Arch. Pharm. Res. **14**(2), 137-142 (1991)

The Crystal Structure of a β-Allyl Type Phenylpropanoid, 2-(4-Allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol, from the Seeds of *Myristica fragrans*

Yang Bae Kim, Il Yeong Park, Jeong Ae Kim and Kuk Hyun Shin*
College of Pharmacy, Seoul National University, Seoul 151-742, Korea
**Natural Products Research Institute, Seoul National University, Korea*
(Received February 26, 1991)

Abstract □ The structure of a β-allyl type phenylpropanoid was determined by single crystal X-ray diffraction analysis. The compound was recrystallized from a mixture of *n*-hexane and benzene in monoclinic crystal system, with $a=24.782$ (2), $b=10.537$ (1), $c=7.871$ (1) Å, $\beta=95.74$ (1)°, $D_x=1.216$, $D_m=1.22$ g/cm^3, space group $P2_1/a$, and $Z=4$. The structure was solved by direct method and refined by least-squares procedure to the final R value of 0.054 for 2824 observed reflections $\{F\geq3\sigma(F)\}$. The molecular geometry shows a most stable *trans*-form with respect to the bulky phenyls, and this conformation is settled by an intramolecular hydrogen bond. In the crystal, the molecules are arranged along with the screw axis, and stabilized by the O-H···O type intermolecular hydrogen bonds. The other intermolecular contacts appear to be the normal *van der Waals'* interactions. The compound is a dimeric phenylpropanoid, and belongs to the neolignan analogues.

Keywords □ Myristicae Semen, X-ray crystallography, three-dimensional structure, hydrogen bond, dimeric phenylpropanoid

Myristicae Semen is the dried seed of *Myristica fragrans*. The drug is used in abdominal disorders in Korea, but sometimes it causes hallucination or psychosis at higher doses[1].

In our continuous search for hepatic mixed function oxydase (MFO) modifiers from herbal medicines, various components were isolated and characterized[2,3]. Recently, in the series of investigation, we isolated four neolignans from Myristicae Semen as the active principles. They were identified as myristicin, dehydrodiisoeugenol, licarin-B, and the title compound (Fig. 1) by spectral analysis, and reported[4,5].

From the above compounds, licarin-B and the title compound were subjected to X-ray crystallographic study to analyse the three dimensional structures. The crystal structure of licarin-B was presented in our previous report[6].

The present study deals with the precise structural analysis of the title compound by single crystal X-ray diffraction technique. We were motivated to investigate the crystal structure of the compound to provide useful informations concerning the structure-activity relationships of their enzyme inhibiting activities and so on.

EXPERIMENTAL METHODS

The fractionation procedure of the compound was reported previously[5]. Colorless prismatic crystals were grown by the slow evaporation method from a mixture of *n*-hexane and benzene at room temperature. The density was measured by the flotation in potassium iodide solution.

The lattice constants were determined from the least-squares refinements of the angular values for 25 reflections recorded on an automatic four-circle diffractometer (Rigaku Denki Co. Ltd.) with graphite-monochromated CuK_α radiations (30 kV, 100 mA). The space group was determined by systematic absences detected on the subsequent data collection. The crystallographic data are listed in

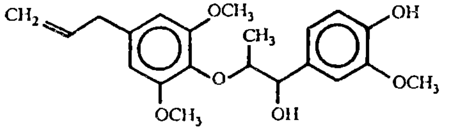

Fig. 1. The title compound.

Table I.

Intensity data with range of $-28 \leq H \leq 28$, $0 \leq K \leq 12$, $0 \leq L \leq 9$ were recorded from a crystal with dimensions of 0.20×0.45×0.45 mm by ω-2θ scan technique (scan speed 8°/min). Three standard reflections, (−2, 3, 2), (8, 0, −2) and (2, 4, −1) were monitored after every 100 data collections and showed no noticeable changes. The reflections were corrected for usual Lorentz and polarization effects, but no absorption corrections were applied. Of all 3738 diffractometer-recorded reflections, 914 reflections which were $F < 3\sigma(F)$ and/or systematic absences were treated as unobserved.

The structure was solved by direct method with *SHELX* 76[7] and *MULTAN* 84[8] programs. *E* values larger than 1.2 were used for phase generation. From the 27 nonhydrogen atoms of the molecule, 26 atoms are appeared on the first *E*-map calculated using the phase set with the highest combined figure of merit. A subsequent Fourier synthesis revealed the position of the remaining atom. The initial *R* value was 0.304.

