The Photochemical Synthesis of 2′-Hydroxychalcones from Phenyl Cinnamates[1]

V. T. RAMAKRISHNAN AND JACQUES KAGAN[2]

Department of Chemistry, University of Illinois at Chicago Circle, Chicago, Illinois 60680

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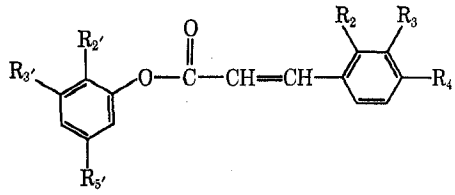
The photolysis of substituted phenyl cinnamates leads to *o*-hydroxychalcones. The examples reported utilized phenol, resorcinol, guaiacol, or phloroflucinol esterified with cinnamic acid or its 2-hydroxy, 4-hydroxy, 4-methoxy, 3,4-dihydroxy, 3-methoxy-4-hydroxy, and 3,4-dimethoxy derivatives. Some 2′,6′-dihydroxychalcones cyclized to the flavanones.

Substituted 2′-hydroxychalcones are widely distributed in plants[3] and they also serve as biosynthetic precursors to all the other classes of flavonoid and isoflavonoid pigments.[4] They can undergo a reversible cyclization to flavanones, and they can also be converted enzymatically into optically active flavanones.[5] Although the conversion of chalcones into the other classes of flavonoids is well understood, their own biosynthesis is still obscure, especially with respect to the origin of the A ring.[4] Our interest in the biosynthetic problem led us to investigate the photochemical conversion of substituted phenyl cinnamates to 2′-hydroxychalcones as a possible model for the biological reaction.[6]

Discussion

The Friedel–Crafts acylation of protected phenols with cinnamoyl chlorides in presence of aluminum chloride has been reported.[8] When the hydroxyls were not protected prior to the reaction with the acid chloride, acylation did proceed, probably *via* Fries rearrangement of the initially formed ester,[9,10] but the hydroxychalcones were not stable under the reaction conditions, and the isomeric flavanones were actually isolated. The photochemical equivalent of the Fries rearrangement is now a well-known reaction,[11] which was recently utilized by Obara, *et al.*,[12,13] in the synthesis of simple 2′-hydroxychalcones from phenyl cinnamates. We independently studied the photochemical reaction, with the goal of obtaining chalcones having the complex substitution patterns usually found in plants.

After confirming that the photo-Fries reaction proceeded with the simple ester **1a**, which yielded **2a** as the major rearranged products,[12] we introduced substituents in the A ring and found that the 2-methoxy- (**1b**) and 3-hydroxy- (**1c**) phenyl cinnamates yielded the products of *ortho* migration, namely **2b** from **1b** and a mixture of **2c** and **2d** from **1c**.[14] Most flavonoid pigments are formally derived from chalcones having hydroxyls at the 2′, 4′, and 6′ positions, and phloro-



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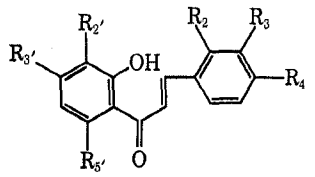

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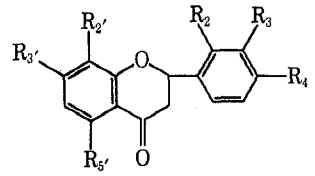

