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Diarylheptanoids from the Rhizome of *Alpinia officinarum* HANCE

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Six diarylheptanoids, including three new compounds, were isolated from the rhizomes of *Alpinia officinarum* HANCE (Zingiberaceae). The structures of the new compounds were determined to be 7-(4′′-hydroxyphenyl)-1-phenyl-4-hepten-3-one (I), 5-methoxy-7-(4′′-hydroxyphenyl)-1-phenyl-3-heptanone (II), and 5-methoxy-1,7-diphenyl-3-heptanone (III) on the basis of the spectroscopic data. This is the first time that compound IV, in which both phenyl rings are substituted, has been isolated from *Alpinia* spp.

Keywords——*Alpinia officinarum*; Zingiberaceae; diarylheptanoid; ^{13}C-NMR; CD; MS; 7-(4′′-hydroxyphenyl)-1-phenyl-4-hepten-3-one; 5-methoxy-7-(4′′-hydroxyphenyl)-1-phenyl-3-heptanone; 5-methoxy-1,7-diphenyl-3-heptanone

The rhizomes of *Alpinia officinarum* (Zingiberaceae) (Japanese name: Ryokyo) are used as a component of some stomachic prescriptions in Chinese medicine.

As regards the chemical components of this plant, some diarylheptanoids have been reported.[1-3] In the present paper, we wish to report the isolation and structure elucidation of three new diarylheptanoids (I, II, and III). The commercial crude drug was extracted with methanol, and the extract was separated into the *n*-hexane-soluble and chloroform-soluble fractions by the usual procedure. The chloroform-soluble fraction was chromatographed on silica gel and silver nitrate-impregnated silica gel to give compounds I—VI.

Compound I was obtained as a colorless oil, having the molecular formula $C_{19}H_{20}O_2$ based on the high-resolution mass spectrum (MS). The infrared (IR) spectrum had prominent bands at 3380 (OH) and 1655 (C=C–C=O) cm^{-1}. The ultraviolet (UV) spectrum showed typical benzenoid absorption (276 nm) with a bathochromic shift on addition of alkali solution. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum ($CDCl_3$) of I showed signals due to four methylenes (δ 2.33—3.00), a hydroxyl group (δ 5.58; disappeared on addition of D_2O), and a non-substituted aromatic ring (δ 7.21). A doublet centered at δ 6.10

