syringe 6.9 g (0.05 mole) of I, 38 ml of 1.8 *M* *t*-butyllithium (0.07 mole), and 40 ml of pentane. A yellow precipitate was observed within 0.5 hr. Subsequent to stirring for 3 days at room temperature, 7.8 g (0.08 mole) of chlorotrimethylsilane was slowly added to the chilled metalation mixture resulting in the formation of a white precipitate. After warming to room temperature and an additional 3 hr of stirring, the reaction mixture was slowly added to a dispersion of 1.75 g (0.055 g-atom) of sulfur in 25 ml of benzene (exothermic reaction) and stirred overnight.

The reacion mixture was then washed thoroughly with aqueous ammonium chloride and concentrated. A ^{31}P nmr spectrum of the concentrate revealed the presence of at least four compounds, as evidenced by distinct signals at −32.4, −36.8, −40.4, and −44.7 ppm, corresponding to *ca.* 26, 49, 19, and 6% of the total phosphorus, respectively. Also, a minimum of four compounds was shown to be present by glpc on a 5-ft 10% Apiezon Fluropak column at 240°. These compounds had the following retention times: 3 min, dimethylphenylphosphine sulfide; 6 min, VI; 9 min, VII; and 13 min, VIII.

The complex reaction mixture was partially resolved by alumina column chromatography. Elution with several solvents afforded the following fractions: (1) hexane–sulfur; (2) 3:2 hexane–carbon tetrachloride, 2.87 g of a mixture of VII and VIII in the ratio of *ca.* 3:1 [The VIII was separated by glpc. A ^1H nmr spectrum consisted of signals centered at τ 2.34 (aromatic), 8.13 and 8.28 (two ABX quartets, J_{AP} = 16.7 cps, J_{BP} = 12.8 cps, and J_{AB} = 13.9 cps, methylene), 8.7 (doublet, J = 16.1 cps, methine), 9.52 (singlet, methyl), 10.02 (singlet, methyl), and 10.08 (singlet, methyl) in the area ratios of *ca.* 5:2:1:9:9:9, respectively. Consistent with the structure assignment, the mass spectrum of VIII exhibited a strong parent peak of 386. In addition, a mass peak of 458 was observed, which suggests the presence of a small amount of the tetrasilyl derivative of I. The VII was shown to be identical with an authentic sample.]; (3) carbon tetrachloride, 0.7 g of VI; (4) benzene, 3.44 g of VI, mp 55–56°.

Anal. Calcd for $C_{11}H_{19}PSSi$: mol wt, 242; C, 54.6; H, 7.85. Found: mol wt (mass spectral), 242; C, 55.1; H, 8.3.

The compound exhibited a ^{31}P nmr signal at −36.6 ppm and ^1H signals centered at τ 2.35 (aromatic), 8.01 (doublet, J = 12.6 cps, methyl), 8.3 (doublet, J = 16.4 cps, methylene), and 9.91 (singlet, methyl) in the correct ratios.

Continued elution with benzene produced fraction 5, a mixture of VI and dimethylphenylphosphine sulfide. No attempt was made to resolve this mixture.

Preparation of Bis(trimethylsilylmethyl)phenylphosphine Sulfide (VII).—To a solution of trimethylsilylmethylmagnesium chloride, prepared[13] from 24.5 g (0.2 mole) of chloromethyltrimethylsilane and an excess (7.2 g, 0.3 g-atom) of magnesium turnings in 200 ml of tetrahydrofuran, there was added dropwise 15.7 g (0.09 mole) of phenyldichlorophosphine dissolved in 65 ml of tetrahydrofuran. Subsequent to the complete addition, the reaction mixture was refluxed for 2.5 hr, cooled, and hydrolyzed with chilled aqueous ammonium chloride. Approximately one-third of the organic layer was removed and added slowly to an excess of sulfur dispersed in benzene and stirred for 0.5 hr. The excess sulfur was removed by filtration and the filtrate was concentrated to give a solid that was dissolved in boiling hexane. On cooling, 6.5 g (65%) of VII, mp 89–91°, crystallized. A second crystallization from the same solvent narrowed the melting point to 90–91.5°.

Anal. Calcd for $C_{14}H_{27}PSSi_2$: C, 53.5; H, 8.6. Found: C, 53.9; H, 9.4.

The phosphine sulfide exhibited a ^{31}P nmr signal at −38.8 ppm and ^1H nmr signals centered at τ 2.35 (aromatic), 8.37 (doublet, J = 15.2 cps, methylene), and 9.98 (methyl).

