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

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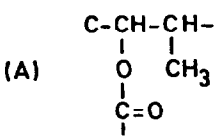
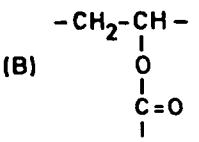
ABSTRACT: Two diterpenes, capitatin 4 and teucapitatin 5 have been isolated from Teucrium capitatum. The X-ray structure of 4, including absolute stereochemistry, is given. Diterpene 4 has been chemically related to picropolin 1 and picropolinone 2, thereby establishing the absolute stereochemistry of these two neoclerodane-type diterpenes.

Diterpenes of the clerodane type are widely represented in the plant kingdom (1-3). Teucrium capitatum L., collected in south-eastern Spain afforded a new diterpenoid, capitatin, to which we assign structure 4.

The ^{1}H NMR spectrum showed signals for a β-substituted furan ring (two α-furan protons at δ7.46 and one β-furan proton at δ6.36), a partially hidden triplet (δ5.58, J 7Hz) assigned to CH-O-CO-, a doublet (δ5.50, J 6Hz) assigned to CH-O-CO- , and an AB system (δ_A 4.60,δ_B 5.00, J 12Hz) assigned to C-CH_2-O-CO-, two CH_3-CO- signals at δ2.10, and a CH-CH_3 doublet (δ0.96, J 7Hz). Spin decoupling experiments indicated a relationship between some of these protons. Thus, irradiating at δ2.26 simultaneously removed the couplings of the doublets observed at δ0.96 and δ5.50. Irradiation at δ2.93 removed a 7Hz coupling from a triplet at δ5.58, collapsing it to a broad singlet. These decoupling experiments suggested the presence of the groupings (A) and (B):





These data can be accommodated on a clerodane skeleton such as 4. In general the ^{13}C NMR spectrum of 4 confirmed these results (see Table I), although comparison with published ^{13}C NMR data on clerodane-type diterpenes (4,5) gave estimated values for ring B carbon atoms that diverged considerably from those observed. This discrepancy could be rationalized either in terms of a departure from the assigned neoclerodane stereochemistry (6) or in terms of a conformational change in ring B. Since both cis and trans-AB ring fused clerodanes have been

found in nature (1-3,7) it was considered advisable to use X-ray crystallographic analysis to determine the complete structure.

Capıtatin 4, $C_{24}H_{28}O_9$, m.p. 165-6°C crystallizes from EtOH:EtOAc in the space group $P4_3$, Z=4, a=b=9.5552(1) Å, c=24.889(1) Å, Dc=1.3455 gr/cm^3. Intensities of 2081 independent Friedel pairs were measured up to θ=65°on an automatic four-circle diffractometer. Graphite-monochromated CuK_α radiation (1.5418 Å) and w/2θ scan technique were used. No crystal decomposition was observed during the data collection process. 1923 Friedel pairs were considered observed if $I \geq 2\sigma(I)$ and were used in the calculations (8). The structure was solved by MULTAN (9) using the 230 normalized structure factors greater than 1.5. After some refinement, the hydrogen atoms were located on a difference map although some methyl hydrogens had to be placed at the expected locations. A convenient weighting scheme (10) was selected to prevent bias in $\langle w\Delta^2F \rangle$ vs. $\langle |Fo| \rangle$ and $\langle \sin\theta/\lambda \rangle$. These weights were applied on several cycles of full matrix anisotropic refinement (fixed isotropic thermal parameters for H atoms) including both hkl and $\bar{h}\bar{k}\bar{l}$ reflections, which converged for the right enantiomer to the discrepancy indices R=0.044 and R_w=0.057. Previously the absolute configuration, which is the one in Fig.1, was determined by comparing the 112 more relevant Bijvoet pairs with $Fo > 10\sigma(Fo)$, $\Delta Fc > .10$ and $\Delta Fo \geq 03$. The average Bijvoet difference for the right enantiomer was 0.28 and 0.35 for the wrong enantiomer, and the averaged Bijvoet ratio was 0.050 (0.064)(11). These differences have proved to be enantiomorph determinant enough for similar compounds (12). The present absolute configuration is the same as those found for other diterpenoids: $C_{24}H_{30}O_9$ (4) and $C_{22}H_{26}O_7$ and $C_{20}H_{24}O_5$ (13). The present molecule and $C_{22}H_{26}O_7$ differ only by one acetyl group, which is an α- substituent on C(7) in the former, producing a conformational change in ring B from chair in $C_{22}H_{26}O_7$ to boat in capitatin 4.Ring C also changes its conformation, although both are envelopes, each molecule has the slope C(11) at a different site of the main plain. In the present molecule the α position of C(11) brings the furan ring closer towards ring B. Ring A is chair-conformated as usual (4,13); the atoms of the furan ring deviate from the main plain less than 0.006 Å. No intra or inter-molecular short contacts are found.

