[Chem. Pharm. Bull. 17(9)1878—1882(1969)]

UDC 581.19 : 547.98.07 : 547.655.1.07

Synthetic Studies on Lignans and Related Compounds. II.[1] Synthesis of 1-Hydroxy-3-hydroxymethyl-6,7-dimethoxy-4-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone and Its Non-identity with Diphyllin

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(Received March 10, 1969)

1-Hydroxy-3-hydroxymethyl-6,7-dimethoxy-4-(3,4-methylenedioxyphenyl)-2-naphthoic acid γ-lactone (II) was synthesized from 3,4-dimethoxy-3′,4′-methylenedioxybenzhydrylidenesuccinic acid (III) by an unambiguous 10-step procedure shown in Chart 1, and was found not to be identical with diphyllin. A revised structure (XII) was proposed to diphyllin by assuming an intermolecular hydrogen bonding to its characteristic lactone carbonyl band of extreme low frequency, 1709 cm^{-1} (Nujol), in the IR spectrum.

In previous paper,[1] there were described the synthesis of 1-hydroxy-3-hydroxymethyl-4-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-2-naphthoic acid γ-lactone (I), which was the structure assigned to diphyllin by Murakami and Matsushima,[3] and its non-identity with diphyllin. The present authors have synthesized 1-hydroxy-3-hydroxymethyl-6,7-dimethoxy-4-(3,4-methylenedioxyphenyl)-2-naphthoic acid γ-lactone (II), a revised structure[4] of diphyllin, and have found that compound II is not identical with diphyllin either.

A mixture of isomeric 3,4-dimethoxy-3′,4′-methylenedioxybenzhydrylidenesuccinic acid[5] (III) was reduced to the corresponding benzhydrylsuccinic acid (IV) by sodium amalgam in bicarbonate buffer solution and then converted to the anhydride. Cyclization of the anhydride with stannic chloride in nitrobenzene followed by esterification with diazomethane gave two isomeric *trans*-tetralonecarboxylates (V) and (VI) in 3% and 42% yield, respectively. The *trans* configuration of V or VI was assigned from the coupling constant ($J_{1,2}$=7.5 or 6.5 cps) between C_1–H and C_2–H in the NMR spectrum. The minor isomer (V) was identical with the tetralone derived from methyl *trans*-1-(3-bromo-4,5-dimethoxyphenyl)-6,7-methylenedioxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoate[1] (VII) by hydrogenolysis.

The major isomer (VI) was condensed with methyl formate in the presence of sodium methoxide in benzene to give, in 49% yield, α-hydroxymethylene-tetralone (VIII), which was converted to an isoxazole (IX) in 81% yield by refluxing with hydroxylamine hydrochloride in acetic acid. On lithium aluminum hydride reduction of IX at −60° followed by ring cleavage with sodium ethoxide was obtained an α-cyano-tetralone (X) in 38% yield, and was converted to a γ-lactone (XI) in 53% yield by treatment with hydrogen chloride in ethanol. Dehydrogenation of XI with selenium dioxide in boiling acetic acid gave II in 58% yield, which showed a positive ferric chloride test and was shown from IR and TLC not to be identical with diphyllin. Constants of II and diphyllin together with those of I are shown in Table I.

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[1] Part I: Z. Horii, K. Ohkawa, S. Kim, and T. Momose, *Chem. Pharm. Bull.* (Tokyo), **16**, 2404 (1968).
[2] Location: *6–5 Toneyama, Toyonaka, Osaka.*
[3] T. Murakami and A. Matsushima, *Yakugaku Zasshi*, **81**, 1596 (1961).
[4] T.R. Govindachari, S.S. Sathe, N. Viswanathan, B.R. Pai, and M. Srinivasan, *Tetrahedron Letters*, **1967**, 3517.
[5] V.G. Joshi, *J. Sci. Ind. Res.* (India), **21 B**, 189 (1962) [*C.A.*, **57**, 11085^a (1962)].