Attempted Base-Catalyzed Hydrogen Exchange of Dimethylphenylphosphine Sulfide.—To a suspension of lithium deuteroxide and deuterium oxide in hexane, obtained from the addition of 1.5 ml (0.1 mole) of deuterium oxide to 14.4 ml (0.02 mole) of 1.4 *M* *n*-butyllithium in hexane, there was added 1.7 g (0.01 mole) of dimethylphenylphosphine sulfide. Subsequent to stirring for 1 hr, the reaction mixture was poured into chilled aqueous ammonium chloride. The organic phase was rapidly extracted with ether, dried over sodium sulfate, and concentrated to give 1.34 g of dimethylphenylphosphine sulfide, mp 40–42°. A mass spectral analysis of the phosphine sulfide revealed the sample to contain 99.4% ≥ P(S)-d_0 and 0.6% ≥ P(S)-d_1.

Acknowledgments.—The authors are grateful to Dr. T. J. Logan for many helpful discussions during the course of this study and to Dr. J. J. McLeskey for the interpretation of one of the nmr spectra.

(13) F. C. Whitmore and H. H. Sommer, *J. Am. Chem. Soc.*, **68**, 481 (1946).

Intramolecular Diels–Alder Reactions. III. Cyclizations of *trans*-Cinnamyl and Phenylpropargyl Phenylpropiolates[1a]

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Intramolecular Diels–Alder reactions on crude *trans*-cinnamyl phenylpropiolate and phenylpropargyl phenylpropiolate produced 1-phenyl-3-hydroxymethyl-3,4-dihydro-2-naphthoic acid lactone (II) and 1-phenyl-3-hydroxymethyl-2-naphthoic acid lactone (V), respectively. Structures were assigned on the basis of conversion of II to V, oxidative degradation of II, and analysis of the nmr spectra of II and its di- and trideuterated compounds.

In an earlier communication[2] we reported the syntheses of γ-apopicropodophyllin and one of its analogs by means of intramolecular Diels–Alder condensation of substituted *trans*-cinnamyl phenylpropiolates. The method represents a simple synthetic approach to lignans of the arylhydronaphthalene type. More generally, one may visualize as starting materials in such cyclizations a series of nine types of unsaturated open-chain esters of the formula $Ar(C_2)CO_2CH_2(C_2)Ar'$, where each C_2 unit may take the form of a *cis*-CH=CH, a *trans*-CH=CH, or a C≡C grouping. We have embarked on a program to synthesize all of these types,[3] including the parent (unsubstituted) esters where Ar = Ar′ = phenyl, in order to study the stereochemical requirements of the cyclization process and to elucidate the structures of such products as may result. The present paper is concerned with the syntheses and successful cyclizations of two parent esters, *viz.*, *trans*-cinnamyl phenylpropiolate (I) (Scheme I) itself, and phenylpropargyl phenylpropiolate (IV). Meanwhile, two other parent esters, *trans*-cinnamyl *trans*-cinnamate

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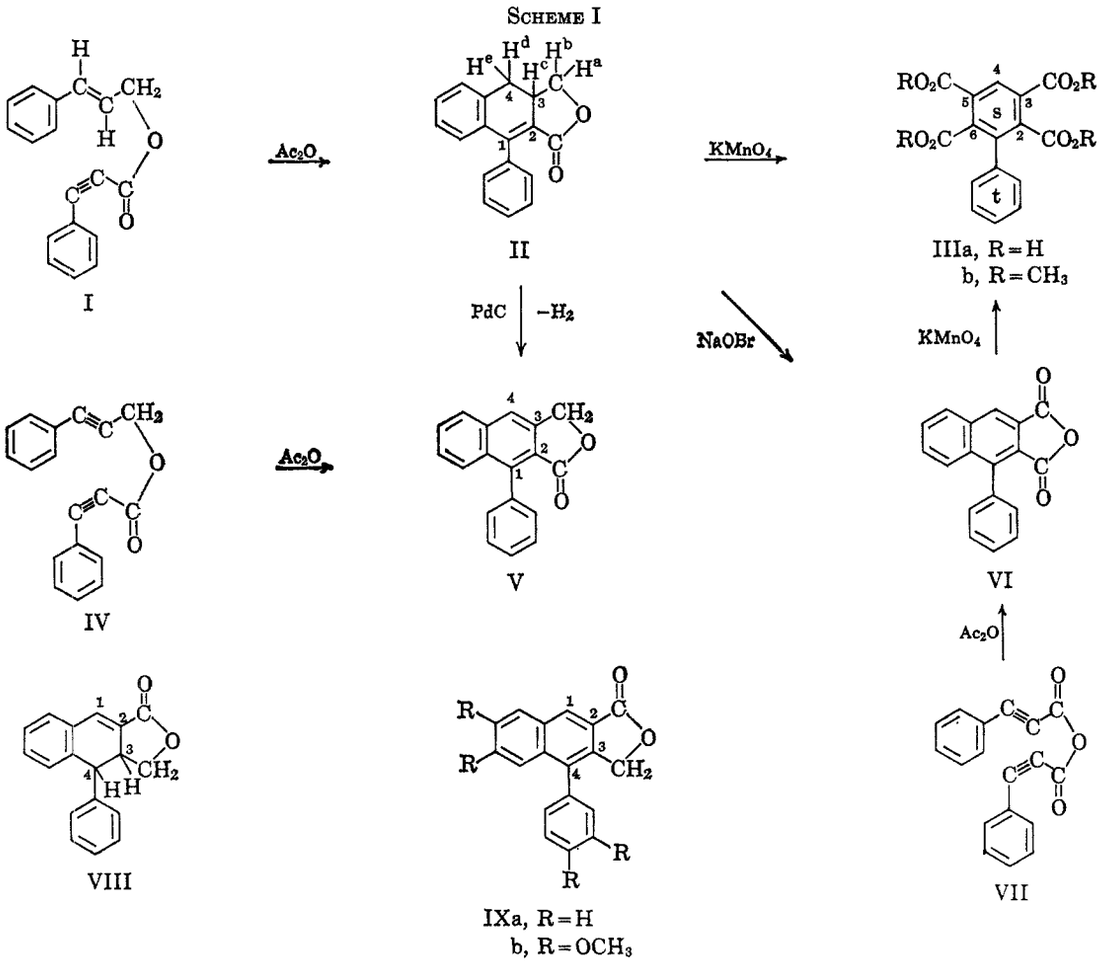
(2) Paper I: L. H. Klemm and K. W. Gopinath, *Tetrahedron Letters*, 1243 1963).