Table I. Crystal data

$C_{21}H_{26}O_6$	M.W. 374.44
2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl)propan-1-ol	
Colorless transparent prism	Monoclinic
$a = 24.782$ (2) Å	$b = 10.537$ (1) Å
$c = 7.871$ (1) Å	$\beta = 95.74$ (1)°
Vol. of unit cell: 2044.9 (4) Å^3	
$D_x = 1.21$ g/cm^3	$D_m = 1.22$ g/cm^3
Space group: $P2_1/a$	$Z = 4$
$F(000) = 800$	$\mu(\mathrm{Cu}K_\alpha) = 6.47$ cm^{-1}

The structure was refined first isotropically to the *R* value of 0.146 by 3 cycles of full matrix least-squares procedure. Successive refinements with anisotropic temperature factors reduced the *R* value to 0.104. Difference Fourier syntheses calculated at this stage revealed all the hydrogen atoms of the compound.

Further refinements by block diagonal least-squares procedure including hydrogen atoms for 2824 reflections $\{F \geq 3\sigma(F)\}$ produced the final *R* value of 0.054 and *wR* of 0.086 (where $wR = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w F_o^2]^{1/2}$). The function minimized in the refinements was $w(|F_o| - |F_c|)^2$, where $w = k/\{\sigma^2(F) + gF^2\}$, k and g were refined to 1.223 and 0.00499. In the final cycle the average and maximum shift/e.s.d. for the parameters are 0.008 and

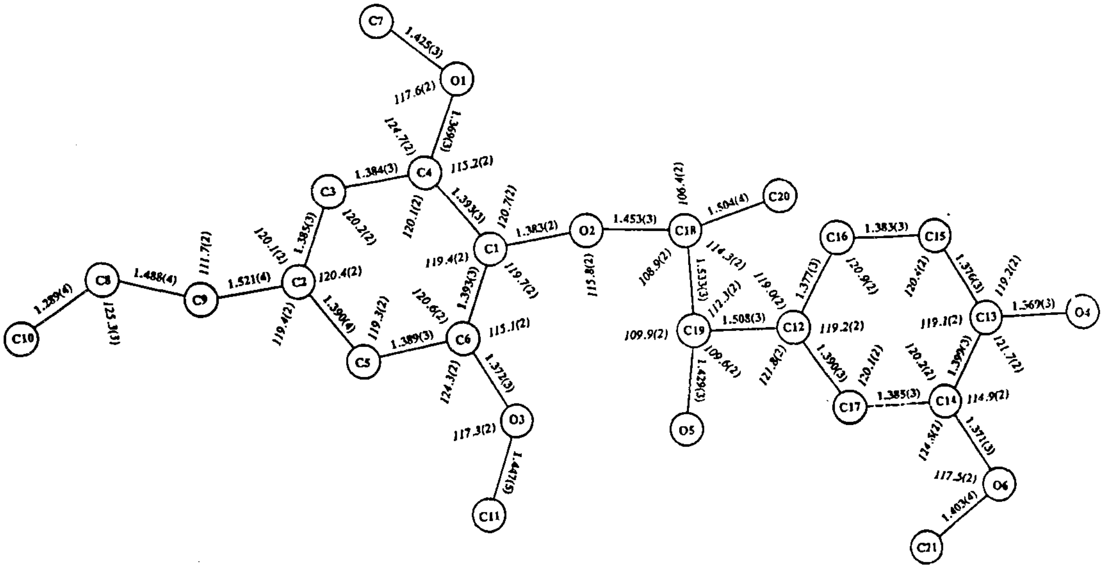

Fig. 2. Bond lengths (Å) and angles (°) of the molecule with their estimated standard deviations in parentheses.

