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THE STRUCTURES OF C_{17}-OBTUSILACTONE DIMER AND TWO C_{21}-OBTUSILACTONES

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In connection with anti-tumor substances, structural studies on many sesquiterpenes with an α-methylene-γ-butyrolactone ring have been extensively carried out.[1] Recently, we isolated the four cytotoxic substances with a novel γ-lactone grouping from the plant Lindera obtusiloba Blume.[2,3] We further examined chemical components of the same plant, and could isolate three new lactones which are expected to have anti-tumor activity. In particular, it is noted that one of them is a dimeric lactone.

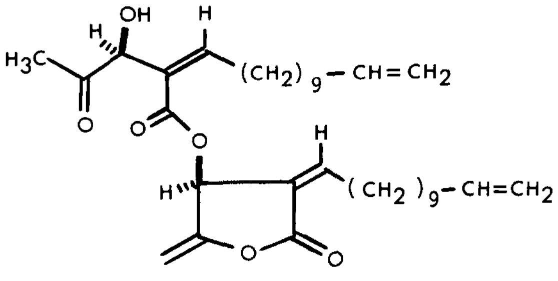
According to the same procedure as described in the previous paper,[2] the benzene extracts of the fresh leaves of the above plant were roughly separated by repeated column chromatography on silica gel and then on florisil using $CHCl_3$ as an eluente. Further separation was also carried out by repeated preparative TLC using Kieselgel 60 PF_{254} and 10%$AgNO_3$-Kieselgel 60 PF_{254} in benzene-EtOAc (3 : 1) to afford three new lactones (I, 0.025%; II, 0.00093%; III, 0.0018%), in each pure state, in addition to the four obtusilactones[2].

C_{17}-Obtusilactone dimer (I), mp 57-58° (from n-hexane), has a molecular formula $C_{34}H_{52}O_6$ [m/e 556(M^+)] with the following spectral data: $[\alpha]_D^{23°}$ = +49.3° in $CHCl_3$ (c = 0.507); $\nu_{max}(CHCl_3)$ 3450, 1795, 1730, 1690 and 1645cm^{-1}; λ_{max}(MeOH) 221nm (ε, 18100); $\delta(CDCl_3)$ 1.30(28H, br.s), 2.06(4H, q, J= 6.5Hz), 2.16(3H, s), 2.52(2H, q, J= 7.5Hz), 2.80(2H, q, J= 7.5Hz), 4.02(1H, br.s, OH), 4.54(1H, s), 4.66(1H, m), 4.8-5.2(5H, complex), 5.80(2H, ddt, J= 17, 10 and 6.5Hz), 6.19(1H, br.s), 6.37(1H, t, J= 7.5Hz) and 6.72ppm(1H, td, J= 7.5 and 1.5Hz).

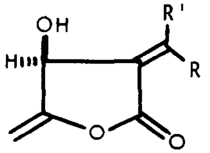
From the above spectral data, this dimer must have the same γ-lactone grouping as that of obtusilactone (IV)[2]. In particular, the NMR spectrum of the former has the signals corresponding to those of IV. The presence of two allyl groups and one exocyclic methylene group attached to the γ-lactone ring is confirmed by the following chemical evidences.

On homogeneous catalytic hydrogenation using $Rh(Ph_3P)_3Cl$ in benzene (room temp., 30min), this dimer was readily converted into a hexahydro-compound (V) in 68% yield [mp 69.5-70°; $C_{34}H_{58}O_6$; $\nu_{max}(CHCl_3)$ 3430, 1760, 1730 and $1670cm^{-1}$; $\lambda_{max}(MeOH)$ 219nm (ε, 17800); $\delta(CDCl_3)$ 0.89(6H, t, J= 6Hz), 1.30(39H, br.s), 2.18(3H, s), 2.47(2H, q, J= 7.5Hz), 2.76(2H, q, J= 7.5Hz), 4.03(1H, br.s, OH), 4.52(1H, br.s), 4.65(1H, quintet, J= 6.0Hz), 5.78(1H, d, J= 6.0Hz), 6.35(1H, t, J= 7.5Hz) and 6.66ppm(1H, t, J= 7.5Hz)]. In the case of catalytic hydrogenation using PtO_2 in EtOAc (room temp., 3hr), hydrogenolysis took place to give a saturated lactone (VI) in 67% yield [mp 53-54°; $C_{17}H_{32}C_2$ [m/e 268(M^+)]; $\nu_{max}(CHCl_3)$ $1775cm^{-1}$; $\delta(CDCl_3)$ 0.88(3H, t, J= 6Hz), 1.26(22H, br.s), 1.41(3H, d, J= 6.5Hz), 2.56(3H, complex) and 4.50ppm(1H, m)]. This lactone (VI) was also obtained from obtusilactone (IV) under the same condition.

