

The Crystal Structure of Licarin-B (C₂₀H₂₀O₄), A Component of the Seeds of *Myristica fragrans*

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Abstract □ The crystal structure of licarin-B, a component of Myristicae Semen was determined by single crystal X-ray diffraction analysis. Crystal of the compound, which was recrystallized from the mixture of hexane and ether, is monoclinic with $a=12.740(1)$, $b=7.219(1)$, $c=9.284(1)$ Å, $\beta=94.75(1)^\circ$, $D_x=1.26$, $D_m=1.27$ g/cm³, space group $P2_1$, and $Z=2$. The structure was solved by direct method and refined by least-squares procedure to the final R value of 0.040 for 1532 independent reflections $\{F \geq 3\sigma(F)\}$. The compound is a dimeric phenylpropanoid, and belongs to the neolignan analogues. The molecules are arranged along with the screw axis. The intermolecular contacts appear to be the normal *van der Waals forces*.

Keywords □ Licarin-B, X-ray crystallography, three-dimensional structure, 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. The psychological effects are suspected due to the essential oils of the drug¹⁾.

Recently, in the series of investigation, it was found that the methanol extracts from Myristicae Semen significantly modified the activities of the hepatic drug-metabolizing enzymes, or more specifically, the mixed function oxidase system^{2,3)}. The extract was fractionated, and some compounds were isolated as active principles. They were identified by various spectral analysis, and reported previously^{4,5)}.

In the present study, we analysed the three dimensional structure of licarin-B (Fig. 1), one of the active principles, by single crystal X-ray diffraction technique. We were motivated to investigate the crystal structure of the title compound to provide useful informations concerning the structure-activity relationships of their enzyme inhibiting activities and so on.

EXPERIMENTAL

The isolation procedure of the compound was reported previously⁴⁾. The compound was recrystal-

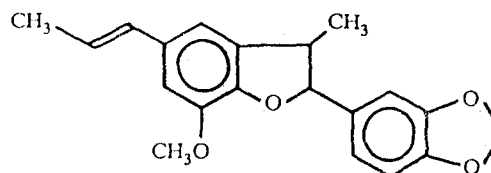


Fig. 1. Licarin-B.

lized by the slow evaporation method as colorless transparent prisms from a mixture of *n*-hexane and ether at room temperature. The density was measured by the flotation method in KI solution.

Then a 0.2×0.2×0.4 mm dimensioned crystal was mounted on an automatic four-circle diffractometer (Rigaku Denki Co., Ltd.) with graphite-monochromated CuK_α radiations (40 kV, 160 mA). The lattice constants were determined from the least-squares refinements of the angular values for 20 diffractometer-recorded reflections. Intensity data with range of $-14 \leq H \leq 14$, $0 \leq K \leq 8$, $0 \leq L \leq 10$ were collected by ω - 2θ scan technique (scan speed 4°/min). Three standard reflections, (0 2 0), (4 0 2), and (0 0 4) were monitored after every 100 reflections and showed no noticeable changes. Of all 1579 independent reflections, 47 reflections which had $F < 3\sigma(F)$ were treated as unobserved. The reflections were corrected for usual Lorentz and polarization effects, but

no absorption corrections were made. The space group was determined from systematic absences. The crystallographic data are listed in Table I.

The structure was solved by the multiresolution tangent refinement method with *MULTAN 84*⁶⁾ and *SHELX 76*⁷⁾ program. *E* values larger than 1.2 were used for phase generation, and the solution was obtained from the set having the highest combined figure of merit. The 18 non-hydrogen atoms were appeared on the first *E* map, and the subsequent successive Fourier syntheses revealed all the remaining non-hydrogen atoms. The initial *R* value was 0.232.

