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A PUNGENT DIARYLHEPTANOID FROM *ALPINIA OXYPHYLLA*

HIDEJI ITOKAWA, RITSUO AIYAMA and AKIRA IKUTA

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo, Japan

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Key Word Index—*Alpinia oxyphylla*; Zingiberaceae; Yakuchi; pungent principle; diarylheptanoid; 1-(4′-hydroxy-3′-methoxyphenyl)-7-phenyl-3-heptanone; 1-(3′-hydroxy-4′-methoxyphenyl)-7-phenyl-3-heptanone; zingerone.

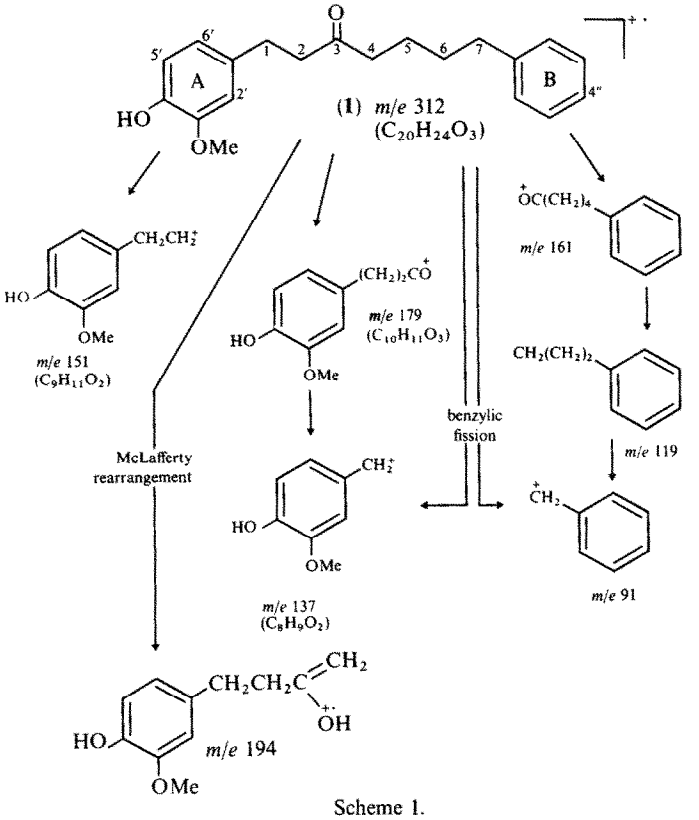
Abstract—From the neutral fraction of the methanolic extract of the fruit of *Alpinia oxyphylla*, a new pungent compound has been isolated, and is shown to be 1-(4′-hydroxy-3′-methoxyphenyl)-7-phenyl-3-heptanone. This compound is 125 times more pungent than zingerone.

INTRODUCTION

The crude drug 'Yakuchi' in Japan, prepared from the fruits of *Alpinia oxyphylla* Miquel (Zingiberaceae) originating in China, has been used in oriental medicine. As for its chemical components, the monoterpenes pinene, camphor and 1,8-cineole and the sesquiterpenes, zingiberene and zingiberol, have been reported [1–2]. In the present paper, we wish to report a new pungent compound from the fruits of *A. oxyphylla*.

RESULTS AND DISCUSSION

Compound **1** was a yellowish oil having pungency and turning deep brown with Fast Blue B reagent on silica gel TLC. It showed a molecular formula $C_{20}H_{24}O_3$ by high resolution MS, and the IR spectrum had prominent bands at 3400 (OH) and 1705 cm^{-1} (C=O). The UV spectrum showed typical benzenoid absorption (282 nm) and there was a bathochromic shift upon the addition of aqueous NaOH. In the ^1H NMR spectrum ($CDCl_3$), a broad



Scheme 1.

signal was shown at δ 5.52 (disappearing with D_2O) and a OMe group attached to an aromatic ring was shown at δ 3.80 (*s*, 3 H). No other hydroxyl groups were present since acetylation proceeded smoothly, yielding a monoacetate, with a signal at δ 2.28 in ^{1}H NMR ($CDCl_3$).

On the other hand in $(CD_3)_2CO$, the aromatic protons of ring A appeared at δ6.64 (*dd*, 1 H, J = 2 Hz, 8 Hz, C-6′), 6.78 (*d*, 1 H, J = 8 Hz, C-5′), 6.82 (*d*, 1 H, J = 2 Hz, C-2′), and those of ring B at δ 7.0–7.4 (*m*, 5 H). The MS spectral base peak occurs at *m/e* 137 which is indicative of a monohydroxy-monomethoxybenzyl cation. A peak at *m/e* 91 indicated a benzyl cation of ring B.