Table II. Fractional non-hydrogen atomic coordinates ($\times 10^4$) and thermal parameters ($\times 10^3$) with their e.s.d.'s in parentheses. The anisotropic temperature factors are in the form of

$$exp[-2\pi^2(U_{11}a^{*2}h^2+U_{22}b^{*2}k^2+U_{33}c^{*2}l^2+2U_{12}a^*b^*hk+2U_{13}a^*c^*hl+2U_{23}b^*c^*kl)]$$

Atom	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	4115(1)	838(2)	6525(3)	54(1)	51(1)	49(1)	−9(1)	4(1)	11(1)
C(2)	4623(1)	−1245(2)	8150(3)	73(2)	58(1)	51(1)	−6(1)	3(1)	18(1)
C(3)	4928(1)	−226(2)	7684(3)	55(1)	62(2)	57(1)	−14(1)	−1(1)	10(1)
C(4)	4677(1)	815(2)	6877(3)	52(1)	55(1)	49(1)	−12(1)	7(1)	4(1)
C(5)	4062(1)	−1234(2)	7813(3)	73(2)	52(1)	66(2)	−9(1)	9(1)	4(1)
C(6)	3810(1)	−188(2)	7004(3)	52(1)	56(1)	63(1)	−12(1)	2(1)	5(1)
C(7)	5519(1)	1841(3)	6534(5)	54(1)	82(2)	80(2)	−21(2)	14(1)	−5(1)
C(8)	5054(1)	−3323(2)	7615(3)	62(1)	62(2)	67(2)	4(1)	7(1)	15(1)
C(9)	4903(1)	−2420(3)	8941(4)	93(2)	67(2)	64(2)	1(1)	−1(2)	26(2)
C(10)	4922(1)	−4506(3)	7523(5)	85(2)	75(2)	85(2)	−6(2)	−2(2)	3(2)
C(11)	2923(2)	−1080(4)	7167(9)	68(2)	86(2)	186(5)	6(3)	5(3)	−17(2)
C(12)	3289(1)	4035(2)	8745(3)	50(1)	47(1)	53(1)	2(1)	11(1)	2(1)
C(13)	3161(1)	6197(2)	10704(3)	53(1)	57(1)	66(1)	−9(1)	11(1)	0(1)
C(14)	2753(1)	5829(2)	9442(3)	51(1)	53(1)	61(1)	1(1)	8(1)	10(1)
C(15)	3628(1)	5486(2)	10950(3)	49(1)	62(1)	63(1)	−6(1)	2(1)	−3(1)
C(16)	3690(1)	4411(2)	9979(3)	47(1)	57(1)	63(1)	0(1)	4(1)	6(1)
C(17)	2819(1)	4759(2)	8464(3)	47(1)	53(1)	54(1)	2(1)	3(1)	4(1)
C(18)	3810(1)	3003(2)	6517(3)	49(1)	46(1)	58(1)	−3(1)	6(1)	6(1)
C(19)	3370(1)	2845(2)	7739(3)	45(1)	48(1)	57(1)	2(1)	3(1)	2(1)
C(20)	3692(1)	4018(3)	5188(4)	74(2)	65(2)	70(2)	12(1)	15(2)	9(1)
C(21)	1872(1)	6243(4)	8093(5)	75(2)	116(3)	93(3)	−23(2)	−21(2)	49(2)
O(1)	4941(1)	1871(2)	6376(2)	51(1)	63(1)	76(1)	−5(1)	13(1)	3(1)
O(2)	3862(1)	1822(1)	5595(2)	56(1)	57(1)	52(1)	−4(1)	1(1)	11(1)
O(3)	3261(1)	−80(2)	6595(3)	52(1)	61(1)	111(1)	−3(1)	0(1)	−4(1)
O(4)	3109(1)	7252(2)	11691(3)	64(1)	76(1)	109(2)	−40(1)	5(1)	7(1)
O(5)	2870(1)	2488(2)	6802(2)	51(1)	62(1)	81(1)	−14(1)	4(1)	−2(1)
O(6)	2302(1)	6589(2)	9301(2)	62(1)	78(1)	84(1)	−18(1)	−5(1)	27(1)

0.039 for non-hydrogen atoms, and 0.015 and 0.134 for hydrogen atoms.

All the calculations were carried out on *VAX*-11/780 computer system at Seoul National University. The atomic scattering factors were taken from "*International Tables for X-ray Crystallography*"[9].

RESULTS AND DISCUSSION

The final atomic coordinates and temperature factors are listed in Table II and III together with their estimated standard deviations. The observed and calculated structure factors are available upon request.

