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Isolation and Structures of Two New Flavonoids from Lindera umbellata

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A new chalcone, neolinderachalcone, and a new dihydrochalcone, neolinderatin, were isolated from the leaves of Lindera umbellata var. lancea. Their structures were established by spectroscopic and chemical method, and syntheses of these compounds were also performed.

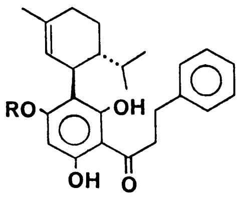
Previously, we have reported the isolation and the structural determination of novel flavonoids, linderatin (**1**), linderatone (**2**), methyllinderatone (**3**), isolinderatone (**4**), linderachalcone (**5**), and methyllinderatin (**6**), having a p-menthene substituent from Lindera umbellata Thunb. var. lancea Momiyama, L. umbellata Thunb., and L. umbellata Thunb. var. membranacea (Maxim.) Momiyama.[1-3] In the course of our further examination of the leaves of these plants,[4] we isolated a new dihydrochalcone, neolinderatin (**7**) and a new chalcone, neolinderachalcone (**8**). We now describe the structural elucidation and syntheses of these new compounds (**7** and **8**).

Neolinderatin (**7**), viscous oil, $[\alpha]_D$ +20.3° (c 0.9, $CHCl_3$) gave a brown color with ethanolic ferric chloride. The IR spectrum showed absorption bands for hydroxyl (3350 cm^{-1}) and conjugated carbonyl (1620 cm^{-1}) groups. The molecular formula was determined to be $C_{35}H_{46}O_4$ by the high-resolution mass spectrum (m/z 530.3378). Acetylation of neolinderatin with acetic anhydride in pyridine gave a triacetate **7a**. In the ^{1}H NMR spectrum ($CDCl_3$) of neolinderatin, signals of six methyl groups (δ 0.80, 0.81, 0.82 and 0.84, 12H, br s x 4, 8"- and 8"'-Me; δ 1.78, 6H, s, 1"- and 1"'-Me), an ethylene group (δ 3.00, 2H, t, J=7.8 Hz, β-H; δ 3.39, 2H, t, J=7.8 Hz, α-H), two benzylic methine protons (δ 3.81 and 3.99, 2H, d x 2, J=10.8 Hz, 3"- and 3"'-H), two olefinic protons (δ 5.50, 2H, s, 2"- and 2"'-H),

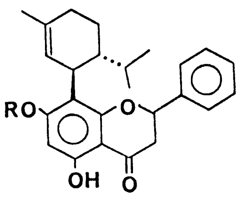
Table 1 ^{13}C NMR Spectrum of 1, 5, 7, and 8

