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ZEDOAROL, 13-HYDROXYGERMACRONE AND CURZEONE, THREE SESQUITERPENOIDS FROM *CURCUMA ZEDOARIA**

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Key Word Index—*Curcuma zedoaria*; Zingiberaceae; zedoary; zedoarol; 13-hydroxygermacrone; curzeone; furanoguaiane; furanocadinane; germacrane; sesquiterpenoids.

Abstract—From the crude drug zedoary (the dried rhizome of *Curcuma zedoaria*), three novel sesquiterpenoids, zedoarol (a furanoguaiane), 13-hydroxygermacrone (a germacrane) and curzeone (a furanocadinane), have been isolated and their structures elucidated by extensive spectral analysis.

INTRODUCTION

In the course of the investigation of the chemical constituents of Japanese zedoary, the dried rhizome of *Curcuma zedoaria* Roscoe, we have isolated the cyclopropanosesquiterpenoid, curcumenone, and two spirolactones, curcumanolide A and curcumanolide B [1]. Further attempts to separate the minor components led to the isolation of three new sesquiterpenoids named zedoarol (**1**), 13-hydroxygermacrone (**3**) and curzeone (**4**). The structure elucidation revealed that these sesquiterpenoids have different carbon skeletons, namely furanoguaiane, germacrane and furanocadinane.

RESULTS AND DISCUSSION

A combination of column chromatographic separations on silica gel and on Sephadex LH-20 of the dichloromethane extract of Japanese zedoary resulted in the isolation of zedoarol (**1**), 13-hydroxygermacrone (**3**) and curzeone (**4**).

Zedoarol (**1**), $C_{15}H_{18}O_3$, was isolated as a colourless oil. Its IR spectrum indicated an unsaturated carbonyl group (1660 cm^{-1}) and a hydroxyl group (3540 cm^{-1}). The presence of another oxygen atom in a furan ring was suggested by a positive Ehrlich reaction; this was further supported by the long range coupled ^1H NMR signals due to the α-H (H-12) and β-methyl group (H-13) in a furan ring (Table 1). Its UV absorption (256 nm) showed that the carbonyl group and the furan ring were conjugated. Furthermore, the ^1H and ^{13}C NMR spectra indicated the presence of a carbonyl group, a tetrasubstituted double bond, a trisubstituted double bond, an exocyclic methylene group, a quaternary oxygen-bearing carbon, two sp^3 methines, three sp^3 methylene groups, one of which was located at an isolated position, a secondary methyl group and a vinylic methyl group. The above spectral data together with the molecular formula indicated that compound **1** was a bicarbocyclic compound with a tertiary hydroxyl group.

The partial structure **A** (Fig. 1) for **1** was deduced by two dimensional proton–proton correlation (COSY) analysis. The AB quartet at δ3.66 and 3.83 (H-9) and the triplet at δ2.98 (H-1) were long-range coupled with the exomethylene signals at δ5.16 and 5.32 (H-15), as was

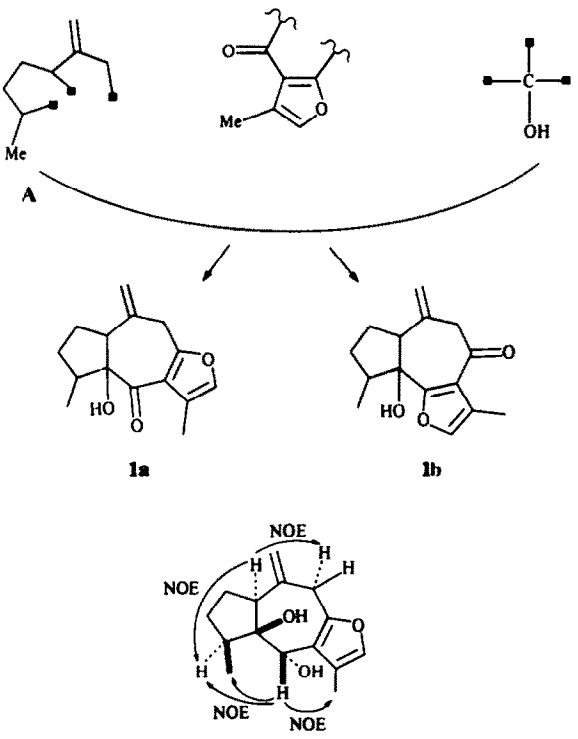

Fig. 1.

