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Synthetic Studies on Lignans and Related Compounds. III.[1)]
Structure and Synthesis of Diphyllin

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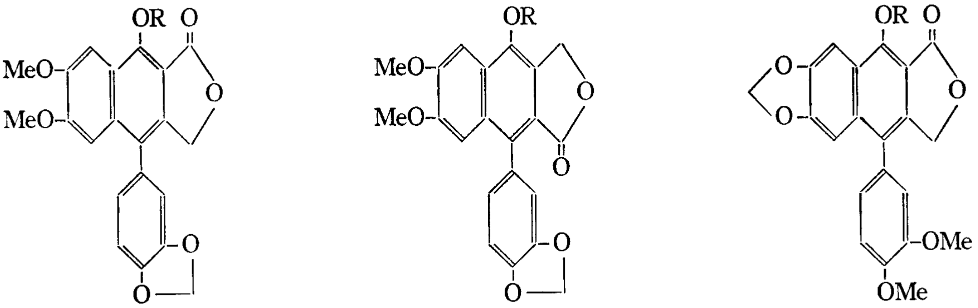
The structure of diphyllin or justicidin A was discussed from nuclear magnetic resonance (NMR) spectral evidences and concluded to be II or IX on the basis of its synthesis.

In the preceding paper,[1)] there was described the non-identity of diphyllin with synthetic 1-hydroxy-3-hydroxymethyl-6,7-dimethoxy-4-(3,4-methylenedioxyphenyl)-2-naphthoic acid γ-lactone (I), which was the structure of diphyllin proposed by Govindachari, *et al.*,[3)] and was proposed the revised structure (II). This paper describes the synthesis of compound II and its complete identity with diphyllin.



I: R=H
III: R=Me

II: R=H
IX: R=Me

IV: R=H
V: R=Me

Chart 1

On consideration of the hitherto porposed structures[3),4)] of diphyllin, in which the orientation of the lactone ring is that capable of intramolecular hydrogen bonding between α-naphthol hydroxyl and lactone carbonyl, it seems to be unusual that diphyllin shows a negative ferric chloride test. α-Naphthols bearing carbonyl group at *ortho* position show a positive ferric chloride test, in most case a greenish coloration in ethanol, and diphyllin is the sole exceptional example. This unusual property can be interpreted by assuming[1)] that the lactone carbonyl group attaches at *meta* position to α-naphthol hydroxyl as shown in structure II and that the hydrogen bonding observed in diphyllin is an intermolecular one in the solid state.[5)]

The nuclear magnetic resonance (NMR) study of α-arylnaphthalene lignan lactones was found to provide an additional evidence to this proposal. The chemical shift of the lactone methylene signal of those lactones is expected to be influenced greatly by an anisotropic shield-

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[1)] Part II: Z. Horii, K. Ohkawa, S. Kim, and T. Momose, *Chem. Pharm. Bull.* (Tokyo), **17**, 1878 (1969).
[2)] Location: *6-5 Toneyama, Toyonaka, Ōsaka.*
[3)] T.R. Govindachari, S.S. Sathe, N. Viswanathan, B.R. Pai, and M. Srinivasan, *Tetrahedron Letters*, **1967**, 3517.
[4)] T. Murakami and A. Matsushima, *Yakugaku Zasshi*, **81**, 1596 (1961).
[5)] Diphyllin shows the lactone carbonyl band at 1709 cm^{-1} (KBr) in the IR spectrum. The spectrum has not been measured in solution because of its insolubility in most solvent.

ing effect of the benzene ring of α-aryl group which is perpendicular to the plane of the naphthalene ring, because the lactone methylene protons of 4-aryl-2,3-naphthalide types are situated on the top of the benzene ring. Natural and syntheticlignans of this type has been summarized in another paper,[6] where it has been shown that the lactone methylene proton signals in the 4-aryl-2,3-naphthalide types always appear at high field from those of 1-aryl-2,3-naphthalide types by approximately 0.1—0.44 ppm or that the former appear above 4.77 τ while the latter below 4.68 τ.

As a model compound for NMR comparison, methyl ether (III) of I, which was the structure assigned by Govindachari, *et al.*[3] to justicidin A, was prepared by methylation of I with methyl iodide and anhydrous potassium carbonate in boiling acetone. Similarly, 1-hydroxy-3-hydroxymethyl-4-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-2-naphthoic acid γ-lactone[7] (IV) was methylated into its methyl ether (V), which was the structure assigned by Munakata, *et al.*[8] to justicidin A.

