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XENICULIN, XENIAPHYLLENOL AND XENIAPHYLLENOL OXIDE, NEW DITERPENOIDS FROM THE SOFT-CORAL XENIA MACROSPICULATA

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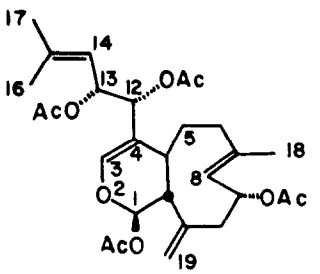
Most recently the structure of a new diterpenoid xenicin (1), isolated from the soft coral xenia elongata, has been reported by the Oklahoma group[1]. From another xenia sp. xenia macrospiculata (the Gulf of Eilat, the Red Sea) we were able to isolate a second compound, with the same bicyclic skeleton, which we have named xeniculin 2. Chromatography on silica gel of the petrol ether extract of the soft coral followed by separation on a Sephadex LH-20 column (elution with chloroform-hexane 7:3) and finally purification, with the aid of HPLC, on a Porasil-A column gave pure xeniculin: m.p. 112°-113° (benzene-petrol ether), $\alpha_D^{25°}$ - 3° ($CHCl_3$, c, 1.7); γ_{max}^{KBr} 2980, 1735br, 1667, 1435, 1380, 1242, 1180, 1010, 940, 910, 875, 830 and 790 cm^{-1}; m/e (%) 476(M^+,$C_{26}H_{36}O_8$,2), 417(M^+-OAc, 36), 416(M^+-HOAc, 17), 357(M^+-OAc-HOAc, 19), 356(M^+-2HOAc, 18), 296(M^+-3HOAc, 15) and 263(100); ^{13}C-NMR[2]: 170.3s, 170.3s, 169.3s (three $OCOCH_3$ groups), 146.9s, 116.1t (>C=CH_2), 140.8d, 116.5s (>C=C<), 134.4s, 126.3d (-CH=C<), 91.9d (-O-CHOAc), 72.2d, 70.6d (two CHOAc's), 60.8d, 57.8s (>C<O>CH-), 49.8d and 37.2d (two methines) 43.0t,40.0t,32.7t, 30.5t (four methylenes) and 24.6, 21.3, 21.3, 20.9, 19.0 and 17.7 all quartets (six methyl groups); ^{1}H-NMR[3]: 5.86d (J=2.6, H-1), 6.57d (J=1.8, H-3), 5.27 brd (J=7, H-8), 5.67 brt (J=7, H-9), 5.54dd (J=6.5 and 7.6, H-12), 1.92m (H-13), 2.73t (J=5.9, H-14), 1.30s ($Me_{16,17}$), 1.72s (Me_{18}), 4.91, 4.98s (H-19, 19'), 2.04s, 2.07s (6H)(three OAc groups). The ^{13}C-NMR spectrum of 2 supplies full evidence for the molecule's functional groups, furthermore, comparison of the ^{1}H-NMR spectrum of 2 with that of xenicin (1)[4,5] proves unequivocally that the bicyclic skeletons, together with their functional groups, in both compounds are the same. Compounds 1 and 2 must therefore differ only in the composition of the side chain; on the one hand the C_{14}-C_{15} double bond of xenicin is oxidised to an oxirane ring in xeniculin and on the other hand one of the two acetates is absent. The location of the remaining acetate was established to be at C-12 according to a double resonance experiment (Table 1). The latter experiment confirmed also some other functional sites.

