3150 (-NH-), 1660 (aromatic aldehyde), 1620, 1600, 1575 (aromatic residue), and 850, 824, 773, 745, and 725 cm^{-1} (substituted benzene derivatives).

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.35; H, 4.70; N, 6.00.

Registry No.—I, 723-97-7; V, 15562-11-5; VI, 14961-29-6; VII, 14960-81-7; VIII, 14961-28-5; IX, 4532-33-6; X, 3909-78-2.

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Intramolecular Diels–Alder Reactions. V. Synthesis of Dehydro-β-peltatin Methyl Ether[1a]

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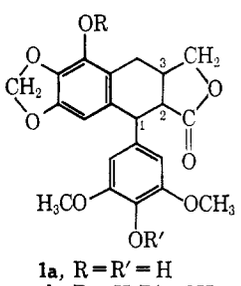
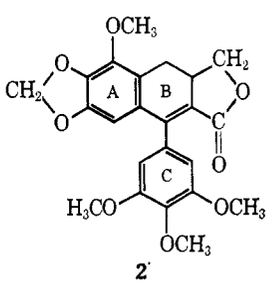
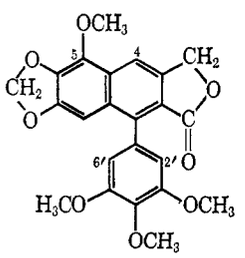
During the period 1947–1953, Hartwell, *et al.*,[2] reported the isolation from podophyllin of the tumor-necrotizing agents α- and β-peltatin and structural investigations on them. The structures proposed (**1a** and **1b**, respectively) were based on (1) oxidative degradations, (2) analogy of spectral characteristics and chemical transformations with those found in the podophyllotoxin system, and (3) conversion of both peltatins into the same permethyl ether (**1c**). These studies clearly established the carbon skeleton of the peltatins and the locations of the phenolic, methoxy, and methylenedioxy substituents thereon. The stereochemistries at C-1, C-2, and C-3[3] as well as the orientation of the lactone ring (*i.e.*, as shown, or alternatively with the carbonyl and methylene moieties reversed) were still open to question. The research presented here serves to establish unequivocally the orientation of the lactone ring.



1a, R = R′ = H
b, R = H, R′ = CH_3
c, R = R′ = CH_3



2



3

The ethyl ester of *trans*-2-methoxy-3,4-methylenedioxycinnamic acid (of established isomeric structure)[4] was reduced by means of lithium aluminum hydride to *trans*-2-methoxy-3,4-methylenedioxycinnamyl alcohol. The crude, open-chain ester formed from this alcohol and 3,4,5-trimethoxyphenylpropiolyl chloride was cyclized by means of refluxing acetic anhydride to a single product, **2**. Dehydrogenation of **2** by means of Pd–C in cymene or by means of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in benzene afforded **3**, identical with the product obtained from dehydrogenation of β-peltatin-B methyl ether **1c** (derived directly from podophyllin). The identity of these products assures that cyclization of the open-chain ester did occur into ring A (where only a single position for cyclization was available) rather than into ring C and, thus, establishes the orientation of the lactone ring as that shown in formulas **1**–**3**. Cyclization into ring A is consistent with expectations for an intramolecular Diels–Alder reaction and with previous results on other *trans*-cinnamyl phenylpropiolates which reacted under similar conditions.[5,6]

It might be noted that the nmr signal for the proton on C-4 in the 1-phenylnaphthalene lignan lactone **3** falls at δ 8.17. The appearance of this singlet at such a low field is ascribed to the deshielding influence of the *peri* methoxy group at C-5. Dudek[7] has observed similar downfield shifts of signals for *peri* protons in naphthalenes which bear an OH, OCH_3, or NH_2 substituent in an α position. In an earlier paper[6] the presence or absence of a singlet at $\delta > 8.0$ was of diagnostic pertinence to the direction of cyclization in the intramolecular Diels–Alder reaction. In those examples, however, one was concerned only with the respective presence or absence of an aromatic hydrogen atom in a position *ortho* to the carbonyl group of the lactonic moiety. In no case was it possible to obtain a cyclized product bearing a methoxy or methylenedioxy group in a position *peri* to an aromatic hydrogen atom. In the present case, on the other hand, either direction of cyclization should give a product with a low-field singlet in its spectrum.

