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A Novel Sesquiterpene Peroxide from *Alpinia japonica* (THUNB.) MIQ.[1)]

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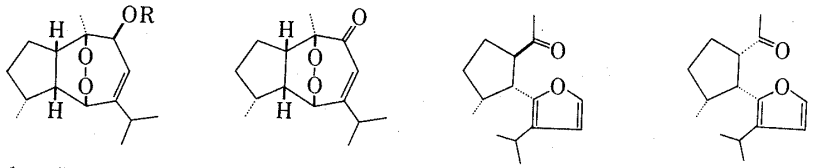
A novel sesquiterpene peroxide, hanalpinol (**1a**), has been isolated from the rhizomes of *Alpinia japonica*. Oxidation of **1a** with pyridinium chlorochromate gave a crystalline, α,β-unsaturated ketone (**2**), whose structure was established by means of X-ray analysis. The IR spectrum of **1a** revealed the presence of intramolecular hydrogen bonding, and acid treatment of **1a** resulted in the formation of furopelargone B (**4**), which was present naturally in the same plant. This conversion reaction suggests that **4** is biosynthesized from **1a** or its analog. Furopelargone A (**3**) was also isolated.

Keywords——Zingiberaceae; *Alpinia japonica*; sesquiterpene; guaiane: cyclic peroxide; X-ray analysis

As a part of our continuing study of *Alpinia japonica* (THUNB.) MIQ. (Zingiberaceae), we previously reported the isolation of various sesquiterpenes (3α,4α- and 3β,4β-oxidoagarofuran, α-agarofuran, 4α-hydroxydihydroagarofuran, β-eudesmol, 10-*epi*-γ-eudesmol, $\Delta^{9(10)}$-eremophilen-11-ol, alpiniol, hanamyol and alpinolide).[2)] Further examination of *A. japonica* has resulted in the isolation and structure elucidation of a novel sesquiterpene cyclic peroxide, hanalpinol (**1a**). Furopelargone A (**3**) and B (**4**) were also isolated.



1a : R=H
1b : R=Ac

2 **3** **4**

Chart 1

Hanalpinol (**1a**) was obtained as one of the major sesquiterpenes from the rhizomes of *A. japonica*, as a fairly stable oil. The molecular formula, $C_{15}H_{24}O_3$, was obtained by elemental analysis, and the presence of an allylic hydroxy group was shown by the infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectra (IR band at 3400 cm^{-1} and one proton signal at δ 4.16). The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra showed three signals due to carbon atoms bearing an oxygen function (δ 73.1, 80.3 and 83.3) and no signal for a carbonyl carbon (also, no IR band due to carbonyl). However, acetylation of **1a** gave only a monoacetate (**1b**) and oxidation of **1a** by pyridinium chlorochromate furnished an α,β-unsaturated ketone (**2**); both **1b** and **2** no longer showed the IR band due to the hydroxy group. Thus, the remaining two oxygen atoms might be present as an intramolecular peroxide linkage. The presence of the cyclic peroxide moiety was also supported by the fact that **1a** gave a reddish-purple spot on thin-layer chromatography (TLC)