The atomic numbering scheme, bond lengths and angles are presented in Fig. 2. All the molecular dimensions with their estimated standard deviations are in the chemically reasonable range[10]. The stereoscopic view of the molecule drawn by *ORTEP*[11] is shown in Fig. 3.

The phenyl groups of the molecule are planar. The equations of the least-squares planes of these planar regions and the deviations of individual atoms from these planes are listed in the Table IV. The phenyl ring of the 4-hydroxy-3-methoxyphenyl group was tentatively designated as plane A, and that of 4-allyl-2,6-dimethoxyphenoxy group was designated as plane B. The plane B seems to be more distorted ($\Sigma\Delta^2 = 0.02137$ Å^2) than the plane A ($\Sigma\Delta^2 = 0.00015$ Å^2) owing to the relatively heavier substitutions. The dihedral angle between these planes is 117.6°. The two rings are connected by the propanol chain. The conformation around C(18)-C(19) is a most stable *trans*-form with respect to the bulky

Table III. Fractional hydrogen atomic coordinates and thermal parameters ($\times 10^3$) with their e.s.d.'s in parentheses. The isotropic temperature factors are in the form of

$$exp(-8\pi^2 U \sin^2\theta/\lambda^2)$$

Atom	Bonded to	*x/a*	*y/b*	*z/c*	*U*
H(3)	C(3)	534(1)	−29(2)	793(3)	58(6)
H(5)	C(5)	386(1)	−203(2)	825(3)	65(7)
H(7-1)	C(7)	565(1)	182(2)	776(4)	69(7)
H(7-2)	C(7)	566(1)	112(2)	589(3)	62(7)
H(7-3)	C(7)	565(1)	263(3)	620(3)	77(8)
H(8)	C(8)	520(2)	−284(4)	655(5)	133(13)
H(9-1)	C(9)	469(1)	−291(3)	975(5)	119(12)
H(9-2)	C(9)	528(1)	−218(3)	965(5)	102(10)
H(10-1)	C(10)	502(1)	−512(4)	664(5)	115(11)
H(10-2)	C(10)	470(2)	−473(4)	852(5)	141(15)
H(11-1)	C(11)	253(2)	−73(3)	700(4)	115(11)
H(11-2)	C(11)	309(2)	−128(4)	845(6)	169(18)
H(11-3)	C(11)	303(1)	−181(3)	641(4)	92(10)
H(15)	C(15)	389(1)	577(2)	1187(3)	56(6)
H(16)	C(16)	400(1)	392(2)	1010(3)	55(6)
H(17)	C(17)	253(1)	455(2)	759(3)	61(7)
H(18)	C(18)	415(1)	316(2)	721(3)	50(6)
H(19)	C(19)	348(1)	215(2)	852(3)	48(6)
H(20-1)	C(20)	336(1)	388(3)	457(4)	85(9)
H(20-2)	C(20)	396(2)	417(3)	434(4)	90(9)
H(20-3)	C(20)	367(2)	478(3)	570(4)	108(12)
H(21-1)	C(21)	203(2)	628(4)	693(5)	126(13)
H(21-2)	C(21)	163(1)	681(3)	814(4)	87(9)
H(21-3)	C(21)	172(1)	536(3)	840(4)	92(11)
H(O4)	O(4)	279(2)	743(4)	1168(5)	122(14)
H(O5)	O(5)	292(1)	172(3)	640(4)	80(9)

phenyls, and this conformation is settled by an intramolecular O(5)-H···O(3) hydrogen bond (2.884 Å). The Newman projections around some selected bonds are shown in Fig. 4. The methoxy groups are nearly coplanar to the phenyl rings as pointed out earlier in the case of other compounds[6,12-16].

In the structure of licarin-B[6], an α-allyl type phenylpropanoid, the double bond of the α-allyl group was nearly coplanar to the phenyl ring (dihedral angle 2.4°) because of the π-conjugation. However in the title compound, a β-allyl type one, the double bond is separated by one sp^3-carbon from the phenyl ring. The π-electrons of the double bond cannot conjugate with those of the ring as in the case of licarin-B. The β-allyl moiety was rotated, and the least-squares plane of the double bond has a perpendicular conformation with respect to the phenyl ring (dihedral angle 75.4°, also see Fig. 4).