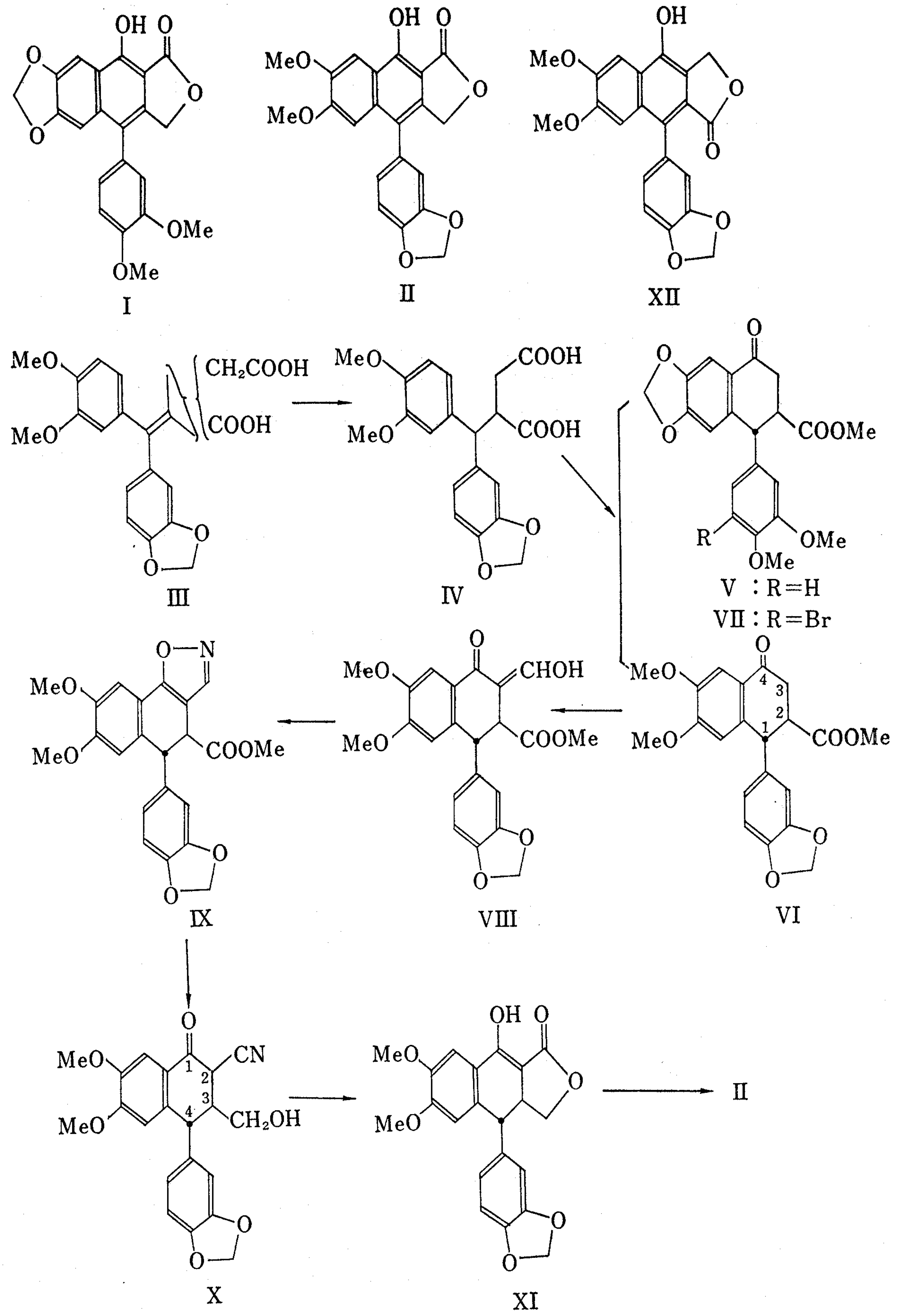

Chart 1

Previous workers[3,4] have assigned the 1-hydroxy-2,3-naphthalide system to diphyllin from its IR spectrum (Nujol) in which the lactone carbonyl band appears at 1709 cm^{-1} and shifts to 1770 cm^{-1} [6] on methylation of the phenolic hydroxyl group. The present result

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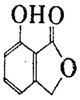
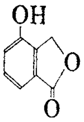
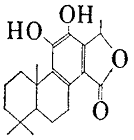
6) Similar value, 1765 cm^{-1} (KBr), was reported in justicidin A, the methyl ether of diphyllin [K. Munakata, S. Marumo, K. Ohta, and Y.-L. Chen, *Tetrahedron Letters*, **1965**, 4167].

