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THE STRUCTURES AND CONFORMATIONS OF TWO NEW LIGNANS, KADSURIN AND KADSURARIN

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The decoction of the stems of Kadsura japonica Dunal (Magnoliaceae) is used in Taiwan as a remedy for snake-bites, and also used as an antipyretic, antispasmodic and anodyne by the local people.[1] In the course of our searching for physiologically active substances of this plant, we have isolated two new schizandrin-type lignans, named kadsurin (I) and kadsurarin (II). In the present paper, we wish to describe the isolation and structures of kadsurin and kadsurarin. In addition, the conformation of these lignans, which have a cyclo-octadiene system, will be also presented.

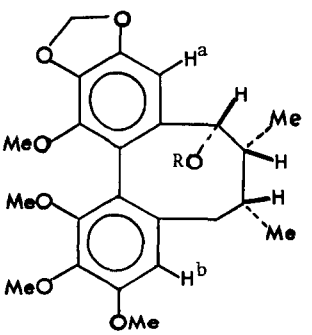
A sample of the dried and pulverized material of the stems of Kadsura japonica Dunal was refluxed with large amounts of n-hexane for 3hr., and then filtered. The filtrates were concentrated under reduced pressure to give a dark green oil, which was chromatographed on silica gel (Kieselgel, E. Merck, Darmstads, Germany) and eluted with n-hexane-EtOAc (4 : 1) to give white needles of kadsurin (I) in ca. 0.0015%. Further elution with n-hexane-EtOAc (2 : 1) afforded white needles of kadsurarin (II) in ca. 0.005%. The physical properties of these two compounds are shown below.

Kadsurin (I): m.p. 157-158° (from EtOH); $C_{25}H_{30}O_8$ [m/e 458(M^+) and 398(M^+- 60)(M*= 346)]; $[\alpha]_D^{25}$ -39°(c= 0.13 in $CHCl_3$); ν_{max}(Nujol) 1735, 1615, 1600, 1585 and 1495cm^{-1}; λ_{max}(MeOH) 278, 254 and 230nm (ε, 3500, 11300 and 26300, respectively); δ($CDCl_3$) 0.95(3H, d, J= 7.0Hz), 1.08(3H, d, J= 7.0Hz), 1.60(3H, s), 1.92-2.20(2H, complex), 2.67(2H, d, J= 4.2Hz), 3.65 (3H, s), 3.83(3H, s), 3.89(3H, s), 3.92(3H, s), 5.67(1H, br.s), 5.99(2H, br.s), 6.48(1H, s)

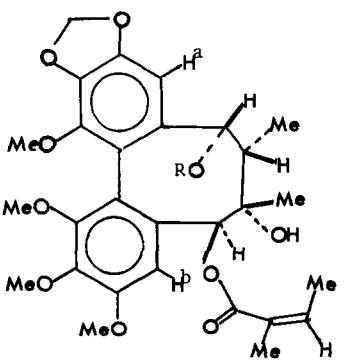
and 6.60ppm(1H, s).

Kadsurarin (II): m.p. 255-256°(in a sealed tube)(from EtOAc); $C_{30}H_{36}O_{11}$[m/e 572(M^+), 512(M^+- 60)(M*= 458) and 412]; $[\alpha]_D^{25}$-65°(c= 0.10 in $CHCl_3$); ν_{max}(Nujol) 3550, 1735, 1720sh., 1643sh., 1620, 1600, 1585sh. and 1500cm^{-1}; λ_{max}(MeOH) 280, 255 and 231nm (ε, 3200, 10600 and 30000, respectively); δ($CDCl_3$) 1.27(3H, d, J= 6.8Hz), 1.36(3H, s), 1.40(3H, fine sprıtted s), 1.60(3H, s), 1.85(3H, d,q, J= 7.5, 1.5Hz), 2.10(1H, br.s, OH), 2.16(1H, q, J= 6.8Hz), 3.64(3H, s), 3.75(3H, s), 3.90(3H, s), 3.95(3H, s), 5.68(2H, br.s), 5.90(2H, s), 6.00 (1H, br.q, J= 7.5Hz), 6.43(1H, s) and 6.60ppm(1H, s).

From the above spectral data, kadsurın (I) can be regarded as a biphenyl-type compound with two aromatic protons (δ 6.48 and 6.60ppm). In particular, ıt should be noted that the UV spectrum of I ıs almost superimposable to that of schızandrın.[2] From the NMR spectral data, kadsurın has four methoxyl groups(δ 3.65, 3.83, 3.89 and 3.92ppm) and one methylene-dıoxy group (δ 5.99ppm), and all of them must be attached to the aromatic rıng. Furthermore, the presence of a partıal structure (III)(⁓CH(OAc)-CH(Me)-CH(Me)-CH_2⁓) can be confirmed by exhaustive analysıs of the NMR spectrum of I with aid of double resonance experıments: ırradıatıon at the center of δ1.92-2.20ppm caused each sıgnal at δ0.95, 1.08, 2.67 and 5.67ppm to collapse to sharp singlet. The presence of the acetoxyl group(AcO-CH⁓) ın III can be confırmed by the mass and NMR spectra (m/e 398; δ 1.60 and 5.67ppm) coupled with the chemical evıdences. When treated wıth $LiAlH_4$ in THF (room temp., 2.5hr.), kadsurin was converted into the corresponding hydroxy-compound (IV)[m.p. 134-135°(from MeOH); $C_{23}H_{28}O_7$ (m/e 416 (M^+)); ν_{max}(Nujol) 3560cm^{-1}]. In the NMR spectrum, the sharp singlet atδ1.60ppm in