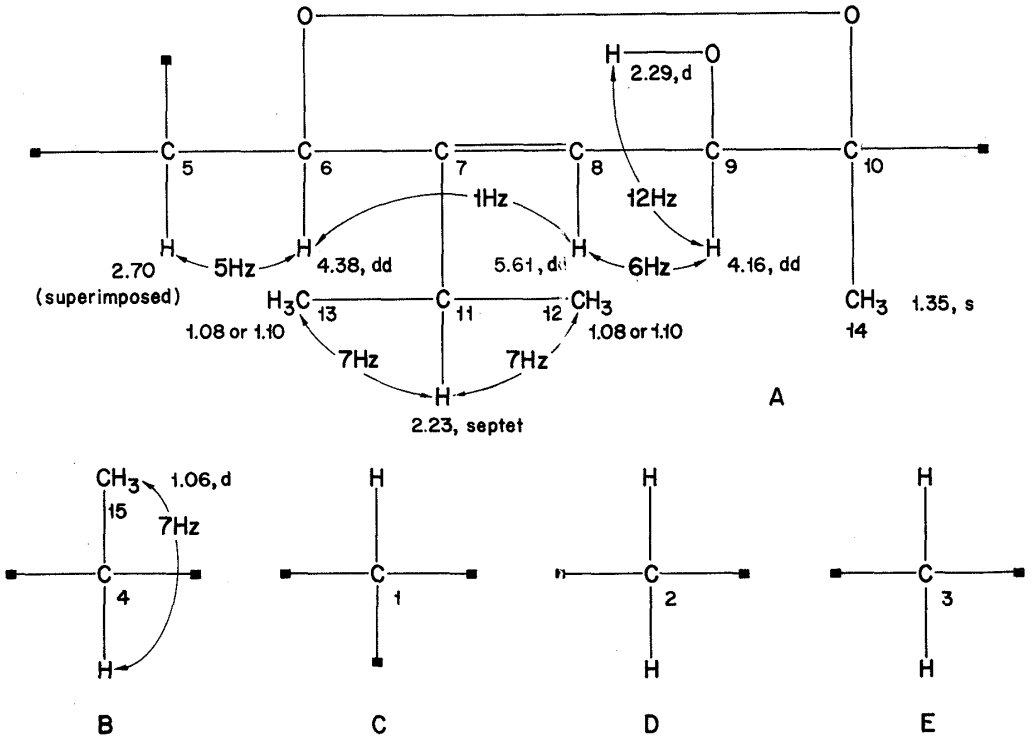


Fig. 1. Partial Structures of Hanalpinol (**1a**) (δ ppm, in $CDCl_3$)

with *N*,*N*-dimethyl-*p*-phenylenediamine spray, which is a well-known detection reagent for peroxides.[3]

Partial structure A where the carbon atoms are numbered as in the final structure was established from the ^{1}H-NMR spectra in $CDCl_3$ (with addition of D_2O) with the usual decoupling sequence, beginning with irradiation of the septet signal of H-11 to reveal the presence of an isopropyl group. The isopropyl group is on a double bond because of the chemical shift of H-11 (δ 2.23). Irradiation at the frequency of a vinylic proton, H-8, at δ 5.61 not only changed the doublet of doublets at δ 4.38 (J=5, 1 Hz) under the peroxide oxygen into a doublet (J=5 Hz) but also collapsed the H-9 proton doublet at δ 4.16 (J=6 Hz) into a singlet, showing that there is no proton on the adjacent carbon, C-10, which was assigned to the remaining quaternary carbon (δ 83.3 in ^{13}C-NMR). In $CDCl_3$ without D_2O, the coupling of J=12 Hz between the hydroxy proton at δ 2.29 and the doublet of doublets of H-9 at δ 4.16 indicated the predominance of an antiperiplanar conformation between the C9-H bond and the O–H bond because of hydrogen bonding to one of the peroxide oxygens.[4] The presence of this hydrogen bonding is also supported by the IR spectrum in highly dilute solution (IR band at 3571 cm^{-1}, 12 mg of **1a** in 5.8 ml of CCl_4). A methyl singlet at δ 1.35 was assigned to H-14 because of the chemical shift. The H-6 proton was converted to a doublet (J=5 Hz) by the irradiation of one of the superimposed signals at δ 2.70. Partial structure B was deduced from the presence of the methyl doublet at δ 1.06 and other partial structures C, D and E were derived from the ^{13}C-NMR spectra.

Biogenetic considerations made it reasonable to combine these partial structures as in **1a**. However, to elucidate the whole structure including the stereochemical configurations, an X-ray analysis of **2** was undertaken. Figure 2 is a stereoscopic drawing of the molecule which shows that the skeleton is *cis*-linked guaiane. Figures 3 and 4 show bond lengths and bond angles of the molecule, respectively. The remaining relative configuration of the hydroxy group on C-9 was assigned to be β because of the hydrogen bonding, as mentioned above.