(3) Paper IV: L. H. Klemm, K. W. Gopinath, D. H. Lee, F. W. Kelly, E. Trod, and T. M. McGuire, *Tetrahedron*, in press.

SCHEME I



(as well as several of its substitution compounds) and phenylpropargyl *trans*-cinnamate have been isolated in crystalline form,[4] but they have resisted cyclization[5] under the same conditions as (and even under more strenuous conditions than) used for I and IV. On the other hand, in a recent extension of the range of Ar′ moieties used, it has been found that *trans*-3-(2- and 3-thienyl)allyl phenylpropiolates cyclize in a manner analogous to that of I.[6]

Crude I, prepared by refluxing a mixture of *trans*-cinnamyl alcohol and phenylpropiolyl chloride with limited or no excess of pyridine, was cyclized preferably in refluxing acetic anhydride (in 46% over-all yield) or by slow distillation *in vacuo*. The cyclization was followed readily by observation of the infrared spectrum which indicated the disappearances of the carbon–carbon triple bond (band at 2240 cm^{-1}) and the *trans*-vinylene group (band at 965 cm^{-1}) as well as formation of an α,β-unsaturated γ-lactone from an open-chain ester (replacement of 1710-cm^{-1} band by one at 1750 cm^{-1}). The structure of the cyclized product A was established as either II or VIII on the basis of degradative studies. Thus, treatment of A with aqueous, alkaline hypobromite produced the known 1-phenylnaphthalene-2,3-dicarboxylic anhydride (VI), derivable separately (probably *via* the intermediate anhydride VII) by heating phenylpropiolic acid with acetic anhydride. In addition, both A and VI were oxidized by aqueous, alkaline permanganate to the same acid, biphenyl-2,3,5,6-tetracarboxylic acid (IIIa), identified by complete methylation with diazomethane to the crystalline, known ester IIIb, for which the nmr spectrum served to establish the structure virtually unambiguously (*vide infra*). Dehydrogenation of A to the naphthalene derivative B (either V from II or IXa from VIII) was effected by means of palladium–charcoal in refluxing *p*-cymene, N-bromosuccinimide in carbon tetrachloride, or lead tetraacetate in glacial acetic acid. Product B was also obtained (in 39% yield from phenylpropiolic acid) as the only isolated product from cyclization of the crude ester phenylpropargyl phenylpropiolate. The ultraviolet absorption spectrum of A exhibits a shape closely similar to that of the spectrum of 3,4-dihydro-2-naphthoic acid,[7] but with maxima in the former shifted bathochromically by as much as 10 mμ from those in the latter. This spectral shift is consistent with the structural feature that A is effectively an alkyl derivative of the latter. Completely analogous spectral and structural relationships occur for the pair B and 1-phenyl-2-naphthoic acid.[8]

Structure V (rather than IXa) was preferred for B on the basis of (a) the consideration that the nmr spectrum of IXa would be expected to show a low-field singlet at $\delta > 8.0$ ppm corresponding to the aromatic hydrogen at C-1 in the naphthalene ring (*cf.* VI, singlet for

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

(5) Some of these tests have been made by Mr. Floyd W. Kelly.

(6) Paper II: L. H. Klemm and K. W. Gopinath, *J. Heterocyclic Chem.*, **2**, 225 (1965).

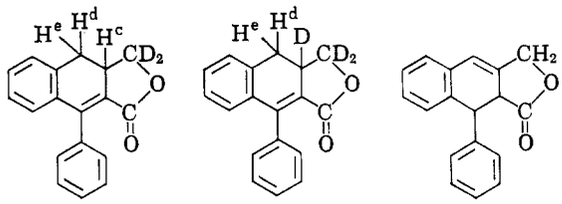
(7) A. W. Schrecker, G. Y. Greenberg, and J. L. Hartwell, *J. Am. Chem. Soc.*, **74**, 5669 (1952).

