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CONSTITUENTS OF COMPOSITAE. XV.[1]

CHLOROHYSSOPIFOLIN A AND B, TWO NEW SESQUITERPENE LACTONES ISOLATED FROM CENTAUREA HYSSOPIFOLIA VAHL.

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Continuing our studies on the sesquiterpene lactones from Centaureae (Compositae, tribe Cynareae) we have investigated Centaurea hyssopifolia Vahl[2] collected near Valdemoro (Madrid). From the ethanolic extract we isolated chlorohyssopifolin A (Ia) and its desacyl derivative chlorohyssopifolin B (Ib). The former compound, Ia, $C_{19}H_{24}O_7Cl_2$, m.p. 217-219°, $[\alpha]_D$ +97° (c, 1.12; MeOH), is an α-methylene-γ-lactone ester as may be seen from its NMR[†] (6.10 and 5.71, 1H each, d, J = 3.5 Hz) and IR spectra (1750 cm^{-1}, v.s.). Upon alkaline saponification it gives a lactone, $C_{15}H_{19}O_5Cl$, M^+ 314, m.p. 192-194°, $[\alpha]_D$ +67° (c, 0.30; $CHCl_3$), which was shown to be identical in all respects with chlorohyssopifolin B (Ib) isolated from the plant, and probably α-chloro-β-hydroxy-isobutyric acid [NMR: 1.60, s, C(Cl)Me, and 3.95, t, 2H, J = 11 Hz, $C\underline{H_2}OH$].

Strongly acetylated, Ia yields the triacetate Ic, $C_{25}H_{30}O_{10}Cl_2$, M^+ 560, m.p. 139°, $[\alpha]_D$ +98° (c, 1.99; $CHCl_3$), thus proving the nature of three of the oxygen atoms present in chlorohyssopifolin A.

Hydrogenation of Ia with Pd/C gives the dihydro derivative IIa, $C_{19}H_{26}O_7Cl_2$, m.p. 192-194°, $[\alpha]_D$ -16° (c, 2.63; MeOH), in which not only $\Delta^{11(13)}$ has been hydrogenated, but also $\Delta^{10(14)}$ is isomerized to $\Delta^{1(10)}$, as is shown by its NMR spectrum which presents the typical signals of a $\underline{Me}-\overset{|}{C}=C<$ group (1.89) and

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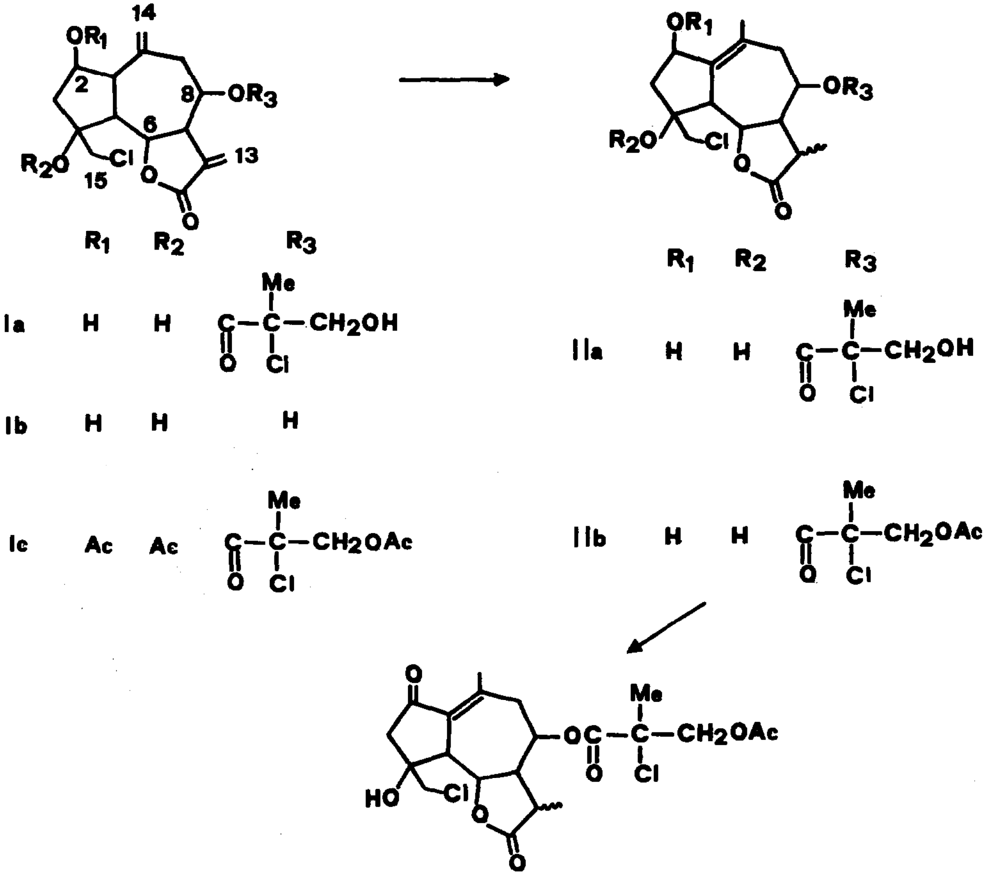
[†] δ-values.

