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STRUCTURE OF ABSINTHOLIDE A NEW GUAIANOLIDE DIMER OF Artemisia absinthium L.

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Absintholide 1 is a new guaianolide dimer whose structure and stereochemistry has been elucidated on the basis of high resolution n.m.r.

During the past few years the structure of several sesquiterpene lactone dimers have been determined, some of them by application of newly developped n.m.r. techniques[1-6]. These dimers continue to be of great interest because of their unusual structural features and in some cases due to their valuable biological activity.[1] We herein report on the attribution of structure 1 to a new guaianolide dimer from Artemisia absinthium L which we call absintholide.

The molecular formula $C_{30}H_{38}O_8$ of 1 [mp 227-228°C (benzene), $[\alpha]_D^{25}$ + 127 (c 1.3, $CHCl_3$), $M^{+\cdot}$ 526] resulted from high resolution mass spectrometry (HRMS). Its i.r. spectrum showed several bands suggesting the presence of hydroxyl (3620, 3470 cm^{-1}), lactone 1780 cm^{-1}) and ketone (1740 cm^{-1}) functionalities. Only one hydroxyl could be acetylated or oxidized to give the acetate 2 or the unsaturated ketone 3 (u.v., λ_{max} 240 nm, ε 5900) respectively, thus indicating the presence of an allylic alcohol.

The ^1H n.m.r. spectrum (400 MHz) of absintholide 1 showed two doublets and four singlets due to two secondary and four tertiary methyls and also two doublets at 5.46 and 5.34 ppm assigned to H-6 and H-6', respectively. The signal at 4.46 ppm was attributed to H-2 since

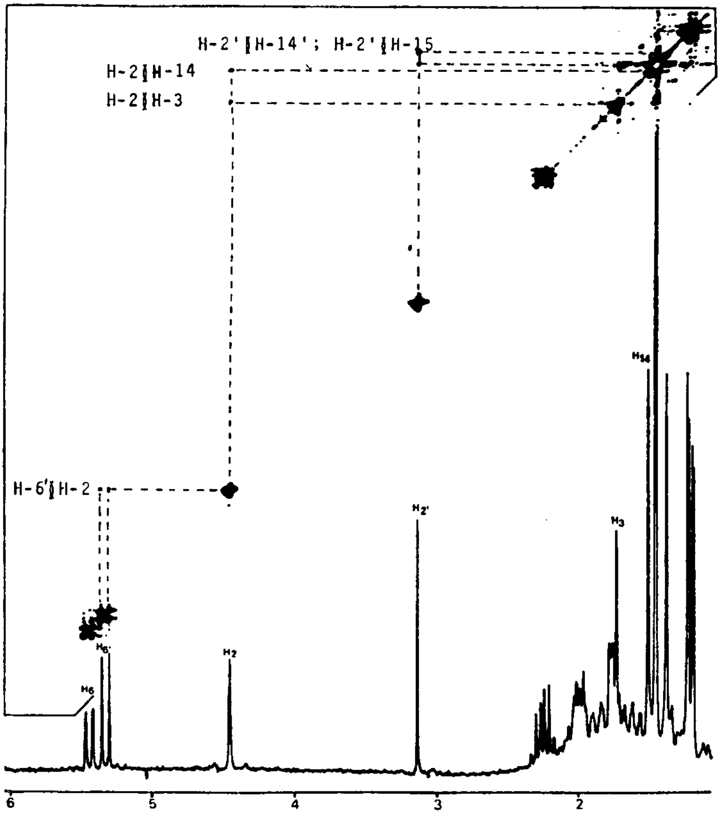
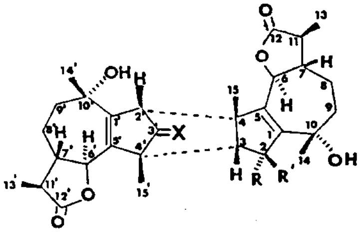
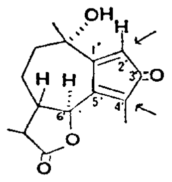
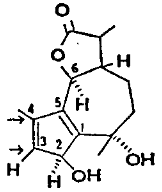


FIGURE : Vertical contours of the 200 MHz proton N.O.E.-correlated 2D spectrum of 1 with the normal ^{1}H spectrum below (the mixing time was .7 sec.).





4'



4

	R	R'	X
1	H	OH	O
2	H	OAc	O
3	O		O
5	O		H,OH
6	O		H,OAc

it was shifted low field ($\Delta\delta$ + 0.9 ppm) after acetylation and was absent in the spectrum of compound 3. A decoupling experiment revealed a homoallylic relationship between H-2 and H-6 (^5J = 1.5 Hz); furthermore, the coupling constant (J = 1.25 Hz) for H-2 and H-3 is in agreement with the stereochemistry indicated on structure 1.

