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REVISED STRUCTURES OF LINDERATONE AND METHYLLINDERATONE

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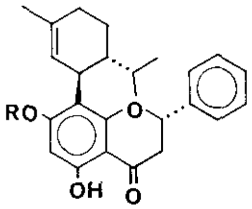
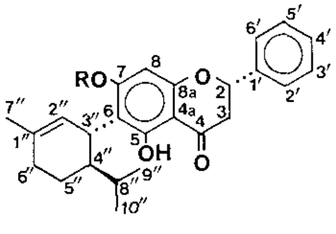
Abstract ——— The structure of a terpenylflavanone, linderatone, was revised to 6-terpenylflavanone by ^{1}H-^{13}C long-range cosy experiment. Therefore, the structure of methyllinderatone was also revised to **4**.

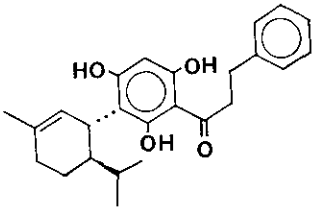
Previously, we have reported the isolation and the structure elucidation of two novel flavanones, linderatone (**1**)[1] and methyllinderatone (**2**),[2] having a cyclic monoterpene on the A ring, from the fresh leaves of Lindera umbellata Thunb. and L. umbellata Thunb. var. membranacea (Maxim) Momiyama. The location of the monoterpene unit in each compound was determined, at first, to C-8 position from the results of Gibbs reaction and bathochromic effect in uv spectrum. And later, terpenylation reaction of 5,7-dihydroxyflavanone afforded a mono-terpenylated flavanone as a main product which was identical with natural linderatone in all respects.[3] However, prenylation of the similar compounds has been shown to give the 6-prenyl derivative as a major product,[4] and recently the location of the alkyl group in some previously reported 6-alkyl flavanones was revised to the C-8



1 : R = H
2 : R = CH$_3$



3 : R = H
4 : R = CH$_3$



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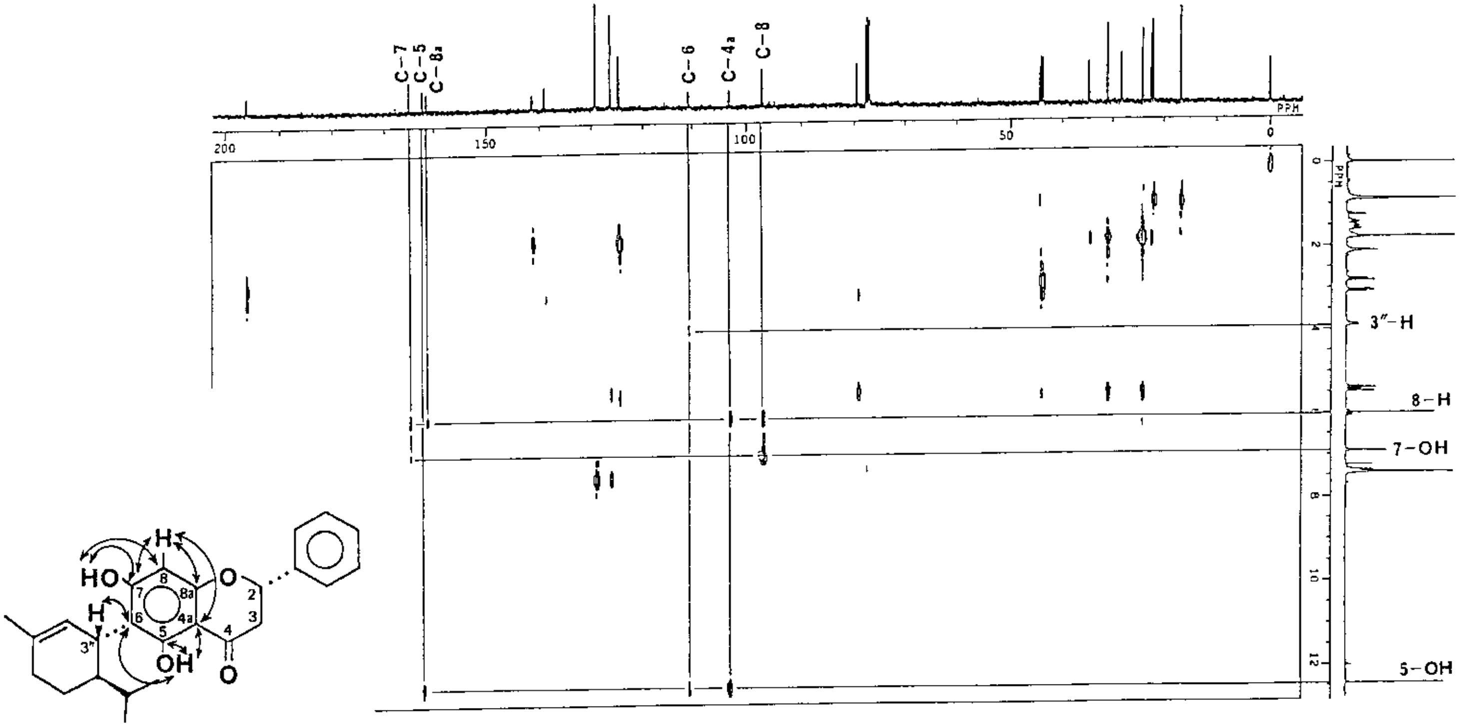