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a, $R_{2'} = R_{3'} = R_{5'} = R_2 = R_3 = R_4 = H$
b, $R_{2'} = OCH_3$; $R_{3'} = R_{5'} = R_2 = R_3 = R_4 = H$
c, $R_{3'} = OH$; $R_{2'} = R_{5'} = R_2 = R_3 = R_4 = H$
d, $R_{5'} = OH$; $R_{2'} = R_{3'} = R_2 = R_3 = R_4 = H$
e, $R_{3'} = R_{5'} = OH$; $R_{2'} = R_2 = R_3 = R_4 = H$
f, $R_{3'} = R_{5'} = R_2 = OH$; $R_{2'} = R_3 = R_4 = H$
g, $R_{3'} = R_{5'} = R_4 = OH$; $R_{2'} = R_2 = R_3 = H$
h, $R_{3'} = R_{5'} = OH$; $R_4 = OCH_3$; $R_{2'} = R_2 = R_3 = H$
i, $R_{3'} = R_{5'} = R_3 = R_4 = OH$; $R_{2'} = R_2 = H$
j, $R_{3'} = R_{5'} = R_4 = OH$; $R_3 = OCH_3$; $R_{2'} = R_2 = H$
k, $R_{3'} = R_{5'} = OH$; $R_3 = R_4 = OCH_3$; $R_{2'} = R_2 = H$

(1) This work was presented at the meeting of the Phytochemial Society of North America, Banff, Canada, Aug 1969.

(2) Author to whom inquiries should be directed.

(3) J. B. Harborne in "Comparative Biochemistry of the Flavonoids," Academic Press, New York, N. Y., 1967, p 78.

(4) H. Grisebach in "Recent Advances in Phytochemistry," T. J. Mabry, R. E. Alston, and V. C. Runeckles, Ed., Appleton-Century-Crofts, New York, N. Y., 1968, p 379.

(5) M. Shimokoriyama, *J. Amer. Chem. Soc.*, **79**, 4199 (1957).

(6) The view that phloroglucinol is not a precursor to chalcones *in vivo* is based on short-term competitive feeding experiments between phloroglucinol and carbon dioxide in cut plants.[7a] While the rate of absorption of phloroglucinol through damaged cells and its translocation to the sites of chalcone biosynthesis may not compete efficiently with direct synthesis from carbon dioxide *via* photosynthesis, the intermediacy of the phenol is not necessarily eliminated. We have secured preliminary evidences (M. A. Ali and J. Kagan, unpublished results) that labeled phloroglucinol was indeed absorbed through the stems of buckwheat cuttings, yielding radioactive flavonoids. This result contrasts with the often quoted but still unpublished work by Watkin and Neish.[7b]

(7) (a) J. E. Watkin, E. W. Underhill, and A. C. Neish, *Canad. J. Biochem. Physiol.*, **35**, 230 (1957); (b) A. C. Neish in "Biochemistry of Phenolic Compounds," H. B. Harborne, Ed., Academic Press, New York, N. Y., 1964, p 341.

(8) H. Simonis and C. Lear, *Chem. Ber.*, **59**, 2908, 2914 (1926).

(9) (a) J. Shinoda and S. Sato, *J. Pharm. Soc. Jap.*, **48**, 791 (1928); (b) *ibid.*, **48**, 791 (1928); (c) *ibid.*, **49**, 64 (1929); (d) *ibid.*, **49**, 71 (1929).

(10) J. Shinoda and Kawagoye, *ibid.*, **48**, 938 (1928).

(11) (a) D. Bellus and P. Hrdlovic, *Chem. Rev.*, **67**, 599 (1967); (b) J. W. Meyer and G. S. Hammond, *J. Amer. Chem. Soc.*, **92**, 2187 (1970), and references therein cited.

(12) H. Obara and H. Takahashi, *Bull. Chem. Soc. Jap.*, **40**, 1012 (1967).

(13) H. Obara, H. Takahashi, and H. Hirano, *ibid.*, **42**, 560 (1969).

(14) The irradiation of **1c** in benzene yielded only **2c**.[13]

glucinol cinnamates, therefore, were required. Since many flavonoids also bear hydroxyls in the B ring, it was necessary to obtain the monoester without forming polyesters and products of selfcondensation from the hydroxycinnamoyl moiety.

Phloroglucinol could not be directly esterified[15] with hydroxycinnamic acids in acceptable yield and we used the following approach. First, the required cinnamic acid was treated with an excess of chloromethyl methyl ether in the presence of base.[16] After saponification, the O-protected cinnamic acid was treated with thionyl chloride, and the acid chloride was allowed to react with phloroglucinol in excess. There is a practical limit to the size of the excess, but we observed that even a sixfold molar excess did not completely eliminate the formation of di- and triesters. The monoester was isolated after column chromatography.

