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Studies on the Agalwood (Jinkō). VI.[1] Structures of Three 2-(2-Phenylethyl)-5,6,7,8-tetrahydrochromone Derivatives, AH_{1A}, AH_{2a} and AH_{2b}

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Three new kinds of phenylethyl chromone derivatives, named AH_{1A}, AH_{2a} and AH_{2b}, were isolated from the crude AH_1 (agarotetrol) and AH_2 (isoagarotetrol) fractions of agalwood (Jinkō) from Kalimantan. AH_{1A} separated from the crude AH_1 fraction through the process of acetylation was characterized as 2-[2-(4-methoxyphenyl)ethyl]-5α,6β,7β,8α-tetraacetoxy-5,6,7,8-tetrahydrochromone, and AH_{2a} and AH_{2b}, from crude AH_2 fraction, were established to be 2-[2-(4-methoxyphenyl)ethyl]- and 2-[2-(2-hydroxyphenyl)ethyl]-5α,6β,7α,8β-tetrahydroxy-5,6,7,8-tetrahydrochromone, respectively.

Keywords——2-(2-phenylethyl)chromone; agalwood; Aquilariaceae; agarotetrol; isoagarotetrol; ^{1}H-NMR spectrum; ^{13}C-NMR spectrum

The isolation and characterization of six constituents, named AH_1 (agarotetrol, **1**), AH_2 (isoagarotetrol, **4**), AH_3, AH_4, AH_5, and AH_6 which were obtained from the ether and acetone extracts of agalwood "Jinkō" from Kalimantan island were described in the previous papers.[1,2] In the course of the elucidation of the structures of AH_1 and AH_2, it was suggested that crude AH_1 and AH_2 were mixtures of hydroxyl and methoxyl derivatives of phenylethylchromone, and three new components, tentatively named AH_{1A} (**3**), AH_{2a} (**5**) and AH_{2b}(**6**) were separated from these fractions. In this paper, the isolation and structure determination of these compounds are described.

The isolation procedures are shown in Charts 1 and 2. Compound **3** was separated as an acetyl derivative, since it was difficult to isolate directly from the crude AH_1 fraction.

AH_{1A} (**3**), $C_{26}H_{28}O_{11}$, $[\alpha]_D+14.3°$ exhibited an absorption maximum at 247 nm in the ultraviolet (UV) spectrum and signals due to a γ-pyrone ring at about 1670 and 1610 cm^{-1} in the infrared (IR) spectrum, as did **1** and **4**. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **3** showed five methyl signals due to one methoxyl and four acetoxyl groups, and **3** was thought to be a methoxyl derivative of agarotetrol peracetate (**2**) based on a comparison of the chemical shifts of the corresponding protons of **2** and **3**, as shown in Table I. In the phenyl skeleton the number of protons was decreased from five to four [6.33(2H) and 7.08(2H), each $J=8.9$ Hz], indicating *para* substitution by a methoxyl group. This conclusion was supported by the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum, since the C-1′ signal of the phenylethyl group showed an upfield shift of about 8 ppm, and the calculated and observed values of the chemical shifts of C-2′—C-6′ were in excellent agreement, as shown in Table II.

Accordingly, AH_{1A} was suggested to be 5α,6β,7β,8α-tetraacetoxy-2-[2-(4-methoxyphenyl)ethyl]-5,6,7,8-tetrahydrochromone, **3**.

