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DITERPENES FROM TEUCRIUM CAPITATUM L.
X-RAY CRYSTAL AND MOLECULAR STRUCTURE OF LOLIN

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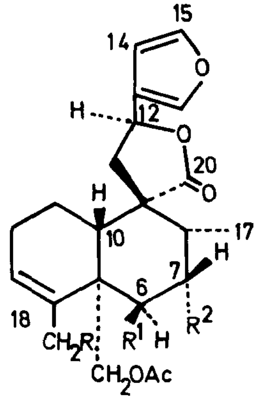
ABSTRACT: Lolin, a new diterpene of the *ent*-clerodane type has been isolated from Teucrium capitatum. The X-ray structure and spectroscopic data of lolin is given.

Diterpenoids with an *ent*-clerodane skeleton have shown biological activity as antifeedant, antitumor, antimicrobial and antifungal agents(1).

Teucrium capitatum L., collected at central Spain afforded a new diterpenoid, lolin, to which we assign structure 1. Column chromatography of the crude extract yielded two known compounds (19-acetylgnaphalin (2) and teucapitatin (3)) plus a mixture of isomeric substances. Preparative layer chromatography of this mixture allowed separation of the major component as an amorphous solid. Acetylation with Ac_2O/Py at 80ºC during four hours yielded a triacetylated substance 2, which could be crystallized after purification from MeOH-EtOAc, m.p. 166-167º C.

The ^1H and ^{13}C NMR of 2 are collected in Tables 1 and 2. Spin decoupling experiments establish the sequences: (C)-CH_2-CH(OR)-(C), (a), and (C)-CH(OR)-CH(OR)-CH(CH_3)-, (b). Assuming a clerodane skeleton, partial structure (a) can be accomodated in the spirolactone ring and partial structure (b) in ring B. The coupling constants existing among the protons of sequence (b) exclude the possibility of diaxial arrangement between them. The usual α-configuration of the C17 methyl group defines as α-axial the configuration of the -OR group on C7. To assign the β-configuration of the -OR group on C6 the chemical shifts of the ring B carbon atoms, showing values almost identical to those found in teucapitatin (3), have been considered. A trisubstituted olefin bond present in lolin has to be placed in ring A. Hydrogenolysis of compound 2 with Pd/C in the presence of Et_3N(4) proceeds with the loss of an acetoxyl group and opening of the lactone ring. This finding points to C3-C4 bond for the location of



1 R=R^1=R^2=OH
2 R=R=OAc R^2=OH

the double bond excluding the alternative site (C1-C10).

A C-13 NMR spectrum obtained with the original mixture of isomeric mono acetates shows duplicate or triplicate lines for most ring B and spirolactone carbon atoms but single lines for ring A and furan carbon atoms. C6 and C7 monoacetate isomers of 1 could probably be present in the original mixture of natural products but, through repeated plc, only chromatographycally pure 1 was isolated,(an amorphous solid, M.W. 420, $C_{22}H_{28}O_8$, IR (nujol) 3400,1755 (sh) and 1720 cm^{-1}).

The C-13 NMR spectrum of 1 (a monoacetate) is shown in Table 2. On acetylation the C3 and C4 chemical shifts of 1 move to higher field indicating that the C18 -OH is one of the acetylated hydroxyl groups. The second acetyl group must enter on C6 according with the downfield shift experimented by this carbon atom and the upfield shift shown by the vicinal C7 atom (5).

Table 1. *PMR chemical shifts (in δ ppm, relative to internal TMS) and coupling constants of compound 2.*

H-6	H-7	H-11	H-12	H-18	H-19	H-3	CH_3
5.40	3.80	2.50	5.60	4.50	4.53, 4.80	5.75	1.20
d	$m \xrightarrow{D_2O} dd$	d	t	s	ABq	m	d
J 3Hz	$J_{6,7}=J_{7,8}$ 3Hz	J 9Hz	J 9Hz		J 12Hz	$W_{1/2}$ 6Hz	J 6Hz

Table 2. *C-13 NMR shifts of compounds 1 and 2.*

	1	2
C-1	19.6	19.4
C-2	25.8	25.2
C-3	133.1	127.3
C-4	139.2	136.5
C-5	47.5	43.9
C-6	70.9	71.2
C-7	74.5	71.7
C-8	35.5	36.3
C-9	53.9	53.4
C-10	45.4	46.7
C-11	44.2	44.3
C-12	74.5	74.2
C-13	124.7	124.4
C-14	107.9	107.7
C-15	139.6	139.6
C-16	144.2	144.2
C-17	12.4	12.5
C-18	64.4	65.1
C-19	64.4	63.1
C-20	181.2	180.4