The ^{13}C n.m.r. spectrum of acetate 2 exhibited thirty two carbon resonances. The peaks due to four carbonyls and four fully substituted olefinic carbons were found in the low field region. Five resonances between 82 and 72 ppm could be attributed to oxygenated carbons. Two of them corresponded to the fully substituted carbons C-10 and C-10' and three others to the methine carbons C-2, C-6 and C-6'. The spectrum also revealed the resonances only due to four methylene carbons attributed to C-8, C-8', C-9 and C-9'.

All these observations could be best interpreted on the basis of a structure such as 1 which results from the coupling of the guaianolide units 4 ($C_{15}H_{20}O_4$) and 4' ($C_{15}H_{18}O_4$) to give a bicyclopentadiene type compound.[7]

Since in 1 (and its derivatives 2 and 3) no coupling was observed between H-3 and H-2' it could be concluded that the binding of the two units 4 and 4' occurs between C-2' - C-4 and C-4' - C-3, respectively. Further evidence for the proposed structure 1 was gained from the chemical reactivity of compound 3. Its reaction with sodium borohydride led to the exclusive reduction of the carbonyl at position C-3' to give alcohol 5 which was acetylated to 6. This reduction behaviour was anticipated because of the presence of a methyl substituent at position C-4'.[10] Moreover, irradiation[11] of 3 provided a cage compound devoid of u.v. absorption thus demonstrating the *endo* stereochemistry of dimer 1.

To establish the relative stereochemical arrangement of the two units 4 and 4' in compound 1 we compared the spectral data of 3 with those of the dimer of 1,2-dehydroisophotosantanic lactone[12] which served as a model compound. This comparison as well as the inspection of the molecular models suggested that absintholide 1 resulted from the cycloaddition of the C-1 - C-2 double bond of unit 4 to the α-side of dienone 4' (i.e. the same side as its proton H-6') to give 1 as the unique possibility.

This view was further confirmed by observing an upfield shift $\Delta\delta$ -0.45 ppm for H-6' after oxidation of absintholide 1 to ketone 3. Accordingly, the H-6' proton of 3 must be located above the plane of the carbonyl at position C-2. Full confirmation of this interpretation was obtained from the NOE experiments. The 2-D spectrum shown (figure) fully establishes the spatial proximity of H-2 and H-6' and also indicates correlations between H-2~H-3, H-2~H-14, H-2'~H-14' and H-2'~H-15. These observations are in complete agreement with structure *1* for absintholide.

REFERENCES

1. K.-H. LEE, Y. IMAKURA, D. SIMS, A.T. McPHAIL and K.D. ONAN, *J. Chem.Soc.Chem.Commun.*, 341 (1976); K.-H. LEE, Y. IMAKURA and D. SIMS, *J.Pharm.Sci.*, *69*, 1044 (1980).
2. N.D. ABDULAEV, M.R. YAGUDAEV, V.A. TARASOV, S.H. KASYMOV, and G.P. SIDYAKIN, *Khim.Prir.Soedin.*, 329 (1979) (*Chem.Abstr.*, 1980, *92* : 31783).
3. J. BEAUHAIRE, J.-L. FOURREY, M. VUILHORGNE and J.-Y. LALLEMAND, *Tetrahedron Letters*, *21*, 3191 (1980).
4. J. BEAUHAIRE, J.-L. FOURREY, J.-Y. LALLEMAND and M. VUILHORGNE, *ibid.*, *22*, 2269 (1981).
5. S.H. KASYMOV, N.D. ABDULAEV, G.P. SIDYAKIN, N.R. YAGUDAEV, *Khim.Prir.Soedin*, 495 (1979) (*Chem.Abstr.*, 1980, *92* : 129115v); Z. KARIMOV, S.H. KASYMOV, M.R. YAGUDAEV and G.P. SIDYAKIN, *ibid.* 446 (1981) (*Chem.Abstr.*, 1983, *96* : 35570v)
6. F. BOHLMANN, A. MANIRUDDIN, J. JAKUPOVIC, R.M. KING, and H. ROBINSON, *Phytochem.*, *22*, 191 (1983).
7. Although neither *4* nor *4'* (nor their corresponding dimers) could be detected after heating absintholide *1* it is assumed that the absolute stereochemistry of the moieties derives from that of artabsin [8] and of the artabsinolides [9] because of their common biosynthetic origin.
8. K. VOKAV, Z. SAMEK, V. HEROUT, and F. SORM, *Coll.Czech.Chem.Commun.*, *37*, 1346 (1972).
9. J. BEAUHAIRE and J.-L. FOURREY, *J.Chem.Soc.*, *Perkin Trans.*, *1*, 861 (1982).
10. B. FUCHS, *Tetrahedron Letters*, 3047 (1972).
11. B. FUCHS, and K. SCHAFFNER, *Helv.Chim.Acta*, *55*, 2643 (1972); K.N. HOUK and D.J. NORTHINGTON, *Tetrahedron Letters*, 303 (1972).
12. J. BEAUHAIRE, A. CHIARONI, J.-L. FOURREY and C. RICHE, *ibid.*, *24*, 4417 (1983).

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