(8) "Organic Electronic Spectral Data," Vol. II, M. J. Kamlet, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 518.

one proton at δ = 8.66 ppm; IXb, at δ = 8.30 ppm)[3,9] and (b) the fact that the nmr spectrum of B showed no such low-field singlet. In addition, the transformation I → II (rather than I → VIII) has a precedent in the analogous conversion of *trans*-3,4-methylenedioxycinnamyl 3,4,5-trimethoxyphenylpropiolate to the known γ-apopicropodophyllin,[2,3] a process wherein the arylvinyl group of the cinnamyl moiety serves as a diene and the carbon–carbon triple bond of the arylpropiolyl moiety serves as a dienophile. Formation of VIII, on the other hand, would involve actions of the phenylethynyl group (in the phenylpropiolyl moiety) as a "diene" and the vinyl group (in the cinnamyl moiety) as a dienophile. Electronically, Diels–Alder cyclization of I to form VIII would be expected to be less favorable than the sterically nearly analogous cyclization of phenylpropargyl *trans*-cinnamate (to form XII),[10] a process which did not occur under identical reaction conditions. The observations that A gives (a) sluggish, partial reaction on perbenzoic acid titration of the carbon–carbon double bond[11] and (b) absorption of more than a 2 *M* quantity of hydrogen on catalytic hydrogenation (perhaps to give reduction of the benzo ring; *cf.* reduction of γ-apopicropodophyllin)[12] are consistent with structure II, but by no means exclude structure VIII.

The nmr spectrum of IIIb consists of four singlets at δ = 8.75 (one proton at C-4), 7.41 (five protons on ring t), 3.96 (six protons for carbomethoxy groups at C-3 and C-5), and 3.57 ppm (six protons for carbomethoxy groups at C-2 and C-6). The assignment of the signal at 3.57 to groups at C-2 and C-6 is based on the consideration that the methyl moieties thereon can project over the inner portion of the induced magnetic field associated with ring t (which is twisted far out of coplanarity with ring s). This magnetic environment should result in an upfield shift of the resonance signal from that for the carbomethoxy groups at C-3 and C-5 which cannot overhang ring t, but instead can buttress the groups at C-2 and C-6 and, hence, enhance overhang by the latter. The difference of 0.39 ppm between signals for the *ortho* and non-*ortho* carbomethoxy groups in IIIb compares favorably with analogous differences for carbomethoxy signals in dimethyl 1-(2-bromo-4,5-methylenedioxyphenyl)-5-bromo-7,8-methylenedioxynaphthalene-2,3-dicarboxylate[13] ($\Delta\delta$ = 0.29 ppm) and for methyl signals in 2,4,2′,4′-tetramethylbiphenyl[14] ($\Delta\delta$ = 0.34 ppm) and decamethylbiphenyl[15] ($\Delta\delta$ = 0.45 ppm).

Finally the structure of A was firmly established as II (rather than VIII) by means of inspection and of computer analysis of its complex nmr spectrum and of the spectra of di- and trideuterated samples of A.[16] The deuterated compounds were synthesized by interaction of phenylpropiolyl chloride with *trans*-α,α-dideuteriocinnamyl alcohol (to form X) and *trans*-α,α,β-trideuteriocinnamyl alcohol (to form XI), respectively.



X XI XII

The nmr spectrum of A showed absorptions in the range δ = 6.7–7.6 (nine aromatic protons) and 2.4–4.9 ppm (at least 18 lines for a total of five aliphatic protons). Spectra of the di- and trideuterated samples showed the same appearance in the aromatic region but became increasingly simple (12 or 13 lines in the dideuterated compound, one broad line in the trideuterated one) in the aliphatic region. The ratio of total integrated intensities of the aromatic/aliphatic proton absorptions was consistent with structure II in all cases, while the large number of lines in the aliphatic region of the dideuterated compound was clearly inconsistent with structure VIII. An interesting feature of the computer analysis was the assignment of negative values to the coupling constants J_{ab} and J_{de} for geminal protons.[17]

Experimental Section[18]

1-Phenyl-3-hydroxymethyl-3,4-dihydro-2-naphthoic Acid Lactone (II).—A mixture of 6 g (0.041 mole) of phenylpropiolic acid (Aldrich Chemical Co., Milwaukee, Wis.), 8 ml of pure thionyl chloride, and 10 ml of benzene was refluxed (2–3 hr) until the solid was completely dissolved. Excess thionyl chloride was removed by repeated distillation (*in vacuo*) with benzene. A solution of the crude, residual acid chloride in benzene was added dropwise to a well-stirred solution of 6 g (0.045 mole) of *trans*-cinnamyl alcohol in 3.2 ml (0.041 mole) of purified pyridine. The mixture was refluxed for 3 hr, cooled, filtered to remove precipitated pyridinium chloride, washed successively with water, dilute aqueous sodium carbonate solution, dilute hydrochloric acid, and water, dried, and evaporated. There resulted a brown liquid (10.5 g) [ν_{max}^{neat} at 2240 (strong, C≡C), 1710 (strong, α,β-unsaturated ester), and 965 cm^{-1} (strong, *trans* CH=CH in the alcohol moiety)][4] presumed to contain ***trans*-cinnamyl phenylpropiolate** (I) but contaminated with chlorine-bearing products (positive test for chloride ion after sodium fusion).

