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SIX NEW DITERPENES FROM SIDERITIS LEUCANTHA Cav. AND SIDERITIS LINEARIFOLIA Lam.(*)

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Six diterpenes (see Table 1) have been isolated from the petroleum ether extracts of S. leucantha by means of successive chromatographic separations on silica gel and silica gel-silver nitrate impregnated columns. S. linearifolia yielded compounds I, III and V only(**).

TABLE 1

Diterpenoids	Formulae	m.w.(ms)	m.p. ºC	$[\alpha]_D^{25º}$ (EtOH)
Foliol (I)	$C_{20}H_{32}O_3$	320	198-200(from Me_2CO:Hex.)	-36 (c̄ 0.52)
Isofoliol (II)	$C_{20}H_{32}O_3$	320	230-231(Me_2CO)	+8.1(c̄ 0.53)
Sidol (III)	$C_{22}H_{34}O_4$	362.2459	165-167(Et_2O:Hexane)	-93 (c̄ 0.85)
Isosidol (IV)	$C_{22}H_{34}O_4$	362	181-183(Et_2O:Hexane)	-27.2(c̄ 0.53)
Linearol (V)	$C_{22}H_{34}O_4$	362.2457	217-219($CHCl_3$:Hexane)	-65.4(c̄ 0.60)
Isolinearol (VI)	$C_{22}H_{34}O_4$	362	187-188(EtOH:H_2O)	-13.3(c̄ 0.03)

Foliol and isofoliol exhibit strong -OH absorption in their IR spectra (3400 cm^{-1}) and no CO band, while compounds III, IV, V and VI show besides the -OH band a strong CO band at 1710 cm^{-1}; the presence of an additional band at 1265 cm^{-1} and of a signal (3H,s) at 2.03δ in the NMR spectra(***) of III, IV, V and VI confirm the existence of an acetate group in their molecules.

When I, III and V are treated with Ac_2O/Py the same product (VII) [$C_{26}H_{38}O_6$, m.p. 129º(EtOH:H_2O), $[\alpha]_D^{25º}$-4.4º(c̄ 0.68, $CHCl_3$)] is obtained. The IR spectrum of VII shows no -OH absorption; there is acetate (1720, 1250 cm^{-1}) and terminal methylene absorption (3050, 1660 and 890 cm^{-1}). At the NMR spectrum of VII there are two

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(*).- Taken in part from the doctoral dissertation of Teresa Gª de Quesada.

(**).- Satisfactory elemental analysis have been obtained for all the products here described.

(***).- Spectra measured at a 60 MHz machine, with TMS as the internal standard.

singlets of tertiary methyl groups (0.82 and 1.11 δ), three acetates singlets(2.04 δ) an AB quartet centered at 3.74 δ (2H, J 12 Hz, $-\overset{|}{\underset{|}{C}}-CH_2-O-Ac$) and at 4.82 δ a complex signal integrating for four protons, a signal which must contain the two protons of the terminal methylene detected in the IR spectrum and probably the two protons geminal to the acetylated secondary alcohols.

Acetylation of II, IV and VI give the same triacetate (VIII) $[C_{26}H_{38}O_6$, m.p. 134-135º(EtOH:H_2O), $[\alpha]_D^{25º}$ +46.2º($\bar{c}$ 0.8, $CHCl_3$)$]$. The NMR spectrum of VIII exhibits two singlets of tertiary methyl groups (0.82 and 1.12 δ), three singlets at 2.03, 2.05 and 2.08 δ ($-O-CO-CH_3$), a doublet at 1.73 δ (3H, J 1.5 Hz, $\underline{CH_3}-\overset{|}{C}=\overset{|}{C}-H$), an AB quartet centered at 3.76 δ (2H, J 12 Hz, $-\overset{|}{\underset{|}{C}}-CH_2-O-Ac$), a complex signal at 4.81 δ(2H, two $-\overset{|}{C}H-O-Ac$) and one olefinic proton at 5.29 δ (small quartet, $W_{\frac{1}{2}}$ 5 Hz, $CH_3-\overset{|}{C}=\overset{|}{C}-\underline{H}$).

