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ANTHELIOLIDE A & B: TWO NEW C_{24}-ACETOACETYLATED DITERPENOIDS OF THE SOFT CORAL *ANTHELIA GLAUCA*

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Abstract - Two new derivatives of xenicin and two novel C_{24} - acetoacetylated diterpenoids, antheliolide A & B (8 & 9)have been isolated from *Anthelia glauca*. The structure of compounds 8 & 9 was established by 2D-NMR techniques and a biogenesis starting from GeGePP *via* xeniaphyllane is suggested.

The soft corals are known to be a source of many diterpenoids. Many of these diterpenes belong to a single class, the cembranoids (e.g. metabolites of the genus *Sarcophyton*, *Nephtea*, *Sinularia* and *Lobophytum*)[1]. The genus *Xenia*, on the other hand produces other prominent bicyclic, 9-membered macrocyclic diterpenes[2]. Included in these *Xenia* diterpenes are the xeniaphyllanes, xenicins and xeniolides (e.g. compounds 1,2 & 3, Scheme 1).

Herewith we report on the diterpenoids of the soft coral *Anthelia glauca* which is closely related to the *Xenia* genus - both belonging to the same family *Xeniidae*. Chromatography of the CH_2Cl_2-extract of *Anthelia glauca* (40 gr dry wt) collected near Shaab Mahamud (The Gulf of Suez, The Red Sea) in July 1986, yielded besides others, compounds 2-9. Four out of these compounds, that is, xeniculin (2), xeniolide A (3), isoxeniolide A (4) and xeniolide B (5) were readily identified according to their spectral data [2].

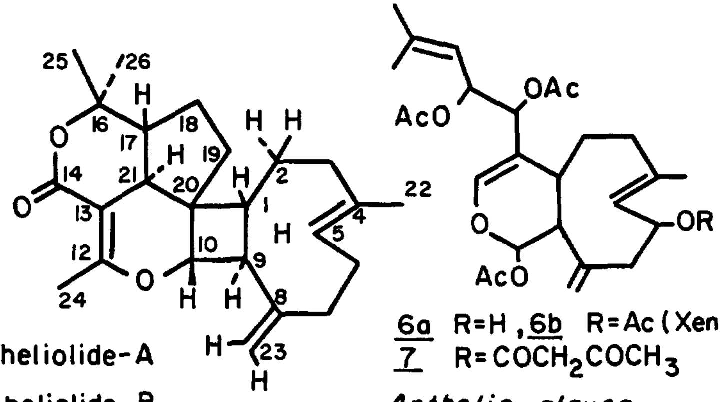
Triacetate 6a[3], $C_{26}H_{36}O_8$, was suggested to be 9-desacetyl xenicin according to overlapping of almost all the proton-signals except for H-9, which is upfield shifted to δ_H 4.75 brt. Indeed, acetylation of 6a with Ac_2O/Pyr. at r.t. afforded xenicin (6b)[2a].

Compound 7[4] showed ^1H NMR absorptions indicative of the xeniane skeleton and very similar to those of xenicin and compound 6a. Outstanding in the NMR spectrum was the downfield shift of one of the four acetates to δ_H 2.39s and an additional two-proton singlet at δ_H 3.40ppm. The chemical shifts (as compared to methylacetoacetate; δ_H 2.30 and 3.50 ppm) and the correlation between the latter two singlets, observed in a COSY experiment, established the replacement of one of the xenicin acetates by an aceto-acetate ester in compound 7. Although no molecular ion could have been seen even in the CI-MS of compound 7, one to five losses of 60 and/or 42 m.u. (HOAc and CH_2=C=O respectively) were observed. Comparison of the proton NMR data of compound 7 and xenicin suggests, tentatively, the 9-acetoacetyl-9-desacetyl xenicin structure for 7. Instability of the compound and the limited available amounts of material avoided, so far, further studies.