A solution of 2.8 g of this crude I in 9 ml of acetic anhydride was refluxed for 6 hr. The solution was cooled and seeded. Further refrigeration gave 1.3 g (46% over-all from phenylpropiolic acid) of yellow prisms of II, mp 185–187°, converted to white needles, mp 194.5–195.5°, on repeated recrystallization from ethanol: $\nu_{max}^{CHCl_3}$ at 1750 cm^{-1} (α,β-unsaturated γ-lactone); λ_{max}^{EtOH} 229.5 mμ (log ε 4.15), 235 (log ε 4.14), 300 (log ε 4.01).

Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38; mol wt, 262; sapon equiv, 262. Found: C, 82.19; H, 5.45; mol wt (Rast, camphor), 231; sapon equiv, 253.

Low pressure microhydrogenation with palladium–charcoal in ethanol at room temperature gave absorption of 2.5 moles of hydrogen gas/mole of II before reaction had virtually ceased. Perbenzoic acid titration in chloroform at 5–10° showed reaction of 0.24 mole of peracid/mole of II in 24 hr (0.53 in 2 weeks).

(9) M. E. Cisney, W. L. Shilling, W. M. Hearon, and D. W. Goheen, *J. Am. Chem. Soc.*, **76**, 5083 (1954).

(10) H. L. Holmes, *Org. Reactions*, **4**, 60 (1948).

(11) D. Swern, *J. Am. Chem. Soc.*, **69**, 1692 (1947); *Org. Reactions*, **7**, 378 (1953); Houben-Weyl, "Methoden der Organischen Chemie," Vol. II, E. Müller, Ed., Georg-Thieme Verlag, Stuttgart, 1953, p 309.

(12) A. W. Schrecker and J. L. Hartwell, *J. Am. Chem. Soc.*, **75**, 5916 (1953).

(13) D. Brown and R. Stevenson, *J. Org. Chem.*, **30**, 1759 (1965); *Tetrahedron Letters*, 3213 (1964).

(14) "NMR Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963, Spectrum 659.

(15) Unpublished data of D. R. Taylor of our laboratory.

(16) Copies of the pertinent spectra and an account of the computer analyses of them will be presented in a subsequent paper.

(17) See J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, **42**, 1339 (1965); P. Loève and L. Salem, *ibid.*, **43**, 3402 (1965), and references therein.

(18) Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill., and by Clark Microanalytical Laboratory, Urbana, Ill. Certain other microanalytical determinations were made by Geller Laboratories, Bardonia, N. Y. Deuterium analyses were performed by Josef Nemeth, Urbana, Ill. Ultraviolet spectra were obtained by means of a Cary Model 11 spectrophotometer; infrared spectra, by means of a Beckman IR-7 spectrophotometer.

Evaporative distillation of 1.7 g of crude I at 190° (0.2 mm) for 24 hr gave 0.7 g of crude yellow II, mp 193–194° after crystallization from ethanol.

1-Phenyl-3-hydroxymethyl-2-naphthoic Acid Lactone (V). A. From Phenylpropargyl Phenylpropiolate (IV).—A mixture of crude phenylpropiolyl chloride (prepared from 6 g of acid, *vide supra*), 6 g of phenylpropargyl alcohol,[4] 3 ml of pyridine, and 40 ml of benzene was refluxed for 4 hr and then washed successively with water, dilute aqueous sodium carbonate solution, dilute hydrochloric acid, and water. Removal of solvent from the dried benzene solution gave 9.9 g of crude brown oily product: ν_{max}^{neat} at 2230 (C≡C), 1760 (γ-lactone), and 1710 cm^{-1} (α,β-unsaturated ester). Chromatography of 1.6 g of this crude product on 45 g of neutral alumina (E. Merck, Darmstadt, Germany) using 250 ml of benzene and then benzene–chloroform as eluents gave 1 g of yellow liquid ($\nu_{max}^{CHCl_3}$ 2225 and 1725 cm^{-1}, assigned structure of **phenylpropargyl phenylpropiolate, IV**) from the first 150 ml of effluent and 0.16 g of crystals (mp 154–161°, $\nu_{max}^{CHCl_3}$ at 1770 cm^{-1}, assigned structure V) from a portion of the mixed solvent effluent.