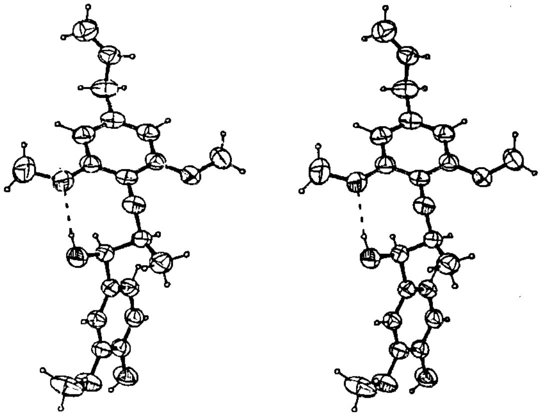

Fig. 3. The stereoscopic view of the molecule. The thermal ellipsoids are drawn at 50% probability level. The broken line indicates the intramolecular hydrogen bond.

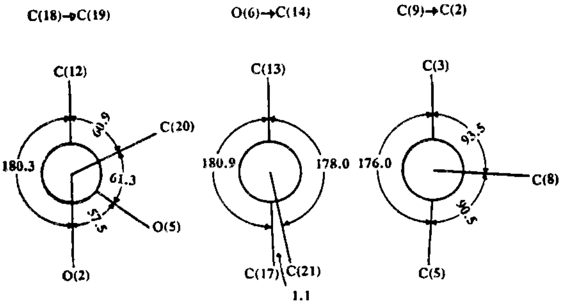

Fig. 4. Newman projections (°) around some selected bonds.

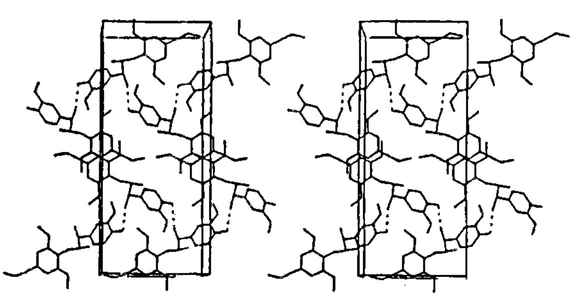

Fig. 5. The stereoscopic packing diagram of the compound. The broken lines indicate the intermolecular hydrogen bonds.

The stereoscopic molecular packing is presented in Fig. 5. The molecules in the crystal are arranged

Table IV. The equations of the least-squares planes of the planar regions of the compound, and the deviations of individual atoms from these planes(Å).

Equations: Plane A (phenyl ring of 4-hydroxy-3-methoxyphenyl group)

$0.4890X+0.5553Y-0.6727Z=1.4091$

Plane B (phenyl ring of 4-allyl-2,6-dimethoxyphenoxy group)

$0.2036X-0.4180Y-0.8854Z=-2.9473$

Deviations from:

Atom	Plane A	Atom	Plane B
C(12)	0.006*	C(1)	0.025*
C(13)	0.004*	C(2)	0.046*
C(14)	−0.000*	C(3)	−0.116*
C(15)	−0.007*	C(4)	0.069*
C(16)	−0.002*	C(5)	−0.002*
C(17)	−0.007*	C(6)	−0.016*
C(18)	−1.281	C(7)	0.286
C(19)	0.035	C(8)	1.558
C(20)	−2.482	C(9)	0.144
C(21)	0.063	C(10)	2.028
O(4)	0.007	C(11)	−0.187
O(5)	0.321	O(1)	0.094
O(6)	0.022	O(2)	0.124
		O(3)	−0.051

*Atoms used for the calculation of the equation

along with the 2-fold screw axis and stabilized by intermolecular hydrogen bonds between hydroxyl O(4)-H and O(5) of a neighboring molecule at (0.5-*x*, *y*-0.5, 2-*z*). The distance of this hydrogen bond is 2.817 Å. The other interatomic contacts appear to be the normal *van der Waals'* interactions.

The compound is a dimeric phenylpropanoid. It seems that the allyl moiety of one phenylpropanoid was coupled to the phenoxy group of the other phenylpropanoid. Though the coupling is thought to occur *via* free radical reaction[17,18], the aromaticity of the phenyl rings was conserved after dimerization. The compound belongs to the neolignan analogues[18].

ACKNOWLEDGEMENT

The authors thank Professor K. Tomita, Faculty of Pharmaceutical Sciences, Osaka University, *Japan* for intensity data measurements.

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