

CARDIOPHYLLIDIN, A SECO-ENT-NEOCLERODANE DITERPENOID FROM SALVIA CARDIOPHYLLA

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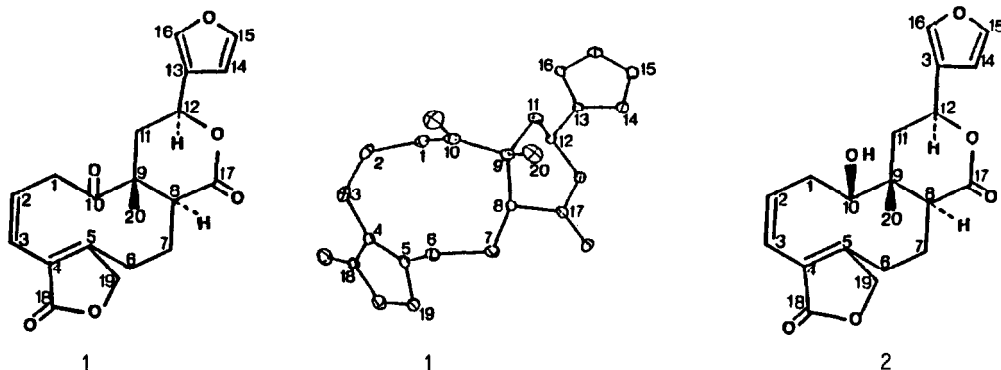
ABSTRACT.- A new seco-ent-neo-clerodane diterpenoid, cardiophyllidin, was isolated from the aerial part of Salvia cardiophylla Benth, and its structure and absolute configuration established as 10-oxo-15,16-epoxy-10,5-seco-ent-neo-cleroda-2,4,13(16),14-tetraen-17,12S:18,19-diolide by spectroscopic means and X ray study.

In our search for new natural substances with biological activity from flora used in Latin American folk medicine (1,2) we studied the aerial part of S. cardiophylla Benth. (3). From this plant we isolated the triterpenes β amyrin, ursolic and oleanolic acids, a mixture of compounds at present under study and a novel diterpenoid, cardiophyllidin 1, the structure of which has been shown to be 10-oxo-15,16-epoxy-10,5-seco-ent-neo-cleroda-2,4,13(16),14-tetraen-17,12S:18,19-diolide following the nomenclature proposed by Rogers et al (4). Cardiophyllidin 1, mp 239-241°, has the molecular formula $C_{20}H_{20}O_6$, which indicates a high degree of unsaturation. The IR spectrum of 1 shows the presence of a furan ring (3140, 1500, 870 cm^{-1}), olefine double bonds (3020, 3010, 1660 cm^{-1}), a δ lactone grouping (1750 cm^{-1}) another carbonyl group (1705 cm^{-1}) and no hydroxy groups. The presence of the furan ring and a cisoid diene system in compound 1 is confirmed by the UV spectrum where absorptions typical these two chromophores appear at 212, 232, 260, 283 nm (5,6,7).

The 1H and ^{13}C NMR spectra of cardiophyllidin are the most informative. ^{13}C NMR has signals for the four carbon atoms of a β -substituted furan ring: three doublets at δ 109.0 (C-14), 140.4 (C-16) and 144.0 (C-15) and a singlet at δ 124.2 with three protons forming an A_2X system (see Table I); for the carbons of the diene system (two as doublets at δ 121.2 and 131.0 and two as singlets at δ 123.6 and 163.9, indicating the presence of a tetra-substituted double

bond), and for a carbonyl (δ 211.6) and two esters (δ 173.1, 173.3) together with two carbons bonded with oxygen as a doublet and triplet, respectively, at δ 69.3 and 71.8. Also to be seen is a single methyl at δ 20.6 as a quartet. These data together with those obtained from the ^1H NMR and the correlation H-H and C-H spectra establish the values shown in Table 1. The Noessy study assigns a boat conformation to ring B.

When 1 was subjected to reduction with NaBH_4 , the major product obtained was



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alcohol 2 in the ^1H NMR of which a proton geminal to a hydroxy group at δ 5.19 appears as a doublet ($J=5\text{Hz}$) coupled with only one H_1 proton; its unusual chemical shift is attributed to the interaction with the C-2, C-4 diene system orbitals which remain on the same plane as H_{10} (8).

On the basis of these data, structure 1 was proposed for cardiophyllidin as far as its relative configuration was concerned and, this substance being the first example of its kind, it was also subjected to X ray analysis.