In the ^{1}H NMR spectrum in C_6D_6, two methylene groups, located between the carbonyl group and an aromatic ring, were observed as two triplets at δ 2.28 (C-2) and 2.78 (C-1). Moreover the remaining four methylene protons, located between the carbonyl group and another aromatic ring, were observed at δ 1.94 (C-4), 2.42 (C-7) as two broad triplets, and at 1.44 (C-5 and 6). The location of a carbonyl group in compound **1** was determined from the MS fragmentation pattern (Scheme 1). Therefore, **1** has the structure 1-(4′-hydroxy-3′-methoxyphenyl)-7-phenyl-3-heptanone. This structure was confirmed when its ^{13}C NMR spectrum was compared with that of zingerone and 6-phenyl-2-hexanone (Table 1). Though this compound has been synthesized by Berlin *et al.* [3] who also reported on its pungency, there have been no reports of its isolation from the natural sources. We have now synthesized **1**, using a different procedure (Scheme 2) from that used earlier [3].

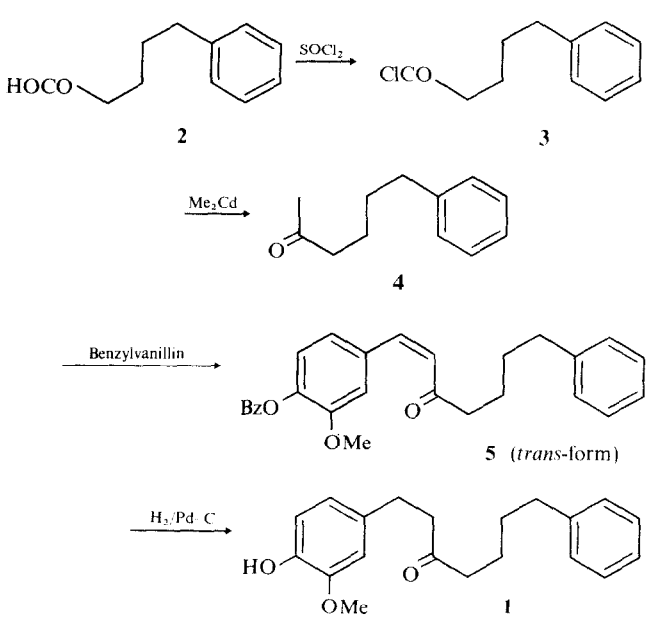
Table 1. ^{13}C NMR of compound **1**

Carbon	Compound **1**	Zingerone	PH†
1	29.5	29.5	
2	44.6	45.5	
3	210.2	208.3	208.7
4	42.8		43.5
5	23.4		23.4
6	30.9		30.8
7	35.7		35.7
1′	132.9	132.8	
2′	111.0	111.0	
3′	146.3	146.4	
4′	143.8	143.9	
5′	114.3	114.3	
6′	120.6	120.6	
1″	142.1		142.0
2″3″	128.2		128.2
4″	125.6		125.6
5″6″	128.2		128.2

† PH = 6-phenyl-2-hexanone.

We initially prepared 6-phenyl-2-hexanone (**4**) by the reaction of dimethylcadmium and 5-phenylvaleryl chloride (**3**) derived from 5-phenylvaleric acid (**2**). When a mixture of benzylvanillin and **4** was stirred with aqueous ethanolic KOH at room temperature, slow condensation occurred with the formation of the α,β-unsaturated derivative (**5**) of **1**. The reduction of **5** in methanol with palladium–charcoal gave **1** in total yield 61% from 5-phenylvaleric acid, and the spectral data were perfectly in agreement with those of the natural product.

The pungency of **1** was compared with the iso-form of **1*** and zingerone. A panel of three male non-smokers were used to assess the pungencies. As shown in Table 2, the threshold concentration of **1** was 3.2×10^{-8} mol/ml, and



Scheme 2.

* The iso-form of **1** is 1-(3′-hydroxy-4′-methoxyphenyl)-7-phenyl-3-heptanone, which is prepared from isovanillin by the same synthesis as **1**.

