Intramolecular Diels-Alder Reactions. VIII. Syntheses of Phenolic Cyclolignan Lactones (1,2)

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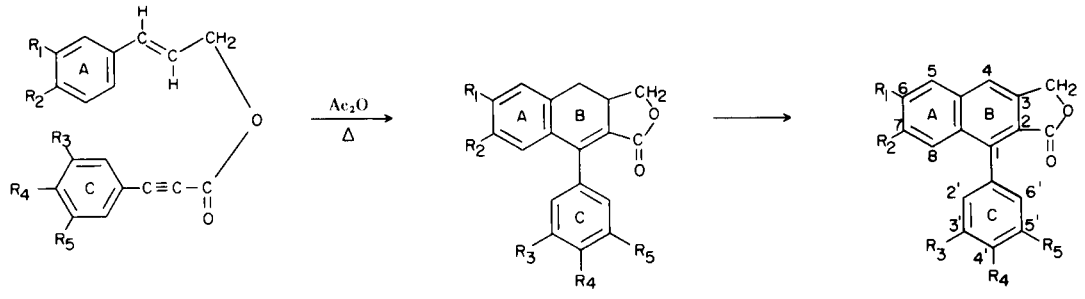
Various phenolic cyclolignan lactones have been reported as constituents of natural products (4). In previous papers we reported use of the intramolecular Diels-Alder reaction as a route to cyclolignan lactones with a total of 0-3 alkoxy substituents on each of the rings A and C (5-9). We have now extended these syntheses to the formation of aromatic cyclolignan lactones bearing a phenolic group in ring A and/or C (Scheme 1).

For use in these studies ethyl *trans*-4-benzyloxy-3-methoxycinnamate was converted into *trans*-4-benzyloxy-3-methoxycinnamyl alcohol (IV) and into 4-benzyloxy-3-methoxyphenylpropiolic acid (V). Four substituted *trans*-cinnamyl phenylpropiolates (Ib, Id, Ig, and Ij) were prepared from these benzyloxy-substituted intermediates and cyclized to the corresponding dihydroaromatic cyclolignan lactones (IIb, IId, IIg, and IIj, respectively) by means of refluxing acetic anhydride. In contrast to the conditions reported (7) for reaction of *trans*-cinnamyl phenylpropiolate (Ia) itself, the present cyclizations were conducted in relatively dilute solution (40-80 ml. of solvent per g. of ester) in an effort to decrease the extent of intermolecular condensation. Overall yields of lactones were 23-39%, as based on the initial phenylpropiolic acids used.

Dehydrogenation of compounds II to the corresponding aromatic cyclolignan lactones IIIb, IIId, IIIg, and IIIj was effected in 30-76% yield by means of dichlorodicyanobenzoquinone (DDQ). Hydrogenolysis of the benzyloxy group(s) was then accomplised by means of palladium-charcoal and hydrogen gas to give the phenolic aromatic cyclolignan lactones IIIc, IIIe, IIIh, and IIIk, respectively (45-82%). Alternatively, in two cases, surface-catalyzed dehydrogenation-hydrogenolysis was brought about in a single laboratory process. Thus refluxing IIb with palladium-charcoal in *p*-cymene gave IIIc directly (33%, as com-

SCHEME 1



I II III

a: $R_1 = R_2 = R_3 = R_4 = R_5 = H$
b: $R_1 = R_2 = R_5 = H$, $R_3 = CH_3O$, $R_4 = C_6H_5CH_2O$
c: $R_1 = R_2 = R_5 = H$, $R_3 = CH_3O$, $R_4 = OH$
d: $R_1 = R_3 = R_4 = CH_3O$, $R_2 = C_6H_5CH_2O$, $R_5 = H$
e: $R_1 = R_3 = R_4 = CH_3O$, $R_2 = OH$, $R_5 = H$
f: $R_1 = R_2 = R_3 = R_4 = CH_3O$, $R_5 = H$
g: $R_1 = R_3 = R_4 = R_5 = CH_3O$, $R_2 = C_6H_5CH_2O$
h: $R_1 = R_3 = R_4 = R_5 = CH_3O$, $R_2 = OH$
i: $R_1 = R_2 = R_3 = R_4 = R_5 = CH_3O$
j: $R_1 = R_3 = CH_3O$, $R_2 = R_4 = C_6H_5CH_2O$, $R_5 = H$
k: $R_1 = R_3 = CH_3O$, $R_2 = R_4 = OH$, $R_5 = H$

pared to 13% overall for the two-step process). Analogously, IId was converted to IIIe (68% for one step, 55% for two steps).