Crystal of cardiophyllidin ($\text{C}_{20}\text{H}_{20}\text{O}_6$) are orthorhombic, $P2_12_12_1$, $a=7.040(1)$, $b=13.442(4)$, $c=18.699(2)$ Å, $V=1769$ Å³, $D_c=1.34$ g.cm⁻³, $z=4$. The intensity of 1059 independent reflections was measured up to $\theta=50^\circ$ with an automatic four-circle diffractometer. Graphite monochromated $\text{CuK}\alpha$ radiation and w/θ scan technique were used. 1012 reflections were considered as observed according to the criterion $I > 3(I)$ and corrected for Lorentz and polarization. The structure was solved by SHELXS-86 (9). A difference synthesis showed all the H-atoms. A final anisotropic l.s. full-matrix refinement (fixed isotropic contribution for H-atoms) has converged to a standard crystallographic residual

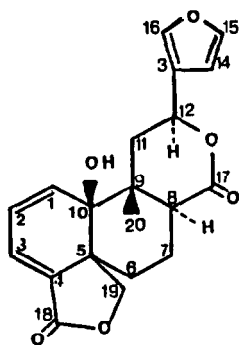
of $r = 0.041$. The absolute configuration was determined by comparing the 23 more relevant Bijvoet pairs (10) with $AF_c > .1$ in the ranges $10. < F_o < 50$ and $.2 < \sin \theta / \lambda < .5$, showing an averaged Bijvoet difference of 1.19 for the right enantiomer vs. 1.24 for the wrong one. The figure shows the absolute configuration of the final X-ray model. The Cremer and Pople parameters (11) indicate that both five-membered rings are planar and the six-membered ring has a boat conformation; the A/B ring junction is trans. Biogenetically, cardiophyllidin may derive from a hypothesized diene compound 3, in a similar way to that proposed by Bohlman *et al* (12,13) for the formation of strictic acid from a similar diene (14).

TABLE 1: CARDIOPHYLLIDIN-CORRELATIONS BETWEEN ^1H AND ^{13}C SPECTRAL VALUES

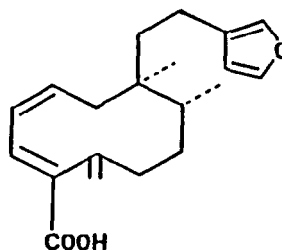
H-1	[3.66, 3.74 dd (16.0, 8.8) 3.11, 3.19 dd (16.0, 7.7)	C-1	35.5 t
H-2		C-2	131.0 d
H-3	6.25 m	C-3	121.2 d
	6.05 d (11.0)	C-4	163.9 s
		C-5	123.6 s
H-6	[1.74 ^a 2.32 ^a	C-6	39.4 t
H-7		C-7	22.4 t
H-8	2.39 ^a	C-8	42.5 d
	3.27 d (10.3)	C-9	48.7 s
		C-10	211.6 s
H-11	[1.85 ^a 2.40 ^a	C-11	23.9 t
H-12		C-12	69.3 d
	5.56, 5.62 dd (12.1,4.1)	C-13	124.2 s
H-14	6.39, 6.40 dd (1.7,0.7)	C-14	109.0 d
H-15	7.41 t (0.7)	C-15	144.0 d
H-16	7.46 bs	C-16	140.4 d
		C-17	173.1 s ^b
		C-18	173.3 s ^b
H-19	[4.67 dd (17.0, 1.5) 4.84 dd (17.0, 2.1)	C-19	71.8 t
H-20		C-20	20.6 q

a partially overlapping signals

b interchangeable



3



4

ACKNOWLEDGEMENTS

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- 2: IR(CHCl₃)_{max} ν cm⁻¹: 3680, 3630, 3000, 1740, 1720, 1600, 1430, 1360, 1230, 1160, 1020, 870. ¹H NMR (DMSO): δ 0.93(3H,s), 1.44(1H,t, J=13 Hz), 1.89(2H,m), 2.49(3H,m), 3.16(1H,d, J=8 Hz), 4.84, 4.94(each 1H,d, J_{AB}= 13 Hz), 5.19(1H,d, J=5 Hz), 5.47(1H,dd, J=7, J=12 Hz), 5.84(1H,d, J=11 Hz), 6.30(1H,m), 6.55(1H,bs), 7.70(1H,s), 7.75(1H,t, J=1.7 Hz). MS m/z: 358 |M|⁺ (99), 340(16), 330(8), 312(20), 301(9), 294(10), 284(9), 268(10), 249(21), 221(31), 203(41). Calculated for C₂₀H₂₂O₆, 358.1414; found 358.1484.
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