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XENIOLIDE-A AND XENIOLIDE-B, TWO NEW DITERPENOIDS FROM THE SOFT-CORAL XENIA MACROSPICULATA

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Xenicin (1), isolated by Schmitz and coworkers[1] from xenia elongata, is the first reported diterpenoid possessing a oxabicyclo[7.4.0]tridecane skeleton. We describe here the structure of several other closely related compounds from another species of the xenia genus, namely, xenia macrospiculata (from the Gulf of Eilat, the Red Sea). Xenia macrospiculata was found to be very rich in diterpenoids; at least seven C_{20}- compounds (2-8) exist in the petrol ether extract of this xenia[2], and at least five others are present in the more polar ethyl acetate extract.

We recently described the structure elucidation of three of the seven less polar compounds[3], namely, xeniculin (2) which closely resembles xenicin (1) (possessing the same new oxabicyclic skeleton), xeniaphyllenol (3) and xeniaphyllenol oxide (4). The two latter compounds differ only in the addition of a 4,5-epoxy group in 4, and both are isoprenologues of caryophyllene.

Two additional olefin-epoxide pairs that accompany 2-4 in the petrol ether extract were identified by us, by spectroscopic and chemical means, to be isoxeniaphyllenol (5), acetoxyxeniaphyllendiol (7) and their corresponding 4,5-epoxides 6 and 8 respectively[4].

As discussed previously,[1,3] the xeniaphyllanes might be intermediates in the biosynthesis of the diterpenoids which possess the oxabicyclo[7.4.0]tridecane skeleton: that is, oxidative cleavage of the cyclobutane ring together with oxidation, to various degrees (vide infra), of the quaternary methyl group (e.g. C_{18} in 3) followed by recyclisation to a di or tetrahydropyran derivative will produce compounds like 1 and 2.

Repeated chromatographies of the ethyl acetate extract on a Sephadex LH-20 column (elution with hexane-chloroform-methanol 2:1:1), followed by a chromatography on a silica gel column (elution with chloroform and rising percentage of ethyl acetate), gave in a pure state two of the more polar compounds (9 and 10), which we named xeniolide-A (9) and xeniolide-B (10).

Compound 9 is a viscous oil, $C_{20}H_{28}O_4$, $\alpha_D^{25°}$ - 6° (c=2.9,$CHCl_3$) with the following spectral data: λ_{max}^{MeOH} 268 nm (ε= 15,500; $\nu_{max}^{CHCl_3}$ 3660, 3600, 3470br (OH), 2970, 2920, 2850, 1715 (C=O), 1635 (C=C), 1605 (C=C), 1380,1315,1180,1100, 1030,970,905 ($C=CH_2$) and 845 cm^{-1}; m/e (%): 332 (M^+,3), 330 (M^+-H_2,10), 314 (M^+-H_2O,80), 299 ($M^+-H_2O-CH_3$,30), 296 (M^+-2H_2O,31), 286(28), 271(50), 218(28), 159(28), 121(33), 119(99.5) and 117(100); ^{13}C-NMR[5]: 171.2s ($-CO_2-$), 147.4s, 115.6t ($>C=CH_2$), 151.1d 136.5d,132.7s,119.8d ($-CH=CH-CH=C<$), 132.7s,130.8d ($>C=CH-$), 71.0t ($-OCH_2-$), 71.0s ($-\overset{|}{\underset{|}{C}}-O$) 67.4d ($>CH-O$ 49.7d,42.6d (two methines), 44.8t,40.1t,38.0t (3 methylenes), 29.8q,29.8q and 17.5q (3 Me's);

^{1}H-NMR^6: 6.92d (J=11.4, H-12), 6.53dd (J= 15.0 and 11.4, H-13), 6.26d (J= 15.0, H-14), 5.32brd (J= 7.6, H-8), 5.09s and 4.91s (H-19,19'), 4.78brt(J=7.0, H-9), 4.08dd (J=11.4 and 5.6, H-1), 3.61t (J=11.4, H-1'), 3.12m (H-4a), 2.52-2.17m (H-6,6' and 10,10'), 2.07m (H-11a), 1.63-1.55m (H-5,5'), 1.70brs (Me_{18}) and 1.38s (6H,$Me_{16 \text{ and } 17}$). The four double bonds and the ester-carbonyl, clearly seen in the ^{13}C-NMR spectrum, count for five of the seven unsaturations of the molecule; thus, xeniolide-A must be bicyclic.

The vicinity of several of the protons was established by double resonance irradiations (Table 1).