Finally, the protecting groups in the B ring of the phloroglucinol monocinnamate were removed in presence of acid, yielding the esters **1e–k**, which were photolyzed at 253.7 or 300 nm in benzene or methanol solution. The yield of chalcone was usually higher in methanol. The photo-Fries reaction of phloroglucinol monoesters is particularly simple since, for reasons of symmetry, the two products of *ortho* migration and that of *para* migration are identical.

Using the procedure outlined above, we synthesized 2′,4′,6′-trihydroxychalcones having either no substituent (**2e**), a 2-hydroxyl (**2f**), 4-hydroxyl (**2g**), 4-methoxyl (**2h**), 3,4-dihydroxyl (**2i**), 3-methoxyl-4-hydroxyl (**2j**), or 3,4-dimethoxyl (**2k**) substitution in the B ring. These substitution patterns correspond to some of the most common natural flavonoid pigments. The procedure, therefore, appears to be equally suited for the synthesis of other polyhydroxylated chalcones and flavanones and their glycosides.

In contrast to the acid-catalyzed acylation reaction, the isomerization of the initially formed chalcones into flavanones did not occur immediately. It took place occasionally during work-up and we thus synthesized the naturally occurring flavanones, pinocembrin (**3e**), isosakuranetin (**3g**), and eriodictyol (**3i**).

The photochemical *cis–trans* equilibration of olefins is well known,[17] but we did not isolate any *cis*-chalcones as judged by the coupling constant between the vinyl protons in the nmr, even though the unreacted cinnamic esters had partially isomerized. Isomerization had also occurred in the methyl cinnamates obtained by fragmentation during photolysis in methanol. Coumarin, for example, which was isolated along with **2f** in the photolysis of **1f** must have been formed by intramolecular transesterification of methyl *cis*-*o*-hydroxycinnamate.

The yield of the chalcones isolated in this work was between 20 and 50% based on the reacted esters. In the related acid-catalyzed acylation reaction, Shinoda, *et al.*, obtained similar products (only as the flavanones) but did not report the yields.[9,10] In a more recent application of Shinoda's method,[18] the synthesis of **3e** was performed with a yield of about 20%, whereas we secured it in about 46% photochemically. The photolysis of phenyl cinnamates, however, does not always proceed with high conversion, probably because their specific absorption is smaller than that of the chalcones, which therefore act as internal filters. Alternatively, the products may quench the reactive triplet state of **1**.[19]

Experimental Section

All uv spectra were recorded in methanol on a Hitachi–Coleman Model 124 spectrophotometer. The nmr spectra were recorded with TMS as internal standard on a Varian A-60A or T-60 spectrometer in DMSO-d_6 except where indicated. They are reported in parts per million on the δ scale. The mass spectra were obtained at 70 eV and at the appearance potential by direct injection into the ion source of a Perkin-Elmer 270 gc-mass spectrometer. The melting points are uncorrected and were determined with a Kofler microscope–hot stage. All the irradiation experiments were carried out under nitrogen in a Rayonet apparatus. The nylon powder chromatography was performed on short column by introducing the sample coated over some powder at the top of a column packed in water and by eluting the components with methanol solutions of increasing concentrations. The structural assignments of flavonoid products derived from spectral shifts is based on Jurd's work.[20]

Phenyl Cinnamate (1a).—Cinnamoyl chloride was prepared by refluxing the acid (10 g) and an excess of thionyl chloride in $CHCl_3$. It was treated with phenol (10 g) in refluxing benzene in presence of Mg. After work-up there was obtained 14.5 g (98%) of ester, mol wt 224 (mass spectrum), mp 75–76° (lit.[21] 75–76°). A solution of 640 mg of ester in 150 ml of methanol or chloroform was irradiated at 253.7 nm for 20 hr. After solvent removal and silica gel chromatography there was obtained 150 mg of chalcone **2a** eluted with benzene, mp 86–88° (lit.[12] 87–88°), with complex nmr signals between 6.77 and 8.05, identical with those of an authentic sample. A lower yield was observed upon irradiation in benzene. Unreacted starting material, phenol, methyl cinnamate, and 4′-OH chalcone were also isolated.