The structure was refined by full-matrix least-squares procedure with isotropic temperature factors to the *R* value of 0.132. Further refinements with anisotropic temperature factors reduced *R* value to 0.078. The difference Fourier syntheses calculated at this stage revealed all the hydrogen atoms of the compound molecule. Refinements by block-diagonal least-squares procedure including hydrogen

atoms for 1532 reflections ($\{F \geq 3\sigma(F)\}$) produced the final *R* value of 0.040 and *wR* of 0.063 (where $wR = [\sum w(|F_o| - |F_c|)^2 / \sum wF_o^2]^{1/2}$). 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 1.000 and 0.137. In the final cycle the average and maximum shift/e.s.d. for the parameters are 0.066 and 0.352 for non-hydrogen atoms, and 0.144 and

Table I. Crystal data

$C_{20}H_{20}O_4$	M.W. 324
2-(3,4-methylenedioxyphenyl)-2,3-dihydro-7-methoxy-3-methyl-5-(1(<i>E</i>)-propenyl)benzofuran	
Colorless transparent prism	Monoclinic
$a = 12.740(1) \text{ \AA}$	$b = 7.219(1) \text{ \AA}$
$c = 9.284(1) \text{ \AA}$	$\beta = 94.75(1)^\circ$
Vol. of the unit cell: $851.6(1) \text{ \AA}^3$	
$D_x = 1.26 \text{ g/cm}^3$	
$D_m = 1.27 \text{ g/cm}^3$ by flotation in KI soln.	
Space group: $P2_1$	$Z = 2$
$F(000) = 344$	$\mu(\text{CuK}\alpha) = 6.28 \text{ cm}^{-1}$

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

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

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	8998(2)	2961(4)	1701(2)	37(1)	52(1)	47(1)	-4(1)	3(1)	2(1)
C(2)	8666(2)	2062(4)	3102(3)	39(1)	49(1)	56(1)	4(1)	9(1)	3(1)
C(3)	7497(2)	2446(3)	2957(2)	36(1)	43(1)	50(1)	1(1)	6(1)	1(1)
C(4)	6649(2)	1741(4)	3654(2)	43(1)	43(1)	54(1)	5(1)	12(1)	0(1)
C(5)	5650(2)	2516(3)	3372(2)	41(1)	42(1)	47(1)	0(1)	6(1)	-2(1)
C(6)	5530(2)	4063(4)	2445(2)	38(1)	57(1)	53(1)	7(1)	8(1)	-1(1)
C(7)	6365(2)	4779(4)	1748(2)	41(1)	60(1)	51(1)	19(1)	7(1)	-1(1)
C(8)	7332(2)	3901(4)	1996(2)	32(1)	55(1)	44(1)	5(1)	2(1)	0(1)
C(9)	10089(1)	3749(3)	1707(2)	33(1)	49(1)	47(1)	1(1)	6(1)	5(1)
C(10)	10333(2)	5416(3)	2423(2)	39(1)	55(1)	53(1)	-9(1)	9(1)	7(1)
C(11)	11330(2)	6088(4)	2302(2)	40(1)	49(1)	56(1)	-5(1)	-1(1)	1(1)
C(12)	12060(1)	5172(4)	1554(2)	33(1)	61(1)	53(1)	9(1)	4(1)	2(1)
C(13)	11857(2)	3533(4)	882(3)	39(1)	66(1)	64(1)	-10(1)	13(1)	11(1)
C(14)	10834(2)	2827(4)	953(2)	46(1)	52(1)	57(1)	-10(1)	13(1)	3(1)
C(15)	12754(2)	7885(5)	2287(4)	50(1)	71(2)	94(2)	-12(2)	11(1)	-16(1)
C(16)	4739(2)	1759(4)	4076(3)	48(1)	49(1)	58(1)	8(1)	14(1)	-2(1)
C(17)	3773(2)	2368(4)	3972(3)	41(1)	51(1)	65(1)	12(1)	10(1)	0(1)
C(18)	2853(2)	1597(4)	4676(3)	51(1)	55(2)	83(2)	5(1)	22(1)	-5(1)
C(19)	9001(2)	41(5)	3276(5)	45(1)	59(2)	106(2)	13(2)	14(1)	12(1)
C(20)	5530(3)	7592(6)	1060(5)	59(2)	81(2)	114(3)	53(2)	15(2)	13(2)
O(1)	8231(1)	4446(3)	1376(2)	34(1)	68(1)	59(1)	17(1)	10(1)	2(1)
O(2)	11755(1)	7692(3)	2907(2)	51(1)	69(1)	110(1)	-30(1)	16(1)	-17(1)
O(3)	12983(1)	6184(3)	1613(2)	34(1)	76(1)	96(1)	-2(1)	11(1)	-6(1)
O(4)	6328(1)	6280(4)	868(2)	44(1)	98(2)	92(1)	54(1)	18(1)	13(1)