A mixture of 5 g of the preceding, unchromatographed product and 15 ml of acetic anhydride was refluxed for 5 hr. The cooled mixture was treated with water and extracted with chloroform. The organic extract was washed with dilute aqueous sodium bicarbonate solution and then water, dried, and evaporated, yield 2.1 g (39%) of V, mp 151–158°. Recrystallization from ethanol (with charcoal) and then from ethyl acetate gave needles, mp 185–186°.

B. From II.—A mixture of 2 g of lactone II, 1 g of 30% palladium on charcoal, and 75 ml of *p*-cymene was stirred and refluxed for 30 hr. The catalyst was separated by filtration and extracted several times with portions of fresh, boiling solvent. Evaporation of the combined organic solutions and crystallization of the residue from ethanol gave 1.17 g (59%) of V, mp 184–186°.

A solution of 3 g of lactone II, 2.2 g of N-bromosuccinimide, and 80 mg of benzoyl peroxide in 410 ml of carbon tetrachloride was refluxed for 1.5 hr, cooled, and filtered (to remove precipitated succinimide). On standing, the cold filtrate deposited pale yellow crystals of V, yield 2.1 g (70%), mp 176–179°, raised to 185–187° on recrystallization from benzene–petroleum ether (60–90°).

A mixture of 4 g of lead tetraacetate, 1 g of lactone II, and 25 ml of glacial acetic acid was refluxed for 25 min, treated with water, and extracted repeatedly with chloroform. Evaporation of the dried, combined organic layers and crystallization of the residue from ethanol gave 0.4 g (40%) of V, mp 175–180°, raised to 183–184.5° on recrystallization from ethanol and then from benzene–petroleum ether: $\nu_{max}^{CHCl_3}$ at 1760 cm^{-1} (γ-lactone); λ_{max}^{EtOH} 242 mμ (log ε 4.65), 281 s (log ε 3.69), 291 (log ε 3.88), 302 (log ε 3.87), 333 s (log ε 3.53), 343 (log ε 3.70); nmr absorptions at δ = 5.48 ppm (singlet or very close doublet, 2 H methylene) and 7.3–8.3 ppm (complex, *ca.* 10 H aromatic).

Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65; CCH_3, none. Found: C, 82.78; H, 4.90; CCH_3, none.

Identities of samples of V produced from A and the three different procedures in B were established by mixture melting points as well as by infrared and ultraviolet spectra.

Oxidation of II to 1-Phenylnaphthalene-2,3-dicarboxylic Anhydride (VI).—A mixture of 0.2 g of lactone II was heated with a solution of 0.1 g of potassium hydroxide in 5 ml of methanol until solution was complete. The solvent was removed by evaporation. To a well-stirred, ice-cold, aqueous solution of the residue was added 4 ml of 1 *M* sodium hypobromite solution.[19] The mixture was kept cold for 30 min, allowed to warm to room temperature, and then heated on a steam bath for 10 min. The solution was treated with excess aqueous sodium bisulfite, acidified with hydrochloric acid, and extracted with chloroform. The residue from evaporation of the dried organic extract was refluxed with 2 ml of acetic anhydride for 2 hr. The cooled solution deposited a solid which was recrystallized from glacial acetic acid and dried *in vacuo* at 100° to give 80 mg (38%) of VI: mp 255–256°; $\nu_{max}^{CHCl_3}$ at 1835 (medium) and 1780 cm^{-1} (strong)[20]; λ_{max}^{EtOH} (>250 mμ) at 277 s mμ (log ε 4.06), 286 (log ε 4.15), 295 s (log ε 4.06), 324 (log ε 3.22), 337 (log ε 3.31); nmr (CH_2Cl_2) absorptions at δ = 8.66 ppm (singlet, 1 H at the 4 position) and 7.3–8.4 ppm (complex, nine other aromatic protons).

Compund VI was also obtained by refluxing 3 g of phenylpropiolic acid with 20 ml of acetic anhydride for 6 hr. The solid which precipitated on cooling the solution was recrystallized and dried in the aforementioned manner, yield 2 g (71%), mp 254–256°, lit.[21] 255–256°, undepressed on admixture with product from oxidation of II and identical in infrared spectrum therewith.

Oxidation of II to Biphenyl-2,3,5,6-tetracarboxylic Acid (IIIa).—As before, 1 g of lactone II was dissolved in methanolic potassium hydroxide and the solvent was removed by evaporation. A stirred solution of the residue in 35 ml of 5% aqueous sodium hydroxide was heated on a steam bath while an aqueous solution of potassium permanganate (quantity used 7.7 g) was added dropwise until a pink color persisted in the reaction mixture for 30 min. The precipitated manganese dioxide was removed by filtration and washed with hot water, The filtrate was concentrated, acidified, and extracted with ether continuously for several hours. The dried ether extract (containing IIIa) was treated with excess diazomethane and then evaporated. The resultant residue was chromatographed by use of 15 g of neutral alumina to give a main product (0.37 g) of **tetramethyl biphenyl-2,3,5,6-tetracarboxylate (IIIb)**, mp 133–134.5° after recrystallizations from benzene–petroleum ether and methanol: nmr absorptions at δ = 8.75 (singlet, 1 H at 4 position), 7.41 (singlet, five aromatic protons on the phenyl group), 3.96 (singlet, 6 H carbomethoxy groups in 3 and 5 positions), and 3.57 ppm (singlet, 6 H carbomethoxy groups in 2 and 6 positions); $\nu_{max}^{CHCl_3}$ at 1730 cm^{-1} (strong, C=O).