(1) (a) This investigation was supported by Research Grant No. GM 12730 from the National Institute of General Medical Sciences, U. S. Public Health Service. (b) Research Associate, 1966–1967.

(2) (a) J. L. Hartwell, *J. Amer. Chem. Soc.*, **69**, 2918 (1947); (b) J. L. Hartwell and W. E. Detty, *ibid.*, **70**, 2833 (1948); (c) *ibid.*, **72**, 246 (1950); (d) J. L. Hartwell, A. W. Schrecker, and G. Y. Greenberg, *ibid.*, **74**, 6285 (1952); (e) A. W. Schrecker and J. L. Hartwell, *ibid.*, **75**, 5924 (1953).

(3) The numbering used in this paper is consistent with *Chemical Abstracts* practice but does not follow that used by Hartwell, *et al.*,[2] and by some other workers in the lignan field.

(4) See the Experimental Section for evidence on aspects of both positional and geometric isomerism in this starting material.

(5) L. H. Klemm, D. H. Lee, K. W. Gopinath, and C. E. Klopfenstein, *J. Org. Chem.*, **31**, 2376 (1966). *Cf.* L. H. Klemm and K. W. Gopinath, *J. Heterocycl. Chem.*, **2**, 225 (1965).

(6) L. H. Klemm, K. W. Gopinath, D. H. Lee, F. W. Kelly, E. Trod, and T. M. McGuire, *Tetrahedron*, **22**, 1797 (1966).

(7) G. O. Dudek, *Spectrochim. Acta*, **19**, 691 (1963).

Experimental Section[8]

o-Vanillin was converted into 3-methoxycatechol by Dakin oxidation[9] and then to 1-methoxy-2,3-methylenedioxybenzene.[10] This ether was formylated to a mixture of isomers, which were separated chromatographically.[11] The isomer[12] of melting point 103–104° was condensed with malonic acid to give *trans*-2-methoxy-3,4-methylenedioxycinnamic acid.[13]

Ethyl *trans*-2-Methoxy-3,4-methylenedioxycinnamate.—A mixture of 6 g of the preceding 2-methoxy-3,4-methylenedioxycinnamic acid, 200 ml of absolute ethanol, and 2 ml of sulfuric acid was refluxed for 12 hr, evaporated to 130 ml, and treated with a cold solution of 5 g of sodium bicarbonate in 1.5 l. of water. The refrigerated mixture deposited a solid which was recrystallized from methanol to give 5.1 g (76%) of prisms: mp 61–62°;[14] $\nu_{max}^{CHCl_3}$ 1720 (ester C=O), 935 (OCH_2O),[15] 985 cm^{-1} (*trans* CH=CH).[16] The nmr spectrum (CCl_4) showed a triplet at δ 1.29 (J = 7 cps, 3 H, CH_3 of ethyl group), a singlet at 4.03 (3 H, CH_3O group) which overlaps the upfield signal of a quartet at 4.17 (J = 7 cps, 2 H, CH_2 of ethyl group), a singlet at 5.93 (2 H, OCH_2O group), a doublet at 6.26 (J = 16 cps, 1 H, vinylic proton α to ester group), doublets at 6.46 and 7.00 (J = 7.6 cps, 1 H each, aromatic protons), and a doublet at 7.72 (J = 16 cps, 1 H; vinylic proton β to ester group).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.47; H, 5.50.

***trans*-2-Methoxy-3,4-methylenedioxycinnamyl Alcohol.**—To a cold (−10°), stirred suspension of 1.5 g (40 mmol) of lithium aluminum hydride in 75 ml of anhydrous ether was added dropwise a solution of 5 g (20 mmol) of the preceding ester in 150 ml of ether. The reaction mixture was stirred at the same temperature for 3 hr longer and then treated first with ethyl acetate and then with water. The residue from evaporation of the water-washed, dried organic phase was chromatographed on 80 g of Woelm neutral alumina. The first fraction of effluent (eluent benzene) was discarded. Elution with 400 ml of 2% methanol in chloroform gave 2.5 g (60%) of colorless liquid; infrared bands were $\nu_{max}^{CHCl_3}$ 3570 (OH) and 935 cm^{-1} (OCH_2O). The nmr spectrum ($CDCl_3$) showed a broad singlet at δ 3.23 (probably OH group), a singlet at 3.94 (3 H, CH_3O group), a doublet at 4.23 (J = 5.5 cps, CH_2 of CH_2OH group), a singlet at 5.86 (2 H, OCH_2O group), and a complex multiplet at 6.0–7.0 (4 H, aromatic plus vinylic protons).