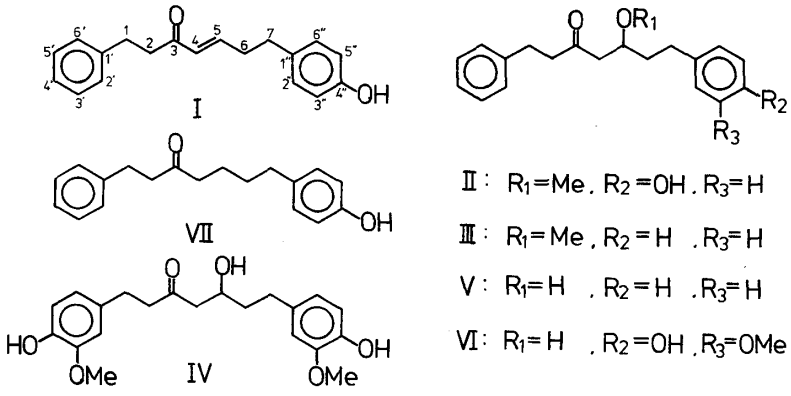


Chart 1

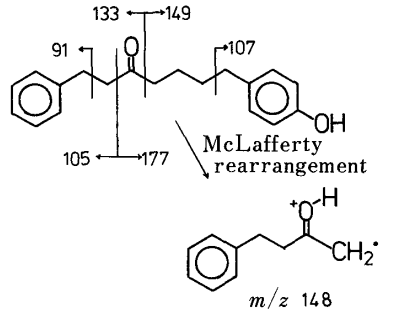


Chart 2. MS Fragment Ions of VII

(1H, $J=16.5$ Hz) was assigned to H-4. Hence the double bond in I was concluded to be *trans*. The β-proton signal of the conjugated ketone overlapped with four proton signals on a disubstituted phenyl ring (δ 6.67—7.10, 5H, m). Catalytic hydrogenation of I gave VII. The MS of VII showed a peak at *m/z* 105, 133, 148, 149, 177, indicating the location of the carbonyl group (Chart 2). The presence of a 4″-hydroxyphenyl ring was assumed based on a direct comparison of the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum with those of analogous compounds.[1] On the basis of these spectral data, the structure of I was confirmed to be 7-(4″-hydroxyphenyl)-1-phenyl-4-hepten-3-one.

Compound II was obtained as colorless needles, mp 68—70 °C, $C_{20}H_{24}O_3$ ($M^+ - MeOH$: *m/z* 280.1473). The IR spectrum clearly showed bands due to a hydroxyl (3640 cm^{-1}) and a ketone group (1715 cm^{-1}). A bathochromic shift in the UV spectrum occurred on addition of alkali. In the ^{1}H-NMR spectrum ($CDCl_3$), signals due to an aliphatic methoxyl at δ 3.27 ppm, a methine proton adjacent to a methoxyl group at δ 3.63 ppm (1H, quintet, $J=6$ Hz), and aromatic protons of a phenyl group at δ 7.10 ppm (5H, s) were observed. The AB-type protons at δ 6.62 and 6.88 ppm (each 2H, d, $J=8$ Hz) indicated the presence of a 1,4-substituted benzene ring. The MS of II, which indicated the location of a ketone and an aliphatic methoxyl group, showed fragment ion peaks at *m/z* 280 ($M^+ - MeOH$), 175, 107, 105, and 91. On the basis of these spectral data as well as the ^{13}C-NMR spectrum, II was suggested to be 5-methoxy-7-(4″-hydroxyphenyl)-1-phenyl-3-heptanone. This structure was confirmed by the fact that base treatment of II gave a conjugated compound identical to compound I.

Compound III was obtained as a colorless oil, $C_{20}H_{24}O_2$ (M^+: *m/z* 296, 1798) with two nonsubstituted phenyl groups based on its UV (260 nm), IR (1500 and 1605 cm^{-1}), and ^{1}H-NMR (δ 7.12 ppm, 10H, br s) spectra. Furthermore, the presence of an aliphatic methoxyl group and ketone was indicated by the ^{1}H-NMR (δ 3.20 ppm) and IR (1715 cm^{-1}), respectively. On the basis of these spectral data as well as the ^{13}C-NMR spectrum and MS,

TABLE I. The ^{13}C-NMR Spectra of I—VI

No.	I	II	III	IV	V	VI
1	30.2 t	29.5 t	29.5 t	32.4 t	31.7 t	31.4 t
2	41.5 t	45.3 t	45.3 t	46.4 t	44.2 t	44.9 t
3	200.7 s	209.2 s	208.2 s	211.9 s	210.7 s	210.9 s
4	130.4 d	47.3 t	47.3 t	51.3 t	49.2 t	49.2 t
5	147.6 d	76.7 d	76.5 d	68.3 d	66.7 d	66.9 d
6	34.4 t	35.8 t	35.6 t	40.4 t	38.1 t	38.3 t
7	33.4 t	30.4 t	31.3 t	30.3 t	29.4 t	29.5 t
1′	140.8 s	140.7 s	140.9 s	134.9 s	141.7 s	140.6 s
2′	128.2 d	128.2 d	128.2 d	113.2 d	128.1 d	128.2 d
3′	128.3 d	128.3 d	128.2 d	148.9 s	128.2 d	128.4 d
4′	126.0 d	126.0 d	125.9 d	145.8 s	126.0 d	126.1 d
5′	128.3 d	128.3 d	128.2 d	116.2 d	128.2 d	128.4 d
6′	128.2 d	128.2 d	128.2 d	121.8 d	128.1 d	128.2 d
1″	132.1 s	133.3 s	141.7 s	134.1 s	140.5 s	133.6 s
2″	129.2 d	129.2 d	128.2 d	113.2 d	128.2 d	111.1 d
3″	115.4 d	115.3 d	128.2 d	148.9 s	128.1 d	146.4 s
4″	154.3 s	154.0 s	125.7 d	145.6 s	125.7 d	143.7 s
5″	115.4 d	115.3 d	128.2 d	116.2 d	128.1 d	114.3 d
6″	129.2 d	129.2 d	128.2 d	121.7 d	128.2 d	120.8 d
3″-OMe				56.4 q		55.8 q
5-OMe		56.9 q	56.9 q			
3′-OMe				56.4 q		