The least polar material isolated from the *A. glauca* extract seemed to be a 1:4 mixture of two components, however, as all attempts to separate the mixture by various chromatographic methods failed we continued with the unresolved mixture (8)[5]. Eventually, it turned out that we had on hand a mixture of two conformers as confirmed by the chemical exchanges observed in an NOE experiment. The existence of two atropoisomers *vide infra*, of course, complicated to a great extent the interpretation of the NMR spectra of compound 8.

Compound 8[5] designated antheliolide A, $C_{24}H_{32}O_3$, 9-unsaturations, νmax 1685 cm^{-1} possesses three double bonds: one three substituted bond (-CH=CMe-), one terminal methylene and one highly polarized tetrasubstituted bond (δ_C 105.0 and 162.7 ppm). The polarization suggested that the latter double bond is conjugated to the lactone carbonyl (δ_C 167.0 ppm), and carries the very low-field resonating methyl (δ_H 2.75, C_6D_6). Two additional methyls (δ_H 1.35, and 1.36 ppm) are proposed to be vicinal to an oxygen ($OCMe_2$). The above functionalities account for four out of the nine unsaturations of the molecule. Antheliolide A has, therefore, to be pentacyclic. As there are no acidic protons in 8 (according to the IR and the carbon NMR spectrum which accounts for all-32 protons) two oxygen bridges and three carbocycles are anticipated. The spectral data suggest that the two heterocycles are a lactone ring and, most likely, a cyclic enol-ether.

A C-H correlation experiment (Table 1) established all one bond C-H correlations and hence also determined the six geminal proton pairs. This assignment assisted considerably with the interpretation of the homonuclear COSY experiment. An experiment which established the complete structure of the three carbocycles [6]. Obtaining of a bicyclo [7.2.0] system, as in caryophyllene and the xeniaphyllanes, explained the two atropoisomers, *vide supra*, as a result of the strained nine membered ring.[2] Next, a long-range CH-correlation experiment (Table 1) not only confirmed the alicyclic part of the molecule but also established the position of the oxygenated site of the moloecule as shown in Fig. 1.



8 Antheliolide-A

9 Antheliolide-B (8,23-epoxy A)

6a R=H, 6b R=Ac(Xenicin)

7 R=$COCH_2COCH_3$

Anthelia glauca

Figure 1

The mass spectrum of antheliolide A is in full agreement with the proposed structure, that is, as with caryophyllene and the xeniaphyllanes, there is a prominent cleavage of the cyclobutane ring to give the unsaturated nine membered ring: $C_{11}H_{16}$ (m/e 148, 100%) and M-148 (31%).

The suggested stereochemistry of antheliolide A, as shown in Fig. 1 is based on dNOE and CONOESY experiments - summarized in Fig. 2.

Of special interest is the biosynthesis of the antheliolides. A possible biogenesis leading from GeGePP *via* the xeniaphyllanes to the xenicins, xeniolides and to the antheliolides is given in Scheme 1. The proposal suggests the new compounds (8 & 9) to be acetoacetylated diterpenes. Isolating of compound 7 together with 8 & 9 supports the availability of the acetoacetate either for simple esterifiatios or in a more complex way, as described, for the C_4 alkylation with a unit which enables, due to its functionalities, further transformations.

Table 1. Proton and Carbon 13 Data for antheliolide A (8).