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(1)	C(1)	892(3)	218(6)	94(4)	70(9)
H(2)	C(2)	893(2)	279(4)	384(3)	36(6)
H(4)	C(4)	673(2)	78(3)	430(2)	20(4)
H(6)	C(6)	479(3)	475(5)	232(4)	68(9)
H(10)	C(10)	980(2)	620(4)	277(2)	40(5)
H(13)	C(13)	1231(2)	293(5)	27(3)	81(9)
H(14)	C(14)	1063(2)	178(3)	44(2)	33(5)
H(15-1)	C(15)	1324(3)	808(5)	299(3)	77(9)
H(15-2)	C(15)	1250(4)	888(13)	144(8)	186(16)
H(16)	C(16)	490(3)	70(6)	471(4)	71(10)
H(17)	C(17)	365(2)	332(5)	363(3)	45(7)
H(18-1)	C(18)	297(4)	30(10)	505(6)	111(18)
H(18-2)	C(18)	278(5)	193(10)	612(7)	139(18)
H(18-3)	C(18)	223(4)	205(10)	457(6)	124(17)
H(19-1)	C(19)	868(4)	-50(8)	249(6)	105(16)
H(19-2)	C(19)	963(3)	-29(4)	314(3)	53(7)
H(19-3)	C(19)	876(3)	-62(6)	422(4)	70(9)
H(20-1)	C(20)	567(4)	887(8)	34(5)	103(13)
H(20-2)	C(20)	477(5)	704(9)	28(6)	135(17)
H(20-3)	C(20)	523(5)	775(9)	199(6)	121(17)

0.656 for hydrogen atoms. The final difference Fourier calculation showed maximum electron density of $0.16 e/\text{\AA}^3$.

All the calculations were carried out on a VAX-11/780 computer system at Seoul National University. The atomic scattering factors were taken from "International Tables for X-ray Crystallography"⁸.

RESULTS AND DISCUSSION

The final atomic parameters are listed in Table II and Table 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 shown in Fig. 2. All the molecular dimensions are in the chemically reasonable range⁹. However the differences of bond lengths in the pentagon moiety caused the interatomic angles around C(2) to be deviated from the ideal value of 109.4° (sp^3 -carbon), suggesting some strains in the moiety.

The equations of the least-squares planes of the planar regions of the molecule and the deviations of individual atoms from these planes are collected in Table IV. Fig. 3 shows torsion angles around

three single bonds which can be rotated with conformational changes. The molecule has a dihydrobenzofuran group and a methylenedioxyphenyl group. The phenyl ring (plane B) of the methylenedioxyphenyl seems to be more planar ($\Sigma\Delta^2=0.00039 \text{\AA}^2$) than that (plane A) of the dihydrobenzofuran ($\Sigma\Delta^2=0.00185 \text{\AA}^2$). Also, the deviations from the planes of the remaining atoms are larger in the latter group. When an alkoxy group is substituted to a phenyl ring (as the oxygens of the title compound) there is some tendency of the effective overlap of unbonded electron lobes of oxygen with the π cloud of the ring as reported previously¹⁰. The distance from the oxygen to the phenyl group is shorter than that to the other side alkyl, and the two bonds of the oxygen tend to be coplanar to the ring plane¹¹⁻¹⁴. The sp^3 -carbon atom lacks such unbonded lobe, and there is no tendency of overlapping. So the geometry of dihydrobenzofuran is more distorted than that of methylenedioxyphenyl. The two group has the dihedral angle of 69.1° . The conjugated π electron system of the ring extends to the double bond of the propenyl group (plane C), and this plane is nearly coplanar to the ring as expected (dihedral angle, 2.42°).