The measurements were made on a JEOL FX-100 spectrometer in CD_3OD (IV) or $CDCl_3$ (I, II, III, V and VI) with tetramethylsilane as an internal reference, and are expressed in terms of ppm.

compound III was concluded to be 5-methoxy-1,7-diphenyl-3-heptanone. This structure was also confirmed by the fact that base treatment of III gave an α,β-unsaturated compound identical to a compound reported in the literature.[2] Since II and III are optically inactive, they may be artifacts formed during the extraction of the crude drug.

Compound IV was identified as hexahydrocurcumin(5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-3-heptanone), which still has undetermined stereochemistry at the 5-position.[4] The specific rotation of authentic hexahydrocurcumin was $+9.0°$, so IV ($[\alpha]_D$ $-10.0°$) was isolated as the enantiomer of hexahydrocurcumin. This is the first time that compound IV, in which both phenyl rings are substituted, has been isolated from *Alpinia* spp.

Compounds V and VI were identified as dihydroyashabushiketol (5-hydroxy-1,7-diphenyl-3-heptanone) and 5-hydroxy-7-(4′′-hydroxy-3′′-methoxyphenyl)-1-phenyl-3-heptanone, respectively, by comparing their spectral data with those of authentic specimens. Compound VI, a pungent principle, has recently been isolated from the same source.[3b] The specific rotation of authentic dihydroyashabushiketol was $+10.8°$ ($CHCl_3$), so the configuration of the 5-position of V must be "*R*" [compound V: $[\alpha]_D$ $-16.9°$ ($CHCl_3$)].

The absolute configuration of the hydroxyl group was determined by comparison of the optical rotations of IV and V with those of similar compounds.[5] The possibility of intermolecular hydrogen bonding is illustrated in Chart 3, which shows the projections in the direction of the carbonyl group. The horizontal plane encompasses C-3, C-4, and C-5. The circular dichroism (CD) spectra of IV, V, VI, and analogous compounds in $CDCl_3$ are shown in Fig. 1. By using a highly simplified model for the n–π^* transition in the region of about 300 nm, a relationship can be obtained between the chirality of the hydroxyl group chromophore and the sign of the Cotton effect, *i.e.*, the hydroxyl group situated in the lower site makes a negative contribution to the Cotton effect, whereas the hydroxyl group situated in the upper site leads to a positive Cotton effect. In this way, it seems that the hydroxyl group determines the sign of the Cotton effect, and the absolute stereochemistry of the hydroxyl group can be established by measuring the sign.

