Phytochemistry, Vol. 28, No. 12, pp. 3548 3550, 1989.
Printed in Great Britain.

TRI-2-(2-PHENYLETHYL)CHROMONES FROM AGALWOOD

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(*Received* 3 *April* 1989)

Key Word Index—Agalwood; Aquilariaceae; chromone; agarotetrol; isoagarotetrol; tri-2-(2-phenylethyl)-chromone.

Abstract—Two new tri-2-(2-phenylethyl)chromones, tentatively named AH_{19a} and AH_{19b}, were isolated from agalwood 'Jinkō' and structurally characterized using ^{1}H and ^{13}C NMR spectra.

INTRODUCTION

Agalwood 'Jinkō' has been used as an incense from ancient times in the Orient, and many kinds of agalwood have appeared on the market. In the course of a study to evaluate the quality of agalwood products [1–3], 24 new 2-(2-phenylethyl)chromone derivatives together with a known substance, agarotetrol [4], have so far been isolated from the ether and acetone extracts of agalwood from Kalimantan [3]. Twenty of the new compounds were characterized as hydroxylated or hydrogenated 2-(2-phenylethyl)chromones, and dimers and trimers, joined by ether and C–C bonds, formed from agarotetrol (**1**), isoagarotetrol (**2**) and 2-(2-phenylethyl)chromone (**3**) [5–10]. We now report on the isolation and characterization of two new tri-2-(2-phenylethyl)chromones from agalwood.

RESULTS AND DISCUSSION

The IR and UV spectra of AH_{19a} (**4**) showed the characteristic absorptions of a γ-pyrone ring whilst FDMS gave a peak at m/z 883 $[M+H]^{+}$. The ^{1}H NMR spectrum of **4** showed three singlet proton signals at δ6.017, 6.127 and 6.156, assignable to each H-3 and three sets of phenylethyl groups indicating the structure of a tri-2-(2-phenylethyl)chromone derivative. Two units (A and B) of the trimer appeared to be 5,6,7,8-tetrahydroxyphenylethylchromone derivatives on the basis of two sets of signals for the four methine proton signals in the moiety of the cyclohexenyl ring. Unit A was characterized as agarotetrol (**1**) linked at C-5 by ether bond to another monomeric unit (unit C), based on the four vicinal methine protons which showed analogous chemical shifts and coupling systems to those of AH_{15} and AH_{18} [9]. Unit B was identified as isoagarotetrol having the ether linkage at C-5 and the *trans* diaxial relationship of the four methine protons as shown in the ^{1}H NMR spectrum of AH_{14} [11]. Furthermore, another monomeric unit, unit C was assumed to be the 6,7-dialkoxylate of **3** because of the presence of two singlet signals of the aromatic protons located at C-5′ and 8′ of the chromone ring. Their assignments were confirmed by ^{1}H–^{13}C COSY (Tables 1 and 2). In order to determine the positions of the two –O– linkages between units A, B and C, **4** was subjected to a NOE study. Irradiation of H-5 at δ5.330 gave an appreciable NOE with H-5′ at δ7.856, and a further NOE was detected between the methine protons at δ5.729 and H-8′ at δ7.806. Therefore, each C-5 of units A and B is linked to the C-6′ and 7′, respectively, of unit C by an ether bond. Accordingly, AH_{19a} was characterized as the trimer **4**.

Compound AH_{19b} (**5**) showed analogous IR, UV and FDMS spectra to those of **4**, and it was inferred from the ^{1}H NMR spectrum to be another trimer of 2-(2-phenylethyl)chromone on the basis of three H-3 protons at δ6.038, 6.097 and 6.149. Two units (D and E) of **5** were suggested to be **1** and **2** based on the two sets of four

Table 1. ^{1}H NMR data for AH_{19a} (**4**) and AH_{19b} (**5**) (J values in Hz)