For the three esters (Id, Ig, and Ij) formed from alcohol IV (R_1 = CH_3O, R_2 = $PhCH_2O$) cyclization into ring A could occur either *ortho* (not shown in formulas) or *para* (as shown) to the methoxy group. Had the dihydroaromatic or aromatic compounds isolated actually contained a methoxy group at C-8 (from *ortho*-cyclization) rather than at C-6, the pmr spectra of the products should have shown a methoxy signal at high field (*ca.* δ 3.2-3.4) (6). In fact, none of these products showed methoxy signals upfield of δ 3.7. Direct chemical proof that the cyclizations went *para* to the methoxy group was also obtained by methylation of the phenolic aromatic compounds. Thus, both IIIe and IIIk were converted into the known dimethyldehydroretrodendrin (IIIf) (6,10) and IIIh was converted into the known dehydroanhydrosikkimotoxin (IIIi) (11).

In an extension of the ester cyclization, acid V was refluxed with acetic anhydride to give a 64% yield of 1-(4-benzyloxy-3-methoxyphenyl)-6-methoxy-7-benzyloxynaphthalene-2,3-dicarboxylic anhydride (VI) and this compound was debenzylated to a phenolic aromatic cyclolignan anhydride.

It is noteworthy that the phenyl protons in the benzyloxy groups located at C-4′ and C-7 in compounds II and III are readily distinguishable in the pmr spectrum (with deuteriochloroform as solvent). For IId, IIId, IIg, IIIg (with a single benzyloxy group at C-7) the spectrum shows a sharp five-proton singlet at δ 7.21-7.28 (*cf.* spectrum of benzyl alcohol) (12). On the other hand, IIb and IIIb (with a single benzyloxy group at C-4′) show only a multiplet in the aromatic region, while IIj and IIIj (with benzyloxy groups both at C-4′ and C-7) show one sharp five-proton singlet (for the latter group) superimposed on a broad multiplet for other aromatic protons. Anhydride VI has a spectrum similar to that of IIIj in the aromatic region, except that the singlet is slightly split. Examination of Stuart-Briegleb molecular models indicates that the phenyl moiety of a 4′-benzyloxy group (in contrast to one at C-7) can assume conformations wherein it approaches closely to the carbonyl oxygen atom at C-2 in compounds of type II, III, and VI. In such conformations the various hydrogens on the juxtaposed phenyl moiety will experience significantly different magnetic environments and produce a broad multiplet, rather than a singlet, in the spectrum.

EXPERIMENTAL (13)

Trans-4-Benzyloxy-3-methoxycinnamyl Alcohol (IV).

To a cold (-25°), stirred suspension of 1.6 g. (0.042 mole) of lithium aluminum hydride in 140 ml. of ether was added dropwise (over a period of 40 minutes) a solution of 5 g. (0.016 mole) of ethyl *trans*-4-benzyloxy-3-methoxycinnamate (15) in 140 ml. of ether. The mixture was stirred at -20° for 1.5 hours and treated with ethyl acetate (to react with excess lithium aluminum hydride) and then with water (cautiously). The residue from evaporation of the dried ether layer was crystallized from carbon tetrachloride, yield 3 g. (69%), m.p. 86-88°, lit. (16) 89°; ir 3630 (OH), 965 cm^{-1} (*trans*-CH=CH); pmr δ 2.29 (s, 1, OH), 3.83 (s, 3, OCH_3), 4.22 (d, 2, J = 4.7 Hz, CH_2OH), 5.10 (s, 2, $C_6H_5CH_2O$), 6.1-7.0 (m, 5, aromatic and vinylic protons), 7.34 ppm (broadened, slightly split s, 5, J = 1.5 Hz, phenyl).

4-Benzyloxy-3-methoxyphenylpropiolic Acid (V).