The **3,5-dinitrobenzoate**[17] derivative of the carbinol formed bright orange needles from chloroform–ethanol, mp 160.5–162°.

Anal. Calcd for $C_{18}H_{14}N_2O_9$: C, 53.73; H, 3.51; N, 6.96. Found: C, 53.87; H, 3.59; N, 7.20.

1-(3,4,5-Trimethoxyphenyl)-3-hydroxymethyl-5-methoxy-6,7-methylenedioxy-3,4-dihydro-2-naphthoic Acid Lactone (2).—A mixture of 1.18 g (5 mmol) of 3,4,5-trimethoxyphenylpropiolic acid,[16] 2.5 ml of fresh reagent-grade thionyl chloride, and 15 ml of anhydrous benzene was refluxed for 45 min. Excess thionyl chloride was removed by repetitive distillation *in vacuo* with benzene. To the residue was added a solution of 1.04 g (5 mmol) of the preceding carbinol in 27 ml of benzene and 1.5 ml of pyridine. The mixture was refluxed for 4 hr, cooled, washed,[18] and evaporated to give 2 g of crude ***trans*-2-methoxy-3,4-methylenedioxycinnamyl 3,4,5-trimethoxyphenylpropiolate** as a viscous brown liquid; infrared bands were $\nu_{max}^{CHCl_3}$ 2240 (C≡C), 1710 (ester C=O), 935 cm^{-1} (OCH_2O). The nmr spectrum ($CDCl_3$) showed singlets at δ 3.81, 3.84 (broad), and 3.97 (CH_3O groups), a singlet at 5.88 (OCH_2O group), and a complex multiplet at 5.7–7.2 (vinylic and aromatic protons).

A solution of this crude ester in 25 ml of acetic anhydride was refluxed for 4.5 hr and evaporated *in vacuo* to leave a solid which was triturated with ether and recrystallized, first from chloroform–cyclohexane (yield 400 mg) and then repeatedly (with use of activated charcoal one time) from acetone–ethanol to give lactone **2** as cream-colored needles: mp 251–252°; $\nu_{max}^{CHCl_3}$ 1750 (α,β-unsaturated-γ-lactone), 940 cm^{-1} (OCH_2O). The nmr spectrum ($CDCl_3$) showed singlets at δ 3.83 (6 H, presumably CH_3O groups at C-3′ and C-5′), 3.91 and 4.02 (3 H each, CH_3O groups) which overlap complex absorption in the region of 2.2–4.9 (aliphatic protons), as well as at 5.96 (2 H, OCH_2O group), 6.29 (1 H, aromatic proton at C-8), and 6.51 (2 H, aromatic protons at C-2′ and C-6′).

Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.59; H, 5.19.

Dehydro-β-peltatin Methyl Ether (3). A. From 2.—A mixture of 250 mg of preceding lactone, 0.5 g of 30% palladium on carbon, and 12 ml of *p*-cymene was refluxed for 18 hr in an atmosphere of nitrogen. Crystallization from chloroform–cyclohexane of the residue obtained from filtration and evaporation of the reaction mixture gave 150 mg (60%) of flakes of **3**: mp 266–268°; $\nu_{max}^{CHCl_3}$ 1755 (lactone C=O), 945 cm^{-1} (OCH_2O); $\lambda_{max}^{100\%\ EtOH}$ 263 mμ (log ε 4.62), 320 (3.92), 355 shoulder (3.61) [lit.[2e] mp 271–272°; $\lambda_{max}^{95\%\ EtOH}$ 264 mμ (log ε 4.71), 318 (3.92), 356 (3.65)]. The nmr spectrum ($CDCl_3$) showed singlets at δ 3.83 (6 H, presumably CH_3O groups at C-3′ and C-5′), 3.97 and 4.21 (3 H each, CH_3O groups), 5.38 (broadened somewhat, 2 H, CH_2 of lactone group), 6.06 (2 H, OCH_2O), 6.56 (2 H, aromatic protons at C-2′ and C-6′), 6.88 (1 H, aromatic proton at C-8), and 8.17 (broad, 1 H, aromatic proton at C-4).