H	AH_{19a} (**4**)			AH_{19b} (**5**)		
	Unit A	Unit B	Unit C	Unit D	Unit E	Unit F
5,5′	5.330 *d* $J=7.5$	5.729 *d* $J=7.8$	7.856 *s*	5.537 *d* $J=7.5$	5.515 *s* $J=7.5$	7.884 *s*
6	4.291 *dd* $J=2.0, 7.5$	3.841 *dd* $J=7.8, 9.6$		3.824 *dd* $J=7.5, 9.0$	4.345 *dd* $J=2.0, 7.5$	
7	3.862 *dd* $J=2.0, 4.0$	3.637 *dd* $J=6.9, 9.6$		3.663 *dd* $J=6.6, 9.0$	3.896 *dd* $J=2.0, 4.0$	
8,8′	4.564 *d* $J=4.0$	4.480 *d* $J=6.9$	7.806 *s*	4.449 *d* $J=6.6$	4.592 *d* $J=4.0$	7.726 *s*
7″–CH_2 8″–CH_2	2.894 *m* (8H), 2.535 *m* (4H)			2.930 *m* (8H), 2.555 *m* (4H)		
C_6H_5	6.911 *dd* $J=2.0, 7.0$ (2H) 6.935 *dd* $J=2.2, 7.1$ (2H) 7.121 *m* (7H), 7.186 *m* (4H)			6.900 *dd* $J=2.0, 8.0$ (2H) 6.940 *dd* $J=2.0, 8.0$ (2H) 7.123 *m* (7H), 7.229 *m* (2H)		

Table 2. ^{13}C NMR data for AH_{19a} (**4**) and AH_{19b} (**5**)

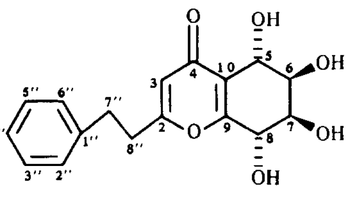
C	AH_{19a} (4)			AH_{19b} (5)		
	Unit A	Unit B	Unit C	Unit D	Unit E	Unit F
2,2′	167.923,	167.965	167.340	167.882,	167.986	167.348
3,3′	113.010,	113.228	109.252	112.958,	113.312	108.849
4,4′	177.815,	178.871	175.797	177.936,	178.849	175.793
5,5′	77.514	77.644	108.852	77.863	77.323	109.264
6,6′	69.174	71.817	147.389	72.127	69.008	147.283
7,7′	73.039	73.305	154.355	72.873	73.197	154.480
8,8′	64.250	68.602	103.832	68.376	64.143	104.055
9,9′	157.782	159.456	151.867	159.040	158.345	151.818
10,10′	121.485	122.006	116.792	122.043	121.467	116.890
1″	139.428,	139.477,	139.854	139.531,	139.480,	139.955
2″,6″ 3″,5″	127.823–128.280			127.770–128.268		
4″	126.106	126.106	126.004	126.087	126.087	126.010
7″	31.185,	31.365,	31.920	31.307,	31.307,	31.890
8″	33.966,	34.107,	34.757	33.954,	34.754,	34.754

Assignments of C_5–C_8 were established by ^1H–^{13}C COSY spectrum.

methine protons of which the chemical shifts and coupling systems were compared with those of **4**. The doublet signals at δ5.537 and 5.515 were respectively assigned to the protons at C-5 in the unit D and E by double irradiation and ^1H–^{13}C COSY (Tables 1 and 2). Another unit (F) was assumed to be 6,7-disubstituted 2-(2-phenylethyl)chromone in accordance with the assignment of the aromatic two protons at δ7.884 and 7.726 as described in **4**. Each ether bond at C-5, 6′ or C-5, 7′ in **5** was also confirmed by NOEs when **5** was subjected to alternate irradiation between the protons at δ5.537 and 7.884 or δ5.515 and 7.726 as in the case of **4**.

Accordingly, AH_{19b} was characterized as an isomer of AH_{19a} in which unit A and B are interchanged. The chemical shift differences between the axial protons at C-5 followed by the ether-linkages at C-5, 6′ and C-5, 7′ positions were about 0.2 ppm both in **1** and **2**.

It is of interest that the polymerizations of 2-(2-phenylethyl)chromones in agalwood are usually carried out between **3** and the polyoxylates **1** or **2** by formation of ether-linkages at C-5, 6′, C-5, 7′ and C-8, 6′ as described above and shown in the other dimers and trimer [8–11].



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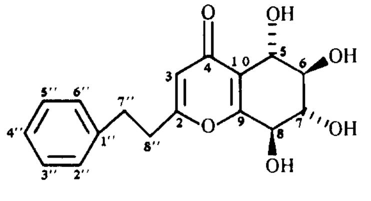

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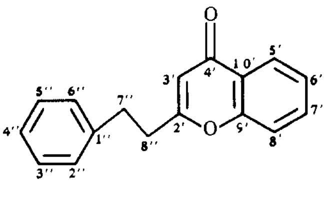

