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# CISTODIOL AND CISTODIOIC ACID, DITERPENOIDS WITH A CIS-FUSED CLERODANE SKELETON

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The petroleum ether extract of Cistus monspeliensis is very rich in diterpenoid derivatives (1). From the neutral part of its saponification product we isolated a small amount of a diol, m.p. 82-84°, $[\alpha]_D$ -6.9° *, which was identified as 8α,15-labdanediol (**1**), previously isolated from Cistus labdaniferus (2), while the main constituent was a new diol, m.p. 86-88°, $[\alpha]_D$ +47.9°, which we shall call "cistodiol". It corresponds to the formula $C_{20}H_{36}O_2$ (element and mass spectral analysis). The acidic fraction of the same extract ** yielded a small amount of the corresponding diacid, "cistodioic acid", m.p. 255-256°, $[\alpha]_D$ +63.6° (EtOH), which was correlated with cistodiol by $LiAlH_4$ reduction. We propose for the new compounds the structures **2a** and **3a**, derived from the unusual cis-clerodane skeleton.

The compounds are bicyclic and contain a trisubstituted double bond (one-proton signals at 5.53 ppm for **2b**, at 6.50 ppm for **3c**)***, which is conjugated with the carboxyl group in **3a** ($\lambda_{max}$ 217 nm, ε 6900, EtOH). Two methyl groups on tertiary (singlets at 0.75 and 1.07 ppm in **2b**, at 0.75 and 1.20 ppm in **3c**) and two on secondary carbon (doublets at 0.73 and 0.92 ppm in **2b**, at 0.71 and 0.92 ppm in **3c**) are present. Two two-proton signals in the spectrum **2b** at 3.97 (triplet) and 4.44 ppm (broad singlet) can be assigned, respectively, to $-CH_2-C\underline{H}_2-OAc$ and $-CH=\underset{C}{C}-C\underline{H}_2-OAc$. A series of signals around 2 ppm (100 Mhz, benzene) in the spectrum of **3c**, can be interpreted as the AB part of an ABX system and assigned to the α protons in the $C-\underset{C}{C}-C\underline{H}_2-CO_2Me$ grouping. The mass spectrum of **3a** shows a peak at *m/e* 221 (loss of the $C_5H_{10}-COOH$ side-chain) and a base peak at *m/e* 125 ($C_7H_9O_2^+$), which is also

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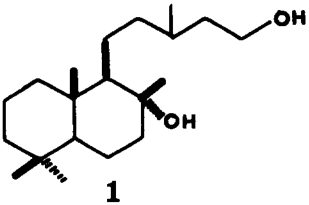
* Specific rotations were determined on ca. 1% solutions in $CHCl_3$, unless stated otherwise.

** The acidic fraction also contains large amounts of liquid acids, part of which are related to **2** and **3**; they are being studied at present in Montpellier by M.me Ch.Tabacik (personal communication).

*** NMR spectra were recorded at 60 Mhz on $CDCl_3$ or $CCl_4$ solutions, unless stated otherwise; chemical shifts are expressed in ppm from internal TMS.



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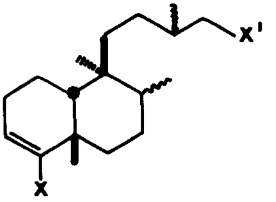
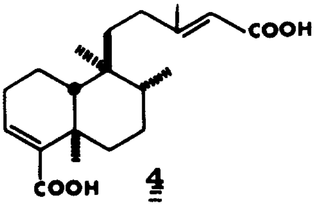


2a $X=X'=CH_2OH$
2b $X=X'=CH_2OAc$
3a $X=X'=COOH$
3b $X=COOH,\ X'=COOMe$
3c $X=X'=COOMe$



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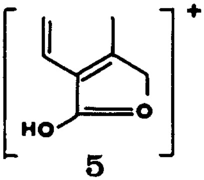

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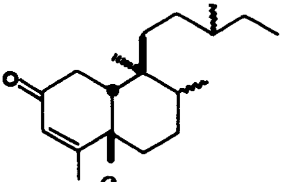

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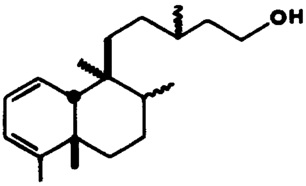

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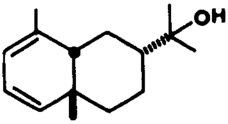

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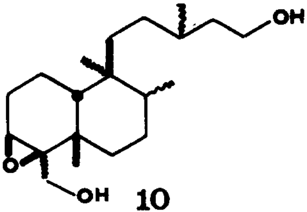

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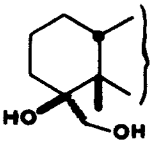

