Studies on the Agalwood "Jinkō." XII. Structures of Pentahydroxy-2-(2-phenylethyl)chromone Derivatives[1)]

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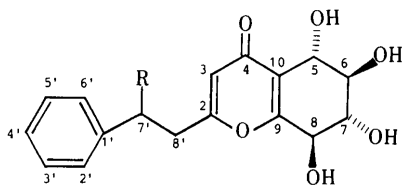
Two new phenylethylchromone derivatives were isolated from a methanol soluble portion of pyridine extract of agalwood (Jinkō). Their structures were elucidated as (5*S*,6*R*,7*S*,8*R*,7′*R*)-7′-hydroxyisoagarotetrol (1) and its (7′*S*)-isomer (2), respectively.

Keywords agalwood; Aquilariaceae; chromone; isoagarotetrol; pentahydroxy-2-(2-phenylethyl)chromone; ^{1}H-NMR; ^{13}C-NMR; NOE

We have already isolated many 2-(2-phenylethyl)chromone derivatives from the acetone and pyridine extracts of the agalwood, "Jinko." They were characterized as hydroxylated or hydrogenated 2-(2-phenylethyl)chromones, and dimers and trimers, joined by ether and C–C bonds, formed from agarotetrol, isoagarotetrol and 2-(2-phenylethyl)chromone.[2)]

Two new compounds, **1** and **2**, were isolated from a methanol soluble fraction of the pyridine extracts of agalwood by silica gel, Sephadex LH-20 and Lichroprep RP-8 column chromatographies followed by preparative high performance liquid chromatography (prep. HPLC).[2c)]

Compound **1**, colorless needles, mp 185—187 °C, $[\alpha]_D$ −67.9°, showed the characteristic absorptions of a γ-pyrone ring in the infrared (IR) and ultraviolet (UV) spectra. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed signals similar to those of isoagarotetrol[2b)] except that the ethylene signals of the latter are replaced by the signals at δ 4.98, 5.60 (OH), 2.83 and 2.90 assignable to the hydroxymethine and adjacent methylene groups (Table I). The chemical shifts and coupling system of the four sets of methine and hydroxy proton signals accorded with those of the tetrahydroxycyclohexenyl ring of isoagarotetrol having (5*S*,6*R*,7*S*,8*R*)-5e′, 6e, 7e, 8e′-tetrahydroxycyclohexene ring in the half-chair conformation (Table I). In the decoupling experiment, irradiation at δ 5.60 caused the multiple signal at δ 4.98 to collapse to a double doublet (J=8.0, 5.5 Hz). Further, irradiation at δ 4.98 transformed each proton of methylene at δ 2.83 (J=14.5, 5.5 Hz) and 2.90 (J=14.5, 8.0 Hz) into doublet signals with J=14.5 Hz. Therefore, it was suggested that the phenylethyl moiety of isoagarotetrol is hydroxylated at C-7′ or C-8′ in the case of **1**. In order to determine the position, **1** was subjected to nuclear Overhauser effect (NOE) study. Irradiation at δ 2.83 and 2.90 gave a remarkable NOE (*ca.* 8.9%) at δ 6.14, and the irradiations at δ 4.98 gave a smaller NOE (*ca.* 4.2%) at δ 6.14. These results indicated the hydroxylation at C-7′.



1, 2: R=OH
isoagarotetrol: R=H

Chart 1

This was also supported by the comparison of the ^{13}C-NMR data of **1** with those of isoagarotetrol in which β-effects (+5 and +9 ppm at C-1′ and C-8′, respectively) and γ-effects (about −3 ppm at C-2′ and C-6′) of hydroxylation at C-7′ were observed (Table II).

Consequently, **1** was characterized as 7′-hydroxyl derivative of isoagarotetrol.

Compound **2**, a white powder (mp 95—98 °C), $[\alpha]_D$ −46.8°, was analogous to **1** in the signal patterns of IR, UV, and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum of **2** a methine proton at δ 4.98 was assigned to C-7′ position by NOE study in which the irradiation at δ 4.98 gave an NOE (*ca.* 3.1%) with H-3 at δ 6.20, and the irradiation at δ 2.89 and 2.81 gave remarkable NOEs (*ca.* 6.1 and 6.7%) with H-3, respectively. The vicinal coupling constants of C-8′ methylene proton signals at δ 2.81 and 2.89 correspond to those of **1** at δ 2.90 and 2.83. Therefore, **1** and **2** were assumed to be stereoisomers at C-7′ asymmetric carbon.