the characteristic doublets of a mixture of the two possible methyl isomers in position α to the lactone carbonyl [1.35 (70%) and 1.13 (30%), 3H total, d each, J = 7 Hz] . The pyrolysis of this mixture with Se affords chamazulene, which proves that Ia has a guaianolide skeleton . On the other hand, upon reduction of Ia with $LiAlH_4$ and subsequent pyrolysis with Se, a mixture of azulenes is obtained from which artemazulene and linderazulene were identified, thus evidencing the existence of two oxygen functions at C_6 and C_8 in Ia.

The partial acetylation of IIa yields IIb which upon oxidation affords a liquid enone, $[\alpha]_D$ +46° (c, 3.42; $CHCl_3$), which on the basis of spectroscopic data [IR: 1680 cm^{-1}; UV: 246 nm, ε = 11033; NMR ($CDCl_3$): 2.18, vinyl protons absent] is assigned structure III.[3] We therefore conclude that a secondary OH is located at C_2 and a second methylene at C_{10}.

The position of the acyl group in Ia is deduced from the paramagnetic shift (0.34 ppm) of the αH-C_{13} observed when Ia is transformed into Ib, and from the appearance of a geminal coupling of ~ 1 Hz which requires the presence of a hydroxyl at C_8 having a nearly parallel orientation with respect to the lactone methylene. [4] In the NMR spectrum of Ia, the signal of the proton geminal to the lactone oxygen is a double doublet (J = 10.5, 9.0 Hz) at approximately 5.00, i.e. at lower field than expected for these compounds; its form is characteristic of the guaian-6,12-olides, but does not allow to decide between the configurations 5βH,6,7αH and 5,7αH,6βH although the magnitude of J and biogenetic reasons suggest the latter possibility.[5]

There only remains now to determine the position of the other Cl atom and the third OH. The absence of Me signals in the NMR spectrum of Ib and the presence of a neat AB quartet (3.85 and 4.27, d each, J = 11 Hz) indicate that the customary Me-C_4 is substituted by $ClCH_2-\overset{|}{\underset{|}{C}}-OH$, the configuration of the hydroxyl being such as to maintain a 1,3-diaxial relation with the H-C_6, which would explain the low resonance of this hydrogen. This hypothesis is supported by the fact that when Ia is transformed into the triacetate Ic the signal of the above mentioned H suffers a diamagnetic shift of ~ 0.5 ppm in consequence of the delocalization of the electron pair of the alcoholic oxygen atom.[6]



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All these reasons lead us to propose structure Ia as the most probable one for chlorohyssopifolin A and hence Ib for chlorohyssopifolin B, both not yet found in nature. To our knowledge, this is the second case of chlorinated sesquiterpene lactones isolated from a natural source. The first one has been reported by Kupchan et al. [7] from Eupatorium species showing cytotoxic properties.

Satisfactory analyses were obtained for all the new compounds cited. If not otherwise stated, the NMR spectra (100 MHz) were determined in d_6-acetone.

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