The values for I, III, IV and V were 4.83, 4.92, 4.77 and 4.85 τ, respectively, while that for justicidin A was 4.48 τ.[8] It is obvious that diphyllin or justicidin A,[3,8] methyl ether of the former, is one of the 1-aryl-2,3-naphthalide types.

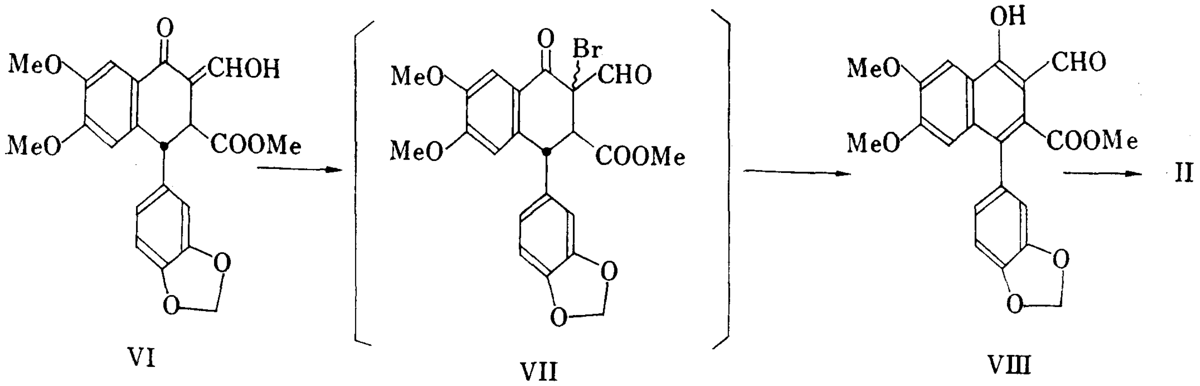

Chart 2

This conclusion was finally confirmed by the synthesis of compound II.

Methyl *trans*-3-hydroxymethylene-6,7-dimethoxy-1-(3,4-methylenedioxyphenyl)-4-oxo-1,2,3,4-tetrahydro-2-naphthoate[1] (VI) was brominated into the bromide (VII) and then dehydrobrominated by heating with β-picoline to give, in 33% yield from VI, methyl 3-formyl-4-hydroxy-6,7-dimethoxy-1-(3,4-methylenedioxyphenyl)-2-naphthoate (VIII). Sodium borohydride reduction of VIII in methanol gave, in 65% yield, II, which was found, by infrared (IR) (KBr) and thin-layer chromatography (TLC)-comparison, to be completely identical with natural diphyllin. The results of this synthesis also lead unambiguously to structure (IX) for justicidin A.

Experimental[9]

3-Hydroxymethyl-1,6,7-trimethoxy-4-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone (III)—— A mixture of 1-hydroxy-3-hydroxymethyl-6,7-dimethoxy-4-(3,4-methylenedioxyphenyl)-2-naphthoic acid γ-lactone[1] (I, 70 mg), acetone (20 ml), MeI (5 ml) and anhyd. K_2CO_3 (5 g) was refluxed for 12 hr. After removal of the solvent, the residual mass was extracted with hot $CHCl_3$ (10 ml × 3), and the $CHCl_3$ layer

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[6] Z. Horii, M. Tsujiuchi, and T. Momose, *Tetrahedron Letters*, **1969**, 1079.

[7] Z. Horii, K. Ohkawa, S. Kim, and T. Momose, *Chem. Pharm. Bull.* (Tokyo), **16**, 2404 (1968).

[8] K. Munakata, S. Marumo, K. Ohta, and Y.-L. Chen, *Tetrahedron Letters*, **1965**, 4167.

[9] All melting points are uncorrected. NMR spectra were taken on Hitachi H-6013 spectrometer with Me_4Si as the internal standard.

was evaporated to give 72 mg of a solid. Recrystallization from MeOH gave 60 mg (83%) of III as colorless needles, mp 264—267°. *Anal.* Calcd. for $C_{22}H_{18}O_7$: C, 66.99; H, 4.60. Found: C, 66.70; H, 4.36. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1740 (C=O). NMR (CDCl$_3$)τ: 6.18 (3H, singlet, OMe), 5.97 (3H, singlet, OMe), 5.65 (3H, singlet, 1-OMe), 4.92 (2H, singlet, 3-CH$_2$O-), 3.95 (3H, singlet, -OCH$_2$O-), 2.31 (1H,singlet, 8-H).