Carbon	1$^{a)}$	5$^{b)}$	7$^{a)}$	7$^{b)}$	8$^{b)}$
1	143.2 s	140.9$^{c)}$s	142.7 s	142.2 s	140.5$^{c)}$s
2	129.4 d	128.8 d	129.0 d	128.4 d	128.9 d
3	129.6 d	128.5 d	129.2 d	128.7 d	128.6 d
4	127.1 d	127.7 d	126.5 d	125.9 d	125.2 d
5	129.6 d	128.5 d	129.2 d	128.7 d	128.6 d
6	129.4 d	128.8 d	129.0 d	128.4 d	128.9 d
1'	105.4 s	106.0 s	105.7 s	105.2 s	105.9 s
2'	161.4$^{d)}$s	159.2$^{d)}$s	158.7$^{d)}$s	157.6$^{d)}$s	157.2$^{d)}$s
3'	110.5 s	109.5 s	109.3 s	108.3$^{c)}$s	108.8 s
4'	163.9$^{d)}$s	162.2$^{d)}$s	161.2$^{d)}$s	160.5$^{d)}$s	161.0$^{d)}$s
5'	95.8 d	96.1 d	109.3 s	108.8$^{c)}$s	108.8 s
6'	165.9$^{d)}$s	164.3$^{d)}$s	163.0$^{d)}$s	162.5$^{d)}$s	163.3$^{d)}$s
C=O	205.9 s	193.1 s	205.7 s	205.2 s	193.5 s
C-α	46.6 t	130.1 d	47.0 t	46.3 t	129.9 d
C-β	31.5 t	142.7 d	31.3 t	30.9 t	142.0 d
1"	135.4 s	135.6$^{c)}$s	141.3 s	141.2$^{e)}$s	135.9$^{c)}$s
1"'	-	-	141.3 s	140.7$^{e)}$s	135.9$^{c)}$s
2"	126.9 d	124.7 d	125.2 d	125.2$^{f)}$d	124.8 d
2"'	-	-	125.2 d	124.8$^{f)}$d	124.8 d
3"	36.0 d	34.9 d	35.6 d	35.0$^{g)}$d	35.0 d
3"'	-	-	35.6 d	34.7$^{g)}$d	35.0 d
4"	43.0 d	44.0 d	44.2 d	43.8 d	43.8 d
4"'	-	-	44.2 d	43.8 d	43.8 d
5"	23.7 t	22.2 t	23.8 t	22.5 t	22.5 t
5"'	-	-	23.8 t	22.5 t	22.5 t
6"	31.5 t	30.7 t	31.3 t	30.9 t	31.0 t
6"'	-	-	31.3 t	30.9 t	31.0 t
7"	23.7 q	23.8 q	23.2 q	23.8 q	23.9 q
7"'	-	-	23.2 q	23.8 q	23.9 q
8"	29.1 d	27.9 d	28.8 d	28.3$^{h)}$d	28.2 d
8"'	-	-	28.8 d	28.1$^{h)}$d	28.2 d
9"	16.9 q	16.6 q	17.0 q	16.7 q	16.7 q
9"'	-	-	17.0 q	16.7 q	16.7 q
10"	22.0 q	21.8 q	21.8 q	21.7 q	21.7 q
10"'	-	-	21.8 q	21.7 q	21.7 q

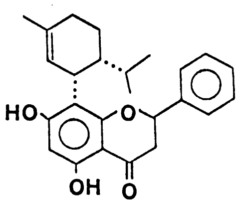
a) Measured in acetone-d_6. b) Measured in $CDCl_3$.
c-h) Assignments may be interchanged in each column.



1 : R=H
6 : R=Me



2 : R=H
3 : R=Me



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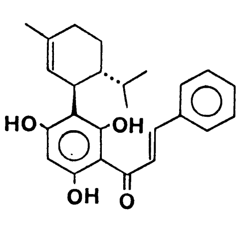

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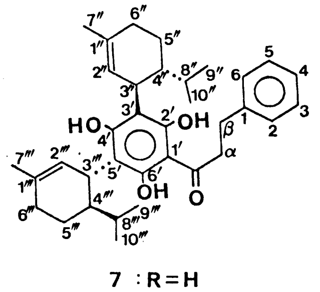
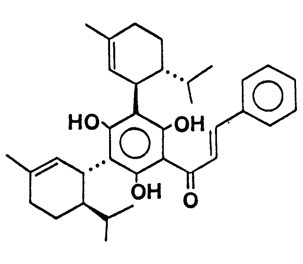


7 : R=H
7a : R=Ac



8

two hydroxyl groups (δ 6.81 and 6.90, 2H, s x 2), a phenyl group (δ 7.20-7.31, 5H, m), and a chelated hydroxyl group (δ 14.02, 1H, s) were observed. The ^{13}C NMR spectrum was very similar to those of linderatin (**1**) except for the signal of C-5' (δ 109.3, s)(Table 1). The mass spectrum of neolinderatin showed a molecular ion peak at m/z 530 which indicates an increase of 136 mass units in comparison with that of linderatin (**1**). This spectrum also had a characteristic fragmentation peak at m/z 460 (M^+-70) which was formed by the retro Diels-Alder reaction of a p-menthene unit as in linderatin (**1**).[1] These results suggested that neolinderatin must be a 5'-terpenylated derivative of linderatin (**1**). Further, the structure of neolinderatin was supposed to be **7**, because the ^{1}H and ^{13}C NMR spectra indicated the symmetry of this compound.