*This work was presented at the 28th Symposium of the Chemistry of Terpenes, Essential Oils and Aromatics of Japan, Kanazawa, October 1984, symposium papers, p. 271.

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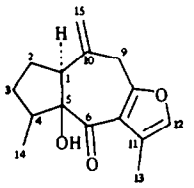
Table 1. ^{1}H NMR data of compounds 1 and 3 (400 MHz, TMS as internal standard)

H	1 ($CDCl_3$)	3 ($CDCl_3$)	3 (C_6D_6)
1	2.98 *t*, *J* = 9.3 Hz	4.99 *d* (*br*), *J* = 10.7 Hz	4.80 *d* (*br*), *J* = 11.8 Hz
2	1.90 *m*	2.08 *m*	1.95 *m*
	2.05 *m*	2.36 *m*	2.17 *m*
3	1.46 *m*	2.08 *m*	1.95 *m*
	1.90 *m*	2.17 *m*	1.84 *m*
4	2.53 *tq*, *J* = 6.8, 9.2 Hz		
5		4.66 *dd*, *J* = 10.4, 3.6 Hz	4.67 *d* (*br*), *J* = 12.2 Hz
6		2.96*	2.87 *d* (*br*), *J* = 12.2 Hz
			3.09 *t* (*br*), *J* = 12.2 Hz
9	3.66 *d*, *J* = 18.1 Hz	3.44 *d*, *J* = 10.3 Hz	2.83 *d* (*br*), *J* = 10.7 Hz
	3.83 *d*, *J* = 18.1 Hz	2.96*	3.32 *d*, *J* = 10.7 Hz
12	7.05 *s* (*br*)	1.82 *s*	1.59 *s*
13	2.12 *d*, *J* = 1.4 Hz	4.19 *d*, *J* = 12.2 Hz	3.81 *d*, *J* = 12.2 Hz
		4.31 *d*, *J* = 12.2 Hz	3.92 *d*, *J* = 12.2 Hz
14	1.14 *d*, *J* = 6.8 Hz	1.44 *s*	1.34 *s*
15	5.16 *s*(*br*)		
	5.32 *s*(*br*)	1.63 *s*	1.63 *s*(*br*)
OH	2.18 *s* (*br*)	1.60 *s* (*br*)	1.60 *s* (*br*)

*The signals were overlapped.



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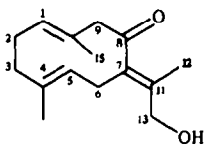

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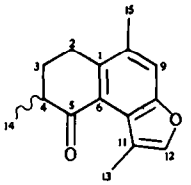

4

evident from the contour plot of the COSY spectrum. This plot also showed that the triple quartet at δ2.53 (H-4) was coupled with the doublet at 1.14 (H-14). Furthermore, H-1 and H-4 showed the expected couplings to the C-2 and C-3 methylene groups (δ1.46, 1.90 and 2.05), respectively. From the above data and from biogenetic considerations, 1 had to belong to the guaiane class of sesquiterpenoids and have either structure **1a** or **1b** (Fig. 1).

Reduction of 1 with sodium borohydride gave a labile diol (2), the ^{1}H NMR of which showed a singlet at δ4.46 (H-6) assigned to a carbinyl proton. The position of the ketone moiety and the stereochemistry of 2 was established by NOE difference spectra (Fig. 1). When the carbinyl proton was irradiated, both methyl signals (H-13 and H-14) were enhanced, as was the H-4 resonance. Furthermore, when H-1 was irradiated, H-4 and one of H-9 (δ3.43) were enhanced. Thus the gross structure of 1 was as shown in the formula.

