THE STRUCTURE OF AH_{16}, NEW TETRAHYDROXY-2-(2-PHENYLETHYL)CHROMONE FROM AGALWOOD

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New tetrahydroxy-2-(2-phenylethyl)chromone, tentatively named AH_{16} was isolated from agalwood, "Jinkō", and the structure was characterized as (5R,-6R,7S,8R)-2-(2-phenylethyl)-5e',6a,7e,8e'-tetrahydroxy-5,6,7,8-tetrahydrochromone, assuming the cyclohexenyl ring to have a boat conformation.

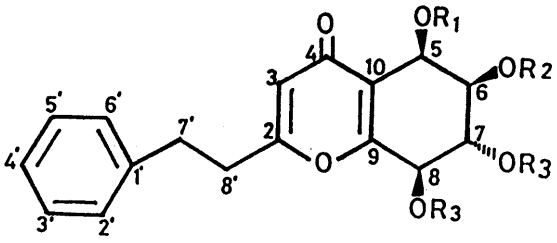
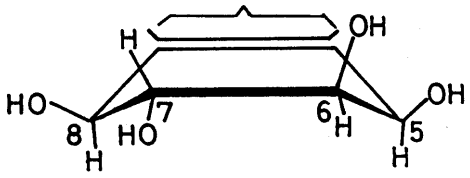
KEYWORDS 2-(2-phenylethyl)chromone; agalwood; Aquilariaceae; polyoxylate; cyclohexenyl ring; boat form; ^{1}H-NMR

New tetrahydroxy-2-(2-phenylethyl)chromone, AH_{16} was isolated from the crude AH_1 fraction.[1] This paper describes the characterization of the structure.

AH_{16} (1), $C_{17}H_{18}O_6$, a white powder (mp 100-105°C), $[\alpha]_D$ +4.76° (MeOH) appeared to be a 2-(2-phenylethyl)chromone derivative according to the IR (KBr), UV (MeOH) and ^{1}H-NMR spectra: 1658, 1595 cm^{-1} and 253 nm, ε=36321 (γ-pyrone ring); 6.30 (s,3-H). The presence of the vicinal tetramethine protons in the ^{1}H-NMR spectrum indicated that it was a polyoxyl derivative related to agarotetrol and isoagarotetrol.[2,3] Refluxing a mixture with anhydrous cupric sulfate and acetone, 1, afforded a single acetonide (2), colorless needles, mp 173-174°C, $[\alpha]_D$ -122.4° ($CHCl_3$), ^{1}H-NMR: 1.31, 1.32 (each s,CH_3), 5.11 (d,J=4.8,7-OH), 5.41 (d,J=3.4,8-OH), which indicated the structure of a 5,6-isopropylidenyl derivative because of the absence of a 5-OH proton signal, that should be found in the down field position at about δ 5.8 ppm.[3] Therefore, the relative stereochemistry of the four hydroxy groups in the cyclohexenyl ring of 1 was shown to be oriented in 5/6 cis, 6/7 trans, and 7/8 trans.[4]

When a half-chair conformation is assumed for the cyclohexenyl ring, the vicinal hydroxy groups of 1 should be in trans diaxial or trans diequatorial relationship at C_6, C_7 and C_8 (Chart 2. A and B). It is said that in conduritol F having the four vicinal hydroxyl groups e'eea', the molecules will be largely in the conformation A from the viewpoint of the energy levels.[5] In the ^{1}H-NMR spectrum of 1 the observed coupling constants are clearly not in accord with those expected for the aaa' system in the vicinal protons at C_6, C_7 and C_8.[3] On the other hand, the conformation B may be stabilized on the intramolecular hydrogen bonding between the pyrone carbonyl and 5e'-OH function. Acetylation (Ac_2O-pyridine) of 1 afforded tetraacetate (3), a white powder, $[\alpha]_D$ +62.3° ($CHCl_3$), ^{1}H-NMR (C_5D_5N,δ): 2.04, 2.05, 2.07, 2.31 (each s,CH_3COO), 6.05 (dd,J=5.0,2.5,7-H), 6.10 (dd,J=5.0,2.5,6-H), 6.67 (d,J=5.0,5-H), 6.78 (d,J=5.0,8-H). As can be seen from the J values observed in the methine protons, the acetylation did not convert the half-chair form from 5e'-OH to 5a'-OAc, which is expected to be the most stable after releasing to the hydrogen bonding.[2] The stereochemistries of 1 and 3 are virtually invariant in the cyclohexenyl ring. Consequently, it is difficult to assume the half-chair conformation for the cyclohexenyl ring of 1.