Hydrogenation of VII and VIII afford the dihydro-derivatives. In the case of VII, the NMR spectrum shows a new signal (3H, doublet, J 6 Hz, $\underline{CH_3}-\overset{|}{\underset{|}{C}}-H$) at 1.01 δ and the disappearance of two of the four protons forming the complex signal at 4.82. The dihydro-derivative of VIII presents the same doublet and shows the absence of the signals due to an olefinic proton (5.29 δ) and to a methyl group attached to a double bond (1.73 δ)(*).

When VII is refluxed in C_6H_6 solution with an I_2 crystal it isomerizes to VIII (1).

The above results indicate that the three oxygen atoms present in foliol and isofoliol are hydroxylic: a primary and two secondary hydroxyl groups. The remaining diterpenes are monoacetyl derivatives of the first two. All of them must be tetracyclic with one unsaturation; the only difference between I and II is due to the position of the double bond, the placement and configuration of the three hydroxyl groups being the same.

All the data point towards a (-)-kaurene structure for foliol and (-)-isokaurene skeleton for isofoliol. In fact when I is oxidized with CrO_3/Py it yields a diketoaldehyde (IX), m.p. 83-84º(hexane), that for reduction by the Huang-Minlon procedure affords, in low yield, a compound (X) whose physical constant and spectroscopic data fit exactly with those published for (-)-kaurene (2). It is thus established the carbon skeleton and absolute stereochemistry of these compounds.

It remains to locate the hydroxyl groups and the acetate group in the natural compounds. Linearol (V) and isolinearol (VI) show in their NMR spectra an AB quartet at low field (see Table 2) indicating that the primary hydroxyl group is the one acetylated. The chemical shift of this quartet, in the case of linearol, is a bit too low for an equatorial configuration on C-4, but the fact that no appreciable shift is observed for the position of the signal due to the angular C-20 methyl

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(*).- The dihydroderivatives of VII and VIII have the same $[\alpha]_D$ (+28º) and superimposables IR and NMR spectra, but the melting points differ in about 6ºC and are not sharp. We suppose that they are in fact formed by different mixtures of C-16 epimers since the steric control of the hydrogenation is not the same for the $\Delta^{15,16}$ than for the $\Delta^{16,17}$ compounds of these series.

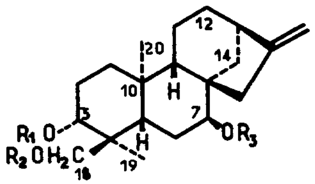
group from III to VI and from VII to VIII (see Table 2) agrees with a C-18 (equatorial) location of the primary alcohol. This is further supported by the fact that in the case of VII and VIII the position of the quartet agrees well with the expected for an equatorial configuration (3, 4).

TABLE 2. Chemical shifts (δ units)

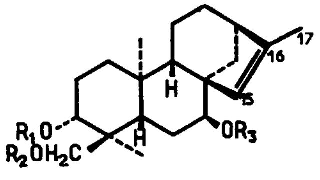
	C-10 Me	C-4 Me	$-CH_2-OR$	H-15	H-3	H-7	C-17
III	1.08(s)	0.68(s)	3.15(q, J 12 Hz)	-	4.92	3.63	4.86(2H, bs)
IV	1.08(s)	0.66(s)	3.17(q, J 12 Hz)	5.58(bs)	4.96	3.65	1.74(3H, d)
V	1.07(s)	0.77(s)	4.04(s)	-	3.60	3.60	4.83(2H, bs)
VI	0.99(s)	0.60(s)	3.77(q, J 12 Hz)	5.57(bs)	3.34	3.34	1.69(3H, d)
VII	1.11(s)	0.82(s)	3.74(q, J 12 Hz)	-	4.82	4.82	4.82
VIII	1.12(s)	0.82(s)	3.76(q, J 12 Hz)	5.29(bs)	4.81	4.81	1.73(3H, d)
XI	1.08(s)	1.04(s)	3.49	5.49(bs)	3.50	3.50	1.76(3H, d)
XII	1.24(s)	1.10(s)	3.46	5.50(bs)	3.48	-	1.75(3H, d)
XIII	1.08(s)	1.03(s)	3.53	5.10(bs)	3.53	-	1.69(3H, d)

All spectra have been run on $CDCl_3$ solution, except VI (DMSO).