Since the peracetylated derivative of the Na BH_4 reduction product of 4 is identical to the peracetylated derivative of the corresponding reduction product of picropolin 1 (tlc and IR spectra), and picropolin had been related (14) to diterpene 2 (picropolinone), the present X-ray results define the absolute stereochemistry of

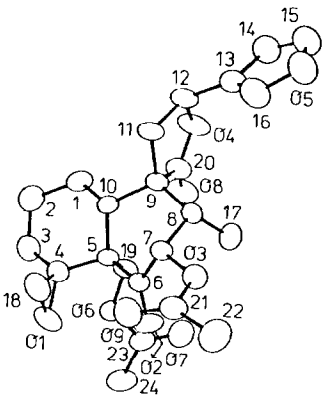
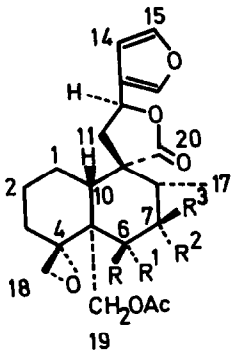


Fig.1

all these three diterpenes.

Table I. ^{13}C NMR shifts of compounds 1-5

	1	2	3	4	5		1	2	3	4	5
C-1	22.8	23.3	22.3	21.5	21.3	C-11	43.7	44.1	44.5	49.3	44.7
C-2	24.5	24.6	24.8	24.9	21.3	C-12	72.0	72.3	72.8	71.6	71.8
C-3	31.1	31.9	30.6	30.6	31.5	C-13	124.6	124.5	124.6	125.9	124.4
C-4	65.6	60.2	66.4	61.0	62.1	C-14	107.8	107.6	107.7	107.4	107.7
C-5	49.0	53.5	52.6	52.8	53.4	C-15	139.6	139.5	139.5	138.2	139.6
C-6	78.5	190.1	74.7	198.3	71.6	C-16	144.1	144.3	144.2	144.3	144.2
C-7	194.0	143.8	72.9	74.6	73.8	C-17	9.2	13.9	13.1	13.0	12.5
C-8	51.0	123.2	40.9	40.9	36.3	C-18	48.8	48.4	48.5	48.2	51.4
C-9	56.5	49.8	48.5	49.3	43.3	C-19	62.5	63.0	62.3	61.7	61.7
C-10	48.2	49.8	53.1	46.4	46.4	C-20	174.7	175.3	178.0	174.4	179.9



1 R=H, R^1=OH; R^2, R^3=O

2 R, R^1=O; R^2, R^3=O (enolic form)

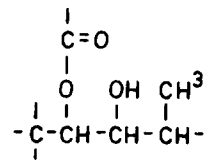
3 R=H, R^1=OH; R^2=OH, R^3=H

4 R, R^1=O; R^2=OAc, R^3=H

5 R=OAc, R^1=H; R^2=OH, R^3=H

A second diterpenoid, teucapitatin **5** , was also isolated from the same plant a solid m.p. 208-210°C (hexane-EtOAc). The ^1H and ^{13}C NMR spectra showed signals for a 8-substituted furan ring (two α-furan protons at δ7.50 and one β-furan proton at δ6.43; see also Table I for pertinent ^{13}C NMR data). Spin decoupling experiments also established partial structures (C) and (B) (the latter identical to the one described for capitatin):

(C)



Irradiation of the triplet appearing at δ3.7 (H-7, $J_{6.7}$= $J_{7.8}$ 3Hz) collapses the doublet at δ5.3(H-6,$J_{6,7}$ 3Hz) to a singlet, while irradiation of a complex signal at δ1.93 (H-8) simultaneously collapses the methyl doublet at δ1.16 (3H, J 7Hz, H-17) to a singlet and the H-7 triplet at δ3.7 to a doublet. Analogously,

irradiation of a triplet (H-12, J 9Hz) at δ5.6 collapses a two- proton doublet (H-11, J 9Hz) appearing at δ2.54 to a singlet. The H-18 epoxide protons showed as doublets at δ2.93 and δ2.53 (J 4.5Hz). Finally, the H-19 methylene is present as a singlet at δ4.83. The $J_{6,7}$ and $J_{7,8}$ coupling constants clearly exclude diaxial couplings. The stereochemistry assigned to teucapitatin 5 takes into consideration the ^{13}C NMR data obtained with the dihydroderivative 3 of picropolin 1, prepared by Na BH_4/H BO_3 reduction of this diterpene. For compound 3 an alpha configuration is assumed for both hydroxyl substituents on C(6) and C(7). When the ^{13}C chemical shifts of C(8) and C(10) of compounds 3 and 5 are compared (see Table I), the shielding effect undergone by the latter compound is apparent. This effect must be due to the β-axial configuration of the -OAc group on C(6). In accordance with the proposed stereochemistry, the epoxide protons of compound 3 appeared as an apparent triplet at δ3.16, and C(18) is deshielded in the case of compound 5.

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