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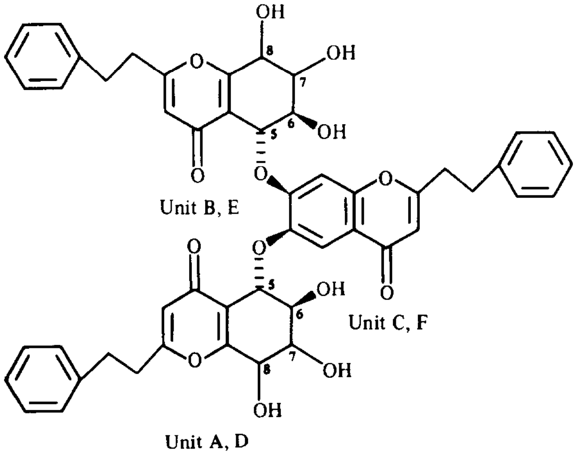

4 Unit A; OH-7β and 8α
Unit B; OH-7α and 8β
5 Unit D; OH-7α and 8β
Unit E, OH-7β and 8α

EXPERIMENTAL

Mps: uncorr; Optical rotations: 20°, 0.1 dm cell; FDMS: 20 mA, 3 kV; ^{1}H NMR: 300 MHz, DMSO-d_6, TMS as int. standard. ^{1}H–^{13}C COSY and ^{1}H–^{1}H NOE: see ref. [11].

Isolation of AH_{19a} (**4**) *and AH_{19b}* (**5**). A pyridine extract (300 g) from residue-2 [5] was refluxed with MeOH to obtain a viscous extract (56.5 g) which on silica gel CC ($CHCl_3$–MeOH–H_2O, 90:10:1) gave four fractions (monitoring by TLC with detection under UV light). Fraction 1 (8.57 g) was chromatographed on silanized silica gel (MeOH–H_2O, 2:3) followed by silica gel ($CHCl_3$–MeOH–H_2O, 100:10:1) to give two fractions, A (543 mg) and B (1.18 g). Fraction B was subjected to CC on LiChroprep Rp-8 (MeOH–H_2O, 13:7) and prep. HPLC (Nova-Pak "C_{18}-Radial Pak", MeCN–H_2O, 12:13) to yield AH_{19} (70.3 mg) as a white powder from *n*-hexane–EtOAc (1:1). AH_{19} was subjected to recycle prep. gel partition chromatography (column: Jaigel-310, elution: MeOH, 4.0 ml/min, detection: UV) to give AH_{19a} (**4**) and AH_{19b} (**5**). **4** (14.3 mg) and **5** (17.4 mg) were obtained as a white powder from EtOAc–MeOH, (1:1).

AH_{19a} (**4**). White powder (mp 165–167°), $[\alpha]_D -33.89°$ (MeOH; *c*, 1.18). IR ν_{max}^{KBr} cm^{-1}: 3380 (OH, vs), 1655, 1648, 1638, 1603 (γ-pyrone ring, vs), 690 (benzene ring, m); UV λ_{max}^{MeOH} nm (log ε): 242 (4.56), 250 (4.57); FDMS *m/z*: 883 $[M+H]^+$ (100), 865 $[M+H-H_2O]^+$ (57), 847 $[M+H-H_2O\times 2]^+$ (32), 829 $[M+H-H_2O\times 3]^+$ (16), 811 $[M+H-H_2O\times 4]^+$ (84), 282 $[C_{17}H_{14}O_4]^+$ (11); ^{1}H NMR and ^{13}C NMR: Tables 1 and 2. (Found: C, 67.7; H, 5.7. $C_{51}H_{46}O_{14}\cdot 1\frac{1}{3}\,H_2O$ requires: C, 67.5; H, 5.4).

AH_{19b} (**5**). White powder (mp 130–133°), $[\alpha]_D -64.04°$ (MeOH; *c*, 0.87); IR ν_{max}^{KBr} cm^{-1}: 3360 (OH, vs), 1655, 1642, 1633, 1600 (γ-pyrone, vs), 690 (benzene ring, m); UV λ_{max}^{MeOH} nm (log ε): 240 (4.59), 250 (4.70); FDMS *m/z*: 883 $[M+H]^+$ (100), 865 $[M+H-H_2O]^+$ (56), 847 $[M+H-H_2O\times 2]^+$ (73), 829 $[M+H-H_2O\times 3]^+$ (54), 811 $[M+H-H_2O\times 4]^+$ (78), 282 $[C_{17}H_{14}O_4]^+$ (7); ^{1}H NMR and ^{13}C NMR: Tables 1 and 2. (Found: C, 67.3; H, 5.5. $C_{51}H_{46}O_{14}\cdot 1\frac{1}{2}\,H_2O$ requires: C, 67.3; H, 5.4).

Acknowledgements—We thank Dr K. Hashimoto, Kyoto Pharmaceutical University, for the FDMS data and the members of the Central Analytical Department, Kyoto University for elemental analyses.

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