2-Methoxyphenyl Cinnamate (1b).—The ester was obtained from cinnamic acid (7 g) by treatment with $SOCl_2$ in $CHCl_3$ at reflux followed by reflux with guaiacol in benzene in the presence of Mg. After work-up, the ester (11.9 g) had mp 139–140° (lit.[22] 130°); mol wt 254 (mass spectrum); nmr 3.81 (s, OCH_3), 6.63 and 7.88 (each a d, J = 16 cps, 1 H), and 6.9–7.6 (m, 9 aromatic H's).

The ester (5 g) was irradiated at 300 nm in $CHCl_3$ under nitrogen for 40 hr. Chromatography over silica gel yielded 1.7 g of starting material and 1.4 g of its *cis* isomer, an oil in which the vinyl protons appeared at 6.09 and 7.07 ppm (J = 13 cps). These, as well as guaiacol (160 mg), were eluted with benzene–hexane (1:3). Elution with benzene–hexane (1:1) yielded 700 mg of chalcone **2b**, mp 120–122°, which showed nmr absorption at 3.87 (s, OCH_3), 6.6–7.9 (m, 10 aromatic and vinyl H's), and 13.0 (s, OH). It showed no tendency to isomerize to **3b** in solution.

3,5-Dihydroxyphenyl Cinnamate (1e).—A mixture of cinnamoyl chloride (from 6 g of acid) in 100 ml of benzene, and phloroglucinol (18 g) in 20 ml of pyridine was stirred with cooling for 5 hr. After work-up and chromatography to separate it from some diester, there was obtained 4 g of phloroglucinol monocinnamate: mp 199–200°; mol wt 256 (mass spectrum); nmr 6.25 (s, 3 A ring H's), 7.6 broad s, 5 aromatic H's), 6.71 and 7.95 (each a d, J = 16 cps, vinyl H's), and 9.61 (s, OH). Acetylation with Ac_2O–pyridine yielded a diacetate: mp 76° (hexane); mol wt 340 (mass spectrum); nmr 2.25 (s, 6 H's), 6.53 and 7.84

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(21) "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., Wiley, New York, N. Y., 1955, p 714.

(22) German Patent 62,176; Beilstein, Vol. 9, 1926, p 585.

(each a d, J = 16 cps, 1 H), 6.90 (3 H's), and 7.2–7.6 (m, 5 H's).

A solution of 3.5 g of ester in 300 ml of MeOH was irradiated at 253.7 nm under nitrogen for 22 hr. Silica gel chromatography yielded 0.9 g of methyl cinnamate (*cis* and *trans*), 0.3 g of starting material, 0.85 g of phloroglucinol, as well as the chalcone–flavanone fraction (1.5 g) which was eluted with EtOAc–$CHCl_3$ (1:19). Careful silica gel chromatography of this last fraction with C_6H_6–$CHCl_3$ (1:1) eluted successively a pure sample (150 mg) of 5,7-dihydroxyflavanone (pinocembrin, **3e**) [mp 198–200° (lit.[9a] 203–204°); λ_{max} 288 nm (log ϵ 4.44); and nmr absorption at 2.85 (q, H-3 *cis* to H-2), 3.55 (q, H-3 *trans* to H-2), and 5.67 (q, H-2) with J_{gem} = 17, J_{cis} = 4, and J_{trans} = 12 cps, 6.05 (s, H-6 and H-8), 7.55 (s, B ring H's), and 12.23 (s, 2 OH's)], and 1.15 g of chalcone **2e** [mp 181–183° (lit.[9a] 189–190°); λ_{max} 341 nm (log ϵ 4.6)]. The latter product partially isomerized into the flavanone upon standing in solution.