Table 2. Evaluation of pungency

Concentration mol/ml	Compound 1	Iso-form*	Zingerone
2.0×10^{-5}	+	+	+
4.0×10^{-6}	+	+	+
8.0×10^{-7}	+	+	−
1.6×10^{-7}	+	−	−
3.2×10^{-8}	+	−	−
6.4×10^{-9}	−	−	−
1.3×10^{-9}	−	−	−

* Iso-form: 1-(3′-hydroxy-4′-methoxyphenyl)-7-phenyl-3-heptanone.

its pungency was 125 times stronger than that of zingerone (4.0×10^{-6} mol/ml). The iso-form of **1** (8.0×10^{-7} mol/ml) also showed a stronger pungency than zingerone.

EXPERIMENTAL

Mps are uncorr. TLC was carried out on Si gel F_{254}, column chromatography was on cellulose powder (Whatman CF-11) and Si gel (wakogel C-200). ^{1}H NMR spectra were recorded at 100 MHz at room temp. Samples were dissolved in $CDCl_3$ or C_6D_6 or $(CD_3)_2CO$ containing TMS as internal standard. The ^{13}C NMR spectra were measured at 25.2 MHz (JEOL FX-100) in 10 mm tubes and samples were dissolved in $CDCl_3$ containing TMS as an internal standard.

Isolation and identification of **1**. Powdered fruit (5.35 kg) was directly extracted with large amounts of MeOH. This MeOH extract was washed with *n*-hexane, evapd and the residue was divided between $CHCl_3$ and water. The former fraction was chromatographed on a cellulose column using *n*-hexane and MeOH respectively and the fraction eluting with *n*-hexane was rechromatographed on Si gel column eluting gradient with *n*-hexane–Et_2O and EtOAc. In this way, **1** was obtained from the fraction eluting with *n*-hexane–Et_2O (1:1) by (SiO_2)HPLC using Bz: EtOAc (19:1). Compound **1** (115 mg) is given in the last column. Compound **1**, yellowish oil $C_{20}H_{24}O_3$ (M^+ 312, Found 312.170, Calc. 312.167). IR ν_{max}^{film} cm^{-1}: 3400, 1705, 1595; UV λ_{max}^{MeOH} nm (log ε): 228 (3.85 sh) and 282 (3.48), $\lambda_{max}^{MeOH+NaOH}$ nm: 244 and 292; ^{1}H NMR ($CDCl_3$): δ 1.58 (*m*, 4 H), 2.37 (*br.t*, 2 H), 2.58 (*br.t*., 2 H), 2.65–2.90 (*m*, 4 H), 3.80 (*s*, 3 H), 5.52 (*br.s*, 1 H, disappeared with D_2O), 6.60 (*d*, 1 H) 6.65 (*s*, 1 H), 6.78 (*d*, 1 H), 7.00–7.34 (*m*, 5 H); (C_6D_6): δ 1.44 (*m*, 4 H), 1.94 (*br.t*, 2 H), 2.28 (*t*, 2 H, J = 7 Hz), 2.42 (*br.t*, 2 H), 2.78 (*t*, 2 H, J = 7 Hz); $(CD_3)_2CO$: 6.64 (*dd*, 1 H, J = 2 Hz, 8 Hz), 6.78 (*d*, 1 H, J = 8 Hz), 6.82 (*d*, 1 H, J = 2 Hz), 7.0–7.4 (*m*, 5 H). MS *m/e* (rel. int.): 312 (M^+, 22), 194 (2), 179 (12), 161 (6), 151 (14), 137 (100), 119 (11), 91 (46).

Acetylation of **1**. Compound **1** (30 mg) on acetylation with Ac_2O–Py at room temp. for 3 hr gave a yellowish oil. $C_{22}H_{26}O_4$, UV λ_{max}^{MeOH} nm (log ε): 272 (4.36) and 278 (4.32), IR ν_{max}^{film} cm^{-1}: 1765, 1705 and 1600; ^{1}H NMR ($CDCl_3$): δ 1.61 (*m*, 4 H), 2.28 (*s*, 3 H), 2.40 (*br.t*, 2 H), 2.60 (*br.t*, 2 H), 2.68–3.00 (*m*, 4 H), 3.78 (*s*, 3 H), 6.72 (*d*, 1 H, 8 Hz), 6.76 (*s*, 1 H), 6.92 (*d*, 1 H, 8 Hz), 7.0–7.4 (*m*, 5 H), MS *m/e* (rel. int.): 354 (M^+, 11), 311 (100), 178 (16), 150 (16), 136 (78), 91 (33). ^{13}C NMR ($CDCl_3$) (OFR) 209.7 (*s*), 169.1 (*s*), 150.8 (*s*), 142.1 (*s*), 140.0 (*s*), 137.9 (*s*), 128.2 (*d*), 125.7 (*d*), 122.5 (*d*), 120.2 (*d*), 112.6 (*d*), 55.8 (*q*), 44.2 (*t*), 42.8 (*t*), 35.7 (*t*), 30.9 (*t*), 29.6 (*t*), 23.4 (*t*), 20.6 (*q*).