In the manner used to prepare 3,4,5-trimethoxyphenylpropiolic acid (14), treatment of 10 g. of ethyl *trans*-4-benzyloxy-3-methoxycinnamate (15) with an equimolar amount of bromine in chloroform solution gave crude ethyl 2,3-dibromo-3-(4-benzyloxy-3-methoxyphenyl)propionate (17). Refluxing this recrystallized (from chloroform-cyclohexane) bromoester (12.7 g., 83%, m.p. 96-99°) with alcoholic potassium hydroxide and subsequent acidification gave the crude acid, purified by continuous extraction into ether and then crystallization from acetone-cyclohexane, yield 3.75 g. (49%) of shiny platelets, m.p. 165-167° dec.; ir (nujol) 2210 cm^{-1} (C≡C); pmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide, 1:1 by volume) δ 3.86 (s, 3, OCH_3), 5.16 (s, 2, $C_6H_5CH_2O$), 7.41 (s, 5, phenyl) superimposed on 6.8-7.7 ppm (m, 8 total, aromatic protons).

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.3; H, 5.0. Found: C, 72.5; H, 5.3.

Substituted *Trans*-cinnamyl Phenylpropiolates (I).

The crude esters Ib, Id, Ig, and Ij were synthesized from the appropriately substituted *trans*-cinnamyl alcohols and phenylpropiolic acids (14,18) in the manner previously described for the unsubstituted compound Ia (7). Pmr data for the esters are as follows: Ib, δ 3.78 (s, OCH_3), 4.85 (d, J = 6 Hz, CH_2OCO), 5.10 (s, $PhCH_2O$), 7.36 (s, phenyl) superimposed on 6.0-7.9 ppm (m, aromatic and vinylic protons); Id, (deuteriochloroform-carbon tetrachloride) δ 3.72, 3.74, 3.77 (3 overlapping s, 9 total, 3 OCH_3), 4.76 (d, 2, J = 6 Hz, CH_2OCO), 5.00 (s, 2, $PhCH_2O$), 6.2-7.5 ppm (m, aromatic and vinylic protons); Ig, δ 3.78 (s, 3, OCH_3), 3.86 (s, 9, 3 OCH_3), 4.86 (d, J = 6 Hz, CH_2OCO), 5.10 (s, $PhCH_2O$), 6.2-7.7 ppm (m, aromatic and vinylic protons); Ij, δ 3.82 (s, 2 OCH_3), 4.80 (d, J = 6 Hz, CH_2OCO), 5.07 (s, $PhCH_2O$), 7.32 (s, phenyl) superimposed on 6.2-7.7 ppm (m, aromatic and vinylic protons).

Cyclization of Substituted *Trans*-Cinnamyl Phenylpropiolates.

Cyclization was effected by refluxing the crude ester in acetic anhydride (40-80 ml. per g. of ester) for *ca.* 10 hours. The residue from evaporation of the solvent was purified as indicated in each case.

Product from Ib was chromatographed (alumina-chloroform) to give a gum which was stirred with ether. Cooling the ether decantate gave a solid which was recrystallized from acetone-ethanol to give cream-colored needles (33%) of 1-(4-benzyloxy-3-methoxyphenyl)-3-hydroxymethyl-3,4-dihydro-2-naphthoic acid lactone (IIb), m.p. 159-160°; pmr δ 3.82 (s, 3, OCH_3), 5.16 (s, 2, $PhCH_2O$), 6.7-7.7 (m, 12, aromatic protons).

Anal. Calcd. for $C_{26}H_{22}O_4$: C, 78.4; H, 5.6. Found: C, 78.3; H, 5.6.

Product from Id was chromatographed, triturated with ether, washed with cold acetone-water, and recrystallized from acetone-

ethanol to give yellow prisms (35%) of 1-(3,4-dimethoxyphenyl)-3-hydroxymethyl-6-methoxy-7-benzyloxy-3,4-dihydro-2-naphthoic acid lactone (IId), m.p. 185-186°; pmr δ 3.73 (s, 3, OCH_3), 3.92 (s, 6, 2 OCH_3), 4.92 (s, 2, $PhCH_2O$), 6.59 (s, 1, aromatic proton), *ca.* 6.8 (broadened s, 4, aromatic protons), 7.22 ppm (s, 5, phenyl).

Anal. Calcd. for $C_{28}H_{26}O_6$: C, 73.4; H, 5.7. Found: C, 73.3; H, 5.7.