3,5-Dihydroxyphenyl *p*-Methoxycinnamate (1h).—A benzene solution of the acid chloride, obtained from 5.35 g of 4-methoxycinnamic acid, was treated with 15 g of phloroglucinol in 15 ml of pyridine at 0° for 5 hr. After work-up and silica gel column chromatography, there was obtained 2 g of pure **1h**: mp 161–163°; nmr 3.82 (s, OCH_3), 6.08 (s, 3 H's), 6.6 and 7.8 (each a d, J = 16 cps, 1 H), 6.98 and 7.72 (each a d, J = 8.5 cps, 2 H), and 9.5 (OH). Acetic anhydride in pyridine treatment yielded a diacetate: mp 78–80°; nmr 2.25 (s, 6 H's), 3.6 (s, OCH_3), 6.38 and 7.78 (each a d, J = 16 cps, 1 H), 6.88 (s, 3 H's), 6.88 and 7.49 (each a d, J = 8.5 cps, 2 H's).

A solution of 1.5 g of **1h** in 300 ml of MeOH was irradiated at 300 nm for 22 hr. Silica gel chromatography yielded 70 mg of 5,7-dihydroxy-4'-methoxyflavanone (**3h**) eluted with benzene–hexane (3:1), 500 mg of 2',4',6'-trihydroxy-4-methoxychalcone (**2h**) eluted with EtOAc-$CHCl_3$ (1:19), as well as methyl 4-methoxycinnamate (350 mg, *cis* and *trans*), 50 mg of starting material, and 300 mg of phloroglucinol. The isolated flavanone (isosakuranetin) had mp 190–192° (lit.[5] 190°), and λ_{max} 289 nm (log ϵ 4.37). Its nmr showed absorption at 2.63 (q, H-3 *cis* to H-2), 3.41 (q, H-3 *trans* to H-2), and 5.43 (q, H-2, with J_{gem} = 17, J_{cis} = 3.5, and J_{trans} = 12 cps), 3.71 (s, OCH_3), 5.86 (s, H-6 and H-8), 6.9 (d, J = 8 cps, H-2' and H-6'), 7.37 (d, J = 8 cps, H-3' and H-5'), and 12.06 (OH). The chalcone **2h** isomerized very readily into **3h** in solution and could not be obtained in pure state.

Resorcinol Monocinnamate (1c).—A solution of cinnamoyl chloride (from 9 g of acid) in 50 ml of benzene was added dropwise to a solution of 20 g of resorcinol in 165 ml of benzene–pyridine (10:1). After overnight stirring and work-up of the upper layer, which was washed with dilute HCl and $NaHCO_3$, the residue was chromatographed over silica gel to yield 7 g of **1c**: mol wt 240 (mass spectrum); mp 102–103° (lit. 112–113°,[13] 129–130°[23]); nmr ($CDCl_3$) 7.83 and 6.53 (each a d, J = 16 cps, vinyl H's), 7.5–6.5 (m, 9 aromatic H's), and 6.06 (OH). A solution of 4 g of **1c** in 500 ml of ethanol was irradiated under nitrogen at 253.7 nm for 45 hr. After removal of the solvent and silica gel chromatography, there was obtained 1.2 g of methyl cinnamate (*cis* and *trans*), 140 mg of **2d**, 600 mg of **2c**, and 1.2 g of starting material and resorcinol. The sample of **2d** had mp 171°; nmr complex signals at 7.8–7.0 (8 H's) and 6.45–6.3 (2 H's); λ_{max} 323 (log ϵ 4.44), shifting to 329 in presence of NaOAc and to 362 nm in presence of $AlCl_3$. The sample of **2c** had mp 145° (lit.[13] 146–147°); complex nmr signals at 8.25–7.3 (8 H's) and 6.5–6.3 (2 H's); λ_{max} 320 (log ϵ 4.34) and 343 (log ϵ 4.32), shifting to 376 in presence of NaOAc and to 352 and 420 nm in presence of $AlCl_3$.

