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DIMERIC SESQUITERPENE LACTONE. STRUCTURE OF ISOABSINTHIN

ACID ISOMERIZATION OF ABSINTHIN DERIVATIVES

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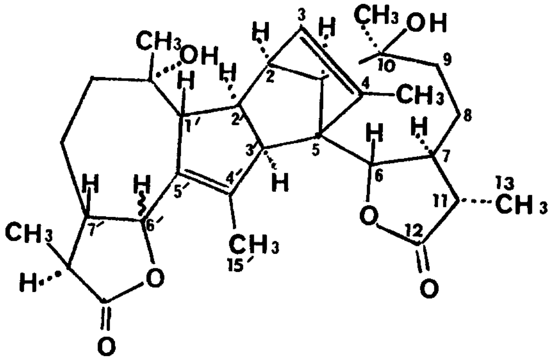
Summary : Isoabsinthin 2 is a new diguaianolide constituent of A. absinthium 1. The acid isomerizations of several derivatives of absinthin have been studied.

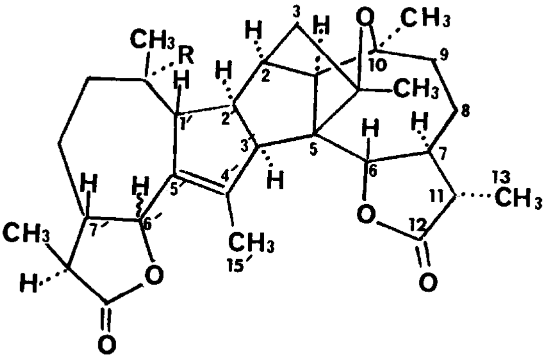
Recently, we and others reported the structure determination of absinthin 1 a dimeric guaianolide of Artemisia absinthium[1,2]. Further examination of the constituents of this plant has now resulted in the isolation of an isomer of absinthin 1 which we call isoabsinthin. On the basis of its spectral data we have secured structure 2 for isoabsinthin.

Absinthin 1 and isoabsinthin 2 (m.p. 172-174°C, MeOH) have identical mass spectra ($C_{30}H_{40}O_6$, found $M^{\ddagger}$ 496,2851). Comparison of their proton - (PMR) and carbon (CMR) NMR spectra shows very minor differences ; thus, in the PMR spectrum of 2 the H-6' proton signal appears as a doublet at 4.95 ppm (J 9.5 Hz) instead of 4.6 ppm (J 11 Hz) in the case of 1. In the CMR spectrum of 2 only the upfield shifts of ca. 3 ppm for carbons C-7' and C-11' are worthy of note. These observations are suggestive of a structural modification affecting the allylic lactone system. Furthermore, it can be seen that the signal patterns and chemical shift values for protons at positions 1,1', 2,2', 3 and 3' as well as the chemical shifts of the corresponding carbons are very similar thereby indicating that both these compounds have in common the same bicyclopentadiene system.

Like absinthin 1, which in acidic medium is isomerized into anabsinthin 3 [3], isoabsinthin 2 leads under the same conditions to an isomer of anabsinthin 3. This new compound has been given structure 4, this assignment is in agreement with the disappearance in its PMR spectrum of the H-3 olefinic proton signal as well as the signal at 1.80 ppm due to the C-15 methyl. The latter shows now a singlet at 1.23 ppm corresponding to a tertiary methyl.

The outcome of this cyclization depends on the reaction conditions. Thus, when the reaction is carried out in benzene in the presence of TsOH only one cyclized derivative is





1 α-$H_{6'}$

2 β-$H_{6'}$

3 α-$H_{6'}$ R = OH

4 β-$H_{6'}$ R = OH

5 α-$H_{6'}$ R = H 1',10'-dehydro

6 β-$H_{6'}$ R = H 1',10'-dehydro

7 α-$H_{6'}$ R = H bis-1',10' ; 11',13'-dehydro

8 β-$H_{6'}$ R = H bis-1',10' ; 11',13'-dehydro

NMR Data[a]