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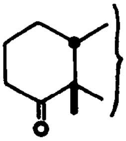

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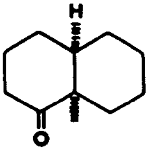

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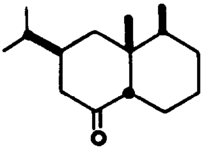

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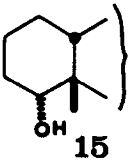

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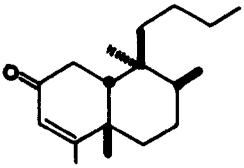

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present in the spectrum of the half-ester 3b, and is shifted to m/e 139 in that of the diester 3c. The same peak is also given by kolavic acid (4), and could be assigned to the ion 5. The mass spectra of the dihydro derivative of 3c and of dimethyl tetrahydrokolavate exhibit almost identical fragmentation patterns, the only differences being in the relative abundances of some of the peaks; however these two compounds have quite different retention times in g.l.p.c., therefore they should have the same skeleton but different relative configurations.

The diol 2a was converted into the corresponding hydrocarbon, *via* tosylation--$LiAlH_4$ reduction, then into the conjugated ketone 6 with $CrO_3$ in acetic acid. In the n.m.r. spectrum of 6 a "deceptively simple" ABX system (in $C_6H_6$, broadened doublet of two protons at 2.76 ppm, and a triplet of one proton at 1.81 ppm, converted into singlets on mutual irradiation) was assigned to protons in positions 1 and 10, and indicated that C-10 is tertiary and C-9 quaternary; furthermore the value of the splitting (3.5 cps) is consistent only with a 10-H equatorial with respect to ring A, and therefore with a cis-fused system in a "steroid-like" conformation (7). The ketone 6 exhibits a positive Cotton effect (a +64, MeOH) for the $n \rightarrow \pi^*$ transition; on the basis of Snatzke's rules (3) for transoid enones, this could be in accordance with absolute configuration 6 in conformation 7.

Reaction of cistodiol with $H_2SO_4$ in methanol gave a cisoid diene 8 ($\lambda_{max}$ 271 nm, $\varepsilon$ 4600, EtOH), the very high specific rotation of which ($[\alpha]_D$ +303°) was consistent with a cis annular junction; e.g., occidentalol (9), $[\alpha]_D$ + 363° (4). Again, in the very likely hypothesis that the preferential conformation of the diene is the same as that of 6, the right-handed helicity of the diene system implies dextrorotation for configuration 8 (5).

The epoxide 10, formed in the treatment of 2a with peroxybenzoic acid, or with ozone (hindered double bond) was converted with $LiAlH_4$ into the triol 11, m.p. 94-96°, $[\alpha]_D$ +6.8°, and into the ketone 12 by periodic acid. An up-field shift of 0.24 ppm in the chemical shift of one of the two methyl singlets of 12 in passing from $CDCl_3$ to benzene is in accordance with the axial nature of the 5-methyl group (6) and therefore with a preferential "steroid-type" conformation; the negative Cotton effect of 12 (a -64, MeOH) is consistent with the assumed conformation and absolute configuration at C-5 and C-10; e.g., 13, a +51 (7); 14, a -39 (8). Reduction of 12 with $LiAlH_4$ gave as the main product an alcohol which was assumed to be 15, because attack by hydride would be expected to be less hindered from the $\beta$ side. Application of Horeau's partial resolution method (9) to 15 gave dextrorotatory recovered 2-phenylbutyric acid; this indicates an (R) configuration at C-4, in agreement with formulation 15.

One of the quaternary methyl group signals in 6 and 12 is found at a rather high field (respectively 0.57 and 0.68 ppm); since this could be due to a shielding effect of the C=O group on an axial methyl group at C-9, we are tentatively proposing the configuration at this chiral centre shown in the formulas.

While it is known that the deduction of configurations of cis-decalin derivatives from physical data can be quite treacherous, the agreement of several lines of evidence seems to provide a reasonably firm ground, even if not a decisive proof for the proposed structures. One point against them could be found in the negative

Cotton effect of the ketone 16, a close analogue of 6 obtained from plathyterpol (10). A possible explanation of this discrepancy would be in the assumption that, while both compounds have the same absolute configuration at the ring junctions, they could differ in the relative configuration at C-8; this could be supported by the fact that their O.R.D. curves are not just mirror images of each other, and that also their n.m.r. spectra exhibit several differences that do not seem to depend only from the different side-chains. An 8α-methyl group could justify the preference for the "steroid-type" conformation, which would otherwise seem to be quite disfavoured because of the bad steric situation at C-9 (analogy with an axial t-butyl group with respect to ring A). Anyway, we consider the proposed configurations as tentative, and hope that an X-ray diffraction study will clear up the remaining uncertainties.

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