Emperical rules for predicting the rotatory effects of asymmetric atoms and conformations have been presented by Brewster.[3)] Therefore, the absolute configurations at C-7′ asymmetric carbons of **1** and **2** may be determined in comparison with the rotatory effects at C-7′ positions between **1** and **2**. The contribution to the overall molecular rotation at C-7′ asymmetric carbon of **1** is predicted on the basis of three staggered conformations of bond C-7′–C-8′, with C-7′, the asymmetric center, forward (Fig. 1. A, B and C). One of these conformations, C, is prohibited owing to the rule; doubly skewed conformations contribute negli-

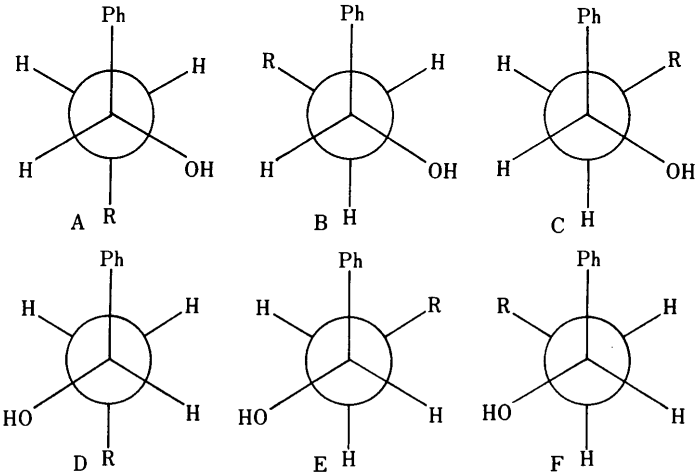


Fig. 1. Stable Conformations of **1** (A, B, C) and **2** (D, E, F) Projected at C-7′ and C-8′

TABLE I. ^{1}H-NMR Data for **1** and **2** (δ in DMSO-d_6, J=Hz)[a]

	1	2
3-H	6.14 (1H, s)	6.20 (1H, s)
5-H	4.30 (1H, dd, J=6.1, 6.0)	4.32 (1H, d, J=6.1)
6-H	3.43 (1H, ddd, J=8.6, 6.5, 4.5)	3.43 (1H, dd, J=8.8, 6.1)
7-H	3.48 (1H, ddd, J=8.6, 5.9, 4.5)	3.48 (1H, dd, J=8.8, 7.5)
8-H	4.47 (1H, dd, J=5.9, 3.0)	4.48 (1H, d, J=5.7)
7′-H	4.98 (1H, ddd, J=8.0, 5.5, 5.0)	4.98 (1H, dd, J=8.5, 5.0)
8′-H	2.83 (1H, dd, J=14.5, 5.5)	2.81 (1H, dd, J=14.5, 8.5)
	2.90 (1H, dd, J=14.5, 8.0)	2.89 (1H, dd, J=14.5, 5.0)
5-OH	5.83 (1H, d, J=6.0)	
6-OH	5.34 (1H, d, J=4.5)	
7-OH	5.23 (1H, d, J=4.5)	
8-OH	5.15 (1H, d, J=3.0)	
7′-OH	5.60 (1H, d, J=5.0)	
C_6H_5	7.25, 7.34, 7.39 (5H, m)	7.26, 7.35, 7.39 (5H, m)

a) Assignments were established by comparison with the data for isoagarotetrol.[2b]

TABLE II. ^{13}C-NMR Data for **1**, **2** and Isoagarotetrol (δ in DMSO-d_6)

Carbon	1	2	Isoagarotetrol
2	167.05	166.81	168.58
3	113.87	113.93	113.88
4	179.30	179.25	179.30
5	69.94	69.95	69.95
6	73.14	73.13	73.15
7	73.45	73.40	73.46
8	68.77	68.72	68.72
9	161.46	161.50	161.55
10	120.08	120.09	120.09
1′	144.44	144.37	139.88
2′,6′	125.66	125.67	128.38
3′,5′	128.06	128.04	128.21
4′	127.10	127.10	126.14
7′	69.94	69.66	31.63
8′	42.91	42.94	34.03