C No.	C	H at C (J,Hz)	Long Range CH-Corr.		C No.	C	H at C (J,Hz)	Long Range CH-Corr.	
			^2J	^3J				^2J	^3J
1	46.8d	1.78t (13.5)		3α,3β,19	13	105.0s		21	17,24
2	30.6t	1.47			14	167.0s			24(^4J)
		1.63			16	84.0s		25,26	
3	39.7t	2.08 (β)		1,22	17	57.8d	1.48		25
		2.19 (α)			18	27.6t	1.28 (α)	17	
4	134.3s		22				1.47 (β)		
5	125.3d	5.47dd(10.5,5.5)		22	19	42.1t	1.97 (α)		1,10
6	29.4t	2.15 (β)		7α,7β			2.04 (β)		
		2.45 (α)			20	40.4s		1	
7	33.7t	2.03 (β)		23en.,23exo	21	37.6d	2.67dd(11,1)		1,10
		2.25 (α)			22	16.7q	1.62s		
8	149.6s			1,6α,10	23	115.4t	5.03brs (exo)		7β,9
9	60.4d	2.40dd (13.5,7.7)		23en.,23exo			5.09brs (endo)		
10	80.8d	4.40d (7.7)	9	19	24	20.8q	2.75brs		
12	162.7s			10	25	30.0q	1.36brs		26
					26	22.7q	1.35brs		25

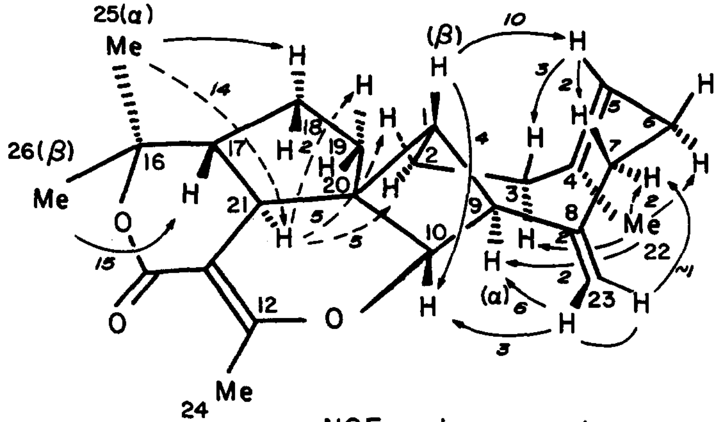
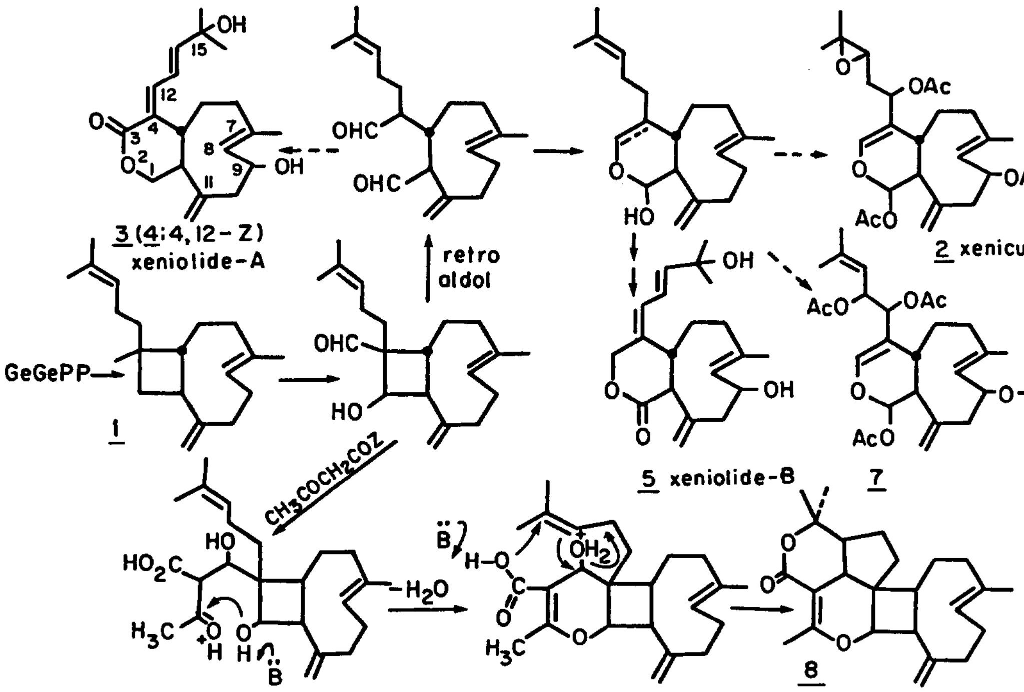


