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DIMERIC SESQUITERPENE LACTONES : STRUCTURE OF ABSINTHIN.

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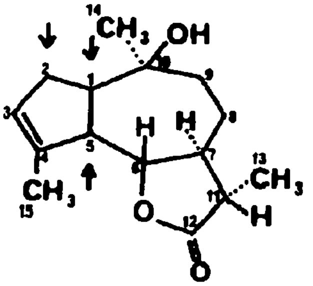
Summary : Absinthin, a constituent of A. absinthium, has been given structure 2.

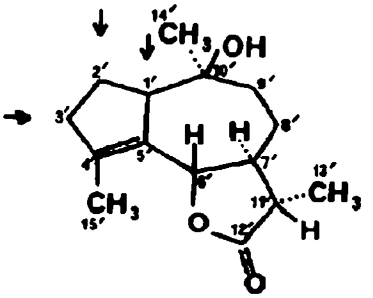
The two main guaianolide constituents [1] of Artemisia absinthium are artabsin [2] and absinthin the complete structure of which has not been elucidated [3,4]. Absinthin (MW 496) is a dimeric sesquiterpene lactone giving rise to artabsin 1 (MW 248) upon heating [4]. This observation strongly suggests that the dimerization process (possibly through a Diels-Alder reaction) to give absinthin, involves the pentadiene system of two guaianolides having the same seven membered ring system fused to the lactone ring as in artabsin 1.

Due to its dimeric nature absinthin exhibits a pseudosymmetry which renders a detailed analysis of its ^{13}C NMR spectrum by standard methods very difficult. However a comprehensive interpretation of the ^{13}C and ^{1}H NMR spectra could be secured from the off-resonance spectra at 62.86 MHz (^{1}H 250MHz) obtained at various decoupling powers [5] leading thereby to structure 2 for absinthin (Table).

The low field region of the ^{13}C NMR spectrum of absinthin 2 exhibits six signals assigned to two lactones carbonyls and to four vinylic carbons (one doublet and three singlets). The presence of a tri- as well as a tetrasubstituted double bond in absinthin 2 is also well established from the ^{1}H NMR spectrum (one vinylic proton and two vinylic



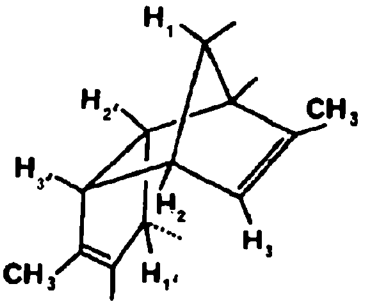
I



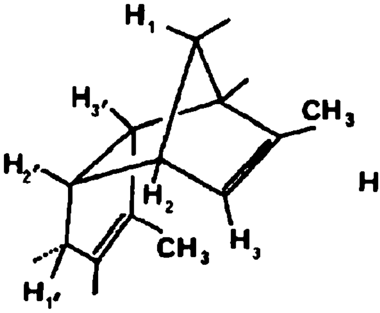
I′

methyls) ; it is compatible with the structural units I and I', arrows indicating the only possible Diels-Alder linkage positions.

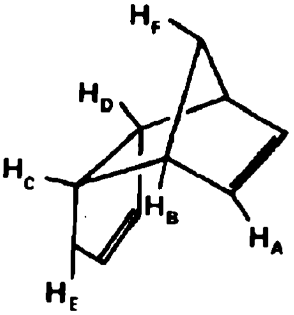
Careful analysis of the ^{13}C NMR off-resonance spectra shows that absinthin 2 has in addition to the above-mentioned six sp^2 type carbons, three quaternary sp^3 carbons (singlet) two of them corresponding to carbon C-10 and C-10', eleven methines (doublet), four methylenes (triplet) and six methyls (quartet). As the four triplets must be attributed to carbons 8, 8', 9 and 9' it clearly appears that carbons 2' and 3', 2 and 5 (the remaining quaternary carbon) are substituted and correspond to the carbons involved in the Diels Alder reaction. In this case, subunits I and I' would derive from 3, as diene and as dienophile respectively, leading to only two types of endo-adducts II and III.



II



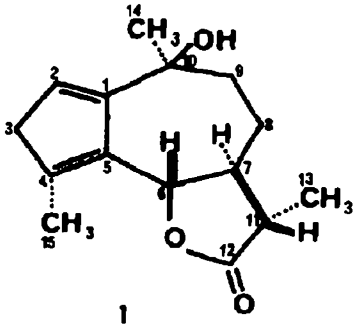
III



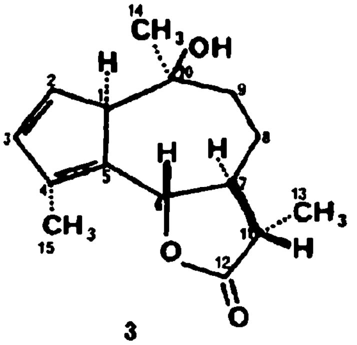
IV

Proton decoupling experiments performed with absinthin 2 at 250 MHz after addition of Eu^{III}(fod)$_3$(LIS) reagent show, in addition to the H-6 and H-6' doublets, six well-separated signals (H$_A$-H$_F$) between ca. 5.5 and 2 ppm. The chemical shifts observed without LIS reagent and coupling patterns (Table)[6] are in agreement with those given for the endo-cyclopentadiene dimer IV [7]. By referring to the chemical shift values of H$_A$, H$_B$ and H$_F$ the assignments of H-3, H-2 and H-1 becomes straightforward. The most important observation is that H$_C$, neighbour of H$_B$, has two further adjacent protons H$_D$ and H$_E$. This is consistent solely with the structure III, protons H$_C$ H$_D$ and H$_E$ being attributed to H-2', H-3' and H-1', respectively.