Synthesis of 6-*phenyl*-2-*hexanone* (**4**). Chloride (**3**) was obtained by adding the $SOCl_2$ (2 ml) dropwise into 5-phenylvaleric acid (4.62 g). **3** in dry ether was added to dimethylcadmium in dry Et_2O, and Et_2O soln after washing with H_2O was evapd. The residue was chromatographed (hexane–Et_2O, 9:1) to afford (**4**) in 73% yield. Colourless oil $C_{12}H_{16}O$, IR ν_{max}^{film} cm^{-1}: 1715 and 1595; ^{1}H NMR ($CDCl_3$): δ 1.62 (*m*, 4 H), 2.12 (*s*, 3 H), 2.42 (*br.t*, 2 H), 2.60 (*br.t*, 2 H), 7.00–7.30 (*m*, 5 H); MS *m/e* (rel. int.): 176 (47), 158 (7), 143 (7), 129 (22), 118 (42), 117 (29), 104 (13), 91 (100); ^{13}C NMR ($CDCl_3$): δ 208.7 (*s*), 142.0 (*s*), 128.2 (*d*), 125.6 (*d*), 43.5 (*t*), 35.7 (*t*), 30.8 (*t*), 29.8 (*q*), 23.4 (*t*).

Synthesis of 1-(4′-*benzyloxy*-3′-*methoxyphenyl*)-7-*phenylhept*-1-*en*-3-*one* (**5**). Benzylvanillin (1.60 g) and **4** (1.17 g) were stirred (room temp. 13 hr) in 25 ml EtOH (+5 ml 10% KOH) and the ppt. was filtered off, washed after the Et_2O soln was evapd, the aq. soln was shaken by ether and the Et_2O evapd. The residue was chromatographed (hexane–Et_2O, 1:1) to afford **5** in 89% yield. **5** was a colourless powder $C_{27}H_{28}O_3$, λ_{max}^{MeOH} nm (log ε): 238 (4.03), 299 (4.13, sh) and 332 (4.28); ν_{max}^{KBr} cm^{-1}: 1620, 1595, 1495, 1445, 1415, 1255, 1225, 1155, 1130. ^{1}H NMR ($(CD_3)_2CO$): δ 1.64 (*m*, 4 H), 2.60 (*br.t*, 2 H), 2.66 (*br.t*, 2 H), 3.86 (*s*, 3 H), 5.14 (*s*, 2 H), 6.69 (*d*, 1 H, J = 16 Hz), 6.96–7.44 (*m*, 13 H), 7.50 (*d*, 1 H, J = 16 Hz). MS *m/e* (rel. int.): 400 (M^+, 10), 309 (5), 240 (5), 117 (12), 91 (100).

Hydrogenation of **5**. **5** (*ca* 610 mg), under presence of 5% Pd–C (50 mg) in MeOH were shaken with H_2 (room temp. 1 atm) for 24 hr. Catalyst and solvent were then removed and the residue chromatographed (hexane–Et_2O, 1:1) to afford **1** in 95% yield). (61% overall yield). The synthetic compound was identical with natural compound **1** by UV, IR, ^{1}H NMR, ^{13}C NMR and MS.

Evaluation of pungency [4]. Each sample dissolved in a small amount of EtOH was adjusted to 5 ml (1.0×10^{-4} mol/ml) with aq. 5% (w/v) sucrose soln. Each solution was diluted to 1 part in 5 (v/v) respectively with aq. 5% sucrose soln. and finally diluted 7.8×10^4 fold (1.3×10^{-9} mol/ml) (Table 2). The minimal concentrations which could be detected by two members of the panel, were regarded as the threshold. Samples (0.2 ml) of each soln were placed on the tip of the tongue of tasters. The results reported represent the average from three panels made up of three tasters in each case.

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