13-Hydroxygermacrone (3), $C_{15}H_{22}O_2$, was isolated as a colourless oil. Its IR spectrum showed the presence of a hydroxyl group (3450 cm^{-1}) and a conjugated carbonyl group (1680 cm^{-1}). The ^{1}H and ^{13}C NMR spectra of 3 (Tables 1 and 2) were similar to those of germacrone [2] except that a vinyl methyl group resonance was replaced by a signal characteristic of a hydroxymethyl group. When the ^{1}H NMR spectrum was measured in C_6D_6, the C-6 and C-9 methylene signals were well separated whilst the vinylic methyl and the hydroxymethyl signals were shifted upfield (Table 1). Hikino *et al.* reported the solvent-induced shifts ($\delta CDCl_3 - \delta C_6D_6$) for the C-12 and C-13 methyl groups in germacrone [3]. The above results indicated that 3 had the same conformation as germacrone and the hydroxyl group was located at C-12 or C-13 of 2. The location of the hydroxyl group was established by NOE difference spectroscopy. When the broad singlet at δ1.82 (H-12) was irradiated in $CDCl_3$, the doublet at δ3.44 (H-9) and the AB quartet at δ4.19 and 4.31 (H-13) were intensified. When the doublet at δ3.92 (H-13) was irradiated in C_6D_6, the broad doublet at δ2.87 (H-6), the broad triplet at δ3.09 (H-6) and the singlet at δ1.59 (H-12) were enhanced. These results indicated that the hydroxyl group was located at C-13 of 3. The structure of 3 was thus established as 13-hydroxygermacrone.

Curzeone (4), $C_{15}H_{16}O_2$, was isolated as colourless needles, which gave a positive Ehrlich reaction. Its UV (290, 323 nm) and IR (1690 cm^{-1}) spectra suggested the presence of a benzofuran system conjugated with a carbonyl group. The ^{1}H and ^{13}C NMR spectra (see

Table 2. ^{13}C NMR data of compounds 1 and 3 (100 MHz, $CDCl_3$, TMS as internal standard)

C	1	3
1	50.8 (*d*)	133.1 (*d*)
2	27.2* (*t*)	24.1 (*t*)
3	29.8* (*t*)	38.1 (*t*)
4	40.5 (*d*)	126.4 (*s*)
5	84.1 (*s*)	125.0 (*d*)
6	197.0 (*s*)	28.6 (*t*)
7	119.8† (*s*)	131.4 (*s*)
8	158.3 (*s*)	207.2 (*s*)
9	39.0 (*t*)	55.5 (*t*)
10	140.8 (*s*)	135.8 (*s*)
11	122.4† (*s*)	139.8 (*s*)
12	138.4 (*d*)	17.8 (*q*)
13	9.5 (*q*)	62.8 (*t*)
14	14.4 (*q*)	15.6 (*q*)
15	115.2 (*t*)	16.7 (*q*)

*† Values with the same superscript in the same column are interchangeable.

Experimental) indicated the presence of an α-proton at δ7.40 (H-12) and β-methyl group at δ2.40 (H-13) long range coupled to each other (J = 1.5 Hz), a proton at δ7.42 (H-9) and a methyl group at δ2.36 (H-15) on a benzene ring, a methine proton at δ2.70 (H-4) and a secondary methyl group at δ1.27 (H-14) coupled to each other (J = 6.8 Hz) and two sp^3 methylene groups at δ1.88, 2.26 (H-3) and 2.86, 2.98 (H-2). Further, in the difference spectrum, NOEs were observed between H-15 and H-9, and between H-15 and H-2. The above data were consistent with the structure **4**, which was previously reported as a synthetic intermediate of curzerenone, although in its racemic form [4].

EXPERIMENTAL

Mps: uncorr; The solvents used for spectral determinations were: TMS–$CDCl_3$ and TMS–C_6D_6 [^1H NMR (400 MHz), ^{13}C NMR (100 MHz)], $CHCl_3$ ($[\alpha]_D$), 95% EtOH (UV); TLC: precoated silica gel (0.25 mm)/F_{254}, *n*-hexane–EtOAc (4:1) or C_6H_6–EtOAc (3:1), spots were detected by UV light (254 nm) or spraying with Fhrlich's reagent.