The absolute configuration was determined by chemical conversion of hanalpinol (**1a**) to

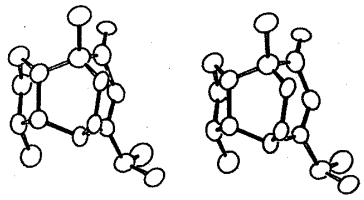


Fig. 2. Streoscopic View of the Structure of Compound **2**

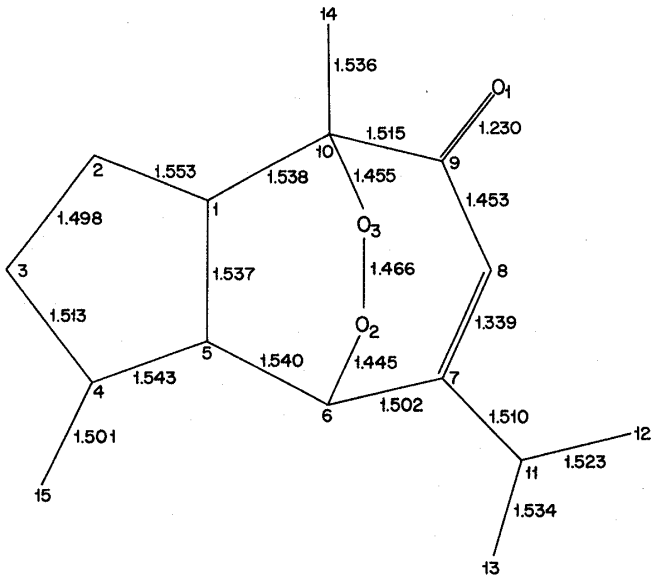


Fig. 3. Bond Lengths of Compound **2** (Å)

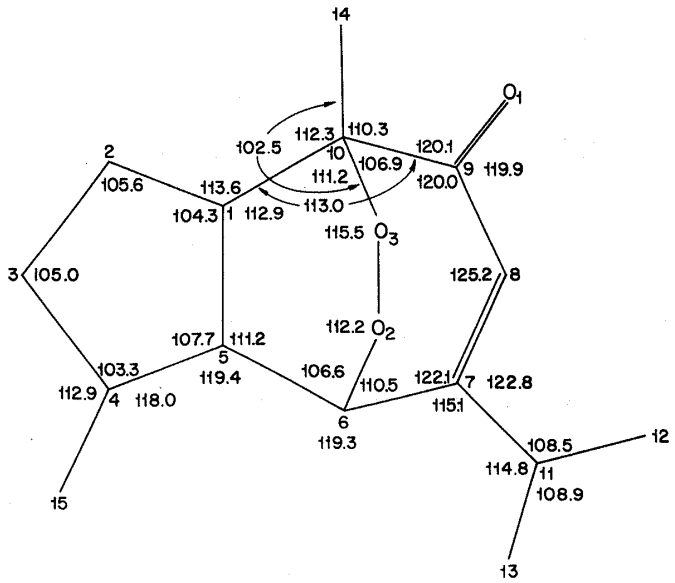


Fig. 4. Bond Angles of Compound **2** (Degree °)

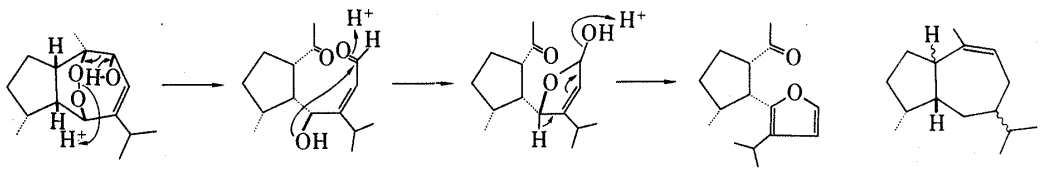


Chart 2

furopelargone B (**4**) whose structure had been established including the absolute configuration by Lukas and co-workers.[5] Treatment of **1a** with *p*-toluenesulfonic acid gave **4** whose spectral data and specific rotation were identical with those of natural furopelargone B (**4**) isolated from the same plant.