The cyclohexenyl ring of the isopropylidenyl derivative can generaly assume a flexible form ranging from the boat to the skew boat conformation.[5] The observed $J_{6,7}$ values of 1 and 2 are 2.0 and 3.2 Hz, respectively, which approximate to J_{ea} in the conduritols.[5] The minor modification of $J_{6,7}$, as well as $J_{5,6}$ and $J_{7,8}$, in the flexible conformation may be made

1: $R_1=R_2=R_3=H$ 2: $R_1,R_2=>C<^{CH_3}_{CH_3}$, $R_3=H$

3: $R_1=R_2=R_3=CH_3CO$ 4: $R_1,R_2=>C<^{CH_3}_{CH_3}$, $R_3=CH_3O$-Ph-CO

5: $R_1=R_2=H$, $R_3=CH_3O$-Ph-CO

Chart 1

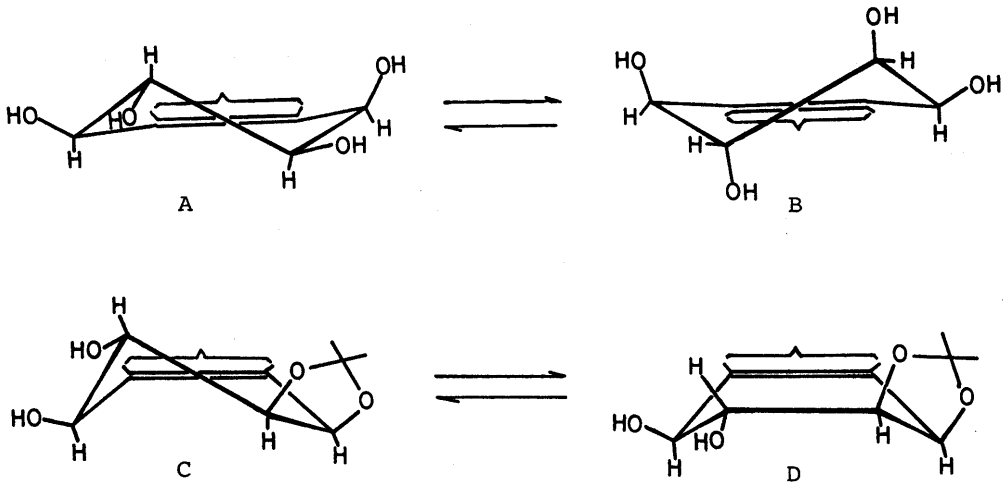


Chart 2

within a small scope of torsion. The dihedral angles in 1 and 2 calculated by the use of the equation $J=11.0\cos^2\psi$ are given in Table II. The interconversions of the angles between 1 and 2 are easily possible by slightly twisting the boat form. Assuming the boat form, the four vicinal methine protons in the cyclohexenyl ring are oriented in 5a', 6e, 7a, and 8a', respectively. Therefore, it appears that the stability of the molecule in the boat conformation rests on the orientations of the hydroxy groups e'aee' system and the intramolecular hydrogen bondings between 5e'-OH and 4-CO, and 8e'-OH and ether oxygen in the γ-pyron ring.

In order to determine the absolute configulation of 1, 7,8-di-p-methoxybenzoate (4) was obtained from 2 followed by hydrolysis with 3% trifluoroacetic acid to give the 5,6-dihydroxylate (5).[6] The ^{1}H-NMR spectra of 4 and 5 were analogous to those of 1 and the other derivatives, 2 and 3, suggesting the stereochemistry of the boat form in the cyclohexenyl ring.[7] Furthermore, the similarity of the conformation between 4 and 5 was indicated by the CD spectra (EtOH) which showed the positive chirality of the 7,8-dibenzoate groups.[8] Therefore, the drawing shown in Chart 1 represents the absolute structure of 1.

Consequently, AH_{16} was defined as (5R,6R,7S,8R)-2-(2-phenylethyl)-5e',6a,7e,8e'-tetra-hydroxy-5,6,7,8-tetrahydrochromone, 1. The conformation of the cyclohexenyl ring of 1 were found in the solution state to be the flexible boat form rather than the rigid half-chair generally assumed.