The chemical shifts of C20 and C12 of compounds 1 and 2 appear at lower fields than in other clerodanes containing the spiro-lactone ring (175-177 and 71-72 ppm respectively) (3,6,7). The formation of a hydrogen bridge between the α-oriented C7 hydroxyl group and the lactone -CO- (apparent from the X-ray data of lolin) (see below), could be responsible for this shift. Such a shift can be taken as an indication of this type of arrangement; in this sense the chemical shifts of C7, C12 of teucapitatin and C6, C12 of compound 3 (see ref.3) may have to be interchanged.

In order to confirm the findings reported above and to settle some further stereochemical points such as the nature of the A/B ring junction and the stereochemistry of the C12 asymmetric center an X-ray study with a single crystal of compound 2 has been carried out.

$C_{26}H_{32}O_{10}$(2) crystallizes in the space group $P2_12_12_1$, Z=4 with a=18.255(1),b=15.253(1) and c=9.2805(2) Å, D_c= 1.295 $g.cm^{-3}$.

Intensities of 2496 independent Friedel pairs were measured up to θ=65º on a computer-controlled four-circle diffractometer. Graphitemonochromated

CuK$_\alpha$ radiation (λ=1.5418 Å) and $\omega/2\theta$ scan technique were used. No crystal decomposition was observed during the data collection process. 2276 Friedel pairs were considered as observed according to the criterion $I>2\sigma(I)$ and were used in the calculations (8). The structure was solved by MULTAN (9) using the 250 greatest normalized structure factors. After a first anisotropic refinement, the hydrogen atoms were located on a difference map. A convenient weighting scheme (10) was selected to prevent bias in $<w\Delta^2F>$ vs. $<|Fo|>$ and vs. $<\sin\theta/\lambda>$.

Several cycles of weighted anisotropic refinement (fixed isotropic thermal parameters for H atoms) were done, including the observed hkl and $\bar{h}\bar{k}\bar{l}$ reflections and those not observed with $|F_c| > |F_o|$. The R factors for the right enantiomer were R=0.051 and R_w=0.069. The absolute configuration was confirmed by comparing the 105 more relevant Bijvoet pairs with $F_o>10\sigma(F_o)$, $\Delta F_c > 0.10$ and $\Delta F_o > 0.03$ (11). The average Bijvoet difference for the right enantiomer was 0.22 vs. 0.38 for the wrong enantiomer and the averaged Bijvoet ratio was 0.033 vs. 0.046. Fig 1 shows the final X-Ray model confirming the <u>ent</u>-clerodane skeleton(12).

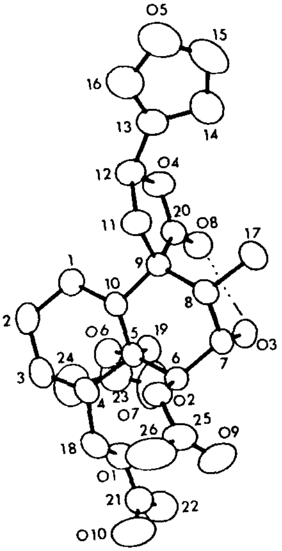


Fig.1

All distances and angles are of the usual values. The acetyl groups show usual CH_2-O-C=O cis conformation. There are no intermolecular contacts less tan 3.2 Å but an intramolecular H-bond O3H...O8 of 2.815(2) Å with an angle of 112.02(1)º.

In the decaline moiety the junction A/B is <u>e-e</u> trans. The sum of the ring torsional angles around the junction is 108º, this is a shorter value than that found of 113.1º, (13), for some <u>e-e</u> trans decalines with the same substitution at the bridge head atoms. That reduction could be due to the bulky substitution at C4 and C6.

The conformation of ring A and B are described by Cremer's parameter (14) θ,ϕ and Q. Ring B with θ=8º, ϕ= 192º (origin at C9) and Q=0.51 Å is a chair slightly distorted to boat. Its deformation could be due to the substituents at C4 and C6, and to the H-bond 03-H...08. The cyclohexene ring A, has envelope conformation with the flap at C10, defined by $\theta=51^{\circ}$, $\phi=304^{\circ}$ (origin at C1), and Q= 0.55 Å. The γ-spirolactone ring is an envelope with the flap at C11, and the keto oxygen approaching to 03.

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