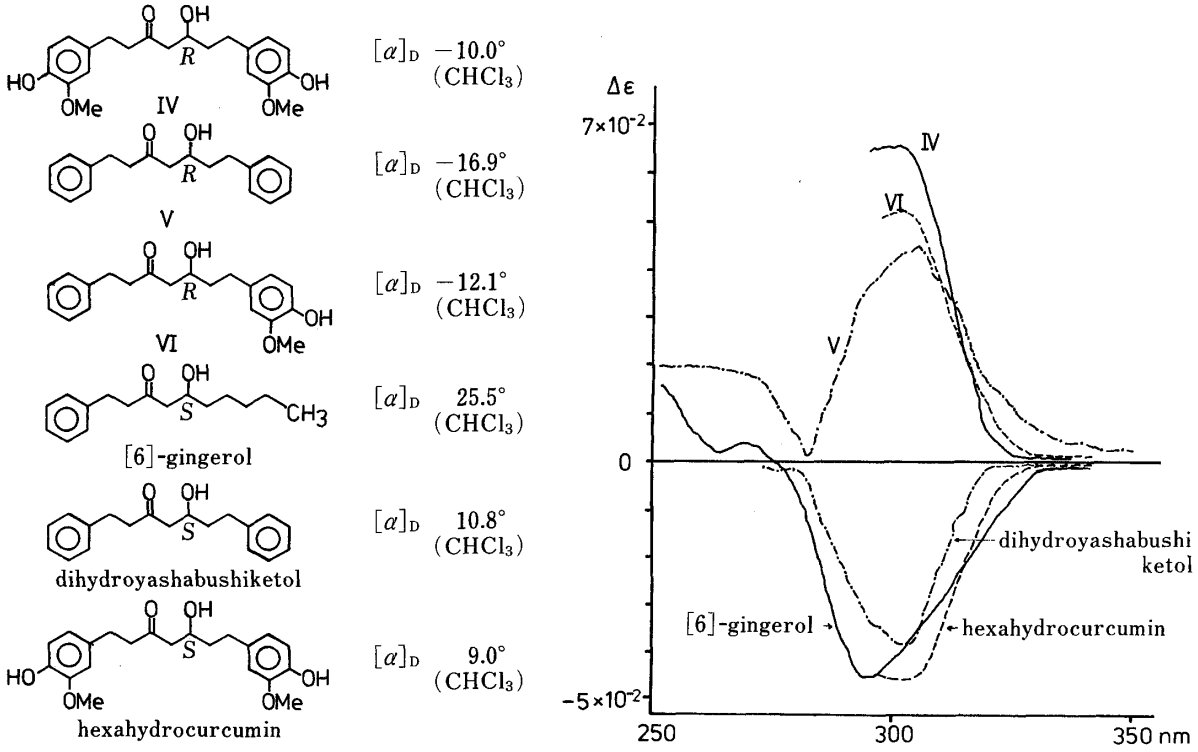
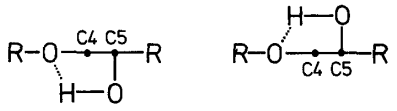


Fig. 1



S-configuration *R*-configuration

Chart 3

On the basis of these data, the configuration of the 5-position of IV and V was concluded to be "*R*" and that of hexahydrocurcumin was determined to be "*S*".

Many diarylheptanoids have been isolated from *Alpinia officinarum*. We have now added three new diarylheptanoids to this group.

Experimental

All melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Spectral data were obtained on the following instruments; optical rotation on a JASCO DIP-4, CD on a JASCO J-500C, IR on a JASCO A-302, UV on a Hitachi 557, ^{1}H-NMR on a Varian EM 390, ^{13}C-NMR on a JEOL FX-100, and MS on a Hitachi M-80. High-performance liquid chromatography (HPLC) was carried out on a CIG column system (Kusano Scientific Co., Tokyo) with IATROBEADS (60 μ silica gel, IATRON Co., Tokyo) as the stationary phase.

Extraction and Isolation——The rhizomes (10 kg) of *Alpinia officinarum* were extracted three times with methanol. The methanol extract was diluted with water to about 10% aq. MeOH and partitioned with *n*-hexane. The aq. MeOH layer was further concentrated and partitioned with $CHCl_3$. Evaporation of the $CHCl_3$-soluble fraction left a brown oil (518 g). The $CHCl_3$ extract (100 g) was subjected to column chromatography on silica gel with a $CHCl_3$–MeOH gradient system. Repeated chromatography of each fraction (HPLC and $AgNO_3$–HPLC) afforded I (80 mg), II (38 mg), III (110 mg), IV (50 mg), V (650 mg) and VI (3.3 g).