Phloroglucinol Hydroxycinnamates. General Procedure.—The hydroxycinnamic acid was added in small portions to a stirred and cooled suspension of sodium hydride in THF–DMF (5:1). After 2 hr, chloromethyl methyl ether was added dropwise with cooling, and the mixture was stirred overnight at room temperature. After filtering off the precipitate, the filtrate was concentrated under vacuum and gave a residue which was refluxed in 3% sodium hydroxide for 2 hr. After ethyl acetate washing, the aqueous layer was acidified with cold dilute HCl and gave the protected acid, which was filtered and dried. The yield was better than 95%.

The acid chloride was prepared in benzene solution by treatment with thionyl chloride and pyridine for 2 hr at room temperature. After removal of the unreacted thionyl chloride under vacuum, the crude chloride was treated with 18 equiv of phloroglucinol in cold benzene–pyridine (4:1). After stirring overnight at room temperature, the mixture was decanted. The lower layer was washed with benzene, which was added to the upper layer. The upper layer was diluted with ethyl acetate, washed with dilute HCl and dilute $NaHCO_3$, dried over $MgSO_4$, and concentrated to yield the esters, contaminated with some phloroglucinol. That mixture was chromatographed over silica gel. $CHCl_3$ eluted the tri- and diesters, whereas $CHCl_3$–MeOH (19:1) eluted the protected monoester which was crystallized from ethyl acetate–hexane. The protecting group was removed by refluxing 1 g of ester in 40 ml of a mixture of trifluoroacetic acid, methanol, and water (1:2:1). The reaction took from 1 to 4 hr and its course was followed by tlc. After work-up, the free ester was purified by silica gel chromatography.

Phlorogulcinol 2-Hydroxycinnamate (1f).—Protection of 2-hydroxycinnamic acid and reaction with phloroglucinol yielded **1f**: mol wt 272; mp 228–230°; nmr spectrum, 10.1 (2 phloroglucinol OH's), 9.25 (OH), 8.05 and 6.78 (each a d, J = 16 cps, vinyl H's), 7.8–6.9 (4 B ring H's), and 6.08 (s, 3 A ring H's). Treatment with acetic anhydride–pyridine yielded a triacetate: mp 110–112°; nmr ($CDCl_3$) 7.4–7.8 (4 B ring H's), 7.0 (s, 3 A ring H's), 6.67 and 8.03 (each a d, J = 16 cps, 1 H), 2.43 (s, 3 H's), and 2.3 (s, 6 H's).

A solution of 350 mg of **1f** in 100 ml of methanol was irradiated at 253.7 nm for a period of 16 hr. After evaporation of the solvent, the residue was chromatographed over silica gel. There was obtained 120 mg of coumarin, mp 70°, identical with an authentic sample, 20 mg of methyl *trans*-2-hydroxycinnamate, and 100 mg of **2f**, in addition to phloroglucinol and starting material. The chalcone **2f** had mp 165–167° (lit.[24] 172–174°); nmr 5.9 (s, 2 A ring H's), 6.7–7.2 (complex, 4 H's), 7.96 and 8.3 (each a d, J = 16 cps, 1 H); λ_{max} 363 (log ϵ 4.25), shifted to 370 with NaOAc, and to 390 nm with $AlCl_3$.