The reaction mechanism of this acid catalyzed reaction is assumed to be as shown in Chart 2. The carbon–carbon bond cleavage between C-9 and C-10 begins with a proton attacking the peroxide oxygen, C6–O, followed by O–O bond cleavage and cyclization to give B, acid-catalyzed dehydration of which affords **4**. Furthermore, **4** was gradually converted into furopelargone A (**3**) under these conditions. On the other hand, it was also possible that this conversion reaction is initiated by intramolecular catalytic action of the hydroxyl proton, but treatment of **1a** under the same condition without acid gave nothing but the starting material.

In 1965, Büchi and Wüest reported the total synthesis of furopelargones A and B.[6] At that time, they suggested that furopelargones A and B could originate in nature from the hypothetical bicyclic sesquiterpene (**5**) by oxidative cleavage of the double bond followed by cyclization. Thus, from the biogenetic point of view, the structure of hanalpinol and the above conversion reaction support their suggestion, and it can be assumed that furopelargones are biosynthesized from hanalpinol or an analog.

Experimental

All melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Spectral data were obtained with the following machines: ultraviolet (UV) on a Shimadzu UV-210, IR on a JASCO IRA-1 or IRA-3, mass (MS) on a Hitachi RMU-7L, ^{1}H-NMR on a JEOL JNM-PS-100 and ^{13}C-NMR on a JEOL JNM-FX-100. A high performance liquid chromatography (HPLC) system was constructed with a glass 22 mm I.D. × 300 mm CIG column system (Kusano Scientific Co., Tokyo) packed with Iatrobeads (60 μ spherically shaped silica gel, Iatron Co., Tokyo). TLC was carried out on Kieselgel 60 F_{254} precoated plates (Merck).

Extraction of *A. japonica*——Rhizomes and roots of *A. japonica* (fresh wt.: 10.8 kg) collected at Kawazu-cho, Shizuoka, Japan, were extracted with methanol and the extract was partitioned with petroleum ether (bp 40.0—60.0 °C) to obtain the petroleum ether-soluble fraction (18.1 g), which was chromatographed on 600 g of silica gel. Sesquiterpenoid fractions were eluted with *n*-hexane : ether (95 : 5—70 : 30); **3** and **4** were eluted with *n*-hexane : ether (90 : 10—80 : 20) and **1a** with *n*-hexane : ether (60 : 40).

Furopelargones A and B (3 and 4)——Further purification by liquid column chromatography (LCC) on silica gel eluted with *n*-hexane : ethyl acetate (19 : 1) and on 10% $AgNO_3$-impregnated silica gel eluted with benzene : ethyl acetate (98 : 2) gave **3** and **4**, each as a colorless oil (yield: 70 mg and 130 mg, respectively). The *Rf* value of **3** is slightly higher than that of **4**.

Furopelargone A (**3**): $[\alpha]_D^{20}$: −128.6° (c=0.07, $CHCl_3$). MS m/z (%): 234 (88, M^+), 191 (76), 163 (100), 109 (47). UV λ_{max}^{EtOH} nm (ε): 220 (6300). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2970, 2880, 1712, 1515, 1470, 1460, 1365, 1170, 1145, 1065 705. ^{1}H-NMR ($CDCl_3$, δ): 0.68 (3H, d, J=6 Hz), 1.13 (6H, d, J=7 Hz), 1.98 (3H, s), 2.80 (1H, septet, J=7 Hz), 3.07—3.57 (2H, m), 6.14 (1H, d, J=2 Hz), 7.14 (1H, d, J=2 Hz). ^{13}C-NMR ($CDCl_3$, δ): 16.3 (q), 23.9 (q), 24.1 (q), 24.3 (d), 28.0 (t), 29.2 (q), 34.3 (t), 39.3 (d), 42.2 (d), 55.5 (d), 108.6 (d), 127.1 (s), 140.2 (d), 149.4 (s), 209.8 (s). These data were identical with those given for furopelargone A in the literature.[5,7]