Compound I (7-(4′′-Hydroxyphenyl)-1-phenyl-4-hepten-3-one): Colorless oil. MS *m/z* (%): 280 (M^+, 18, Calcd for $C_{19}H_{20}O_2$, 280.1463; Found 280.1463), 176 (2), 107 (100), 91 (13). IR (liquid film) cm^{-1}: 3380, 1655, 1615, 1595, 1520,1500, 1455, 1370, 1265, 1225, 1170, 1105, 975, 830, 700. UV λ_{max}^{EtOH} nm (ε): 216 (infl. 7800), 223 (8100), 276 (1400); UV $\lambda_{max}^{EtOH+NaOH}$ nm: 214, 236, 295. ^{1}H-NMR ($CDCl_3$) δ: 2.33—3.00 (8H, m), 5.58 (1H, s, disappeared on addition of D_2O), 6.10 (1H, d, J=16.5 Hz), 6.67—7.10 (5H, m), 7.21 (5H, s).

Compound II (5-Methoxy-7-(4′′-hydroxyphenyl)-1-phenyl-3-heptanone): Colorless needles, mp 68—70 °C. MS *m/z* (%): 280 (M^+ − MeOH, 25, Calcd for $C_{19}H_{20}O_2$, 280.1463; Found 280.1473), 175 (4), 147 (12), 133 (24), 107 (100), 105 (42), 91 (44), 36 (15). IR (CCl_4) cm^{-1}: 3640, 1715, 1615, 1595, 1520, 1255, 1170, 1095, 700. UV λ_{max}^{EtOH} nm (ε): 209 (24800), 224 (infl. 16400), 279 (3600); UV $\lambda_{max}^{EtOH+NaOH}$ nm: 214, 241, 296. ^{1}H-NMR (CCl_4) δ: 1.47—1.80 (2H, m), 2.10—2.93 (8H, m), 3.27 (3H, s), 3.63 (1H, quintet, J=6 Hz), 6.60 (1H, s, disappeared on addition of D_2O), 6.62 (2H, d, J=8 Hz), 6.88 (2H, d, J=8 Hz), 7.10 (5H, s).

Compound III (5-Methoxy-1,7-diphenyl-3-heptanone): Colorless oil. MS *m/z* (%): 296 (M^+, 53, Calcd for $C_{20}H_{24}O_2$, 296.1775; Found 296.1798), 262 (32), 191 (6), 159 (17), 133 (28), 117 (20), 105 (50), 91 (100). IR (CCl_4) cm^{-1}: 2940, 1715, 1605, 1500, 1455, 1365, 1100, 1030, 700. UV λ_{max}^{EtOH} nm (ε): 210 (12600), 260 (500). ^{1}H-NMR (CCl_4) δ: 1.53—1.83 (2H, m), 2.12—2.93 (8H, m), 3.20 (3H, s), 3.58 (1H, quintet, J=6 Hz), 7.12 (10H, br s).

Compound IV (5-Epihexahydrocurcumin): Colorless needles, mp 90—91 °C, $[\alpha]_D$ −10.0° (c=0.28, $CHCl_3$). MS *m/z* (%): 374 (M^+, 4), 356 (2), 194 (23), 180 (17), 137 (100), 124 (14), 91 (9). IR (CCl_4) cm^{-1}: 3560, 2950, 1705, 1610, 1515, 1370, 1270,1150, 1125. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (2H, m), 2.40—3.00 (8H, m), 3.81 (6H, s), 4.02 (1H, m), 5.72 (2H, br s), 6.61 (2H, d, J=8 Hz), 6.65 (2H, s), 6.79 (2H, d, J=8 Hz). CD (c=0.30, $CHCl_3$) [θ] (nm): +218 (302).

