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THE ISOLATION AND STRUCTURE OF C_{19}-OBTUSILACTONE DIMER

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C_{19}-Obtusilactone dimer, a cytotoxic substance, has been isolated from Lindera obtusiloba Blume, and its structure also been elucidated on the basis of its spectral data coupled with chemical evidence.

In connection with antitumor substances, we have isolated the cytotoxic compounds with a novel γ-lactone grouping from Lindera obtusiloba Blume ("Dankobai" in Japanese).[1,2] We further examined chemical components of the same plant, and could isolate C_{19}-obtusilactone dimer (1).

According to the same procedure as described in the previous paper,[2] the benzene extracts of the fresh leaves of the above plant were roughly separated by repeated column chromatography on silica gel and then on Florisil using $CHCl_3$ as an eluent. Further separation was carried out by repeated preparative TLC [1) Kieselgel 60 PF_{254}. 2) 10% $AgNO_3$ - Kieselgel 60 PF_{254}] using benzene - EtOAc (3 : 1) to give four fractions. The second less polar fraction was further purified by preparative TLC (Kieselgel PF_{254}; 10% Et_2O - $CHCl_3$) to give colorless crystals of C_{19}-obtusilactone dimer (1) in a 0.0054% yield.

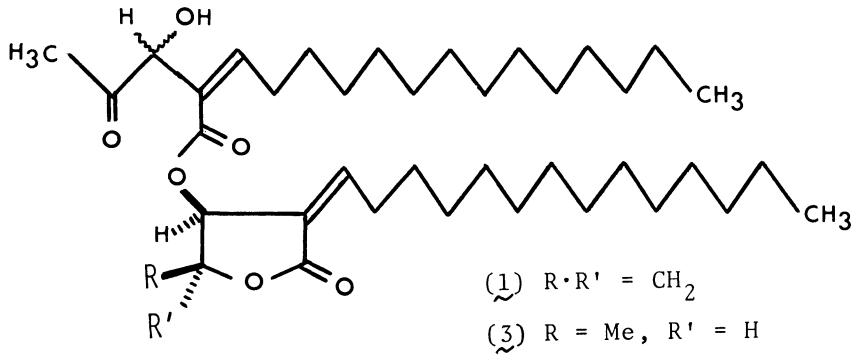
C_{19}-Obtusilactone dimer (1), mp 62 - 63°C (from hexane), has a molecular formula $C_{38}H_{64}O_6$ [m/e 616(M^+)] with the following spectral data: $[\alpha]_D^{23°}$ = +42.7° (c = 0.867 in $CHCl_3$); ν_{max} ($CHCl_3$) 3440, 1790, 1725 and 1680cm^{-1}; λ_{max} (MeOH) 221nm (ε, 18100); δ($CDCl_3$) 0.89(6H, t, J= 6.0Hz), 1.28(44H, br.s), 2.18(3H, s), 2.52(2H, q, J= 7.0Hz), 2.81(2H, q, J= 7.5Hz), 4.02(1H, d, J= 3.0Hz, OH), 4.54(1H, d, J= 3.0Hz) (this doublet is changed to a sharp singlet on addition of D_2O), 4.66 (1H, dd, J= 3.0, 1.5Hz), 4.94(1H, dd, J= 3.0, 1.5Hz), 6.18(1H, br.s), 6.37(1H, t, J= 7.0Hz) and 6.72(1H, td, J= 7.5, 2.0Hz),

From the above spectral data, this dimer has the same γ-lactone grouping as that of obtusilactone A (2).[2] Clearly, the NMR spectrum of the former has the signals corresponding to those of 2 except for the following point: 2 has the NMR signal at δ5.22, while 1 has the corresponding signal at δ6.18, suggesting that the latter has a -CH(OH)-O-CO-R grouping. Furthermore, on the basis of the NMR signals at δ6.72 and 2.81, this dimer adopts the same geometry as that of obtusilactone A (δ 6.68 and 2.78) at the tri-substituted double bond conjugated with the lactone CO group.[3]

On homogeneous catalytic hydrogenation using $Rh(Ph_3P)_3Cl$ in benzene (room temp, 30min), this dimer was converted into a dihydro compound (3) in a 51% yield [mp 64 - 66.5°C (from hexane) $C_{38}H_{66}O_6$ [m/e 618(M^+)]; ν_{max} ($CHCl_3$) 3450, 1765, 1730 and 1675cm^{-1}; λ_{max} (MeOH) 219nm (ε, 19800); δ ($CDCl_3$) 0.89(6H, t, J≃6Hz), 1.30(47H, br.s), 2.19(3H, s), 2.48(2H, q, J= 7.5Hz), 2.76(2H, q, J= 7.5Hz), 4.00(1H, d, J= 4.0Hz, OH), 4.52(1H, d, J= 4.0Hz) (this doublet is changed to a sharp singlet on addition of D_2O), 4.66(1H, quintet, J= 6.0Hz), 6.36(1H, t, J= 7.5Hz) and 6.67(1H, t, J= 7.5Hz)]. In the case of catalytic hydrogenation using PtO_2 in EtOAc (room temp, 3h), hydrogenolysis took place to give a saturated lactone (4) in a 59% yield [mp 49 - 53°C (from hexane); $C_{19}H_{36}O_2$ [m/e 296(M^+)]; ν_{max} ($CHCl_3$) 1775cm^{-1}; δ($CDCl_3$) 0.89(3H, t, J≃6Hz), 1.27(26H, br.s), 1.43(3H, d, J= 6.0Hz), 2.56(3H, complex) and 4.50(1H, m)].

Thus, the structure of C_{19}-obtusilactone dimer is established as 1 on the basis of its remaining NMR signals (δ 2.18, 2.52, 4.02, 4.54 and 6.37) except for the signals corresponding to those of obtusilactone A (2). In the structure of 1, the geometry at the tri-substituted double bond conjugated with the ester CO group is based on the δ-value of the olefinic proton (δ 6.37).[4]

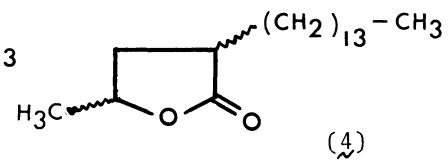
Cytotoxic activity of C_{19}-obtusilactone dimer (1) is also observed, but lower than that of the corresponding C_{19}-lactone, obtusilactone A (2). Further studies on this point are in progress.



(1) R·R' = CH_2

(3) R = Me, R' = H

(2)



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References

1. M. Niwa, M. Iguchi, and S. Yamamura, Tetrahedron Lett., 1975, 1539.
2. M. Niwa, M. Iguchi, and S. Yamamura, Chem. Lett., 1975, 655.
3. In the case of isoobtusilactone A, a geometrical isomer at the tri-substituted double bond, two NMR signals are observed at δ 7.05 and 2.46.
4. Methyl angelate has an olefinic proton signal at δ5.97, while the corresponding signal is observed at δ 6.72 in the case of methyl tiglate.[5] Therefore, this dimer (1) should have the same geometry as that of the former, because the olefinic proton in 1 is much deshielded by an $CH_3COCH(OH)$- grouping.
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