PROTOSAPPANIN B, A NEW DIBENZOXOCIN DERIVATIVE FROM SAPPAN LIGNUM

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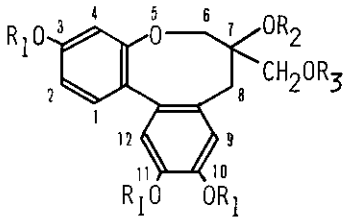
Abstract ——— A new dibenzoxocin derivative, named protosappanin B, $C_{16}H_{16}O_6$, white amorphous powder, $[\alpha]_D^{15}$ -11.4° (MeOH) was isolated from the heart-wood of Caesalpinia sappan L. (Leguminosae). It yielded a trimethyl ether (2) on methylation with diazomethane, a tetraacetate (5) and a pentaacetate (6) on acetylation, and sappanin (4) on alkali fusion. Protosappanin B (1) was chemically correlated with trimethyl ether (3) of protosappanin A (7). On the basis of the chemical and spectroscopic evidence, the chemical structure of 1 was established as 3,7,10,11-tetrahydroxy-7,8-dihydro-7(6H)-dibenz[b,d]oxocinmethanol. The cd spectrum of 1 indicated that its biphenyl system preferentially takes S configuration, from which S configuration was tentatively assigned to C-7 of 1.

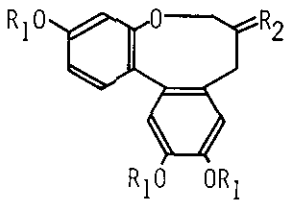
The methanolic extract of Sappan Lignum, the heart-wood of Caesalpinia sappan L. (Leguminosae) has sleeping-time elongation effect in mice. In the course of our study on its chemical components responsible for the effect, sappanchalcone[1] and protosappanin A[2] have been isolated. Present communication deals with protosappanin B (1), another dibenz[b,d]oxocin isolated from the heart-wood.

Protosappanin B (1), white amorphous powder, $[\alpha]_D^{15}$ -11.4° (MeOH) has a molecular formula, $C_{16}H_{16}O_6$ (observed molecular ion in ms, m/z 304.093; Calcd, 304.095). Its ir (KBr) spectrum showed absorptions due to hydroxyl groups at 3650-3100 cm^{-1} and aromatic rings at 1610 and 1500 cm^{-1}. The ^{13}C-nmr spectrum[3] of 1 exhibited

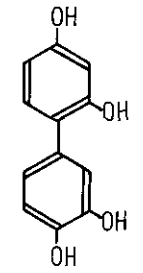
sixteen signals comprising aromatic carbons (seven singlets at δ 122.6, 126.6, 130.5, 143.6X2, 157.8 and 158.3 ppm, and five doublets at δ 107.5, 110.6, 116.7, 118.9 and 131.5 ppm), a quaternary carbon joined to an oxygen atom (δ 71.5 ppm), a methylene (δ 40.9 ppm)[4] and two oxygenated methylenes (δ 66.1 and 75.4 ppm). Protosappanin B (1) afforded a trimethyl ether (2) $C_{19}H_{22}O_6$,[5] $[\alpha]_D^{25}$ -55.5° ($CHCl_3$) on methylation with diazomethane, and a tetraacetate (5), $C_{24}H_{24}O_{10}$,[5] $[\alpha]_D^{25}$-36.8° ($CHCl_3$) and a pentaacetate (6), $C_{26}H_{26}O_{11}$,[5] $[\alpha]_D^{25}$ -62.5°($CHCl_3$), on acetylation with acetic anhydride in pyridine. In the ir (KBr) spectra, the former acetate (5) showed a hydroxyl absorption at 3460 cm^{-1} yet but the latter one (6) showed it no longer. In comparison of the ^{13}C-nmr spectra[6] of 5 and 6, the signal patterns ascribable to the sp^2 carbons were almost the same. In the sp^3 carbon region,



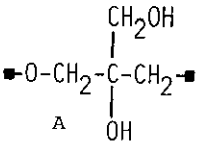
protosappanin B (1)
: R_1=H, R_2=H, R_3=H
2 : R_1=CH_3, R_2=H, R_3=H
5 : R_1=Ac, R_2=H, R_3=Ac
6 : R_1=Ac, R_2=Ac, R_3=Ac



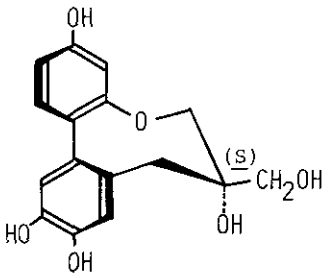
protosappanin A (7)
: R_1=H, R_2=O
3 : R_1=CH_3, R_2=O
8 : R_1=H, R_2= 
9 : R_1=CH_3, R_2= 



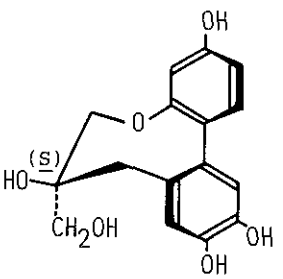
sappanin (4)



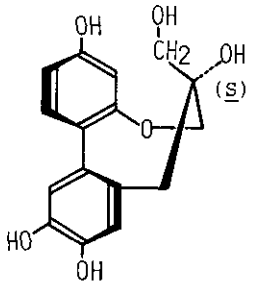
A



B (TBC form)



C (TBC form)



D (TB form)

Chart 1

however, the quaternary carbon signal of 5 was observed at higher field by 9.4 ppm, and three methyene signals of the former acetate (5) were at lower field by 3.7-4.6 ppm than those of the latter acetate (6). These data indicated that 6 is a peracetate formed from 5 through acetylation of the tertiary hydroxyl. The ^{1}H-nmr spectrum[6] of the pentaacetate (6) exhibited five three-proton singlets due to acetoxyl groups (δ 2.01-2.25 ppm), five aromatic protons (δ 6.80-7.35 ppm) and three-paired methylene protons. Each of the methylene protons showed no other coupling than geminal one (three AB types) : [δ 4.83, 3.97 ppm (J=12 Hz)], [δ 4.51, 4.38 ppm (J=12 Hz)], [δ 3.45, 2.68 ppm (J=14 Hz)]. These data supported existence of a partial structure A in the molecule of 1.