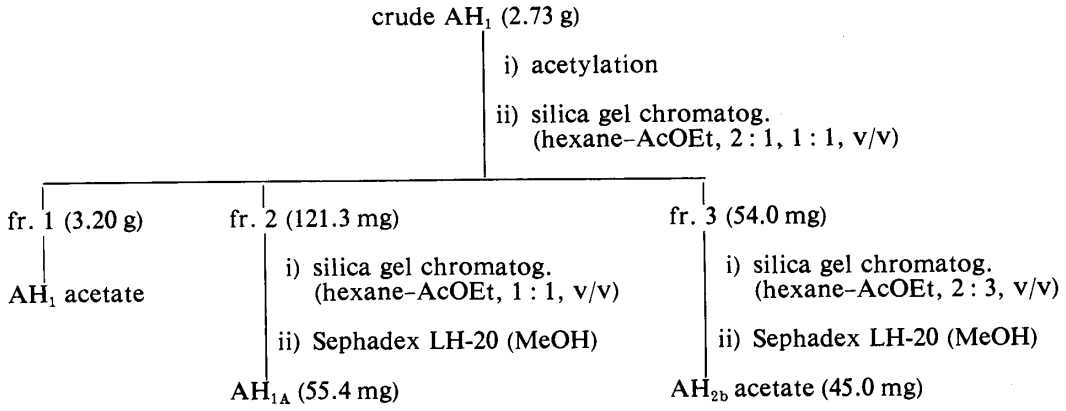

Chart 1

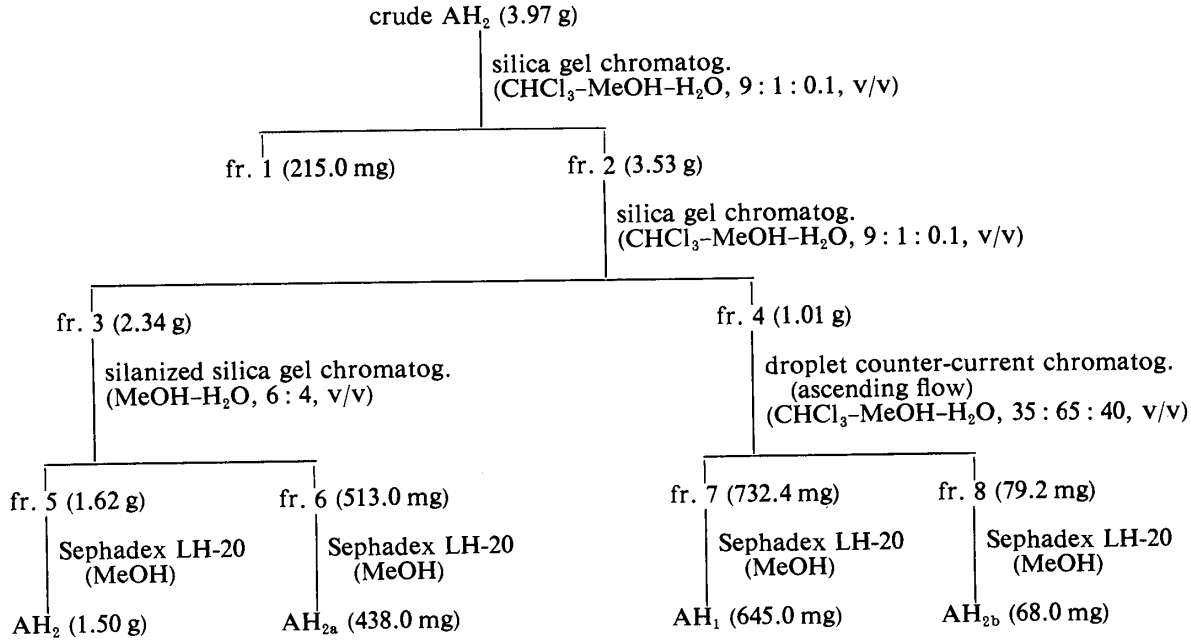

Chart 2

1: $R=R^1=H$
2: $R=CH_3CO$, $R^1=H$
3: $R=CH_3CO$, $R^1=CH_3O$

4: $R=R^1=R^2=H$
5: $R=R^2=H$, $R^1=CH_3O$
6: $R=R^1=H$, $R^2=OH$
7: $R=CH_3CO$, $R^1=H$, $R^2=CH_3COO$

Chart 3

AH_{2a} (**5**), $C_{18}H_{21}O_7$, mp 198—199 °C, was thought to be another methyl ether of 2-(2-phenylethyl)-5,6,7,8-tetrahydrochromone on the basis of its molecular formula, and UV and IR spectra. The ^{1}H-NMR spectrum exhibited the signals of phenylethyl protons bearing one methoxyl function linked at C-4′, as in **3**, but the signal pattern of four methine protons attached to the hexenyl ring was analogous to that of isoagarotetrol (**4**), and their chemical shifts and coupling constants were in fairly good accord with those of **4**, as shown in Table I.

Therefore, it was thought that the hexenyl ring of **5** was in a half-chair conformation bearing pseudo axial and axial protons in all *trans* relationship at 5/6, 6/7 and 7/8. The proposed identity of the hexenyl ring in **4** and **5** was also supported by the ^{13}C-NMR spectrum of **5**, summarized in Table II.

Accordingly, AH_{2a} was concluded to be 5α,6β,7α,8β-tetrahydroxy-2-[2-(4-(methoxyphenyl)ethyl]-5,6,7,8-tetrahydrochromone, **5**.

AH_{2b} (**6**), $C_{17}H_{18}O_7$, mp 135—137 °C, $[\alpha]_D$ −40.0°, was also suggested to be a 2-(2-phenylethyl)-5,6,7,8-tetrahydrochromone on the basis of its UV and IR spectra. The ^{1}H-NMR spectrum of **6** showed the signals of four methine protons fairly analogous to those of **4** and **5** (Table I).