Table 1

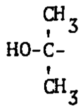
Irradiated proton	Observed changes	Irradiated proton	Observed changes
6.92 (H-12)	6.53dd(H-13)→d(J=15)	4.08dd (H-1)	3.61t(H-1')→d(J=11)
6.26 (H-14)	6.53dd(H-13)→d(J=11.4)		2.07m(H-11a)→a
5.32 (H-8)	4.78brt(H-9)→brd(J=7)	3.61t (H-1')	4.08dd(H-1)→d(J=5,6)
4.78 (H-9)	5.32brd(H-8)→brs		2.07m(H-11a)→a
	2.35m(H-10,10')→a	3.12m (H-4a)	2.07m(H-11a)→a
			1.59m(H-5,5')→a

a- change in multiplicity

The following functional moieties were deduced from the above spectral data:

$>C=CH_2$

a

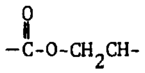


$HO{-}\overset{CH_3}{\underset{CH_3}{C}}{-}$

b

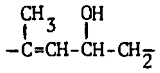
$>C{-}CH{=}CH{-}CH{=}C<$

c



$-\overset{O}{\overset{\|}{C}}{-}O{-}CH_2CH{-}$

d



$-\overset{CH_3}{\overset{|}{C}}{=}CH{-}\overset{OH}{\overset{|}{CH}}{-}CH_2{-}$

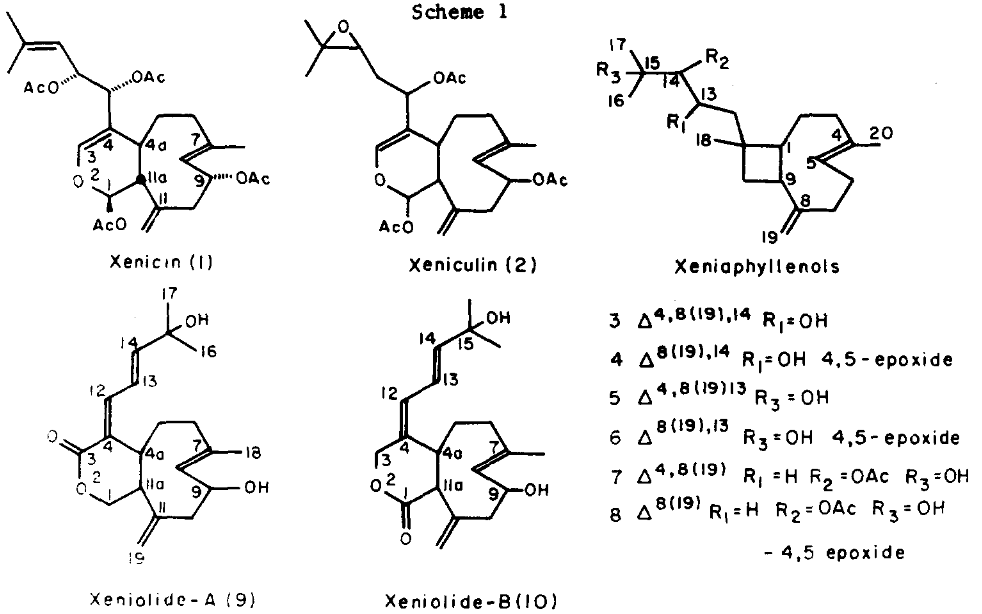
e

Fragments a-e (after combining b with c, as segment b contains the only quaternary sp^3 C-atom), account for 17-carbon atoms out of the molecule's twenty, the additional three being two CH_2 and one CH group. The 268nm absorption in the UV spectrum can be explained best by coupling of fragment c to d^7,this conjugation was further confirmed by the ^{1}H-NMR data. That is, H-12 being β- to the lactone-carbonyl,resonances as would be expected,at the lowest field (δ 6.92).

Assuming normal biosynthesis, i.e. validity of the isoprene rule and a common synthetic pathway for compounds 1,2,9 and 10 (vide infra), structure 9 (Scheme 1) is the one suggested for xeniolide-A. Although an oxabicyclo[6.5.0]tridecane structure cannot be immediately excluded, the [7.4.0] structure like that in compound 1, for which a x-ray analysis has been performed^1, seems to us to be the correct one based on the following observations: a) the chemical shifts of C-5 to C-11, taking into consideration substituent effects, are similar in compounds 2,9 and 10 (see below); b) the expected chemical shift of H-4a and the number of its neighbouring protons (confirmed by a double irradiation experiment), should differ in the [6.5.0] alternative from the observed data (δ 3.12ppm fits well an allylic proton like ours and only in this case were there three rather than five vicinal-protons) As for the configuration of the double bonds, an E-configuration for Δ^7 and Δ^{13} seemed to be unquestionable. The former assignment was based on the ^{13}C-NMR data (Me_{18} appearing at δ 17.5ppm, rather than

22-25ppm in the Z-configuration, due to a γ-effect)[8] and the Δ^{13} assignment was based on the coupling constant between H-13 and H-14 (15.0 Hz). As for the $\Delta^{4(12)}$ configuration, we prefer tentatively also the E-configuration (Scheme 1), based on preliminary NOE-experiments. According to these measurements there seem to be a spatial closeness between H-4a and H-13, whereas no NOE-effect could be found between H-4a (or H-5) and H-12, as would be expected were the Z-configuration the correct one.