Processing product from Ig gave cream-colored platelets (from chloroform-cyclohexane) (39%) of 1-(3,4,5-trimethoxyphenyl)-3-hydroxymethyl-6-methoxy-7-benzyloxy-3,4-dihydro-2-naphthoic acid lactone (IIg), m.p. 189-191°; pmr δ 3.77 (s, 6, 2 OCH_3 at C-3′ and C-5′), 3.92, 3.95 (2s, 3 each, 2 OCH_3 at C-4′ and C-6), 4.95 (s, 2, $PhCH_2O$), 6.43 (s, 2, H-2′ and H-6′), 6.58, 6.82 (2s, 1 each, H-5 and H-8), 7.27 ppm (s, 5, phenyl).

Anal. Calcd. for $C_{29}H_{28}O_7$: C, 71.3; H, 5.8. Found: C, 70.9; H, 5.7.

Crude product from Ij was stirred with ether to give crystals which were washed with acetone-ether and recrystallized from acetone-ethanol as faintly cream-colored prisms (23%) of 1-(4-benzyloxy-3-methoxyphenyl)-3-hydroxymethyl-6-methoxy-7-benzyloxy-3,4-dihydro-2-naphthoic acid lactone (IIj), m.p. 196-197°; pmr δ 3.77, 3.89 (2s, 3 each, 2 OCH_3), 5.03, 5.20 (2s, 2 each, 2 $PhCH_2O$), 7.21 (s, 5, $C_6H_5CH_2O$ at C-7) superimposed on 6.5-7.7 ppm (m, 15 total, aromatic protons).

Anal. Calcd. for $C_{34}H_{30}O_6$: C, 76.4; H, 5.7. Found: C, 76.2; H, 6.1.

Aromatization of Dihydroaromatic Cyclolignan Lactones.

A solution of *ca.* 0.7 g. of preceding lactone and a three-molar quantity of DDQ in 60 ml. of benzene was refluxed for 4-7 hours, cooled, and percolated through a column of 100 g. of alumina. For IIb, elution with benzene-chloroform (1:1) gave a product (30%) which formed needles of 1-(4-benzyloxy-3-methoxyphenyl)-3-hydroxymethyl-2-naphthoic acid lactone (IIIb) on crystallization from acetone-ethanol: m.p. 177-178°; pmr δ 3.83 (s, 3, OCH_3), 5.20 (s, 2, $PhCH_2O$), 5.37 (s, 2, CH_2OCO), 6.8-8.1 ppm (m, aromatic protons).

Anal. Calcd. for $C_{26}H_{20}O_4$: C, 78.8; H, 5.1. Found: C, 78.7; H, 5.2.

For reactions of IId, IIg, and IIj the chromatographic column was eluted with 1% methanol in chloroform to give a highly fluorescent (in ultraviolet light) effluent, from which the dehydrogenated product was isolated. 1-(3,4-Dimethoxyphenyl)-3-hydroxymethyl-6-methoxy-7-benzyloxy-2-naphthoic acid lactone (IIId) (yield 67%) was recrystallized from acetone-ethanol to give faintly yellow prisms, m.p. 196-197°; pmr δ 3.80, 3.99, 4.02 (3s, 3 each, 3 OCH_3), 5.06 (s, 2, $PhCH_2O$), 5.32 (slightly broadened s, 2, CH_2OCO), 6.7-7.25 (m, 5, aromatic protons), 7.28 (s, 5, phenyl), 7.67 ppm (broad s, 1, H-4).

Anal. Calcd. for $C_{28}H_{24}O_6$: C, 73.7; H, 5.3. Found: C, 73.6; H, 5.4.

By the same processing as for IIId there were obtained white, sparkling platelets (76%) of 1-(3,4,5-trimethoxyphenyl)-3-hydroxymethyl-6-methoxy-7-benzyloxy-2-naphthoic acid lactone (IIIg), m.p. 223.5-224.5°; pmr δ 3.78 (s, 6, 2 OCH_3 at C-3′ and C-5′), 4.01, 4.03 (2s, 3 each, 2 OCH_3 at C-4′ and C-6), 5.08 (s, 2, $PhCH_2O$), 5.33 (broadened s, 2, CH_2OCO), 6.49 (s, 2, H-2′ and H-6′), 7.13, 7.21 (2s, 1 each, H-5 and H-8), 7.27 (s, 5, phenyl), 7.69 ppm (broad s, 1, H-4).

Anal. Calcd. for $C_{29}H_{26}O_7$: C, 71.6; H, 5.4. Found: C, 71.4; H, 5.5.