Similarly, IIIb was prepared by oxidation of 1 g of anhydride VI (by use of 4.8 g of potassium permanganate) and methylation of the resultant acid, mp 134–135.5°, lit.[22] 130–133°. Esters from the two oxidation procedures showed identical infrared and nmr spectra and gave no depression of melting point (133–134.5°) on admixture.

***trans*-α,α-Dideuteriocinnamyl Alcohol.**—To a cold (−7°), stirred solution of 0.5 g of lithium aluminum deuteride in 75 ml of ether was added dropwise a solution of 4.2 g of ethyl cinnamate in 25 ml of ether. The mixture was stirred for 2 hr at <0° and treated with water. The dried ether layer (including ether extracts of the precipitate) was evaporated and the residue was distilled, yield 2.9 g, bp 155–162° (70 mm). An infrared spectrum indicated that the product was contaminated with some unreacted ethyl cinnamate.

1-Phenyl-3-hydroxydideuteriomethyl-3,4-dihydro-2-naphthoic Acid Lactone (X).—By the same method as used for the synthesis of I there was obtained from 3 g of phenylpropiolic acid and the preceding distilled *trans*-α,α-dideuteriocinnamyl alcohol 4.1 g of a crude product, presumed to be ***trans*-α,α-dideuteriocinnamyl phenylpropiolate**: $\nu_{max}^{CHCl_3}$ at 2200, 1710, and 965 cm^{-1}. This crude ester was refluxed with 15 ml of acetic anhydride for 6 hr. The crystals which deposited from the cooled solution were collected and washed once with cold acetic anhydride and several times with methanol, yield 1.5 g (28%), mp 186–190°. Three recrystallizations from ethyl acetate–methanol gave needles, mp 193–194°, $\nu_{max}^{CHCl_3}$ at 1750 cm^{-1}.

Anal. Calcd for $C_{18}H_{12}D_2O_2$: D, 14.29 atom % excess. Found: D, 14.15 atom % excess.

***trans*-α,α,β-Trideuteriocinnamyl Alcohol.**—A solution of 1.5 g of *trans*-α-deuteriocinnamic acid[23] (mp 131–133°) in 10 ml of 4% ethanolic hydrogen chloride was refluxed and processed in the usual manner[4,24] to give 1.5 g of ethyl ***trans*-α-deuteriocinnamate**,[25] bp 82–85° (5 mm). To a stirred, cold (<−10°) solution of this ester in 10 ml of ether was added dropwise (over a period of 30 min) a solution of 0.31 g of lithium aluminum deuteride in 25 ml of ether. The mixture was stirred for 30 min longer and processed in the manner used for the dideuterio alcohol, yield 1.1 g. The infrared spectrum showed that very little unreacted ester was present.

1-Phenyl-3-hydroxydideuteriomethyl-3-deuterio-4-hydro-2-

(19) L. T. Sandborn and E. W. Bousquet, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, pp 526–527.

(20) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Methuen and Co., Ltd., London, 1959, pp 127–129.

(21) F. G. Baddar and L. S. El-Assal, *J. Chem. Soc.*, 1267 (1948).

(22) A. Michael and J. E. Bucher, *Am. Chem. J.*, **20**, 89 (1898).

(23) D. S. Noyce, P. A. King, F. B. Kirby, and W. L. Reed, *J. Am. Chem. Soc.*, **84**, 1632 (1962).

(24) R. D. Haworth, W. H. Perkin, and T. S. Stevens, *J. Chem. Soc.*, 1764 (1926).

(25) Direct α-deuteration of ethyl cinnamate as reported by M. F. Zinn, T. M. Harris, D. G. Hill, and C. R. Hauser [*J. Am. Chem. Soc.*, **85**, 71 (1963)] was not successful in our hands.

naphthoic Acid Lactone (XI).—In the same manner as used for the synthesis of I there was obtained from 1.2 g of phenylpropiolic acid and the preceding trideuteriocinnamyl alcohol 1.6 g of brown oil, presumed to be *trans*-α,α,β-**trideuteriocinnamyl phenylpropiolate**: $\nu_{max}^{CHCl_3}$ at 2210, 1710, and 965 cm^{-1}. Cyclization of 1.5 g of this ester gave 0.6 g (30%) of product, mp 190–192°, obtained as needles (mp 193–194°) on recrystallization from methanol: ν_{max} at 1750 cm^{-1}.