Scheme 1



Xenicin (1) Xeniculin (2) Xeniaphyllenols

3 $\Delta^{4,8(19),14}$ R_1=OH
4 $\Delta^{8(19),14}$ R_1=OH 4,5-epoxide
5 $\Delta^{4,8(19)13}$ R_3=OH
6 $\Delta^{8(19),13}$ R_3=OH 4,5-epoxide
7 $\Delta^{4,8(19)}$ R_1=H R_2=OAc R_3=OH
8 $\Delta^{8(19)}$ R_1=H R_2=OAc R_3=OH
- 4,5 epoxide

Xeniolide-A (9) Xeniolide-B (10)

The second compound xeniolide-B (10), which is slightly more polar than 9 turned out to be quite unstable[9]. Attempts to crystallize this compound in a pure state have thus far failed. Xeniolide-B, $C_{20}H_{28}O_4$, $\alpha_D^{25°}$ - 4° (c=0.3,$CHCl_3$) possesses the following spectral data: λ_{max}^{MeOH} 241nm (ε= 15.900); $\nu_{max}^{CHCl_3}$ 3670,3600,3440br(OH),2960,2920,1735 (C=O), 1635 (C=C), 1460,1380, 1325,1150,1020,970 and 910 cm^{-1} ($C=CH_2$); m/e (%):[10] 332 (M^+,4), 314(M^+-H_2O,5), 296(M^+-2H_2O,2), 271 (14), 107(16), 59(52) and 41(100); ^{13}C-NMR[5]: 173.2s (-CO_2-), 145.2d,137.2s,127.6d,121.3d (-CH=CH-CH=C<), 142.3s,119.7t (>C=CH_2), 134.3s,130.4d (-CH=C<), 71.6t (O-CH_2-), 70.9s (-C-O) 70.1d (-CH-O), 57.3d,37.1d (two methines), 43.6t,39.8t,37.5t (three methylenes), 29.8q,29.8q and 19.2q (three Me's); ^{1}H-NMR[6]: 6.40dd (J= 15.3 and 11.1, H-13), 6.06d (J= 11.1,H-12), 5.97d (J=15.3,H-14), 5.40brd (J=9,H-8), 5.07s and 5.00s (H-19,19'), 4.88d (J= 11.7,H-3) and 4.43d(J= 11.7,H-3'), 4.69dt (J= 5.6 and 9,H-9), 3.14brt (J=7,H-4a), 2.92m (H-10 and H-11a), 2.10-2.30m (H-6,6' and 10'). 1.67brs (Me_{18}), 1.38s and 1.37s (3H each, Me_{16} and Me_{17}). The vicinity of the various protons were confirmed by a double irradiation experiment, summarized in Table 2. It is clear from the above data that compound 10 contains the same functional sites as in xeniolide-A (moieties a-e), except for a different mutual arrangement. Most significant were the ν_{max} of the CO-group, and the λ_{max} of the diene values. Both suggest the separation of c from d; a λ_{max} of 241nm fits well a three substituted diene[11], and the carbonyl's 1735 cm^{-1} absorption suits a saturated δ-lactone. The ^{1}H-NMR spectrum of the diene protons confirmed the disconnection (of the lactone-carbonyl from the diene), as the H-13 signal appeared now at lowest field (vide supra).

Table 2

Irradiated proton	Observed changes
6.40 (H-13)	6.06d(H-12)→s 5.97d(H-14)→s
4.69 (H-9)	5.40brd(H-8)→brs 2.90m(H-10)→a 2.15m(H-10')→a
4.43 (H-3)	4.88d(H-3')→s
3.14 (H-4a)	2.92m(H-11a)→a 1.80m(H-5,5')→a

a- changes in multiplicity

Furthermore, the $-CH_2O-CO-$ proton signals, being part of an ABX pattern in 9, changed in the spectrum of 10 into an AB quartet. The appearance of this AB at relatively low field compared to 9 suggested that it belongs to a CH_2O group which, being allylic, is further paramagnetically shifted. Structure 10 proposed for xeniolide-B (Scheme 1) explains the observed changes and is in good agreement with all the spectral data.

The configuration of the above discussed three substituted double bonds in 10 is the same as in 9, based on similar considerations. A NOE-experiment performed on compound 10 suggested, in addition to the H-4a/H-13 proximity seen before, a spatial vicinity of H-3 to H-12.

The biosynthesis of compounds 9 and 10 can be explained as starting from an intermediate of type g, or a closely reduced form. Dialdehyde g can be in equilibrium with the hemiketal enol ether f, which is an immediate precursor of xenicin (1) and xeniculin (2) (the last step in the biosyntheses of 1 and 2 being the acetylation of the 1-hydroxy group). It is difficult to determine whether g undergoes different modes of oxidation-reduction processes to give the desired hydroxy acids required for lactonization to give xeniolide-A and B, or whether they are produced from a precursor of g which may still be in a lower oxidation state.

f

g

Noteworthy are the large variations in the terpenoid content of the xenia macrospiculata specimens collected at different seasons of the year.

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References and Footnotes

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