Table I. ^{1}H-NMR Chemical Shifts (ppm from TMS, J=Hz) and Assignments[a]

	2 ($CDCl_3$)	**3** ($CDCl_3$)	**5** (Pyridine-d_5)	**6** (Pyridine-d_5)
3-H	6.13 (s)	6.11 (s)	6.33 (s)	6.39 (s)
5-H	6.01 (d, J=4.3)	5.99 (d, J=3.6)	5.11 (d, J=6.4)	5.08 (d, J=6.4)
6-H	5.50 (dd, J=4.3, 2.4)	5.52 (dd, J=3.6, 2.3)	4.42 (dd, J=7.0, 6.4)	4.41 (dd, J=7.0, 6.4)
7-H	5.47 (dd, J=8.9, 2.4)	5.45 (dd, J=7.2, 2.3)	4.46 (dd, J=7.0, 6.7)	4.46 (dd, J=7.0, 6.7)
8-H	6.05 (d, J=8.2)	6.07 (d, J=7.2)	5.35 (d, J=6.7)	5.36 (d, J=6.7)
7′,8′	2.88 (m)	2.83 (m)	2.84 (m)	3.09 (m)
C_6H_5	7.26 (m)	6.83 (d, J=8.9), 7.08 (d, J=8.9)	6.91 (d, J=8.9), 7.15 (d, J=8.9)	7.16 (m)
CH_3CO	2.06 (3H, s), 2.09 (6H, s), 2.18 (3H, s)	2.06 (3H, s), 2.08 (6H, s), 2.16 (3H, s)		
CH_3O		3.78 (3H, s)	3.64 (3H, s)	

a) Assignments of 5-, 6-, 7- and 8-H followed those for AH_1 (**1**) and AH_2 (**4**).[2]

Table II. ^{13}C-NMR Chemical Shifts (ppm) of **2**, **3**, **5** and **6**[a]

Carbon	**2**	**3**	**5**	**6**
2	168.26	168.35	169.28	170.12
3	114.03	114.07	113.55	113.31
4	176.60	176.69	180.93	181.11
5	66.41	66.46	71.78	71.75
6	68.15	68.17	74.74	74.77
7	69.07	69.07	75.07	75.05
8	63.77	63.79	70.79	70.86
9	159.00	158.92	162.51	162.54
10	119.14	119.22	121.42	121.25
1′	139.32	131.22 (132.74)[b]	132.26 (132.67)	127.23 (127.67)
2′	128.76	129.17 (129.84)	129.67 (129.91)	156.66 (155.81)
3′	128.21	114.21 (114.17)	114.44 (114.25)	115.76 (115.95)
4′	126.72	158.48 (158.04)	158.71 (158.12)	128.16 (128.12)
5′	128.21	114.21 (114.17)	114.44 (114.25)	119.66 (121.35)
6′	128.76	129.17 (129.54)	129.67 (129.91)	130.50 (130.30)
7′	32.46	31.67	31.90	28.15
8′	35.06	35.45	35.46	33.87
CH_3CO	20.55	20.60		
	169.02	169.12		
	169.67	169.75		
CH_3O		55.22	55.16	

a) Assignments of 5-, 6-, 7- and 8-C followed those for AH_1 (**1**) and AH_2 (**4**).[2] b) Values in parentheses were calculated based on the increment values of Levy *et al.*[3]

The peracetate (**7**) derived from **6** by treatment with anhydrous acetic acid and pyridine showed the presence of five acetoxyl groups at δ 2.03, 2.05, 2.07, 2.17 and 2.33 ppm. One of them, at δ 2.33, should be assigned to the acetoxyl function linked to the phenyl group because it is further downfield than the others. Therefore, **6** was thought to be a monohydroxyl derivative of **4**.

Since the C-1′ signal of the phenylethyl group in the ^{13}C-NMR spectrum of **6** was shifted upfield by 13.2 ppm in comparison with that of **4**, it was suggested that the hydroxy group is located at the *ortho* position with respect to C-1′, and the observed values of the other carbon signals, C-2′, C-3′, C-4′, C-5′ and C-6′, were in excellent agreement with the values calculated on this basis, as shown in Table II.

Accordingly, AH_{2b} was considered to be 5α,6β,7α,8β-tetrahydroxy-2-[2-(2-hydroxyphenyl)ethyl]-5,6,7,8-tetrahydrochromone, **6**.