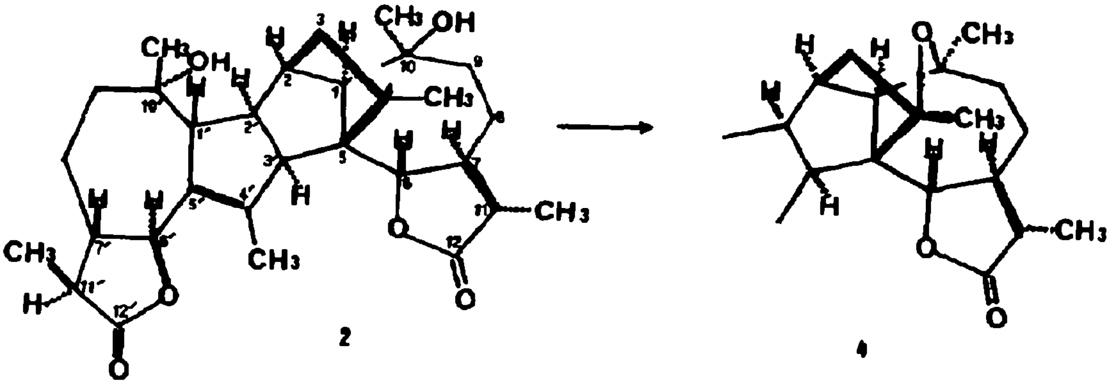
The upfield shift of the proton H-1' in the standard ^{1}H NMR spectrum of absinthin 2 is in agreement with the proposed stereochemistry, this proton being in the shielding zone of the C-3, C-4 double bond.



1



3



2

4

Position	1 1'	2 2'	3 3'	4 4'	5 5'	6 6'	7 7'	8,8'[b]	9,9'[b]	10,10[b]	11,11'[b]	12,12'[b]
$^{13}C^{a}$	71.3 57.0	45.6 46.5	122.4 58.8	146.6 135.4	64.0 147.8	82.7 81.5	46.3 49.2	27.5 23.6	43.6 42.4	73.9 71.6	42.2 42.0	179.3 179.8
$^{1}H^{a}$	2.16 2.29	2.86 2.84	5.50 3.21	-- --	-- --	4.70 4.60	1.80 1.64	1.80[c] 1.60[c]	1.80[c] 1.60[c]	-- --	2.30 2.30	-- --

Position	13,13'[b]	14 14'	15 15'
$^{13}C^{a}$	13.0 12.1	29.4 32.2	13.6 18.3
$^{1}H^{a}$	1.25 1.21	1.20[d] 1.31	1.78 1.90

^{1}H coupling constants (Hz).

$J_{2,3} = 2,5$ $J_{2,2'} = 3,5$ $J_{2',3'} = 8$

$J_{2',1'} = 1,5$ $J_{2,1} \simeq 0,5$.

Table [6]

[a] Chemical shifts in ppm/TMS : upper and lower lines refer to numbering of subunits I and I' respectively.

[b] Assignments of upper and lower lines may be reversed.

[c] Assigned from ^{1}H-^{13}C selective decoupling experiments [5].

[d] Assigned from ^{1}H LIS experiments.

The last point deserving a discussion is the stereochemistry at C-10 and C-10'. The configuration at C-10 (hence C-1) follows from the acid isomerisation of absinthin 2 into anabsinthin 4[3]. This compound is devoid of a trisubstituted double bond and possesses three tertiary methyls and one vinylic methyl. Examination of the ^{13}C NMR spectrum of 4 suggests that the cyclization of 2 into anabsinthin 4 takes place without skeletal rearrangement and involves the hydroxyl at C-10 which must lie close to the C-3, C-4 double bond as indicated on structure 2. Moreover, dehydration of anabsinthin 4 to yield a diene [8] (λ_{max} =256nm) denonstrates that the hydroxyl at C-10' does not participate in this reaction. Finally, LIS experiments on 2 also clearly show that the main binding site of Eu^{III} is the hydroxyl at C-10', the most shifted signals being the methyl at C-10' and H-2'. This observation supports the stereochemistry at C-1' as depicted in structure 2 and accordingly the two putative Diels-Alder partners must have the same structure 3 [9].

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1 For pertinent reviews see : N.H. Fischer, E.J. Olivier and H.D. Fischer in "Progress in the Chemistry of Organic Natural Products", Springer Verlag, (1979) 38, 47 and R.G. Kelsey and F. Shafizadeh, Phytochemistry, (1979), 18, 1591.

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4 K. Vokac, Z. Samek, V. Herout and F. Sorm, Tetrahedron Letters, (1968), 3855.

5 The following acquisition conditions were used on a F.T. Cameca TSN 250 spectrometer : a) Presaturation of protons during 0.7 sec. at high decoupling power ($\gamma H_2 \sim 3.000$Hz), b) ^{13}C acquisition with ^1H decoupler turned to low power ($\gamma H_2 \sim 200$–400 Hz). This kind of experiments which will be described elsewhere by one of us (J.Y. L.) allow the assignments of carbons bearing identified protons separated by ≈ 10 Hz. Line distortion are minimized by proton presaturation, which also restores NOE sensitivity enhancement.

6 The chemical shifts given are those observed in the absence of shift reagent.

7 R.G. Foster and M.C. Mc Ivor, J. Chem. Soc. (B), (1969), 188.

8 The ease of this reaction is indicative of a trans-elimination.

9 After completion of this work we have been aware (Chemical Abstracts, (1980), 92, 59025q) that S.Z. Kazymov et al. have communicated (11th I.U.P.A.C. Natur. Prod. Symp., 1978) a planar structure for absinthin in accord with 2.

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