Table I. Comparison of Diphyllin and Synthetic 1-Hydroxy-2,3-naphthalides (I) and (II)

Compound	$FeCl_3$ test	Melting point	IR absorption (KBr, cm^{-1}) Hydroxyl	IR absorption (KBr, cm^{-1}) Carbonyl
Diphyllin	negative	291°	3220	1709
I	green	275°	3368	1724
II	green	219°	3369	1710

suggests that the hydrogen bonding between the phenolic hydroxyl and the lactone carbonyl group observed in diphyllin is not an intramolecular one but probably an intermolecular one, and that the structure of diphyllin should be revised to 4-hydroxy-3-hydroxymethyl-6,7-dimethoxy-1-(3,4-methylenedioxyphenyl)-2-naphthoic acid γ-lactone (XII). The intermolecular hydrogen bonding of similar hydroxy-lactone system to that in XII has been observed in 4-hydroxyphthalide[7] (XIII) in the solid state or in picrosalvin[8] (XIV) even in solution as shown in Table II, supporting the above proposal.

Table II. Carbonyl Stretching Frequencies of Some Hydroxy Lactones (as Solids and in Solution) (cm^{-1})

Compound		Solid	Solution in CCl_4	Solution in $CHCl_3$
		1726	1749[a)]	1738[b)]
	XIII	1723	—	1760[b)]
	XIV	1712	1712[c)] 1742[c)]	

a) 0.005M solution
b) 0.02M solution
c) two bands of similar intensity in saturated solution

Experimental[9)]

3,4-Dimethoxy-3',4'-methylenedioxybenzhydrylsuccinic Acid (IV)——To a stirred solution of 3,4-dimethoxy-3',4'-methylenedioxybenzhydrylidenesuccinic acid[5)] (III, 35 g) in satd. $NaHCO_3$ (800 ml) was added 5% Na-Hg (450 g) over 6 hr, during which time CO_2 was led into the mixture. After removal of Hg, the aqueous layer was acidified with conc. HCl and extracted with AcOEt (150 ml × 2). The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 25.1 g (71%) of IV as a glass, whose dimethyl ester prepared by treatment with CH_2N_2 was identified with the authentic sample[1)] by IR ($CHCl_3$) and TLC comparison.

Methyl *trans*-1-(3,4-Dimethoxyphenyl)-6,7-methylenedioxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (V)——A suspension consisting of Raney nickel (1 g), KOH (160 mg) and MeOH (10 ml) was shaken in an atmosphere of H_2, and to this was added a solution of methyl *trans*-1-(3-bromo-4,5-dimethoxyphenyl)-6,7-methyl-

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7) L.A. Duncanson, J.F. Grove, and J. Zealley, *J. Chem. Soc.*, **1953**, 1331.
8) C.H. Brieskorn and A. Fuchs, *Chem. Ber.*, **95**, 3034 (1962).
9) All melting points are uncorrected. NMR spectra were taken on Hitachi H-6013 spectrometer with Me_4Si as the internal standard.

enedioxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoate[1] (VII, 250 mg) in MeOH (20 ml). The suspension was shaken in H_2 until theoretical amount of H_2 was consumed, and then filtered. The filtrate was poured into satd. NaCl (50 ml), and extracted with AcOEt (20 ml × 3). The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 200 mg of a solid, which was recrystallized from MeOH to give 180 mg (87%) of V as colorless micro needles, mp 145—148°. *Anal.* Calcd. for $C_{21}H_{20}O_7$: C, 65.61; H, 5.24. Found: C, 65.47; H, 5.20. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1727, 1669 (C=O). NMR ($CDCl_3$) τ 6.44 (3H, singlet), 6.17 (3H, singlet), 6.13 (3H, singlet), 5.49 (1H, doublet, $J=7.5$ cps, C_1-H), 4.02 (2H, singlet, $-OCH_2O-$).