Likewise, there resulted cream-colored prisms (50%) of 1-(4-benzyloxy-3-methoxyphenyl)-3-hydroxymethyl-6-methoxy-7-benzyloxy-2-naphthoic acid lactone (IIIj), m.p. 197.5-198.5°; pmr δ 3.81, 4.00 (2s, 3 each, 2 OCH_3), 5.03 (s, 2, $PhCH_2O$), 5.28 ± 0.04 (2 overlapping s, 4 total, CH_2OCO and $PhCH_2O$), 7.25 (s, 5, $C_6H_5CH_2O$ at C-7) superimposed on 6.6-7.7 ppm (m, 16 total, aromatic protons).

Anal. Calcd. for $C_{34}H_{28}O_6$: C, 76.7; H, 5.3. Found: C, 76.8; H, 5.4.

Debenzylation of Aromatic Cyclolignan Lactones.

A suspension of 0.6 g. of 30% palladium-charcoal and *ca.* 0.5 g. of aforementioned lactone III in 75 ml. of ethyl acetate was shaken with hydrogen gas at 3-4 atmospheres pressure for 20 hours. The residue from evaporation of the filtered solution (plus acetone washings of the catalyst) was recrystallized to give an analytical sample of phenolic lactone.

Compound IIIb produced faintly cream-colored needles (45%) of 1-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-2-naphthoic acid lactone (IIIc), m.p. 216-217.5° (from methanol).

Anal. Calcd. for $C_{19}H_{14}O_4$: C, 74.5; H, 4.6. Found: C, 74.6; H, 4.5.

Compound IIId yielded crystals (from chloroform-cyclohexane) (82%) of 1-(3,4-dimethoxyphenyl)-3-hydroxymethyl-6-methoxy-7-hydroxy-2-naphthoic acid lactone (IIIe), m.p. 261-263°; pmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide) δ *ca.* 3.37 (broad s, OH?), 3.82, 3.91, 3.99 (3s, 3 each, 3 OCH_3), 5.35 (broadened s, 2, CH_2OCO), 6.7-7.3 (m, 5, aromatic protons), 7.72 ppm (s, 1, H-4).

Anal. Calcd. for $C_{21}H_{18}O_6$: C, 68.8; H, 5.0. Found: C, 68.5; H, 4.9.

From IIIg were obtained white needles (from acetone-ethanol) (81%) of 1-(3,4,5-trimethoxyphenyl)-3-hydroxymethyl-6-methoxy-7-hydroxy-2-naphthoic acid lactone (IIIh), m.p. 273-274° dec.

Anal. Calcd. for $C_{22}H_{20}O_7$: C, 66.7; H, 5.1. Found: C, 66.8; H, 5.3.

From IIIj were obtained needles (from acetone-ethyl acetate) (72%) of 1-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-6-methoxy-7-hydroxy-2-naphthoic acid lactone (IIIk), m.p. 283-284.5° dec.

Anal. Calcd. for $C_{20}H_{16}O_6$: C, 68.2; H, 4.6. Found: C, 68.3; H, 4.5.

Direct Aromatization-Debenzylation of Dihydroaromatic Cyclolignan Lactones.

A mixture of 0.3 g. of lactone IIb, 0.6 g. of 30% palladium-charcoal, and 14 ml. of *p*-cymene was refluxed for 22 hours in an atmosphere of nitrogen. Evaporation of the filtered solution gave IIIc (33%), identical with product from IIIb.

Likewise lactone IId gave a 68% yield of IIIe.

Methylation of Phenolic Aromatic Cyclolignan Lactones.

A mixture of 0.37 g. of lactone IIIe, 1.7 g. of dimethyl sulfate, 3 g. of anhydrous potassium carbonate, and 65 ml. of acetone was refluxed for 24 hours and filtered. Evaporation of the filtrate gave a residue which was washed (in chloroform solution) with water and crystallized from chloroform-methanol to give 0.28 g. (72%) of 1-(3,4-dimethoxyphenyl)-3-hydroxymethyl-6,7-dimethoxy-2-naphthoic acid lactone (IIIf), m.p. 253-254°, identical with an authentic sample previously described (6).

Similarly, lactone IIIk was methylated to IIIf (75%).

Also, methylation of lactone IIIh gave crystals (after chromatography with alumina-chloroform plus crystallization from methanol-chloroform) (79%) of 1-(3,4,5-trimethoxyphenyl)-3-hydroxy-

methyl-6,7-dimethoxy-2-naphthoic acid lactone (IIIi), identical with an authentic sample furnished by E. Schreier (11).