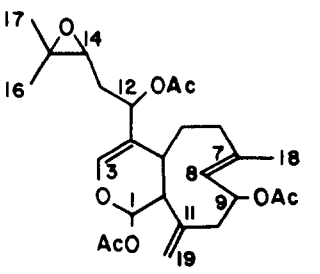
Table 1

Irradiated-H	Observed Changes	Irradiated-H	Observed Changes
5.27(H-8)	5.67brt(H-9)→brd	2.73t(H-14)	1.92m(H-13)→change in multiplicity
2.60dd(J=14.3 & 7,H-10)	5.67brt(H-9)→brd	5.54dd(H-12)	1.92m(H-13)→ "
2.37dd(J=14.3 & 1.5,H-10')	5.67brt(H-9)→t	1.92m(H-13)	2.73t(H-14)→ s
			5.54dd(H-12)→ s

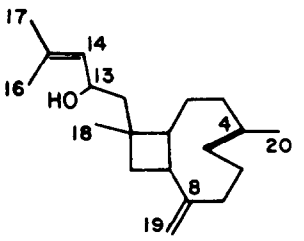
Schmitz et al[1] have suggested that the biosynthesis of xenicin (1) which will of course apply also to xeniculin (2) may involve cyclisation of geranyl geraniol in a manner analogous to that proposed for caryophyllene and related compounds or alternatively, by oxidative cyclisation of geranyl linalool directly to the nine-membered ring. The first biogenesis should then, after cyclisation to the caryophyllene like skeleton, be followed by oxidative cleavage of the resulting cyclobutane ring and eventual closure of the dihydropyran ring.



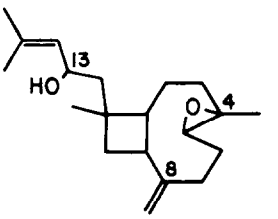
Xenicin (1)



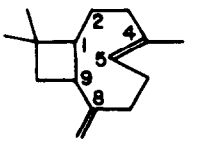
Xeniculin (2)



Xeniaphyllenol (3)



Xeniaphyllenol (4) - oxide



Caryophyllene

Repeated chromatographies of the crude extract as described above led to the isolation, in addition to compound 2, of three new compounds closely related to xenicin and xeniculin which may support the hypothesis of the via caryophyllene analog biosynthesis.

These three compounds, isolated from xenia-macrospiculata, were named xeniaphyllenol[6] (3), xeniaphyllenol oxide (4) and isoxeniaphyllenol (5). The structure of the two first compounds (3 and 4) follows: Compound 3[7] is a crystalline material, m.p. 50°-52° (CCl_4, petrol ether); $\alpha_D^{25°}$ -2° ($CHCl_3$, c 1.5); ν_{max}^{KBr} 3350, 3060, 1660, 1625, 1435, 1377, 1010, 970 and 880 cm^{-1}; m/e (%) 288(M^+, $C_{20}H_{32}O$,2) 270(M^+-H_2O,3); 189(12); 148(16); 133(39); 119(23); 109(23); 95(44); 93(52) and 85(100); ^{1}H-NMR: 5.31m(H-5), 5.20brd (J=9, H-14), 4.46brq (J=9,H-13), 4.83 and 4.94s (H-19,19'), 1.70brs ($Me_{16,17}$), 1.59brs (Me_{20}) and 1.04s (Me_{18}). According to the ^{1}H-NMR spectrum the following functional groups could have been put forward: CH_3-C-, -CH=C(CH_3)-, >C=CH_2 and $(CH_3)_2$C=CHCH(OH)CH_2-. The existence of the last fragment, the side chain of the molecule, could have been proposed according to a double resonance experiment[8] as well as by the mass spectrum fragments m/e 189(M^+-$(CH_3)_2$C=CHCH(OH)CH_2-, 12%) and 85 ($(CH_3)_2$C=CHCH=$\overset{+}{O}$H, 100%).