The spectroscopic properties of protosappanin A (7) and protosappanin B (1) have following resemblances to each other. The ^{1}H-nmr spectrum[3] of 1 showed two singlets at δ 6.61 and 6.67 ppm [1,2,4,5-tetrasubstituted benzene] and an ABX pattern at δ 6.40 (d, J=2.3 Hz), 6.49 (dd, J=8.3, 2.3 Hz) and 6.90 ppm (d, J=8.3 Hz) [1,2,4-trisubstituted benzene], suggesting that the two benzene rings of 1 have the same substitution pattern as those of 7. A prominent fragment at m/z 229 ($C_{13}H_9O_4$)[7] was observed in the both ms spectra of 1 and 7. And their uv spectra were superimposable to each other : the absorptions owing to the biphenyl chromophore [1, λ_{max}^{EtOH} (log ε) : 210 (end absorption 4.61), 255 (4.08), 288 (3.86); 7, λ_{max}^{EtOH} (log ε) : 210 (end absorption 4.59), 260 (4.00), 284 (3.84)]. Since above findings suggested that protosappanin B (1) is a dibenz[b,d]oxocin derivative, it was subjected to alkali fusion. Sappanin (4), $C_{12}H_{10}O_4$, mp 203.5-204°C was obtained, which could also be prepared from the methanolic extract of this heart-wood[8] and protosappanin A (7).[2] On the basis of the all above findings the structure of protosappanin B was presumed as 1 (Chart 1).

In order to confirm the structure of protosappanin B (1), 1 was chemically correlated to 7 as follows. The 1,2-diol system of the trimethyl ether (2) was cleaved with lead tetraacetate to afford an optically inactive ketone (3) $C_{18}H_{18}O_5$.[5] Protosappanin A (7), after protection of its carbonyl group as a ketal (8), was methylated with diazomethane (9), and then deketalized to give its trimethyl ether (3), which was completely identical with 3 derived from protosappanin B (1) on the direct comparison by tlc, ir, and ms. Consequently, the structure of protosappanin B (1) except for its stereochemistry was established as 3,7,10,11-tetrahydroxy-7,8-dihydro-7(6H)-dibenz[b,d]oxocinmethanol.

Cis-cis-1,3-cyclooctadiene exists in two interconvertible conformers, a twist-

boat-chair (TBC) form and a twist-boat (TB) form in solution.[9] The X-ray crystallographic analysis of protosappanin A (7)[2] showed that its dihydrooxocin ring takes a TBC conformation in the solid state, which was also found in the dibenzocyclooctadiene type lignans such as schizandrin.[10] In the case of 1 and its derivatives, two substituents at C-7 seem to destabilize more a TB form of the ring system than a TBC form, because of steric interaction between one of the substituents and one of the benzene rings (e.g. D in Chart 1). Since in the case of protosappanin A and B, protons at C-1 and C-12, two ortho positions of their biphenyl system are not bulky enough to restrict rotation around the C-C single bond between the two benzene rings, the biphenyl system could more or less exist as an equilibrated mixture of rotomers in solution. In fact, owing to this property, optically inactive 3 was derived from optically active 1, and broadened or split signals were often observed in the nmr spectra of 1, 2, 5 and 6 on the measurement at room temperature. Protosappanin B (1), nevertheless, showed Cotton effects in its cd spectrum[11] ($[\theta]^{25}$ (nm) : +5600 (224), -5400 (238), -4600 (251), -1400 (290)). The negative Cotton at 251 nm corresponding to the conjugation band of biphenyl derivatives indicated that the biphenyl system exists as a rotomer with S configuration in preference to one with R in the solution.[12] The biased population in favor of the S rotomer apparently depends on relative stability of stereoisomers at the sole asymmetric carbon C-7 of protosappanin B (1). On the basis of the above discussion, the preferred rotomer with S configuration of the biphenyl system suggests that the carbinol group at C-7 in the S rotomer of 1 exists as an equatorial substituent (B in Chart 1) of a TBC conformer of the dihydrooxocin ring rather than as an axial one (C in Chart 1), because the carbinol group must be more bulky than the hydroxyl group at C-7. In other words, S configuration was tentatively assigned to C-7 of protosappanin B (1) (B in Chart 1).

Protosappanin B (1) extended the sleeping time of mice induced by hexobarbital. The activity is weaker than that of protosappanin A (7), and seems to be minor in relation to the sleeping-time-elongation effect of the methanol extract of Sappan Lignum.

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3. This spectrum was measured in DMSO-d_6 at 90°C.
4. This chemical shift (δ40.9 ppm) is the value on the measurement in pyridine-d_5 at 90°C since it was hidden in signals of DMSO-d_6.
5. The molecular formula was determined by analysis of the high resolution ms.
6. This spectrum was measured in $CDCl_3$ at room temperature.
7. This fragment ion showed intensities 43% and 72% in the case of 1 and 7, respectively, relative to the base ion peak (M^+).
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11. The cd spectrum was measured in MeOH. Negative Cottons at about 245 nm were also observed in the case of 2, 5 and 6.
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