Figure 1 ${}^{1}H$-${}^{13}C$ Long-Range COSY Spectrum of Linderatone (3) in $CDCl_3$ (J_{CH} = 10 Hz; Sample, 50 mg; 20 h Run).

position by the result of $^1H[^{13}C]$ long-range coupling experiment.[5] Furthermore, ambiguities of Gibbs reaction and $AlCl_3$ induced bathochromic shift in uv spectra for structure elucidation were also suggested. We therefore had to reinvestigate the structure of linderatone by means of two dimentional $^1H[^{13}C]$ long-range shift correlation spectroscopy (^1H-^{13}C long-range cosy) experiment.

In the ^1H-^{13}C long-range cosy spectrum of linderatone (Figure 1), the proton of chelated hydroxyl group at δ 12.47 (5-OH) is correlated with the carbons at δ 162.1 (C-5), δ 110.3 (C-6) and δ 102.6 (C-4a), and the carbon at δ 110.3 (C-6) is correlated with the proton at δ 3.90 (3"-H). Similarly, the proton of the another hydroxyl group at δ 6.90 and 6.92 (7-OH)[6] is also correlated with the carbons at δ 164.8 (C-7), δ 96.5 and 96.6 (C-8),[6] and the proton at δ 6.02 (8-H) is correlated with the carbons at δ 164.8 (C-7), δ 161.2 (C-8a) and δ 102.6 (C-4a). These significant long-range ^1H-^{13}C correlations are indicated by arrows. From these results, the position of the p-menthene moiety was unambiguously concluded to be at C-6 but not at C-8. The stereochemistry of the p-menthene moiety was established to be trans relationship by hydrogenolysis of linderatone,[11] and the flavanone skeleton determined to be 2S[7] from a positive maximum at 316 nm and a negative maximum at 287 nm in the cd spectrum. Therefore, the structure of linderatone must now be revised to **3**.

Next, methylation of the linderatone (3) with CH_2N_2 afforded a flavanone (**4**) which was identical with methyllinderatone in all respects. Therefore, the structure of methyllinderatone must also be revised to **4**.

EXPERIMENTAL

Ir spectra were recorded on a JASCO IR-810 spectrophotometer. Ms and high-resolution ms were determined on a Hitachi M-80 mass spectrometer. ^1H Nmr, ^{13}C nmr and ^1H-^{13}C long-range cosy spectra were recorded on a JEOL GX-270, FX-100 and GX-400 spectrometer, respectively. Optical rotations were measured on a JASCO DIP-181 digital polarimeter. Cd spectra were recorded on a JASCO J-600 spectropolarimeter.

Extraction and Separation of Compounds —— The fresh leaves (8.3 Kg) of Lindera umbellata Thunb. collected in Gifu prefecture in September 1988, were extracted with MeOH (67 l) at room temperature for seven days. The MeOH extract was divided into the n-hexane-soluble (172 g) and $CHCl_3$-soluble (38 g) fractions. A portion of the n-hexane-soluble fraction (111 g) was chromatographed on Florisil. Elution with benzene gave linderatone (**3**, 68 mg), methyllinderatone (**4**, 11 mg), linderachalcone[8] (188 mg), neolinderachalcone[8] (9 mg) and 2',6'-dihydroxy-4'-methoxy-3'-(3"-methyl-6"-methylethyl-2"-cyclohexenyl)chalcone[9] (methyllinderachalcone, 43 mg). Further elution with benzene-$CHCl_3$ (10:1) gave pinocembrin[11] (31 mg) and pinostrobin[11] (274 mg).