Methyl *trans*-1-(3,4-Methylenedioxyphenyl)-6,7-dimethoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (VI)——A mixture of IV (39 g) and AcCl (100 ml) was refluxed for 2 hr. After removal of AcCl, the residue was dissolved in benzene (300 ml), and the solution was washed with satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated to give the anhydride (31.7 g, 85%) as a pale yellow glass. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 1857, 1780 (C=O).

To an ice cooled and stirred solution of $SnCl_4$ (55.5 g) in dry nitrobenzene (200 ml) was added a solution of the anhydride (31.5 g) in dry nitrobenzene (200 ml) over 30 min, and the mixture was stirred for 6 hr at room temperature and poured into 5N HCl (300 ml). The nitrobenzene layer was shaken with 5N HCl (100 ml × 3) and extracted with satd. $NaHCO_3$ (150 ml × 5). The alkaline layer was shaken with ether (50 ml × 2), acidified with conc. HCl and extracted with AcOEt (70 ml × 3). The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 29 g of the acid, which was esterified with CH_2N_2 in ether to the ester. Column chromatography of the ester on alumina in benzene gave 17 g of crystals. Recrystallization from MeOH gave 13.6 g (42%) of VI, colorless crystals, mp 149—150°, as the first crop and 850 mg (3%) of V as the second, the latter of which was identified with the authentic sample obtained above by IR (KBr) and TLC comparison. *Anal.* Calcd. for $C_{21}H_{20}O_7$: C, 65.61; H, 5.24. Found: C, 65.85; H, 5.20. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1725, 1659 (C=O). NMR ($CDCl_3$) τ 6.43 (3H, singlet), 6.23 (3H, singlet), 6.02 (3H, singlet), 5.44 (1H, doublet, $J=6.5$ cps, C_1–H), 4.08 (2H, singlet, $-OCH_2O-$).

Methyl *trans*-3-Hydroxymethylene-6,7-dimethoxy-1-(3,4-methylenedioxyphenyl)-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (VIII)——To a suspension of NaH (58% in oil, 3.4 g) in dry benzene (50 ml) was added anhyd. MeOH (1.5 ml), and the suspension was stirred at room temperature for 3 hr under N_2. To this was added methyl formate (5.81 g) and subsequently a solution of V (6 g) in dry benzene (50 ml) over 1 hr, and the mixture was stirred at room temperature for 6 hr under N_2 and allowed to stand overnight. The mixture was poured into ice water (200 ml) and shaken thoroughly. The benzene layer was shaken with 1% NaOH (50 ml × 2), and the combined alkaline layer was shaken with ether (30 ml × 2), poured into 1% H_2SO_4 (300 ml) and extracted with AcOEt (30 ml × 3). The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 6.5 g of a brownish oil. Column chromatography on silica gel in $CHCl_3$ gave 3.6 g (49%) of VIII as colorless prisms (from MeOH), mp 190—193°. *Anal.* Calcd. for $C_{22}H_{20}O_8$: C, 64.07; H, 4.89. Found: C, 63.75; H, 4.81. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1730, 1631 (C=O).

***trans*-3,4-Dihydro-6,7-dimethoxy-3-methoxycarbonyl-4-(3,4-methylenedioxyphenyl)naphth[2,1-*d*]isoxazole (IX)**——A mixture of VIII (3.6 g), $H_2NOH \cdot HCl$ (1.82 g) and AcOH (40 ml) was refluxed for 30 min and poured into ice water (150 ml). The deposited solid was washed with H_2O, dried and recrystallized from MeOH to give 2.9 g (81%) of IX, as colorless needles, mp 168—170°. *Anal.* Calcd. for $C_{22}H_{19}O_7N$: C, 64.54; H, 4.68. Found: C, 64.25; H, 4.58. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1710.