Compound V (5-Epidihydroyashabushiketol): Colorless needles, mp 48.5—49.5 °C, $[\alpha]_D$ −16.9° (c=1.2, $CHCl_3$). MS *m/z* (%): 282 (M^+, 1), 264 (9), 159 (15), 148 (33), 134 (18), 105 (55), 91 (100). IR (KBr) cm^{-1}: 3160, 3030, 2940, 2920, 2860, 1705, 1605, 1500, 1455, 1080, 750, 700. UV λ_{max}^{EtOH} nm (ε): 298 (sh, 50), 279 (sh, 140), 268 (390), 259 (520), 253 (490), 248 (430), 212 (2020). ^{1}H-NMR ($CDCl_3$) δ: 1.60—1.88 (2H, m), 2.44—3.00 (8H, m), 3.12 (1H, d, J= 4 Hz, disappeared on addition of D_2O), 4.04 (1H, quintet, J=3 Hz), 7.20 (10H, br s). CD (c=0.06, $CHCl_3$) [θ] (nm): +146 (306).

Compound VI (5-Hydroxy-7-(4′′-hydroxy-3′′-methoxyphenyl)-1-phenyl-3-heptanone): Colorless needles, mp 60.0—61.5 °C, $[\alpha]_D$ −12.1° (c=0.7, $CHCl_3$). MS *m/z* (%): 328 (M^+, 33), 310 (10), 180 (33), 148 (61), 137 (100), 105 (47), 91 (50), 77 (15). IR (liquid film) cm^{-1}: 3390, 2940, 1710, 1605, 1520, 1455, 1430, 1370, 1040, 755, 710. UV λ_{max}^{EtOH} nm (ε): 288 (sh, 2500), 281 (3000), 227 (sh, 6200), 213 (9300). ^{1}H-NMR ($CDCl_3$) δ: 1.44—1.96 (2H, m), 2.36—2.96 (8H, m), 3.26 (1H, br s, disappeared on addition of D_2O), 3.75 (3H, s), 4.00 (1H, br quintet, J=6 Hz), 5.84 (1H, br s, disappeared on addition of D_2O), 6.50—6.80 (3H, m), 6.96—7.28 (5H, m). CD (c=0.68, $CHCl_3$) [θ] (nm): +173 (302).

Hydrogenation of I——A solution of I (20 mg) in MeOH (5 mg) was stirred with Pd/C (5 mg) for 6 h at room

temperature under an H_2 atmosphere, then the catalyst was removed by filtration and the filtrate was evaporated to give a colorless oil (VII). MS *m/z* (%): 282 (M^+, 45), 177 (6), 175 (9), 160 (10), 149 (4), 148 (3), 134 (53), 133 (46), 107 (100), 105 (30), 91 (42). IR (CCl_4) cm^{-1}: 3620, 3420, 3030, 2930, 2860, 1715, 1615, 1595, 1520, 1500, 1455, 1410, 1370, 1260, 1220, 1170, 1110, 1090, 1030, 700. ^{1}H-NMR ($CDCl_3$) δ: 1.43—1.70 (4H, m), 2.27—3.00 (8H, m), 6.72 (2H, d, J=8 Hz), 7.00 (2H, d, J=8 Hz), 7.10—7.30 (5H, m).

Reaction of II with 2 N NaOH to Give I——A solution of II (30 mg) in dioxane (1.5 ml) containing 5 drops of 2 N NaOH solution was refluxed with stirring for 30 min, then neutralized with 1 N HCl solution. The reaction mixture was evaporated and the residue was subjected to HPLC (*n*-hexane : ethyl acetate = 7 : 3) to give a colorless oil, I (20 mg).

Reaction of III with 2 N NaOH to Give 1,7-Diphenyl-4-hepten-3-one——A solution of III (30 mg) in dioxane (1.5 ml) containing 5 drops of 2 N NaOH solution was refluxed with stirring for 30 min, then neutralized with 1 N HCl solution. The reaction mixture was evaporated and the residue was subjected to HPLC (*n*-hexane : ethyl acetate = 9 : 1) to give a colorless oil.

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