gibly, and two conformational isomers, A and B contribute equally. Taking into account the proper direction of the skew turns one has, for the staggered conformation, $[M]_A = k(Ph \cdot H - H \cdot OH + OH \cdot R - R \cdot H + H \cdot H - H \cdot Ph) = k(OH - H)(R - H)$. For conformation B, $[M]_B = k(Ph \cdot H - H \cdot OH + OH \cdot H - H \cdot H + H \cdot R - R \cdot Ph) = -k(Ph - H)(R - H)$. Since both weigh equally, $1/2([M]_A + [M]_B) = 1/2\ k(R - H)(OH - Ph)$. Using empirical rules OH=50 and Ph=140 with R=C, $1/2([M]_A + [M]_B)$ is $-45°$. In the case of **2**, the three skewed conformations at C-7′ may be shown as D, E and F (Fig. 1). In a similar manner to **1**, conformation F is disregarded. For conformation D we have $[M]_D = k(Ph \cdot H - H \cdot H + H \cdot R - R \cdot OH + OH \cdot H - H \cdot Ph) = -k(R - H)(OH - H)$, and conformation E, $[M]_E = k(Ph \cdot R - R \cdot H + H \cdot H - H \cdot OH + OH \cdot H - H \cdot Ph) = k(R - H)(Ph - H)$. Since $1/2([M]_D + [M]_E) = 1/2\ k(R - H)(Ph - OH)$, $+45°$ is obtained with the empirical values of Ph and OH. It is reasonable to presume the same rotatory effect as isoagarotetrol for the other rotatory contributions of **1** and **2** owing to the similar structure except at C-7′ position. The molecular rotation of isoagarotetrol is taken as $-186°$ on the basis of $[\alpha]_D$ $-58.6°$.[2b] Since it is assumed that the rotatory contributions of individual conformations are additive, the predicted molecular rotations for **1** and **2** are $-231°$ and $-141°$, respectively. Each observed rotation of **1** and **2** is $-226.8°$ and $-154.0°$. Thus the predicted rotation values at the asymmetric C-7′ of **1** and **2** are correct in sign and order of magnitude, and the absolute configurations are determined to (*R*) and (*S*), respectively.

1 and **2** were then characterized as (5*S*,6*R*,7*S*,8*R*,7′*R*)-7′-hydroxyisoagarotetrol and its (7′*S*)-isomer, respectively. They are the first examples bearing the hydroxyl function at C-7′ position of the 2-phenethylchromone derivatives.

Experimental

Melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. The UV spectra were obtained in MeOH with a Shimadzu UV-200S spectrometer and IR spectra (in KBr disks) with a Shimadzu IR 27G spectrometer. The ^{1}H (300.0 MHz) and ^{13}C (75.4 MHz)-NMR spectra were taken on a Varian XL-300 spectrometer in dimethyl sulfoxide-d_6 (DMSO-d_6) solution. Chemical shifts are given in δ (ppm) with tetramethylsilane as an internal standard (s, singlet; d, doublet; dd, double doublet; ddd, double double doublet; m, multiplet). The H–H NOE experiments in the difference mode were performed at 23 °C.

Column chromatographies were performed on Kiesel gel 60 (70—230 mesh, Merck), Kiesel 60 silanisiert (70—230 mesh), Sephadex LH-20 (Pharmacia Fine Chemicals) and LiChroprep Rp-8 (40—63 um) pre-packed column (Merck).

Isolation of Compounds 1 and 2 A pyridine extract (300 g) from residue-2 was refluxed with MeOH to obtain a viscous extract (56.5 g) which on silica gel column chromatography ($CHCl_3$–MeOH–H_2O, 90:10:1 (v/v)) gave four fractions: fr.-1 (8.6 g), fr.-2 (11.1 g), fr.-3 (7.7 g), and fr.-4 (18.5 g).[2d] Fraction-4 (18.5 g) was chromatographed on Sephadex LH-20 (MeOH) further to give another three fractions: fr.-5 (5.11 g), fr.-6 (3.60 g) and fr.7 (9.26 g). A mixture of **1** and **2** was obtained from fr.-6 by LiChroprep Rp-8 column chromatography (MeOH–H_2O, 7:3 (v/v)) and followed by prep. HPLC on Resolv "C_{18} Radial PAK" (MeOH–H_2O, 1:5 (v/v)) to yield **1** (11.3 mg) and **2** (11.0 mg).

Compound 1: Colorless needles, mp 185—187 °C, $[\alpha]_D$ $-67.9°$ (c=0.84 MeOH). UV λ_{max}^{MeOH} nm (ε): 254 (11100), 218 (7800). IR (KBr, cm^{-1}): 3350 (OH), 1657, 1579 (γ-pyrone), 1600, 1460, 1420, 750 (benzene ring). ^{1}H- and ^{13}C-NMR: Tables I and II.

Compound 2: A white powder (mp 95—98 °C), $[\alpha]_D$ $-46.1°$ (c=1.4, MeOH). UV λ_{max}^{MeOH} nm (ε): 254 (13040), 215 (11400). IR (KBr, cm^{-1}): 3400 (OH), 1657, 1590 (γ-pyrone), 1600, 1440, 750 (benzene ring). ^{1}H- and ^{13}C-NMR: Tables I and II.

References and Notes

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