Compounds **3**, **5** and **6** were characterized as *o*-hydroxy- and *p*-methoxy-phenylethyl derivatives of 5,6,7,8-tetrahydrochromones. Accordingly, oxidation of phenylethylchromones is possible at C-5—C-8 of the chromone ring and C-2—C-4 of the phenylethyl group, as judged from the structures of these compounds and homologous compounds obtained from the agalwoods.[1,2,4] Isolation and characterization of other derivatives of 2-(2-phenylethyl)chromones are in progress.

Experimental

Melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. The UV spectra were obtained in EtOH with a Shimadzu UV-200s machine and IR spectra in KBr disks with a Shimadzu IR 27G spectrometer. The ^{1}H- and ^{13}C-NMR were taken in pyridine-d_5 and $CDCl_3$ solutions on a Varian CFT-20 instrument at 79.54 and 20 MHz, respectively, and chemical shifts are given in δ (ppm) with tetramethylsilane (TMS) as an internal standard (s, singlet; d, doublet; t, triplet; m, multiplet).

Isolation——As described previously, AH_1 (**1**) and AH_2(**4**) were isolated from the acetone extractives of agalwood. The residues after isolation of the above compounds were tentatively named crude AH_1 (2.73 g) and crude AH_2 (3.9 g), respectively.

Crude AH_1 (2.73 g) added to a solution (30 ml) of anhydrous acetic acid–pyridine (1 : 1, v/v) and the mixture was allowed to stand for 5 h at room temperature, then evaporated to dryness under reduced pressure to give a residue (3.6 g), which was fractionated as shown in Chart 1. The isolation procedure from crude AH_2 is shown in Chart 2.

AH_1, AH_1 acetate, AH_2 and AH_{2b} acetate were identified by comparison with previously obtained authentic samples (mixed fusion and comparisons of IR and ^{1}H-NMR spectra).

AH_{1A} (3)——Amorphous (mp 58—60 °C (dec.)) (hexane–AcOEt), $[\alpha]_D^{14}$ −14.3° (c=1.2, MeOH). IR (KBr) cm^{-1}: 1755 (ester), 1670, 1610 (γ-pyrone ring), 1179, 1105, 1030, 1022, 820(1,4-disubstituted benzene ring). UV λ_{max}^{EtOH} nm (ε): 210 (18800), 213 (16800), 247 (11900). High-resolution MS *m/z*: Calcd for $C_{26}H_{28}O_{11}$: 516.1630. Found: 516.1634. ^{1}H- and ^{13}C-NMR: Tables I and II.

AH_{2a} (5)——Colorless needles (MeOH), mp 198—199 °C (dec.), $[\alpha]_D^{35}$ −67.7° (c=0.96, MeOH). IR (KBr) cm^{-1}: 3500—3200 (OH), 1650, 1610 (γ-pyrone ring), 1179, 1105, 1035, 1027, 821(1,4-disubstituted benzene ring). UV λ_{max}^{EtOH} nm(ε): 202 (18900), 223 (18300), 253 (14800). *Anal.* Calcd for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.28; H, 5.93. ^{1}H- and ^{13}C-NMR: Tables I and II.

AH_{2b}(6)——Colorless needles (MeOH), mp 135—137 °C (dec.), $[\alpha]_D^{32}$ −40.0° (c=0.85, MeOH). IR (KBr) cm^{-1}: 3500—3200 (OH), 1660, 1590 (γ-pyrone ring), 1190, 1126, 1029, 1004, 775 (1, 2-disubstituted benzene ring). UV λ_{max}^{EtOH}nm (ε): 202 (22400), 214.8 (20500), 253 (15300). *Anal.* Calcd for $C_{17}H_{18}O_7 \cdot 2/3H_2O$: C, 58.95; H, 5.63. Found: C, 58.71; H, 5.82. ^{1}H- and ^{13}C-NMR: Tables I and II.

Acetylation of 6——**6** (20 mg) was dissolved in a mixture of Ac_2O (3 ml) and pyridine (3 ml). The mixture was left to stand overnight and then evaporated to dryness under reduced pressure. The residue (32 mg) was chromatographed on silica gel by using hexane–AcOEt (1 : 1, v/v). The product thus obtained afforded a powder (23 mg) from hexane–AcOEt: (mp 62—64 °C), $[\alpha]_D^{22}$ +21.9° (c=2.01, MeOH). IR (KBr) cm^{-1}: 1755 (ester), 1672, 1636 (γ-pyrone), 1172, 1098, 1023, 971, 750 (1,2-disubstituted benzene ring). UV λ_{max}^{EtOH} nm (ε): 250 (9554), 204 (15147). High-resolution MS *m/z*: Calcd for $C_{27}H_{28}O_{12}$: 544.1578. Found: 544.1554.

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