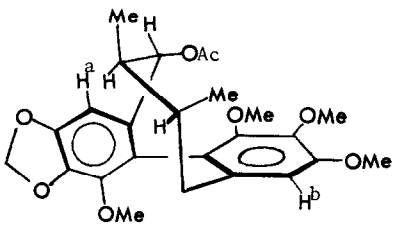
(I) R = Ac
(IV) R = H



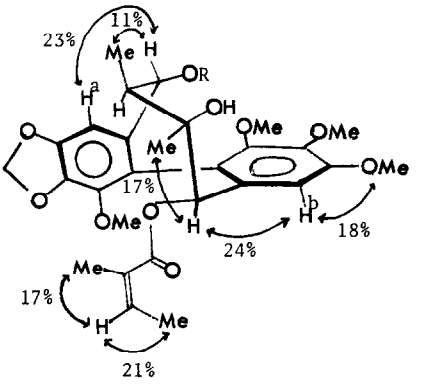
(II) R = Ac
(V) R = H

I was not observed, but instead the signal at δ 5.67ppm in I was shifted to δ 4.64ppm (1H, br.s). Finally, the structure including the position of each functional group and conformation of kadsurin were elucidated by measurements of intramolecular nuclear Overhauser effects (NOE), which were focused on the signals corresponding to two aromatic protons.

Low-intensity irradiation at δ 5.67ppm caused a 21% increase in the integrated intensity of the aromatic proton signal at δ 6.48ppm (H^a), whereas any enhancement of the signal intensity of H^b was not detected. Furthermore, it should be noted that the signal intensity of H^a was not increased by irradiation at frequencies corresponding to the absorbance of each methoxyl group, indicating that the methylenedioxy group must be located at the position adjacent to H^a, as shown in [A]. On the other hand, low-intensity irradiation at δ 3.92, 2.67 and 0.95ppm caused 11, 13 and 9.6% enhancements of the signal intensity of H^b (δ 6.60ppm), respectively. These observations indicate that one of four methoxyl groups (δ 3.92ppm) must be located at the position adjacent to H^b, and one of sec.methyl groups (δ 0.95ppm) also be placed in such a space as depicted in [A]. Finally, configuration of the remaining sec.methyl group can be elucidated as follows: low-intensity irradiation at



[A]



[B] (II) R = Ac
(V) R = H

δ 1.08ppm caused a 12% increase of the signal intensity of the proton attached to the carbon atom bearing the acetoxyl group (δ 5.67ppm), whereas any interaction between the sec.methyl group (δ 1.08ppm) and H^a was not detected. These facts are in good agreement with J-value ($\sim$ 0Hz) of the NMR signal at δ 5.67ppm. Thus, the above results can be

explained only by the conformation [A] for kadsurin (I).

Kadsurarin (II) has the same carbon skeleton as that of kadsurin (I) except for some functional groups. In the comparison of the NMR spectra between I and II, the former has two sec.methyl groups and one methylene group, whereas II has one sec.methyl group (δ 1.27ppm) and no methylene group. But instead, II has a tertiary methyl group (δ 1.36ppm) on the carbon atom having a hydroxyl group, and a proton (δ 5.68ppm)[3] attached to the carbon atom bearing an oxygen atom constituting a part of the angelate (δ 1.40, 1.85 and 6.00ppm). When treated with 0.5N KOH in MeOH-dioxane (room temp., 4.5hr.), II was selectively converted into desacetylkadsurarin (V) in high yields, m.p. 227-228° (from n-hexane-EtOAc); $C_{28}H_{34}O_{10}$ (m/e 530 (M^+), 512 and 412); ν_{max}(Nujol) 1715cm^{-1}; δ ($CDCl_3$) 1.32(3H, s), 1.36(3H, d, J= 7.2Hz), 1.39 (3H, fine spritted s), 1.73(2H, br.s, OH), 1.85(3H, d,q, J= 7.5, 1.7Hz), 1.98(1H, q, J= 7.2Hz) 3.73(6H, s), 3.87(3H, s), 3.90(3H, s), 4.84(1H, s), 5.66(1H, s), 5.88(1H, d, J= 1.2Hz), 5.92 (1H, d, J= 1.2Hz), 5.99(1H, q,q, J= 7.5, 1.5Hz), 6.28(1H, s) and 6.76ppm(1H, s). Finally, the stereostructure of II was established by measurements of NOE (in V). The results are shown in [B]. In particular, an interaction between the tertiary methyl group (δ1.32ppm) and H^b was not detected, but instead irradiation at δ1.32ppm caused a 17% enhancement of the integrated intensity of the signal at δ 5.66ppm. This finding indicates that the configuration of the tertiary methyl group in II is clearly different from that of the corresponding sec.methyl group in I. As the first example, the stereostructures of schizandrin-type lignans were established in the present study.

The NMR spectra were taken on a Varian HA-100D NMR spectrometer using $CDCl_3$ as a solvent.

REFERENCES AND FOOTNOTES

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2. N.K.Kochetkov, A.Khorlin, O.S.Chizhov and V.I.Sheichenko, Tetrahedron Letters, 20, 730 (1961) and references cited therein.
3. The signal at δ 5.68ppm is due to two protons, one of which is attached to the carbon atom bearing the acetoxyl group, as shown in I.