Linderatone (3): Amorphous powder. $[\alpha]_D$ -32.4° (c 0.5, $CHCl_3$). Ms m/z: 392 (M^+), 349, 322, 307, 270. High-resolution ms m/z: 392.1985 Calcd for $C_{25}H_{28}O_4$ (M^+). Found: 392.1952; 322.1204 Calcd for $C_{20}H_{18}O_4$ (M^+-70). Found 322.1226. Ir ($CHCl_3$): 3370, 1635, 1620, 1580, 1450 cm^{-1}. Uv (EtOH): 234(sh), 295, 335(sh) nm. Uv (EtOH + $AlCl_3$): 315, 366. Cd (c 0.033, MeOH): $[\theta]_{223}$ +5.5 x 10^3, $[\theta]_{287}$ -7.6 x 10^2, $[\theta]_{316}$ +1.2 x 10^2. ^{1}H-Nmr ($CDCl_3$) δ: 0.88, 0.88, 0.89, 0.90 (ca. 3/2H x 4, d x 2, J=6.7 Hz, 8"-Me), 1.79, 1.79 (ca. 3/2H x 2, s x 2, 1"-Me), 2.81, 2.83 (ca. 1/2H x 2, dd x 2, J=3.0, 17.1 Hz, 3β-H), 3.09, 3.09 (ca. 1/2H x 2, dd x 2, J=13.1, 17.1 Hz, 3α-H), 3.90 (1H, br d, J=7.2 Hz, 3"-H), 5.40, 5.44 (ca. 1/2H x 2, dd x 2, J=3.0, 13.1 Hz, 2-H), 5.49, 5.50 (ca. 1/2H x 2, s x 2, 2"-H), 6.02, 6.02 (ca. 1/2H x 2, s x 2, 8-H), 6.90, 6.92 (ca. 1/2H x 2, s x 2, OH), 7.38-7.48 (5H, m, Ar-H), 12.47, 12.47 (ca. 1/2H x 2, s x 2, OH). ^{13}C-Nmr ($CDCl_3$) δ: 195.9 (s, C-4), 164.8 (s, C-7), 162.1 (s, C-5), 161.2 (s, C-8a), 141.0 (s, C-1"), 138.8 (s, C-1'), 128.9 (d, C-3',4',5'), 126.2 (d, C-2',6'), 124.5 (d, C-2"), 110.3 (s, C-6), 102.6 (s, C-4a), 96.5, 96.6 (2 x d, C-8),[6] 79.1 (d, C-2), 44.1 (d, C-4"), 43.5 (t, C-3), 34.4 (d, C-3"), 30.7 (t, C-6"), 28.0 (d, C-8"), 23.7 (q, C-7"), 22.1 (t, C-5"), 21.8 (q, C-10"), 16.5 (q, C-9").

Hydrogenolysis of 3 with Raney Ni (Formation of 5) —— A mixture of **3** (9 mg) and Raney Ni (W-3) in EtOH (2 ml) was stirred at room temperature for 4 h under the hydrogen atomosphere. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by preparative tlc ($CHCl_3$-acetone, 40:1) to afford a viscous oil (2 mg, 22 %). $[\alpha]_D$ +20.9° (c 0.067, $CHCl_3$). High-resolution ms m/z: 394.2142 Calcd for $C_{25}H_{30}O_4$ (M^+). Found: 394.2118; 324.1360 Calcd for $C_{20}H_{20}O_4$ (M^+-70). Found: 324.1342. This compound was identical with linderatin (**5**)[11] by direct comparison (ir, ^{1}H nmr, ms, co-tlc in a variety of solvent systems).

Methylation of 3 with CH_2N_2 (Formation of 4) —— A solution of **3** (5 mg) in CH_2N_2-ether (1 ml) was stirred at room temperature overnight and then concentrated in vacuo. The residue was purified by preparative tlc (n-hexane-ether, 3:1) to afford a viscous oil (3.7 mg, 69 %). $[\alpha]_D$ +67.6° (c 0.185, $CHCl_3$). High-resolution ms m/z: 406.2142 Calcd for $C_{26}H_{30}O_4$ (M^+). Found: 406.2094; 336.1360 Calcd for $C_{21}H_{20}O_4$ (M^+-70). Found: 336.1352. This compound was identical with methyllinderatone (**4**) by direct comparison (ir, ^{1}H nmr, ms, co-tlc in a variety of solvent systems).

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6) The θ values of the Cotton effect at 287 and 316 nm were very small, and some signals (2-H, 3α-H, 3β-H, 5-OH, 7-OH, 8-H, 1"-Me, 2"-H and 8"-Me in ^{1}H nmr; C-8 in ^{13}C nmr) attributed to the 2-epi-derivative were observed in its ^{1}H and ^{13}C nmr spectra. Therefore, the flavanone skeleton of this linderatone was supposed to be considerably racemizated.

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