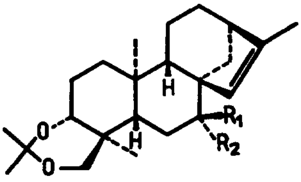
Sidol (III) and isosidol (IV) show a signal that integrates for one proton in the same region. The shape of this signal, partially overlapped with the terminal methylene in the case of III, is a clear quartet in the NMR spectrum of IV (J_{aa}, 9.3 Hz, J_{ae}, 6.6 Hz). This requires that the proton geminal to the secondary acetate group be axial and coupled with a single methylene (2). Compound III treated with a trace of acid in chloroform solution it is partially transformed in V; treating V in the same conditions affords III. With the primary hydroxyl group on C-18 the transacetylation requires that the secondary hydroxyl group participating in the reaction be placed on C-3 or C-6. The last position must be excluded considering the NMR spectrum of IV that points to C-3 hydroxyl group in equatorial configuration. This partial structure also explain the low field in which appears the AB quartet of V, since it allows the formation of hydrogen bridge (4).



I : $R_1=R_2=R_3=H$
III : $R_1=Ac; R_2=R_3=H$
V : $R_2=Ac; R_1=R_3=H$
VII : $R_1=R_2=R_3=Ac$



II : $R_1=R_2=R_3=H$
IV : $R_1=Ac; R_2=R_3=H$
VI : $R_2=Ac; R_1=R_3=H$
VIII : $R_1=R_2=R_3=Ac$



XI: $R_1=OH; R_2=H$
XII: $R_1R_2=O$
XIII: $R_1=R_2=H$

The presence of a C-3, C-18 diol is in accord with ready formation of the acetonide XI $\left[C_{23}H_{36}O_3\right.$, m.p. 265-270º(acetone), $[\alpha]_{D}^{25^{\circ}}$ +13º($\bar{c}$ 0.56, $CHCl_3$)$\left.\right]$ from isofoliol.

These results prove the structure and the configuration of all diterpenoids as I to VI except for the position and the configuration of the other secondary hydroxyl group. This was determined as follows:

The NMR spectra of III and IV show a small quartet ($W_{\frac{1}{2}}$ 5.5 Hz) at 3.63 and 3.65 δ respectively, i.e. the X part of an ABX system; it follows that this hydrogen is coupled with only two adjacents protons; mereover it must be equatorial, any diaxial interaction being excluded by the small width of the signal. Positions C-6, C-11, C-12 and C-2 can be thus excluded. An axial -OH excludes positions C-6, C-12 and C-14 as well, since there is no appreciable shift in the position of the C-20 methyl in none of the products from III to VIII. The remaining possibilities are C-1 and C-7.

The strong deshielding (Δ=0.29δ) undergone by the H-15 vinyl protons from VIII to IV presents as likely the C-7β-configuration (3). Oxidation of XI by Sarett's method gives XII $\left[C_{23}H_{34}O_3\right.$, m.p. 181-183º, $[\alpha]_{D}^{25^{\circ}}$-22.5º($\bar{c}$ 0.54, $CHCl_3$)$\left.\right]$ that by Huang-Minlon reduction affords XIII $\left[C_{23}H_{36}O_2\right.$, m.p. 187-189º($EtOH:Et_2O$), $[\alpha]_{D}^{25^{\circ}}$ -13.0º($\bar{c}$ 0.44, $CHCl_3$)$\left.\right]$; the keto group on C-7 agrees with the deshielding (Δ=0.4δ) of H-15 and the small deshielding of the angular methyl group from XIII to XII (see Table 2). Horeau's method (5) applied to XI affords (-)-α-phenyl butyric acid defining as 7S the absolute configuration of this carbon atom.

Thus the six new diterpenoids are: foliol = 3α,7β,18-trihydroxy-(-)-kaur-16-ene; isofoliol = 3α,7β,18-trihydroxy-(-)-kaur-15-ene; sidol = 7β,18-dihydroxy-3α-acetoxy-(-)-kaur-16-ene; isosidol = 7β,18-dihydroxy-3α-acetoxy-(-)-kaur-15-ene; linearol = 3α,7β-dihydroxy-18-acetoxy-(-)-kaur-16-ene, and isolinearol = 3α,7β-dihydroxy-18-acetoxy-(-)-kaur-15-ene.

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