Phloroglucinol 4-Hydroxycinnamate (1g).—The *p*-coumaric acid was converted into the 4-methoxymethyleneoxycinnamic acid, mp 154°. The preparation of the acid chloride often resulted in polymeric products; in order to minimize them, the chloride from 4.5 g of acid was immediately treated with phloroglucinol in excess without removing the excess of thionyl chloride. After removal of the protecting group and chromatography, there was obtained 1.0 g of **1g**: mp 220–222° (lit.[25] ~200°); nmr 6.05 (s, 3 A ring H's), 6.53 and 7.73 (each a d, J = 16 cps, 1 vinyl H), 6.83 and 7.62 (each a d, J = 8.5 cps, 2 B ring H's), and OH's at 9.4 (2 H's) and 10.0 (1 H). Treatment with acetic anhydride–pyridine yielded a triacetate: mp 107–108°, nmr 2.28 (s, 6 H's), 2.32 (s, 3 H's), 6.5 and 7.87 (each a d, J = 16 cps, 1 H), 6.8–7.0 (3 H's), 7.18 and 7.62 (each a d, J = 8.5 cps, 2 H's). A solution of 0.8 g of **1g** in 200 ml of methanol was irradiated at 253.7 nm for a period of 22 hr. Following chromatography over silica gel and nylon powder, there was obtained 300 mg of methyl *cis*- and *trans*-*p*-coumarate, 50 mg of starting material, 120 mg of phloroglucinol, and 260 mg of **2g**. The chalcone was purified by paper chromatography and recrystallized from MeOH. It had mp 184° (lit.[26] 173–174°); nmr 5.9 (s, 2 H's), 6.9 and 7.6 (each a d, J = 8.5 cps, 2 H's), 7.7 and 8.1 (each a d, J = 16 cps, 1 H); λ_{max} 362 (log ϵ 4.44) shifted to 373 with NaOAc, to 400 nm with $AlCl_3$. The chalcone isosalipurpol (**2g**) did not isomerize to the flavanone naringenin (**3g**) during work-up, even when it was placed in acetic acid solution.

Phloroglucinol 3,4-Dihydroxycinnamate (1i).—Caffeic acid was converted into the dimethoxymethyleneoxy derivative, mp 127–129°. The protected acid (7.0 g) was converted into 4.0 g of pure phloroglucinol ester: mp 169–171°; nmr spectrum, 3.5 (s, 6 H's), 5.33 (s, 4 H's), 6.18 (s, 3 H's), 6.75 and 7.83 (each a d, J = 16 cps, 1 H), 7.0–7.6 (m, H's), and 9.56 (2 H's). Removal of the protecting group yielded **1i** in 50% yield: mp 218–220°; nmr spectrum, 6.1 (s, 3 H's), 6.43 and 7.67 (each a d, J = 16 cps, 1 H), 6.7–7.2 (m, 3 H's), and 9.4 (4 H's). Treatment with acetic anhydride–pyridine yielded a tetraacetate: mp 110–111°; nmr 2.27 (s, 6 H's), 2.3 (s, 6 H's), 6.5 and 7.83 (each a d, J = 16 cps, 1 H), 6.91 (s, 3 H's), 7.2–7.5 (m, 3 H's).

A solution of 1.0 g of **1i** in 200 ml of methanol was irradiated at 253.7 nm under nitrogen for 36 hr. Following chromatography

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(24) British Patent 914,248; *Chem. Abstr.*, **58**, 124,723 (1963).

(25) A. Sonn, *Chem. Ber.*, **46**, 4050 (1913).

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over silica gel and nylon, there was obtained 250 mg of methyl caffeate (*cis* and *trans*), 200 mg of phloroglucinol, 100 mg of starting material, and 300 mg of eriodictyol (**3i**): mp 264–266° (lit.[27] 267°); nmr 2.8–3.6 (m, H-3's), 5.6 (qu, H-2) 5.9 (s, H-6 and H-8), and 6.6–6.8 (m, 3 B-ring H's); λ_{max} 289 and 330, identical with that of an authentic sample. The chalcone was originally present but it isomerized completely during the nylon powder chromatography.