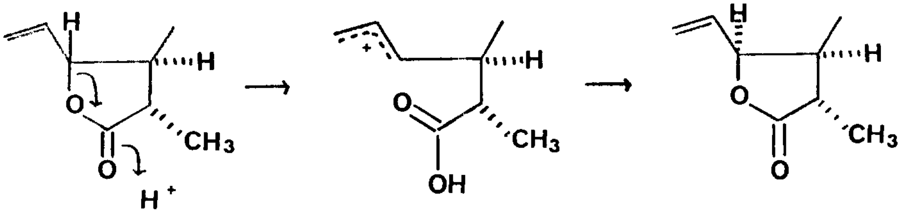
	Position ^{13}C							Position ^{1}H				J (Hz)
	1 1'	2 2'	3 3'	4 4'	5 5'	6 6'	7 7'	1 1'	2 2'	3 3'	6 6'	$J_{6,7}$ $J_{6',7'}$
1	71,3	45,6	122,4	146,6	64,0	82,7	46,3	2,16	2,86	5,50	4,70	10
	57,0	46,5	58,8	135,4	147,8	81,5	49,2	2,29	2,84	3,21	4,60	11
2	71,1	46,8[b]	121,5	139,9	65,1	82,6	46,6[b]	2,24	2,85	5,60	4,80	10,5
	59,7	43,6[b]	60,3	133,4	148,2	80,9	46,8[b]	2,24	2,75	3,30	4,95	9
3	62,9	41,3[b]	34,7	88,3	62,1	82,4	49,4[b]	2,35	2,19	-	4,15	10
	56,7	43,2[b]	52,5	132,5	148	81	49,2[b]	2,51	2,71	3,46	4,70	11
4	62,6	41,1	35,2	88,3	62,6	82,4	47[b]	2,04	2,23	-	4,16	10,5
	59,7	41,1	53,7	131,2	140,4	80,7	49,3[b]	2,37	2,67	3,56	5,06	9
5	62,5	40,3[b]	35,3	89	62,7	82,4	48,1[b]	2,35	2,40	-	4,10	10
	138,1[b]	47,7[b]	50,8	124,9[b]	145,8[b]	80,7	49,4[b]	-	3,05	3,40	4,95	10,5
6	63,2	39,7[b]	35,3	88,6	62,1	82,3	49,2[b]	2,43	2,43	-	4,18	10
	137,1[b]	47,5[b]	50,8	129,1[B]	148,9[b]	78,1	45,2[b]	-	3,16	3,49	5,44	6

[a] Chemical shifts in ppm/TMS Solvent $CDCl_3$

[b] Assignments may be interchanged

obtained ; compounds 1 and 2 yielding 3 and 4, respectively. However, treatment of 1 or 2 in 80 % formic acid produces a 9:1 mixture of 3 and 4 suggesting that under these conditions both ethers undergo interconversion. This can be confirmed by following the equilibration of 4 into a 3 + 4 mixture by PMR. This experiment indicated the decrease in intensity of the H-6' signal at 5.05 ppm as well as the C-15 methyl signal at 1.84 ppm which were replaced by signals at 4.70 and 1.95 ppm, respectively. Mass spectrometry showed that the products recovered after deuterated acid (CF_3COOD) isomerization were devoid of deuterium.

Conditions for the dehydration of anabsinthin 3 to give diene 5 have been reported [1]. As expected, in the presence of $MsCl/NEt_3$ 4 yields the new diene 6 (λ_{max} 256 nm) which results from the introduction of a double bond between C-1' and C-10'. The PMR spectrum of both dienes 5 and 6 differ mainly by the position of the H-6' doublets which are found at 4.95 ppm and 5.44 ppm, respectively. More interestingly in the case of diene 6 the value of the coupling constant $J_{6',7'}$ = 6 Hz is significantly smaller than that of the other isomer ($J_{6',7'}$ = 10 Hz). This observation, as well as the downfield position of the H-6' signal in compounds 2, 4 and 6 compared to their isomers derived from absinthin 1 strongly suggest that in compound 2 the allylic lactone is cis-fused whereas it is trans-fused in absinthin 1 [4]. Moreover, the finding that the equilibration reaction 3 $\rightleftarrows$ 4 takes place without deuterium incorporation is in favour of the mechanism depicted in the Scheme [5].



Also, we wanted to establish that a methylene lactone such as 7 did undergo this acid induced rearrangement. The bis-methylene lactone 7 was prepared [6] from anabsinthin 3 and submitted to aqueous formic acid to give its isomer 8. On the PMR spectrum of 8 the H-6' signal is found at δ 5.24 ppm that is, at lower field than in the case of 7 (δ 4.67 ppm, J 3.4 Hz) ; it is noteworthy that the coupling constant $J_{13',7'}$ 3.5 Hz does not fit the Samek rule [7].

In conclusion, although the acid isomerization of a trans-into a cis-lactone is well known in sesquiterpene chemistry, we consider that isoabsinthin 2 is a genuine constituent of A. absinthium. This compound is certainly not an artefact since the acid conditions necessary for the rearrangement are not mild enough to avoid the formation of an ether bridge as in anabsinthin 3.

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4 In this work we compare three pairs of isomeric γ-lactones and we find that $J_{6',7'}$ (trans) > $J_{6',7'}$ (cis) and $\delta_{H-6'}$ (trans)<$\delta_{H-6'}$ (cis). Such observations are in accord with numerous literature data and application of this criterium can be considered reliable when the two isomers are available for NMR measurements.

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