Figure 2

NOE-enhancements

Compound 9[7], $C_{24}H_{32}O_4$, named antheliolide B, the major constituent of the crude extract (up to 10% dry wt.) was determined on the grounds of NMR comparisons to be the 8,23-epoxy derivative of antheliolide A. Apart from δ- changes in the 8,23 moiety (δ_C 56.4s, 55.8t, δ_H 2.31d & 2.97d, J_{gem} = 5Hz) and small changes in the α and β vicinal groups, the chemical shifts of the rest of the atoms are very close to the corresponding ones in compound 8.

Already earlier it has been shown by us that the xeniaphyllanes as well as caryophyllene readily oxidise by air to give the 4,5 - epoxides[2]. The same was now found to be the case with compound 8 which produces in high yield the 4,5-epoxide by air oxidation of its thin film on glass. The same epoxide was also obtained by m-CPBA epoxidation of 8. Obtaining of the 4,5-epoxide by the above epoxidations ascertains that compound 9 is a natural product and not an oxygenation artefact.



Z = OH or Enz. Proposed biogenesis of xeniolides, xenicines and antheliolides

Scheme 1

References and Notes

1. A.J. Weinheimer, C.W.J. Chang and J.A. Matson, Fortschr. Chem. Org. Naturst, 36, 281 (1979).

2a. D.J. Vanderah, P.A. Steudler, L.S. Ciereszko, F.J. Schmitz, J.D. Extrand and D. Van der Helm, J. Am. Chem. Soc., 99, 5780 (1977).

b. A. Groweiss and Y. Kashman, Tetrahedron Lett. 2205 and 4833 (1978).

c. A. Groweiss and Y. Kashman, Tetrahedron 39, 3385 (1983) and references therein.

3. Compound 6a, an oil; δ_H5.85d(H-1,J=2), 6.56d(H-3,J=2), 5.21d(H-8,J=7), 4.75brt(H-9), 5.35d (H-12,J=9), 5.78t(H-13,J=9), 5.02brd(H-14,J=9), 4.96s & 4.75s(H_2-19)2.04, 2.03 & 2.02(3xOAc), 1.85, 1.72, 1.65(3xMe's).

4. Compound 7, an oil; EIMS m/e 500(28%,M^+-HOAc), 442(75), 441(100), 440(20) & 312(5); δ_H5.82brs (H-1),6.55brs(H-3),5.24d(H-8,J=7),5.76d(H-9,J=9),5.34d(H=12,J=9),5.72dd(H-13),5.04brd(H-14), 4.95 & 4.79(H_2-19), 2.03(3xOAc), 1.82, 1.71 & 1.61(3xCH_3's), 2.29s & 3.50s (acetoacetate).

5. Antheliolide A(8), mp 160°C; EIMS m/e 368(M^+,2%),324(1),338(4),220(31),148(100) & 133(19).

6. The carbon chemical shifts of the four and nine membered rings are in very good agreement with the corresponding ones in caryophyllene and the xeniahyllanes[2].

7. Antheliolide B(9), an oil; EIMS m/e 385(28%), 221(36), 204(22), 164(50), 148(100); $\delta_H(C_6D_6)$:5.72brt(H-5,J=7.6), 1.78m(H-1), 2.04d(H-9,J=6.6), 3.98d(H-10,J=6.6), 2.53brd(H-21, J=12), 2.31d and 2.97d(H_2-23,J=5), 2.65, 1.53, 1.17, 1.16(4xMe's); δ_C35.0(C-3), 56.4s(C-8), 56.1d(C-9), 77.8d(C-10), 55.8t(C-23) all the other δ_C-values are almost identical with the corresponding ones in 8.

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