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THREE NEW TERPENOID QUINONE METHIDES FROM THE SEED OF *CHAMAECYPARIS OBTUSA*

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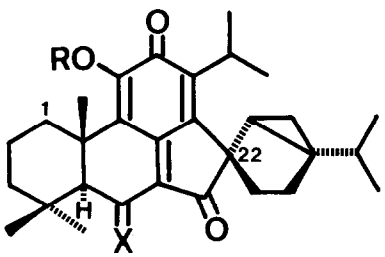
Abstract : The structures of three terpenoids with a new skeleton, isolated from the seed of *Chamaecyparis obtusa* (Cupressaceae), have been elucidated by spectral analyses, chemical transformations and X-ray diffraction analysis.

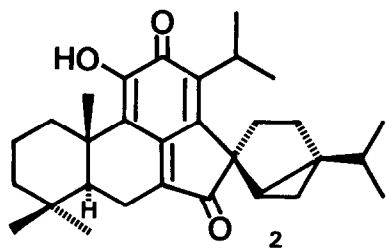
During the course of our investigation of the constituents of the seed of *Chamaecyparis obtusa* Endl., we isolated three new terpenoid quinone methides, named chamaecydin (1), isochamaecydin (2), and chamaecydinol (3), together with a number of mono-, sesqui- and diterpenes. [1] We now wish to report structural elucidation of these new compounds including the absolute configurations by spectroscopic, chemical and crystallographic evidence.

Chamaecydin (1), mp 196-7° (yellow prisms), $[\alpha]_D^{25}$ +40°(c=0.96,$CHCl_3$), $C_{30}H_{40}O_3$(m/z 448.2947, M^+, base peak), λ_{max}^{EtOH}(log ε): 330(4.35),346(4.42),396nm(3.47), showed the presence of an enolic hydroxyl group [a positive iron(III)chloride test and IR(KBr): 3290, 1295cm^{-1}; the mono acetate, 4, mp 181-2°] and two carbonyl groups [IR: 1700, 1615cm^{-1}; ^{13}C NMR(25MHz,$CDCl_3$): 205.7, 182.6ppm]. The ^1H NMR(400MHz,$CDCl_3$) spectrum of 1 showed the presence of two isopropyl groups attached to quaternary carbons [δ 3.18(1H, septet, J=6.8Hz), 1.31, 1.29(each 3H, d, J=6.8Hz); δ 1.80(1H, septet, J=6.8Hz), 1.06, 0.81(each 3H, d, J=6.8Hz)], three tertiary methyl groups [δ 1.17, 0.99, 0.97(each 3H, s)], a 1,1,2-trisubstituted cyclopropane ring [δ 1.05(1H, dd, J=8 and 4Hz), 0.78 (1H, dd, J=6 and 4Hz), 0.72(1H, ddd, J=8,6 and 2Hz)] and the partial structure, $(-\overset{|}{C}-)_2CH-CH_2-\overset{|}{C}-$,[δ2.72(1H, dd, J=19.5 and 3.7Hz), 2.21(1H, dd, J=19.5 and 12.7Hz), 1.52(1H, dd, J=12.7 and 3.7Hz)]. The presence of cyclopropane ring was also confirmed by a methylene carbon signal at 13.3ppm and a methine carbon signal at 33.5ppm in the ^{13}C NMR spectrum of 1 using a proton selective decoupling technique. The ^{13}C NMR spectrum of 1 showed the signals of six olefinic carbon atoms bearing no proton at δ 151.8, 149.4, 145.1, 144.7, 136.4 and 123.6ppm. Judging from the presence of two carbonyl groups and three fully substituted double bonds, 1 was deduced to be hexacarbocyclic.

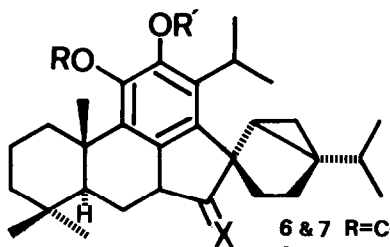
Hydrogenation of 1 over Adams' catalyst gave an unstable dihydro derivative 10 [λ_{max}^{EtOH} 294nm (log ε 3.32)] which was readily oxidized to 1 on standing in the air. The chemical and spectral characteristics (UV and IR) suggested 1 possessing a quinone methide moiety conjugated with a

carbonyl group such as in taxodione [2], 17. LAH reduction of 5 (mp 225-6°), obtained from 1 by treatment with CH_2N_2, gave two diols, 6 [mp 220-1°, λ_{max}^{EtOH} 288nm(log ε 3.46)] and 7 [mp 200-1°, λ_{max}^{EtOH} 289nm(log ε 3.46)]. One of two hydroxyl groups in both 6 and 7 must have been formed by reduction of the carbonyl group in the quinone methide moiety because the ^1H NMR spectra of both the diacetate 8 (mp 281-2°) from 6 and the one 9 (mp 252-3°) from 7 showed the presence of only one proton attaching to the carbon atom bearing an acetoxyl group, *i.e.* 8 : δ 5.28(1H, d, J=10.0Hz) ; 9 : δ 5.01(1H, d, J=10.5Hz).