Table I. ^{1}H-NMR Data for 1 and 2 (ppm, 300 MHz)

	1 (C_5H_5N, Hz)	2 (DMSO-d_6, Hz)
3-H	6.30 (s)	6.17 (s)
5-H	5.06 (d, J=4.1)	5.02 (d, J=6.4)
6-H	4.96 (dd, J=4.1, 2.0)	4.52 (dd, J=6.4, 3.2)
7-H	4.77 (dd, J=4.9, 2.0)	3.79 (ddd, J=5.6, 4.8, 3.2)
8-H	5.79 (d, J=4.9)	4.66 (dd, J=5.6, 3.4)
C_6H_5	7.20 (m, 5H)	7.19 (m, 1H), 7.26 (m, 4H)
CH_2	2.71, 2.72 (each m, 2H)	2.91 (m, 4H)
CH_3		1.31, 1.37 (each s, 3H)
OH		5.11 (d, J=4.8, 7-OH) 5.41 (d, J=3.4, 8-OH)

Table II. Calculated Dihedral Angles from J Values in 1 and 2

	5,6-H (a'e)	6,7-H (ea)	7,8-H (aa')
1	52°	115°	132°
2	40°	123°	136°
Conduritols[5]	53°	116°	151°

This indicates that, assuming the conformation of cyclohexenyl ring, the possibility of the boat form should be investigated at length in connection with the stereochemistry of the substituted groups. It is of interest that AH_{16} and isoagarotetrol are epimers with respect to carbon atom 5.

REFERENCES AND NOTES

1) Crude AH_1 (4.8 g)[a] was chromatographed on a silica gel column ($CHCl_3$-MeOH-H_2O, 9:1:0.1, V/V) to give three fractions (A, 340 mg; B, 650 mg; C, 1.925 g). The fraction B (650 mg) was further subjected to column chromatography ($CHCl_3$-MeOH, 9:1 V/V) to give a crude fraction (65 mg) of AH_{16} from which AH_{16} (43 mg) was obtained as a white powder by sephadex LH-20 column chromatography (MeOH).
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3) Y. Shimada, T. Konishi, S. Kiyosawa, M. Nishi, K. Miyahara, and T. Kawasaki, Chem. Pharm. Bull., 34, 2766 (1986).
4) When p-toluene sulfonic acid was used as a catalyst, the isoagarotetrol 5e',6e,7e,8e'-tetrahydroxylate afforded a monoacetonide having the trans-6,7-isopropylidenedioxy group in the half-chair conformation, but the reaction was not accelerated by refluxing a mixture with anhydrous cupric sulfate and acetone.[3]
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6) N. Harada and K. Nakanishi, Accounts Chem. Res., 5, 257 (1972).
7) ^{1}H-NMR of 4 (DMSO-d_6, δ, 300MHz): 1.33, 1.43 (each 3H, s, CH_3), 2.95 (4H, m, CH_2CH_2), 3.80, 3.82 (each 3H, s, CH_3O), 4.87 (1H, dd, J=5.9, 2.8, 6-H), 5.11 (1H, d, J=5.9, 5-H), 5.64 (1H, dd, J=7.0, 2.8, 7-H), 6.67 (1H, d, J=7.0, 8-H), 6.05 (1H, s, 3-H), 6.83 (2H, d, J=9.0, aromatic H), 6.87 (2H, d, J=9.0, aromatic H), 7.25 (5H, m, aromatic H), 7.90 (2H, d, J=9.0, aromatic H), 7.98 (2H, d, J=9.0, aromatic H).
   ^{1}H-NMR of 5 (DMSO-d_6, δ, 300MHz): 2.91 (2H, m, 7'-CH_2), 2.985 (2H, m, 8'-CH_2), 3.79, 3.82 (each, s, CH_3O), 4.28 (1H, dd, J=3.5, 2.0, 6-H), 4.96 (1H, dd, J=3.5, 1.0, 5-H), 5.34 (1H, dd, J=7.0, 2.0, 7-H), 6.11 (1H, s, 3-H), 6.45 (1H, dd, J=7.0, 1.0, 8-H), 6.98, 7.04 (each 2H, d, J=8.5, aromatic H, 7.24, (1H, m, 4'-H), 7.29 (4H, m, aromatic H), 7.77, 7.92 (each 2H, d, J=8.5, aromatic H).
8) CD of 4 ($c=0.44\times10^{-5}$, MeOH) λ_{max} : -27.59 (247 nm) (negative maximum), +30.65 (268 nm) (positive maximum). CD of 5 ($c=0.95\times10^{-5}$, MeOH) λ_{max} : -28.8 (237 nm) (negative maximum), +34.5 (255 nm) (positive maximum).

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