 202 (10), 195 (55), 177 (100), 159 (80), and 149 (90); NMR: δ 0.80–1.00 three doublets (J = 6, Me_{12}, Me_{13} and Me_{14}), 1.58 s(Me_{15}), 3.44 t (J = 9 Hz, H-5) and 5.24 m (H-9).

Overnight hydroboration followed up by the same procedure as described above resulted in a triol which was directly oxidized by Jones reagent to give 5; an oil, ν_{max}^{neat} 1705–1710 cm^{-1}, mass spectrum see Scheme 2. NMR: δ 0.68–1.05 all four Me's (the compound may be more than one stereoisomer).

Acknowledgement—We wish to express our appreciation to Dr. Y. Loya and Y. Benayahu for collecting the soft coral.

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