***trans*$_{3,4}$-2-Cyano-3-hydroxymethyl-6,7-dimethoxy-4-(3,4-methylenedioxyphenyl)-3,4-dihydro-1(2*H*)-naphthalenone (X)**——A suspension of $LiAlH_4$ (3.4 g) in dry ether (50 ml) was cooled to −60°, and to this was added a solution of IX (2.9 g) in dry tetrahydrofuran (200 ml) over 1.5 hr with stirring. The mixture was stirred at −60° for 6 hr, and to this was added AcOEt (50 ml) and subsequently dil. HCl (100 ml). The organic layer was separated, and the aqueous layer was extracted with AcOEt (20 ml × 2). The combined organic layer was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 2.18 g of an oily material. The reduction product was dissolved in anhyd. EtOH (30 ml), and the solution was added to an ice cooled solution of Na (0.5 g) in anhyd. EtOH (30 ml) and stirred at room temperature for 2 hr. The mixture was poured into ice water (400 ml) and shaken with AcOEt (100 ml). The organic layer was shaken with 5% NaOH (30 ml × 3), and the aqueous and alkaline layers were combined. The combined alkaline layer was shaken with ether (50 ml × 2), acidified with dil. HCl and extracted with AcOEt (50 ml × 3). The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 1.35 g of a solid, which was triturated with $CHCl_3$ to afford 1.0 g of crystals. Recrystallization from AcOH gave 0.9 g (45%) of X as pale yellow plates, mp 212—214°. *Anal.* Calcd. for $C_{21}H_{19}O_6N$: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.07; H, 4.88; N, 3.58. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3436 (OH), 2242 (C≡N), 1675 (C=O).

***trans*-3-Hydroxymethyl-6,7-dimethoxy-4-(3,4-methylenedioxyphenyl)-1-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid γ-Lactone (XI)**——An ice cooled solution of X (400 mg) in anhyd. EtOH (50 ml)was saturated with dry HCl, allowed to stand overnight at room temperature, poured into satd. NaCl (200 ml) and extracted with $CHCl_3$ (30 ml × 3). The extract was washed with satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 350 mg of an oily material, which was purified by column chromatography on silica gel in $CHCl_3$ to give 130 mg (32%) of XI as colorless prisms (from AcOEt), mp 225—226°. *Anal.* Calcd. for $C_{21}H_{18}O_7$: C, 65.96; H, 4.75. Found: C, 65.73; H, 4.64. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3401 (enolic OH), 1770, 1654 (C=O), 1594 (arom.).

1-Hydroxy-3-hydroxymethyl-6,7-dimethoxy-4-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone (II)——A mixture of XI (175 mg), SeO_2 (61 mg) and AcOH[10] (10 ml) was refluxed for 2.5 hr, poured into H_2O (50 ml) and extracted with AcOEt (20 ml × 3). The extract was washed with satd. $NaHCO_3$ and H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 110 mg of a glassy solid. Column chromatography on silica gel in $CHCl_3$ gave 100 mg (58%) of II as colorless crystals (from EtOH), mp 217—219°. *Anal.* Calcd. for $C_{21}H_{16}O_7$: C, 66.31; H, 4.24. Found: C, 66.27; H, 4.18. IR ν_{max}^{KBr} cm^{-1}: 3369 (OH), 1710 (C=O), 1631, 1617 (arom.). $FeCl_3$ test: green (EtOH).

Compound II was shown not to be identical with diphyllin (reported,[3] mp 291°; IR ν_{max}^{Nujol} cm^{-1}: 3220, 1709, 1613; a negative $FeCl_3$ test) from IR (KBr) and TLC measurements.

Acknowledgement The authors are grateful to Professor T. Murakami for providing the sample and IR spectrum of diphyllin.

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[10] Distilled over SeO_2.