Furopelargone B (**4**): $[\alpha]_D^{25}$: +66.8° (c=0.36, EtOH). $C_{15}H_{22}O_2$ (high MS: Calcd for $C_{15}H_{22}O_2$: 234.1620. Found: 234.1619). MS m/z (%): 234 (M^+, 70), 219 (16), 191 (54), 163 (100), 149 (70), 135 (32), 123 (62), 109 (81), 91 (62). UV λ_{max}^{EtOH} nm (ε) 222 (6450). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2960, 1715, 1465, 1360, 1220, 1160, 1075, 890. ^{1}H-NMR ($CDCl_3$, δ): 0.72 (3H, d, J=6 Hz), 1.15 (6H, d, J=6 Hz), 1.86 (3H, s), 2.80 (1H, septet, J=6 Hz), 3.15 (1H, m), 3.59 (1H, t, J=7 Hz), 6.18 (1H, d, J=3 Hz), 7.17 (1H, d, J=3 Hz). ^{13}C-NMR ($CDCl_3$, δ): 16.1 (q), 23.6 (q), 24.3 (q), 24.5 (d), 24.7 (t), 28.6 (q), 31.8 (t), 40.3 (d), 43.8 (d), 57.8 (d), 108.0 (d), 128.4 (s), 140.9 (d), 147.2 (s), 208.2 (s). These data were identical with those given for furopelargone B in the literature.[5]

Hanalpinol (1a)——Further purification by LCC on silica gel eluted with *n*-hexane : ethyl acetate (9 : 1) and on 10% $AgNO_3$-coated silica gel eluted with benzene–ethyl acetate (90 : 10) gave **1a** as a colorless oil (yield: 500 mg): $[\alpha]_D^{25}$: +167.8° (c=0.42, EtOH). *Anal.* Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.84. MS m/z (%): 252 (M^+, 0.8%), 234 (65), 219 (15), 204 (18), 191 (65), 163 (98), 149 (71), 135 (45), 123 (79), 109 (90), 81 (100). IR ν_{max}^{neat} cm^{-1}: 3400, 2940, 1460, 1370, 1250, 1010, 980; νO–H: 3571 cm^{-1} (12 mg in 5.8 ml of CCl_4, cell length: 2 mm). ^{1}H-NMR ($CDCl_3$, δ): 1.06 (3H, d, J=7 Hz), 1.08 (3H, d, J=7 Hz), 1.10 (3H, d, J=7 Hz), 1.35 (3H, s), 2.23 (1H, septet, J=7 Hz), 2.29 (1H, d, J=12 Hz, disappeared on addition of D_2O), 2.5—2.9 (2H, m), 4.16 (1H, dd, J=6, 12 Hz, changed into d, J=6 Hz on addition of D_2O), 4.38 (1H, dd, J=5, 1 Hz), 5.61 (1H, dd, J=6 Hz). ^{13}C-NMR ($CDCl_3$, δ): 15.2 (q), 20.3 (q), 23.2 (q), 25.4 (q+t, superimposed signals), 32.7 (d), 33.0 (t), 37.3 (d), 44.7 (d), 46.4 (d), 73.1 (d), 80.3 (d), 83.3 (s), 124.7 (d), 152.4 (s).