3-Hydroxymethyl-1-methoxy-4-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-2-naphthoic Acid γ-Lactone (V)——A mixture of 1-hydroxy-3-hydroxymethyl-4-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-2-naphthoic acid γ-lactone[6] (IV, 6.5 mg), tetrahydrofuran (10 ml), MeI (2 ml) and anhyd. K_2CO_3 (3 g) was refluxed for 6 hr, and then treated in the similar manner to that for III to give 5.1 mg (76%) of V as colorless crystals (from acetone), mp 220—224°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1745 (C=O). NMR (CDCl$_3$)τ: 6.11 (3H, singlet, OMe), 6.02 (3H, singlet, OMe), 5.64 (3H, singlet, OMe), 4.85 (2H, singlet, 3-CH$_2$O-), 3.86 (2H, singlet, -OCH$_2$O-), 2.20 (1H, singlet, 8-H).

Methyl 3-Formyl-4-hydroxy-6,7-dimethoxy-1-(3,4-methylenedioxyphenyl)-2-naphthoate (VIII)——To an ice-cooled solution of methyl *trans*-3-hydroxymethylene-6,7-dimethoxy-4-(3,4-methylenedioxyphenyl)-4-oxo-1,2,3,4-tetrahydro-2-naphthoate[1] (VI, 710 mg) in CHCl$_3$ (20 ml) was added a solution of Br$_2$ (280 mg) in CHCl$_3$ (20 ml) with stirring over 100 min, and the mixture was stirred at room temperature for 20 min, washed with aq. NaHCO$_3$–Na$_2$S$_2$O$_3$ solution and H$_2$O, dried over anhyd. Na$_2$SO$_4$ and evaporated to give 820 mg of a brownish glass. The bromide was dissolved in β-picoline (4 ml), and the solution was heated at 100° for 1.5 hr, poured into ice water, acidified with conc. HCl and extracted with CHCl$_3$ (20 ml × 2). The extract was washed with satd. NaHCO$_3$ and H$_2$O, dried over anhyd. Na$_2$SO$_4$ and evaporated to give 700 mg of a brownish glass, which was purified by column chromatography on silica gel in CHCl$_3$ to afford 230 mg (33%) of VIII as yellow prisms (from AcOH), mp 227—230°, FeCl$_3$ test (in EtOH): greenish brown. Unchanged bromide (220 mg), probably of *cis* 2-H/3-Br configuration, was recovered. *Anal.* Calcd. for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42. Found: C, 64.20; H, 4.27. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1705, 1634 (C=O).

4-Hydroxy-3-hydroxymethyl-6,7-dimethoxy-1-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone (Diphyllin) (II)——To an ice-cooled solution of VIII (110 mg) in tetrahydrofuran (5 ml) was added NaBH$_4$ (200 mg) and MeOH (10 ml), and the resulting clear solution was stirred under ice-cooling for 30 min and refluxed for 1 hr. After removal of the solvent, H$_2$O (10 ml) was added to the residue, and the resulting solution was acidified with conc. HCl. The precipitates were washed with H$_2$O, dried and recrystallized from AcOH to give 71 mg (65%) of II as pale yellow prisms, mp 277—281°, which held 1 mole of AcOH. *Anal.* Calcd. for $C_{21}H_{16}O_7 \cdot$AcOH: C, 62.72; H, 4.58. Found: C, 62.96; H, 4.53. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3378 (OH), 1709 (C=O).

The crystalline AcOH was removed after 12 hr's drying at 120°. mp 285—289°, a negative FeCl$_3$ test. *Anal.* Calcd. for $C_{21}H_{16}O_7$: C, 66.31; H, 4.24. Found: C, 66.12; H, 4.45. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3175 (OH), 1698 (C=O), 1613 (arom.). NMR (D$_6$-DMSO) τ: 6.34 (3H, singlet, OMe), 6.05 (3H, singlet, OMe), 4.65 (2H, singlet, 3-CH$_2$O-), 3.88 (2H, singlet, -OCH$_2$O-), 2.35 (1H, singlet, 5-H), −0.35 (1H, singlet, 4-OH).

The sample was shown to be completely identical with natural diphyllin (reported[4]: mp 291°; IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3220, 1709, 1613; a negative FeCl$_3$ test) from IR (KBr) and TLC measurements.