To distinguish between the suggested structure and a second biogentically possible one, in which the tert. methyl group is located at C-9 rather than at C-11, an LIS experiment was under taken. The following sequence of shifts, $H_{13}>H_{14}>Me_{16}>Me_{18}>Me_{17}>H_{19}>H_6, H_{19'}>Me_{20}$ strongly supports the proposed structure (the Me_{18} being between Me_{16} and Me_{17}). There was no doubt that xeniaphyllenol (3) must be a bicyclic compound however, more than one bicyclic skeleton could have been taken into consideration. Thus we thought it of utmost importance to compare the ^{13}C-NMR spectrum of 3 with that of caryophyllene by itself, the results of which are given in Table 2:

Table 2

Carbon No.[a]	8	4	15	14	5	19	13	1	12	9
Caryophyllene	154.5s	135.0s			124.5d	111.8t		53.7d		48.6d
Xeniaphyllenol	154.4s	135.1s	133.7s	129.5d	124.5d	112.1t	66.0d	52.3d	51.2t	49.3d

3[c]	10[c]	11	2[c]	6[b]	7[b]	16	18	d	17	20
40.6t	40.1t	29.5s	34.9t	30.0t	28.5t		22.6q	22.6q		16.2q
39.9t	39.9t	35.1s	34.5t	29.4t	28.7t	25.7q	20.4q		18.1q	16.4q

[a] Carbon No. according to 3

[b] Assignment may be reversed

[c] Tentative assignment

[d] The second gem dimethyl of caryophyllene

Apart from C-1,10,11 and 18, which are expected to be influenced by the side chain, all other carbon atoms fit very well in both compounds[9], thus strongly supporting the proposed structure of 3.

Compound 4 was obtained in minute quantities only, and was not able to be crystallised, ν_{max}^{neat} 3420, 3060, 1630, 1460, 1380 and 790 cm^{-1}; m/e (%): 304(M^+,$C_{20}H_{32}O_2$,1), 286(M^+-H_2O,1), 205(5), 145(10), 133(15), 123(20), 109(29), 107(45) and 85(100); ^{1}H-NMR ($CDCl_3$, δ): 1.08s (Me_{18}), 1.18s(Me_{20}), 1.70brs($Me_{16,17}$), 2.90dd(J=10 and 4,H-5), 4.45brq(J=9, H-13), 4.85 and 4.97s (H-19,19') and 5.20dt(J=9 and 1,H-14). The latter spectrum clearly indicates that compound 4 is the 4,5-epoxide of 3. The structure elucidation of additional more polar compounds obtained from the ethyl acetate extract as well as of isoxeniaphyllenol (5) are the subject of a foregoing study.

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FOOTNOTES AND REFERENCES

1. F.J. Schmitz et al, J.Am.Chem.Soc. 99, 5780 (1977) and F.J. Schmitz in "Marine Natural Product Chemistry", p. 293, Plenum Press, 1977.
2. The ^{13}C-NMR spectra were recorded on a Bruker WH-90 instrument, δ-values are in ppm from internal TMS; multiplicities were assigned by off-resonance and PRFT experiments.
3. The ^{1}H-NMR spectra were recorded on a Bruker 270 MHz instrument; the spectra were taken in $CDCl_3$ and quoted in δ-values ; coupling constants are given in Hz.
4. The ^{1}H-NMR of 1 according to Ref. 1 is: 5.86d(J=2,H-1), 6.58d(J=2,H-3), 5.27brd(J=8-9, H-8), 5.70brt(J=8-9,H-9), 5.38d(J=9-10,H-12), 5.82t(J=9-10,H-13), 5.08brd(J=10,H-14), 1.74, 1.84s($Me_{16,17}$), 1.74s(Me_{18}), 4.83, 4.96s(H-19,19'), 2.04s, 2.06s(6H) and 2.08s (40Ac groups).
5. A good agreement of the spectra of 1 and 2 in C_6D_6 has been established.
6. We suggest naming the new skeleton xeniaphyllane.
7. Compound 3 undergoes ready acetylation by Ac_2O/Pyr. mixture.
8. Irradiation of either one of the signals at δ4.46 or 5.20 changed its counterpart as expected.
9. Same results were obtained while recording the spectra in C_6D_6.