Isolation of sesquiterpenoids from zedoary. A CH_2Cl_2 extract (310 g) of zedoary [1] was directly chromatographed on silica gel (2.6 kg) using an *n*-hexane–EtOAc gradient. The eluant was collected as 1 l. fractions. Fraction 11 was concd and the residue was rechromatographed on Sephadex LH-20, using $CHCl_3$–MeOH (1:1) to give curzeone (**4**) (81 mg) as colourless needles, mp 72–74°; $[\alpha]_D^{28}$ +24° (*c* 2.0); IR $\nu_{max}^{liq.}$ cm^{-1}: 1690; UV λ_{max} nm (log ε): 290 (4.5), 323 (4.3); HRMS *m/z*: 228.1201 (calc. for $C_{15}H_{16}O_2$: 228.1151); MS *m/z* (rel. int.): 228 (98), 213 (10), 199 (23), 186 (100), 158 (9), 149 (6), 129 (16), 128 (17), 127 (8), 105 (21); ^1H NMR ($CDCl_3$): δ1.27 (*d*, J = 6.8 Hz, H-14), 1.88 and 2.26 (each *m*, H-3), 2.36 (*s*, H-15), 2.40 (*d*, J = 1.5 Hz, H-13), 2.70 (*m*, H-14), 2.86 and 2.98 (each *m*, H-2), 7.40 (*s* (*br*), H-12), 7.42 (*s*, H-9); ^{13}C NMR ($CDCl_3$): δ12.7 (*q*), 15.5 (*q*), 20.1 (*q*), 26.5 (*t*), 31.2 (*t*), 42.4 (*d*), 117.0 (*d*), 117.7 (*s*), 124.8 (*s*), 128.0 (*s*), 132.2 (*s*), 138.6 (*s*), 143.7 (*d*), 155.2 (*s*), 201.8 (*s*).

The residue obtained from Fr. 21 was rechromatographed on silica gel using *n*-hexane–EtOAc (97:3) to give an oil, which was rechromatographed on Sephadex LH-20 ($CHCl_3$–MeOH, 1:1) to afford zedoarol (**10**, 250 mg), as a colourless oil; $[\alpha]_D^{28}$ +11.6° (*c* 2.0); IR $\nu_{max}^{liq.}$ cm^{-1}: 3540, 1660; UV λ_{max} nm (log ε): 256 (3.7); HRMS *m/z*: 246.1178 (calc. for $C_{15}H_{18}O_3$: 246.1256); MS *m/z* (rel. int.): 246 (25), 229 (33), 228 (100), 213 (66), 175 (40), 162 (30), 159 (34), 149 (60), 148 (38), 147 (32), 119 (37), 109 (62), 105 (28), 95 (31), 91 (58), 77 (43).

Fraction 63 was concd and the residue was rechromatographed on silica gel (CH_2Cl_2) and on Sephadex LH-20 ($CHCl_3$–MeOH, 1:1) to give 13-hydroxygermacrone (**3**, 160 mg), as a colourless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3450, 1680; UV λ_{max} nm (log ε): 240 (3.4); HRMS *m/z*: 234.1611 (calc. for $C_{15}H_{22}O_2$: 234.1620); MS *m/z* (rel. int.): 234 (8), 216 (19), 201 (15), 188 (10), 173 (13), 159 (15), 145 (21), 133 (23), 121 (31), 107 (42), 105 (52), 91 (46), 79 (38), 77 (31), 59 (100).

Reduction of zedoarol (**1**). To a MeOH soln of **1** (100 mg) was added $NaBH_4$ at 0°. After 1 hr, the reaction mixture was extracted as usual. The residue was chromatographed on silica gel eluting with CH_2Cl_2 to yield an oil (**2**, 39 mg); $[\alpha]_D^{28}$ +58.7° (*c* 2.0); IR $\nu_{max}^{liq.}$ cm^{-1}: 3520, 3400; MS *m/z* (248, M^+: $C_{15}H_{20}O_3$); ^1H NMR ($CDCl_3$): 1.05 (*d*, J = 6.8 Hz, H-14), 1.47 (*m*, H-3), 1.84 (*m*, H-2 and H-3), 1.98 (*m*, H-2), 1.65–1.95 (OH × 2), 2.01 (*d*, J = 1.5 Hz, H-13), 2.52 (*m*, H-4), 3.17 (*t*, J = 9.3 Hz, H-1), 3.43 and 3.50 (each *d*, J = 15.6 Hz, H-9), 4.46 (*s*, H-6), 5.05 and 5.20 (each *s* (*br*), H-15), 7.03 (*s* (*br*), H-12).

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