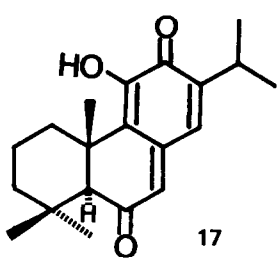




1 R=H ; X=H_2
3 R=H ; X=H, OH
4 R=$COCH_3$; X=H_2
5 R=CH_3 ; X=H_2
14 R=CH_3 ; X=H, OOH
15 R=CH_3 ; X=OOH, H
16 R=CH_3 ; X=H, OH



6 & 7 R=CH_3 ; R'=H ; X=OH, H
8 & 9 R=CH_3 ; R'=$COCH_3$; X=$OCOCH_3$, H
10 R=H ; R'=H ; X=O
13 R=CH_3 ; R'=H ; X=O ; $\Delta^{6,7}$



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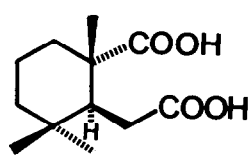

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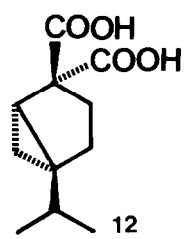

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The molecular structure of 1 was finally determined by X-ray diffraction analysis except for the absolute configuration.

Crystals of 1 grown in an ether solution were yellow plates with predominant (0 1 0) faces. The specimen with approximate dimensions 0.45 x 0.35 x 0.12mm was cut from the crystal for X-ray diffraction study. The lattice constants and intensities were measured on a Philips PW 1100 diffractometer with CuKα radiation monochromated by a graphite plate.

Crystal data : Chamaecydin, $C_{30}H_{40}O_3$, MW = 448.6. Orthorhombic, space group $P2_12_12_1$, Z = 4, $Dx = 1.167\ gcm^{-3}$. a = 12.980(6), b = 18.558(9), c = 10.598(5) Å, V = 2552.9 $Å^3$, μ(CuKα) = 5.37 cm^{-1}.

Intensities of 2076 reflections were measured as above the 2σ(*Iobs*) level out of 2180 within the 2θ range of 6°-120°. They were corrected for Lorentz and polarization factors but not for absorption.

The crystal structure was solved by the direct method using MULTAN program [3] and refined by the block-diagonal least-squares method. Hydrogen atoms were located on the difference electron density maps. The final *R* factor was 0.044 including anisotropic temperature factors for heavier atoms and isotropic ones for all the 40 hydrogen atoms. [4] The molecular structure is illustrated in Fig.1 denoting bond lengths between covalently bonded atoms. The intramolecular hydrogen bond distance between O2 and the hydrogen atom of O1 is also indicated. Double bonds are shown by black stick bonds. The figure was drawn by ORTEP program [5] with 30% probability ellipsoid. The quinone methide chromophore has the conjugated system extending to O3 through C7 and C21.

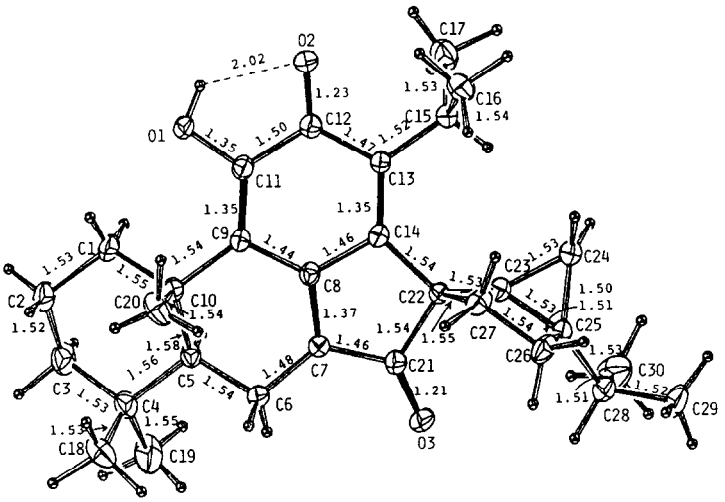

Fig.1 An ORTEP drawing of the molecular structure of Chamaecydin
The average e.s.d.'s of the bond lengths is 0.007 Å

The absolute configuration was determined by the degradation experiment as follows. Ozonolysis of 1 gave two dicarboxylic acids, 11 [6] [the dimethyl ester : $[\alpha]_D^{25}$ -9.0°(c=0.30 $CHCl_3$); $\nu_{max}^{CCl_4}$: 1735, 1300, 1170, 1155, 1440cm^{-1}; δ(100MHz,$CDCl_3$): 3.64, 3.62(each 3H,s), 2.30(m), 1.18(3H,s), 0.88 (6H,s); MS m/z(rel.int.); 256(M^+, $C_{14}H_{24}O_4$, 3), 224(31),197(59),196(44),181(44),174(31),142(54),123 (100),114(60),69(59)] and 12 [the dimethyl ester: $[\alpha]_D^{25}$ + 62.9°(c=0.27,$CHCl_3$); MS m/z(rel.int.); 240(M^+,$C_{13}H_{20}O_4$, 4), 208(10), 180(100),137(63), 121(47); $\nu_{max}^{CCl_4}$ 1740, 1253, 1080cm^{-1}; δ(100MHz,$CDCl_3$): 3.73, 3.72(each 3H, s), 1.85(1H,septet,J=7Hz), 0.95, 0.89(each 3H, d,J=7Hz), 0.45(2H,m)], and the former was identical in all respects ($[\alpha]_D$, MS, IR and ^1H NMR) with the one from known 7-oxo -totarol [7] by the same treatment. Thus the structure of chamaecydin including the absolute configuration was represented by 1.