Acetylation of 1a——Hanalpinol (**1a**) (52 mg) was reacted with acetic anhydride (275 mg) in pyridine (1.5 ml) for 24 h at room temperature. The reaction mixture was worked up in the usual way and the product was subjected to

LCC (silica gel; *n*-hexane : ethyl acetate = 19 : 1 as the eluent) to afford **1b** (44 mg) as a colorless oil. MS *m/z* (%): 294 (M^+, 2), 278 (2), 252 (4), 234 (21), 191 (38), 163 (34), 128 (58), 123 (75), 109 (58), 95 (98), 94 (100). IR ν_{max}^{neat} cm^{-1}: 2940, 1730, 1470, 1380, 1245, 1025, 970. ^{1}H-NMR ($CDCl_3$, δ): 1.04 (3H, d, J = 7 Hz), 1.07 (3H, d, J = 7 Hz), 1.08 (3H, d, J = 7 Hz), 1.23 (3H, s), 2.14 (3H, s), 2.5—3.0 (2H, m), 4.39 (1H, dd, J = 5, 1 Hz), 5.42 (1H, dd, J = 5, 1 Hz), 5.66 (1H, dd, J = 5, 1 Hz). ^{13}C-NMR ($CDCl_3$, δ): 15.3 (q), 20.3 (q), 21.2 (q), 23.0 (q), 25.3 (q), 26.5 (t), 33.3 (t), 33.8 (d), 37.3 (d), 44.6 (d), 45.8 (d), 75.8 (d), 79.9 (d), 82.2 (d), 120.6 (d). 153.2 (s), 170.8 (s).

Oxidation of 1a——Hanalpinol (**1a**) (64 mg) was treated with pyridinium chlorochromate (87 mg) in methylene chloride (2 ml) for 3 h at room temperature. Then, dry ether (20 ml) was added and the reaction mixture was filtered and evaporated. Purification by LCC (silica gel; *n*-hexane : ethyl acetate = 19 : 1 as the eluent) and recrystallization from *n*-pentane gave **2** (48 mg) as colorless plates; mp 80.5—82.0 °C. MS *m/z* (%): 250 (M^+, 56), 207 (29), 179 (50), 165 (45), 126 (100), 111 (42), 97 (58), 81 (71). UV λ_{max}^{EtOH} nm (ε): 237 (9330), 345 (107). IR ν_{max}^{KBr} cm^{-1}: 2960, 1665, 1645, 1380, 1240, 980, 885. ^{1}H-NMR (C_6D_6, δ): 0.59 (3H, d, J = 7 Hz), 0.77 (3H, d, J = 7 Hz), 0.95 (3H, d, J = 7 Hz), 1.51 (3H, s), 2.06 (1H, septet, J = 7 Hz), 2.15—2.8 (2H, m), 4.22 (1H, dd, J = 7, 1 Hz), 6.20 (1H, d, J = 1 Hz). ^{13}C-NMR ($CDCl_3$, δ): 15.6 (q), 20.0 (q), 22.4 (q), 22.5 (q), 26.8 (t), 32.9 (t), 36.4 (d), 37.1 (d), 41.7 (d), 43.7 (d), 81.8 (d), 88.5 (s), 128.7 (d), 166.6 (s), 201.3 (s).

Conversion of 1a to 4——Hanalpinol (**1a**) (60 mg) was stirred with *p*-toluenesulfonic acid (257 mg) in benzene (3 ml) for 17 h at room temperature, then the reaction mixture was filtered, washed with sat. sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated. The product was purified by HPLC (silica gel; benzene : ethyl acetate = 99 : 1 as the eluent) to give **4** (29.6 mg) whose spectral data including specific rotation were identical with those of natural furopelargone B.

X-Ray Analysis of 2——A single crystal of **2**, prepared by slow crystallization from *n*-pentane, was orthorhombic, space group $P2_12_12_1$, with a = 9.837 (5) Å, b = 19.419 (12) Å, c = 7.414 (4) Å, and d_{Calcd} = 1.1725 g cm^{-3} for Z = 4 ($C_{15}H_{22}O_3$). The intensity data were measured on a Philips diffractometer with graphite-monochromated CuK_α radiation.

A total of 1502 independent reflections out of 1715 theoretically possible reflections were measured for $6° < 2\theta < 156°$. The structure was solved by a multiple-solution procedure and was refined by the least-squares methods. The final R value was 0.069 for 1502 reflections including 18 heavier atoms (anisotropic thermal parameters) and 22 hydrogen atoms (isotropic thermal parameters).

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