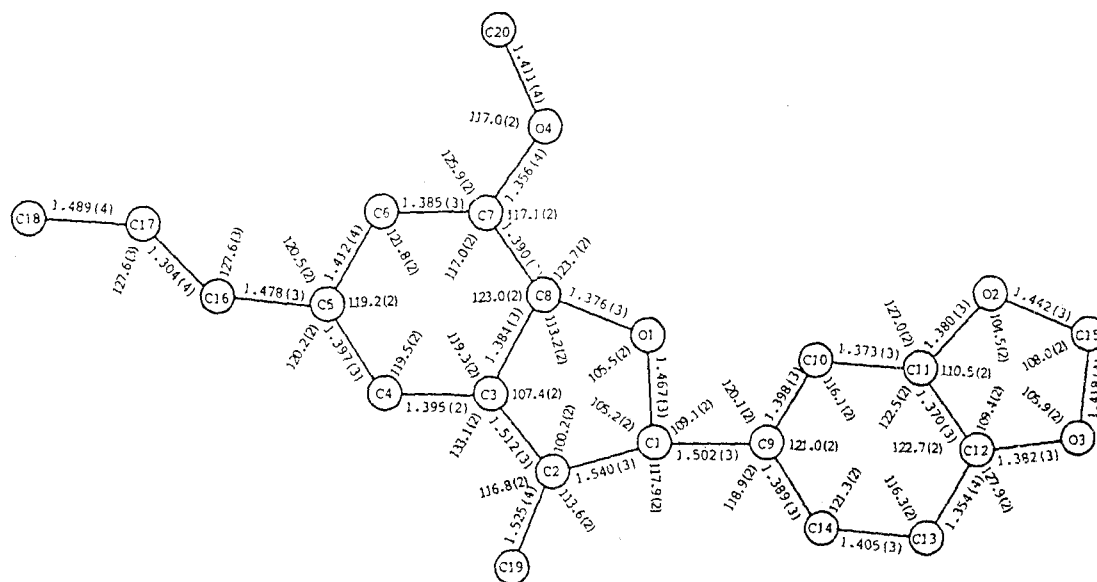


Fig. 2. Bond lengths (Å) and angles (°) of licarin-B with their e.s.d.'s in parentheses.

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).

*: Atoms used for the calculation of the equation

Equations:							
Plane A (phenyl group of the dihydrobenzofuran moiety)							
$0.1522X + 0.6297Y + 0.7618Z = 4.6082$							
Plane B (phenyl group of the methylenedioxyphenyl moiety)							
$0.2492X - 0.4977Y + 0.8308Z = 3.1467$							
Plane C (propenyl group)							
$0.1522X + 0.5966Y + 0.7880Z = 4.6072$							
Deviations from:							
Atom	Plane A	Plane B	Plane C	Atom	Plane A	Plane B	Plane C
C(1)	0.334	0.074	0.363	C(13)	0.090	-0.012*	0.152
C(2)	-0.166	-1.198	-0.193	C(14)	0.559	0.006*	0.603
C(3)	-0.013*	-0.580	-0.027	C(15)	-3.039	0.209	-2.907
C(4)	-0.012*	-1.088	-0.602	C(16)	0.056	-0.793	-0.002*
C(5)	0.024*	-0.281	0.002*	C(17)	0.039	-0.190	-0.002*
C(6)	-0.011*	1.011	0.026	C(18)	0.078	-0.704	0.002*
C(7)	-0.014*	1.528	0.057	C(19)	0.566	-2.161	0.487
C(8)	0.025*	0.718	0.069	C(20)	-0.652	3.321	-0.497
C(9)	-0.239	0.006*	-0.194	O(1)	0.034	1.096	0.106
C(10)	-1.541	-0.011*	-1.472	O(2)	-3.189	-0.009	-3.076
C(11)	-1.957	0.005*	-1.868	O(3)	-1.842	0.033	-1.734
C(12)	-1.162	0.007*	-1.077	O(4)	-0.077	2.741	0.051