Isochamaecydin (2), mp 213-4°(yellow needles), $[\alpha]_D^{25}$ + 226°(c=0.74,$CHCl_3$), $C_{30}H_{40}O_3$ (m/z 448.2951, M^+, base peak), λ_{max}^{EtOH}(log ε): 348(4.43), 333(4.37), 392nm(3.77), ν_{max}^{KBr}: 3350, 1710, 1615, 1330cm^{-1}, δ(400MHz,$CDCl_3$): 3.01(1H, septet, J=6.8Hz), 1.32(6H, d, J=6.8Hz), 1.94(1H, septet, J=6.8Hz), 1.01, 0.62(each 3H, d, J=6.8Hz), 1.19, 1.00, 0.96(each 3H, s), 2.85(1H, broad s, J=12.7Hz), 2.72(1H, dd, J=19.5 and 3.4Hz), 2.22(1H, dd, J=19.5 and 12.2Hz), 1.47(1H, dd, J=12.2 and 3.4Hz), 1.34(1H, dd, J=8.0 and 4.0Hz), 1.26(1H, m), 0.57(1H, ddd, J=8.0, 6.0 and 2.0Hz), 7.73(1H, s, -OH).

The close similarity between the MS and IR spectra of 1 and 2 suggested that 2 was a stereo isomer of 1. The isopropyl group on the quinoid ring was considered to be free from a restricted rotation which was caused by a sterically neighbouring cyclopropane ring, because the isopropyl group revealed a doublet signal at δ 1.32 ppm in the ^{1}H NMR spectrum of 2 while in the case of 1 the isopropyl group under consideration revealed two doublet signals at δ 1.31 and 1.29 ppm in the ^{1}H NMR. The structure of isochamaecydin, therefore, was supposed to be an epimer of 1 at C-22 and the configuration was deduced to be 22*R*.

Chamaecydinol (3), mp 220-1°(yellow prisms), $[\alpha]_D^{25}$ - 113.8°(c=0.91,$CHCl_3$), MS m/z(rel.int.): 464.2949($C_{30}H_{40}O_4$, M^+, 100), 446.2825($C_{30}H_{38}O_3$, M^+-H_2O, 95), λ_{max}^{EtOH}(log ε): 332(4.24), 346(4.29), 396nm(3.44), ν_{max}^{KBr}: 3530, 3330, 1690, 1610, 1295cm^{-1}, δ (100MHz, $CDCl_3$): 5.02(1H, d, J=10.0Hz), 1.71 (1H, d, J=10.0Hz), 3.17(1H, septet, J=6.8Hz), 1.31, 1.29, 1.03, 0.80(each 3H, d, J=6.8Hz), 1.22, 1.18, 1.14(each 3H, s), 7.76, 4.09(each 1H, s, -OH).

The ^{13}C NMR spectrum of 3 showed the signal at δ 67.5 ppm ascribed to the C-6 methine as well as downfield shifts of the C-5 and C-18 signals compared with the ^{13}C NMR of 1. The structure of chamaecydinol, therefore, was presumed to be a hydroxy derivative of 1 at C-6, and was confirmed by partial synthesis from 1, that is, treatment of 5 with p-TsOH in benzene to give an unstable enol 13 [λ_{max}^{EtOH}(log ε): 346(3.82), 254(4.08); δ 6.53(1H, d, J=3Hz, H-6)] which was readily oxidized to afford two hydroperoxides, 14 [mp 193-4°, λ_{max}^{EtOH} 340nm(log ε 4.31); δ 5.08(1H, d, J=11Hz, H-6β)] and 15 [mp 180-1°, λ_{max}^{EtOH} 339nm(log ε 4.36); δ 5.31(1H, d, J=4Hz, H-6α)], on standing in the air. 14 was reduced with $(Ph)_3P$ in ether to give an alcohol 16 (mp 196-7°), which was identical with the methyl ether of 3 in all respects (MS, IR, ^{1}H and ^{13}C NMR). Thus the structure of chamaecydinol was determined as 6α-hydroxy-chamaecydin.

These C_{30} compounds representing an unusual type of terpenoids, not likely being normal triterpenoids might be produced biogenetically by coupling of an abietane-type diterpenoid with a thujane-type monoterpenoid since both types of terpenoids described above have been found to occur in the same source.[1)]

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References and Notes

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