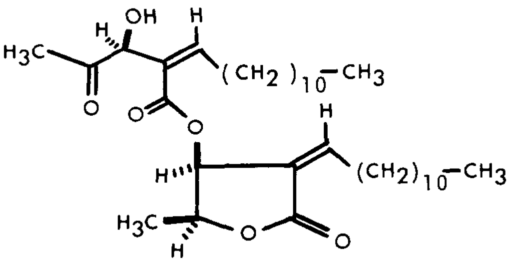
Thus, on the basis of the above chemical evidences coupled with the spectral data, the structure of this dimer can be represented by I, in which the configuration at the carbon atom bearing the hydroxyl group may be the same as that of obtusilactone (IV). Furthermore, the geometry at the tri-substituted double bond conjugated with the ester CO group in I is based on the δ-value of the olefinic proton (δ6.37ppm). However, another possibility is not



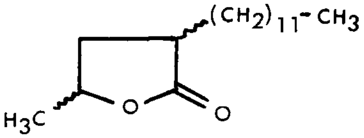
(I)



(II) R $=-CH_2-(CH_2)_4-CH=CH-(CH_2)_7-CH_3$
R'= H
(III) R = H
$R'=-CH_2-(CH_2)_4-CH=CH-(CH_2)_7-CH_3$
(IV) R $=-CH_2-(CH_2)_8-CH=CH_2$
R'= H



(V)



(VI)

necessarily ruled out, in which the ester CO group and the side-chain both are in an E-configuration to each other.

Obtusilactone-B (II) and isoobtusilactone-B (III) both are colourless liquid with a molecular formula $C_{21}H_{34}O_3$, and their physical data are shown below.

Obtusilactone-B (II): $C_{21}H_{34}O_3$ [m/e 334(M^+), 306, 291 and 153]; $\nu_{max}(CHCl_3)$ 3575, 3000sh., 1790 and 1685cm^{-1}; λ_{max}(MeOH) 224nm (ε, 10800); $\delta(CDCl_3)$ 0.88(3H, t, J= 6Hz), 1.28(br.s) and 1.40(br.s)(total 18H), 2.01(4H, br.s), 2.50(1H, br.s, OH), 2.80(2H, q, J=7.0Hz), 4.68 (1H, br.s), 4.89(1H, br.s), 5.13(1H, br.s), 5.37(2H, complex) and 6.67ppm(1H, td, J= 7.0 and 2.0Hz).

Isoobtusilactone-B (III): $C_{21}H_{34}O_3$ [m/e 334(M^+), 306 and 291]; $\nu_{max}(CHCl_3)$ 3580, 3000sh., 1785 and 1680cm^{-1}; λ_{max}(MeOH) 222nm (ε, 12100); $\delta(CDCl_3)$ 0.89(3H, t, J= 6Hz), 1.28(br.s) and 1.39(br.s)(total 18H), 2.02(4H, br.s), 2.47(2H, q, J= 7.5Hz), 2.71(1H, br.s, OH), 4.70(1H, br.s), 4.92(1H, br.s), 5.22(1H, s), 5.33(2H, complex) and 7.04ppm(1H, td, J= 7.5 and 2.5Hz).

From the above spectral data, these two lactones must be the geometrical isomers to each other at the tri-substituted double bond. In particular, the NMR spectra of both lactones indicate that obtusilactone-B has the same lactone moiety as that of IV [δ2.80 and 6.67ppm], whereas the isomer (III) has the different geometry at the tri-substituted double bond [δ2.47 and 7.04ppm] as seen in the case of isoobtusilactone[2].

Finally, the structures of both lactones were determined, as follows. In the NMR spectra of II and III, the following signals are due to the side-chain moiety: II, δ0.88, 1.28, 1.40, 2.01 and 5.37ppm; III, δ0.89, 1.28, 1.39, 2.02 and 5.33ppm. Clearly, one di-substituted double bond is included in the side-chain, the position of which is further determined by the following chemical evidences. When treated with $KMnO_4$ in benzene containing dicyclohexyl-18-crown-6 (room temp., 50hr), obtusilactone-B and its isomer both were oxidized to give nonanoic acid ($C_8H_{17}COOH$). Accordingly, the structures of obtusilactone-B and isoobtusilactone-B can be represented by II and III, respectively, in which the di-substituted double bond in the side-chain seems to be in a Z-configuration [II, δ5.37ppm; III, δ5.33ppm] analogous to Bohlmann's lactone[4].

Further studies on the chemical constituents of Lindera obtusiloba Blume as well as on chemical modification of these novel lactones are in progress.

REFERENCES AND FOOTNOTES

1. S.M. Kupchan, "Recent Advances in The Chemistry of Terpenoid Tumor Inhibitors", Pure Appl. Chem., 21, 227 (1970), and references cited therein.
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3. Obtusilactone, the main product of the plant, has been proved to have cytotoxic activity. The authors wish to thank Dr. T. Takita (Institute of Microbial Chemistry) for these experiments.
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