A solution of 32 mg of lactone **2** and 68 mg of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in 20 ml of benzene was refluxed for 3 hr. Elution chromatography of the cooled solution by means of Woelm neutral alumina and chloroform gave 21 mg (55%) of **3**, identical with the product obtained from dehydrogenation with palladium–charcoal.

B. From β-Peltatin-B Methyl Ether.—A solution of 0.21 g of β-peltatin-B methyl ether[19] and 0.91 g of DDQ in 50 ml of benzene was refluxed for 6 hr and processed as in the preceding paragraph. Crystallization of the chromatographic product from chloroform–cyclohexane afforded 0.15 g (72%)[20] of **3**, mp 265–267°, identical with the product from part A as based on mixture melting point, as well as infrared, ultraviolet, and nmr spectra.

Registry No.—**2**, 15619-23-5; **3**, 15656-72-1; $C_{13}H_{14}O_5$, 15619-24-6; *trans*-2-methoxy-3,4-methylenedioxycinnamyl alcohol, 15619-25-7; $C_{18}H_{14}N_2O_9$, 15619-26-8; *trans*-2-methoxy-3,4-methylenedioxycinnamyl 3,4,5-trimethoxyphenylpropiolates, 15619-27-9.

(8) Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Ultraviolet spectra were obtained by means of a Cary Model 15 spectrophotometer, infrared spectra by means of a Beckman IR-5 spectrophotometer, and nmr spectra by means of a Varian Associates A-60 instrument and using tetramethylsilane as an internal standard.

(9) A. R. Surrey, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 759.

(10) K. N. Campbell, P. F. Hopper, and B. K. Campbell, *J. Org. Chem.*, **16**, 1736 (1951).

(11) A. F. Wagner, E. Walton, A. N. Wilson, J. O. Rodin, F. W. Holly, N. G. Brink, and K. Folkers, *J. Amer. Chem. Soc.*, **81**, 4983 (1959).

(12) This isomer was identified as croweacic aldehyde by Wagner, *et al.*,[11] and by W. B. Brownell and A. W. Weston [*ibid.*, **73**, 4971 (1951)]. The structure of croweacic aldehyde was established as 2-methoxy-3,4-methylenedioxybenzaldehyde by A. R. Penfold, G. R. Ramage, and J. L. Simonsen [*J. Chem. Soc.*, 756 (1938)].

(13) Penfold, *et al.*,[12] described this product as the "β-form" of 2-methoxy-3,4-methylenedioxycinnamic acid. Their observations indicate that the "β-form" has the *trans* configuration, expected for the product from the Doebner modification of the Knoevenagel reaction on an aromatic aldehyde. See J. R. Johnson in "Organic Reactions," Vol. I, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1942, p 210; H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 225; J. J. Bloomfield and R. Fuchs, *J. Org. Chem.*, **26**, 2991 (1961). An infrared absorption band at 985 cm^{-1} and the coupling constant of J = 16 cps for the vinylic protons in our ethyl ester are also consistent with the *trans* configuration (*vide infra*). *Cf.* A. J. Speziale and C. C. Tung, *ibid.*, **28**, 1353 (1963).

(14) After drying for 48 hr *in vacuo* at room temperature. A sample dried for 2 hr in air melted at 51–52°.

(15) An absorption band at 935 cm^{-1} is also found for methylenedioxybenzene in chloroform.

(16) L. H. Klemm, K. W. Gopinath, G. C. Karaboyas, G. L. Capp, and D. H. Lee, *Tetrahedron*, **20**, 871 (1964).

(17) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, New York, N. Y., 1956, p 212.

(18) In the previous manner.[16]

(19) Derived by methylation[2d] of β-peltatin, isolated in our laboratory from Podophyllin, N. F. (Merck) by Mrs. B. Haxby according to the chromatographic procedure of Hartwell and Detty.[2c]

(20) Schrecker and Hartwell[2e] reported a yield of 17% for this dehydrogenation process when palladium–charcoal plus benzoquinone in diphenyl ether was used.