Anal. Calcd for $C_{18}H_{11}D_3O_2$: D, 21.43 atom % excess. Found: D, 20.60 atom % excess.

Nmr Spectra—All nmr spectra were determined by means of a Varian Associates A-60 instrument by use of tetramethylsilane as an internal standard and (unless otherwise specified) deuteriochloroform as solvent. Lactone II showed a spectrum which consisted of a complex of peaks for nine aromatic protons in the region δ = 6.7–7.6 ppm and a series of at least 18 lines (for a total of five aliphatic protons) in the region 2.4–4.9 ppm. The latter absorption lines occurred at 164, 174, 180 (most intense), 187, 189, 195, 201, 203, 210, 216, 218, 225, 232, 240, 249, 273, 282, and 290 cps, of which the trios in the regions 230–250 and 270–290 appeared as two pseudotriplets. The dideuteriolactone X showed a spectrum which was virtually superimposable on that of II except that both pseudotriplets (corresponding to protons on the CCH_2O grouping) were missing. The trideuteriolactone XI showed the same aromatic multiplet plus a broad band for two protons (benzylic type) at δ = 2.93 ppm. Through the courtesy of Varian Associates the spectra of these three compounds were also run on an HA-100 instrument. Computer analysis of the two sets of spectra gave nearly consistent values for the parameters of chemical shifts (ν in cycles per second) and coupling constants (J in cycles per second). Parameters for the A-60 spectrum of II are as follows (*cf.* formula II): ν_a = 281.2 ± 0.1, ν_b = 240.0 + 0.1, ν_c = 203.8 ± 0.2, ν_d = 170.8 ± 0.2, ν_e = 180.4 ± 0.4; J_{ab} = −8.7 ± 0.2, J_{ac} = 8.9 ± 0.3, J_{bc} = 8.9 ± 0.2, J_{cd} = 17.2 ± 0.3, J_{ce} = 5.7 ± 0.4, and J_{de} = −15.2 ± 0.2 cps. The variations in the values given are probable errors and the root-mean-square error of all values is 0.42 cps.[16]

Some 4-Aryl-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridines Derived from Histamine

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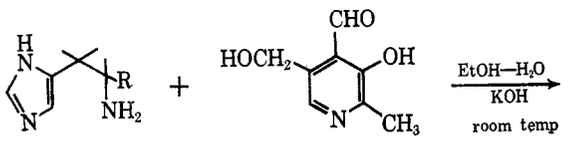
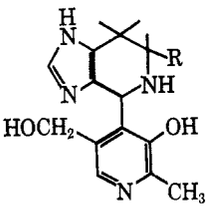
A number of 4-aryl-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridines (VI) and their isomeric Schiff bases (VII) have been prepared from histamine and aromatic aldehydes. The scope of the cyclization reaction was investigated and the structure for VI was firmly established by means of nmr analysis.

In 1948 Folkers and co-workers reported the preparation of 4-aryl-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridines (III) from both histidine (Ib)[2] and histamine (Ia)[3] by treatment with pyridoxal (vitamin B_6, II) in alkaline solution. The desired products were the corresponding Schiff bases (IV). Indeed, in the absence of alkali, histamine condenses with pyridoxal in alcoholic solution to yield IVa, a bright yellow compound which readily absorbs a molar equivalent of hydrogen. In contrast to their isomeric Schiff bases, compounds IIIa and IIIb are colorless and resistant to hydrogenation. These facts, plus structures previously formulated for spinaceamine (Va)[4] and spinacine (Vb)[5] which were prepared by the acid-catalyzed Pictet–Spengler[6] reaction, caused Folkers to postulate the 4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridine ring system for compounds IIIa and IIIb.

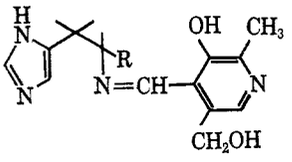


Ia, R = H
b, R = COOH

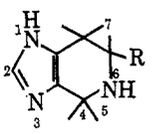
II



IIIa, R = H
b, R = COOH

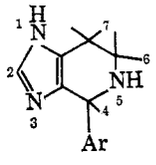


IVa, R = H
b, R = COOH



Va, R = H
b, R = COOH

We embarked on this research with the intention of finding evidence that would unequivocally establish the structure of these new ring-closure products. Furthermore, because of histamine's remarkable physiological acitivity and also because products of carbonyl compounds and β-arylethylamines (*e.g.*, tetrahydroharman, narcotine, laudanosine, hydrastine, etc.) are generally pharmacologically important, we wanted to



VI

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(2) D. Heyl, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **70**, 3429 (1948).
(3) D. Heyl, E. Luz, S. A. Harris, and K. Folkers, *ibid.*, **70**, 3669 (1948).
(4) S. Frankel and K. Zeimer, *Biochem. Z.*, **110**, 234 (1920).
(5) J. Welisch, *ibid.*, **49**, 173 (1913).
(6) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 151 (1951).