1-(4-Benzyloxy-3-methoxyphenyl)-6-methoxy-7-benzyloxynaphthalene-2,3-dicarboxylic Anhydride (VI).

A solution of 0.56 g. of acid V in 100 ml. of acetic anhydride was refluxed for 8 hours and then evaporated to dryness. The residue was triturated with ether and crystallized from chloroform-hexane as yellow needles, yield 0.35 g. (64%), m.p. 194-197°; ir (nujol) 1770 and 1820 cm^{-1} (anhydride); pmr δ 3.85, 4.10 (2s, 3 each, 2 OCH_3), 5.11, 5.33 (2s, 2 each, 2 $PhCH_2O$), 7.28 (slightly split s, J = 1 Hz, 5-6, $C_6H_5CH_2O$ at C-7) superimposed on 6.7-7.8 (m, 15 total, aromatic protons), 8.32 ppm (s, 1, H-4).

Anal. Calcd. for $C_{34}H_{26}O_7$: C, 74.7; H, 4.8. Found: C, 74.4; H, 4.9.

1-(4-Hydroxy-3-methoxyphenyl)-6-methoxy-7-hydroxynaphthalene-2,3-dicarboxylic Anhydride.

Hydrogenolytic debenzylation of the preceding anhydride was conducted with palladium-charcoal in the aforestated manner. The product formed a cream-colored powder (80%) from ethyl acetate; m.p. 320-322° dec.; ir (nujol) 3410 (OH), 1760 and 1820 cm^{-1} (anhydride).

Anal. Calcd. for $C_{20}H_{14}O_7$: C, 65.6; H, 3.9. Found: C, 65.7; H, 3.9.

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REFERENCES

(1) This investigation was supported by research grant No. GM 12730 from the National Institutes of General Medical Sciences, U. S. Public Health Service. For Paper VII, see ref. 9.

(2) We use the term "cyclolignan lactone" to refer to a compound with the skeletal structure of 1-(or 4-)phenyl-3-hydroxymethyl-2-naphthoic acid lactone, irrespective of the degree of reduction of ring B or of whether or not the compound occurs in nature. Where it becomes desirable to identify the degree of reduction of ring B, we use the adjectives "aromatic," "dihydroaromatic," and "tetrahydroaromatic" to precede "cyclolignan lactone." Specific compounds are named and numbered as derivatives of naphthalene. This usage contrasts with that of K. Freudenberg and K. Weinges [*Tetrahedron*, 15, 115 (1961)] who use the term "cyclolignanolide" to refer to a naturally occurring tetrahydroaromatic cyclolignan lactone and who employ a different numbering system.

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(13) Infrared spectra were obtained by means of a Beckman IR-5 or IR-7 spectrophotometer with chloroform as solvent (unless otherwise indicated); pmr spectra, by means of a Varian A-60 spectrometer with deuteriochloroform as solvent (unless otherwise indicated) and tetramethylsilane as internal standard. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. General infrared spectral observations on esters I and lactones II were the same as previously reported (6,14). The aromatic lactones III show γ-lactone absorption at 1750-1760 cm^{-1}. Phenolic lactones III also show OH absorption at 3540 ± 20 cm^{-1} (3440 cm^{-1} for IIIh in nujol). The complex pattern in the pmr spectrum for the three-proton aliphatic system $-CH_2CHCH_2O-$ present in compounds II is observed, but it is not reported here for individual compounds (6,7).

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(15) This compound [pmr δ 1.28 (t, 3, J = 7 Hz, OCH_2CH_3), 3.80 (s, 3, OCH_3), 4.22 (q, 2, J = 7 Hz, OCH_2CH_3), 5.07 (s, 2, $PhCH_2O$), 6.94 (AB system, $\Delta\delta$ = 78 Hz, J = 16 Hz, *trans*-CH=CH), 7.33 (s, 5, phenyl) superimposed on 6.6-7.4 ppm (m, aromatic protons)] was prepared in three steps from vanillin. R. M. Anker, A. H. Cook, and I. M. Heilbron, *J. Chem. Soc.*, 917 (1945); H. Kataoka, *Ann. Rept. IISUU Lab. (Tokyo)*, No. 8, 1 (1957) [*Chem. Abstr.*, 51, 16501 (1957)]; I. A. Pearl and D. L. Beyor, *J. Org. Chem.*, 16, 216 (1951).

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