Fig. 4 shows the stereoscopic molecular packing in the crystal. The molecules are arranged along with the screw axis. The intermolecular contacts appear to be the normal *van der Waals'* interactions.

The compound is a dimeric phenylpropanoid.

The stereoscopic *ORTEP*⁽⁵⁾ drawing of the molecule is presented in Fig. 5. 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

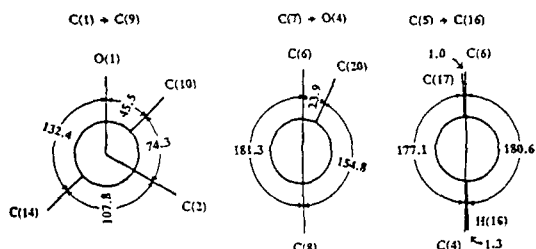


Fig. 3. Newman projections around the single bonds of licarin-B.

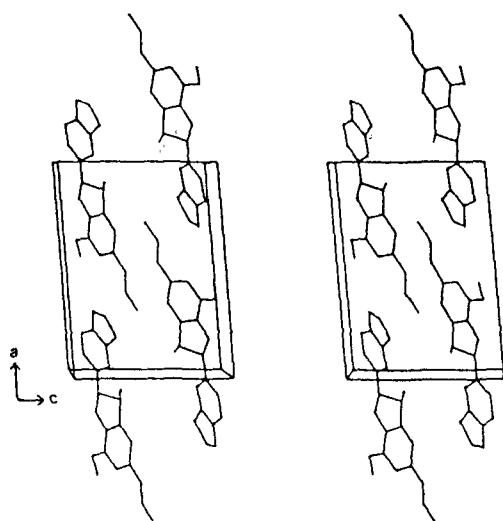


Fig. 4. The stereoscopic packing diagram for licarin-B.

reaction^{16,17}, the aromaticity of the phenyl rings was conserved after dimerization. The compound belongs to a neolignan analogue¹⁷. In this work, we didn't determined the absolute configuration of the compound. The configuration around the C(1) and C(2) atoms were temporarily assigned as (*R,R*), but the compound may have its enantiomeric configuration (*S,S*).

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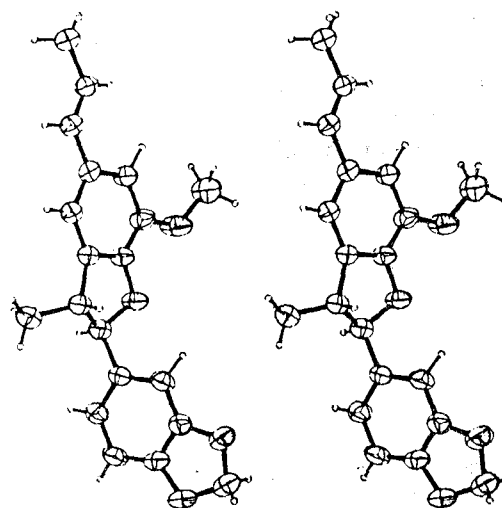


Fig. 5. The stereoscopic view of the licarin-B. The thermal ellipsoids are drawn at the 50% probability level

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