The structure of neolinderatin was confirmed by a following synthesis.[5] Treatment of 2',4',6'-trihydroxydihydrochalcone with 3.0 equivalent of (R)-(-)-α-phellandrene in the presence of p-toluenesulfonic acid in benzene at room temperature for 45 min gave 7 (45%) as a major product: $[\alpha]_D$ +24.7° ($CHCl_3$, c 0.9). This compound was identical with neolinderatin in all respects (^{1}H and ^{13}C NMR, IR, UV and MS), and both samples had (+)-rotation. Therefore the structure of neolinderatin was established to be (3"S,4"R)-(3"'S,4"'R)-2',4',6'-trihydroxy-3',5'-bis-(4-isopropyl-1-methylcyclohex-1-en-3-yl)dihydrochalcone (**7**).

Neolinderachalcone (**8**), viscous oil, $[\alpha]_D$ +26.5° (c 0.15, $CHCl_3$) gave a brown color with ethanolic ferric chloride. The IR spectrum showed absorption bands for hydroxyl (3350 cm^{-1}) and conjugated carbonyl (1620 cm^{-1}) groups. The molecular formula was determined to be $C_{35}H_{44}O_4$ by the high-resolution mass spectrum (m/z 528.3215). In the ^{1}H NMR spectrum ($CDCl_3$), signals of six methyl groups (δ 0.80, 0.83, 0.84 and 0.85, 12H, s x 4, 8"- and 8"'-Me; δ 1.55, 6H, s, 1"- and 1"'-Me), two benzylic methine protons (δ 3.86 and 4.01, 2H, d x 2, J=11.4 Hz, 3"- and 3"'-H), two olefinic protons (δ 5.53 and 5.56, 2H, s x 2, 2"- and 2"'-H), two hydroxyl groups (δ 6.88 and 7.01, 2H, s x 2), a phenyl group (δ 7.23-7.65, 5H, m), a trans-olefinic group (δ 7.78 and 8.01, 2H, d x 2, J=15.5 Hz) and a chelated hydroxyl group (δ 14.25, 1H, s) were observed. The ^{13}C NMR spectrum of neolinderachalcone was very similar to those of linderachalcone (**5**) except for the signal of C-5' (δ 108.8, s)(Table 1). The mass spectrum of neolinderachalcone showed a molecular ion peak at m/z 528 which indicates a decrease of 2 mass units in comparison with that of neolinderatin (**7**). This spectrum also had a characteristic fragmentation peak at m/z 458 (M^+-70) which was formed by the retro Diels-Alder reaction of a p-menthene unit as in neolinderatin (**7**). These results suggested that neolinderachalcone must be also a 5'-terpenylated derivative of linderachalcone and was supposed to be a chalcone derivative corresponding to neolinderatin.

The structure of neolinderachalcone was confirmed as follows. Treatment of 2',4',6'-trihydroxychalcone with (R)-(-)-α-phellandrene in the similar manner as the synthesis of **7** afforded **8** (40%): $[\alpha]_D$ +27.8° ($CHCl_3$, c 0.35). This compound was identical with neolinderachalcone in all respects (^1H and ^{13}C NMR, IR, UV, and MS). These results established that neolinderachalcone was (3"S,4"R)-(3"'S,4"'R)-2',4',6'-trihydroxy-3',5'-bis(4-isopropyl-1-methylcyclohex-1-en-3-yl)chalcone (**8**).

These new compounds (**7** and **8**) were very curious flavonoids in which two cyclic monoterpenes are linked to the same benzene ring, in contrast to several aromatic compounds posessing a cyclic monoterpene (cannabidiol,[7] rubranine,[8] murrayazoline,[9] and linderatin[1]).

References

1) K. Ichino, H. Tanaka, and K. Ito, Tetrahedron, 44, 3251 (1988).

2) K. Ichino, H. Tanaka, and K. Ito, Chem. Pharm. Bull., 35, 920 (1987).

3) K. Ichino, Phytochemistry, in press.

4) **8** was obtained only from L. umbellata var. lancea, though **7** was found in all of the three plants.

5) Crombie and co-workers[6] have already synthesized linderatin (**1**) in 46% yield by treatment of 2',4',6'-trihydroxydihydrochalcone with 1.5 equivalent of (R)-(-)-α-phellandrene in the presence of p-toluenesulfonic acid. On the other hand, we synthesized neolinderatin (**7**) using an excess of (R)-(-)-α-phellandrene under the same condition.

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