Phloroglucinol 3-Methoxy-4-hydroxycinnamate (1j).—Protection of 3-methoxy-4-hydroxycinnamic acid yielded the 3-methoxy-4-methoxymethyleneoxycinnamic acid, mp 137–139°. The protected acid (5 g) was converted into the phloroglucinol monoester (2.3 g): mp 166–168°; nmr spectrum, 3.4 (s, 3 H's), 3.85 (s, 3 H's), 5.22 (s, 2 H's), 6.07 (s, 3 H's), 6.72 and 7.75 (each a d, J = 16 cps, 1 H), 7.0–7.5 (3 H's), and 9.47 (2 H's). Removal of the protecting group yielded the free ester **1j**: mp 234–236; 3.83 (s, 3 H's), 6.07 (s, 3 H's), 6.63 and 7.75 (each a d, J = 16 cps, 1 H), 6.9–7.4 (3 H's), 9.4 (2 OH's), and 9.6 (1 OH). Treatment with acetic anhydride–pyridine yielded a triacetate: mp 111–112°; nmr ($CDCl_3$) 2.18 (s, 6 H's), 2.23 (s, 3 H's), 3.75 (s, 3 H's), 6.32 and 7.6 (each a d, J = 16 cps, 1 H), 6.73 (3 H's), and 6.9–7.1 (3 H's). A solution of 1.5 g of **1j** in 200 ml of methanol was irradiated for a period of 17 hr at 253.7 nm. Chromatography over silica gel yielded 250 mg of methyl 3-methoxy-4-hydroxycinnamate (*cis* and *trans*). The remainder was chromatographed over nylon powder, and yielded 500 mg of starting material, 200 mg of phloroglucinol, and 400 mg of chalcone **2j**, which was further purified by paper chromatography. It had mp 205–208° (lit.[28] 210–212°); nmr 3.8 (s, 3 H's), 5.8 (s, 2 H's), 6.6–7.1 (3 H's), and 7.5 and 7.9 (each a d, J = 16 cps, 1 H); λ_{max} 373 (log ϵ 4.52), shifted to 384 with NaOAc, to 406 with $AlCl_3$.

Phloroglucinol 3,4-Dimethoxycinnamate (1k).—The acid chloride from 10.0 g of 3,4-dimethoxycinnamic acid in 100 ml of benzene was added dropwise with stirring and cooling to a solution of 30.0 g of phloroglucinol in benzene–pyridine (10:3). After 4 hr, the upper layer was worked up as above, and it yielded a mixture which was chromatographed over silica gel. The di- and triesters were eluted with $CHCl_3$, while elution with ethyl acetate–chloroform (1:9) gave 6.0 g of monoester **1k**: mp 204–205; nmr 3.83 (s, 6 H's), 6.0 (3 H's), 6.67 and 7.73 (each a d, J = 16 cps, 1 H), 6.9–7.4 (m, 3 H's), and 9.47 (2 OH's). Acetic anhydride–pyridine treatment yielded a diacetate: mp 146–147°; nmr ($CDCl_3$) 2.3 (s, 6 H's), 3.93 (s, 6 H's), 6.47 and 7.85 (each a d, J = 16 cps, 1 H), and 6.9–7.3 (m, 6 H's). Irradiation of a solution of 2.0 g of **1k** in 300 ml of methanol for 36 hr at 253.7 nm gave, after chromatography over silica gel and nylon, 550 mg of methyl 3,4-dimethoxycinnamate (*cis* and *trans*), 400 mg of starting material, 400 mg of phloroglucinol, and 450 mg of chalcone **2k**, which was recrystallized from methanol and had mp 173: nmr 3.8 (s, 6 H's), 5.9 (s, 2 H's), 7.0–7.3 (3 H's), and 7.65 and 8.1 (each a d, J = 16 cps, 1 H); λ_{max} 366 (log ϵ 4.51), shifted to 378 with NaOAc, and to 400 nm with $AlCl_3$.

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Registry No.—**1b**, 531-40-8; **1c**, 22129-63-1; **1f**, 25518-27-8; **1f** (triacetate), 25518-28-9; **1g**, 25568-73-4; **1g** (triacetate) 25518-29-0; **1h**, 25528-10-3; **1i**, 25528-11-4; **1i** (tetraacetate), 25528-12-5; **1j**, 25528-13-6; **1j** (triacetate), 25528-14-7; **1k**, 25528-15-8; **1k** (diacetate), 25528-16-9; **2b**, 25515-42-8; **2c**, 25515-43-9; **2d**, 25515-44-0; **2f**, 25515-45-1; **2g**, 25515-46-2; **2j**, 25515-47-3; **2k**, 25515-48-4; **3e**, 6307-93-3; **3h**, 480-43-3; **3i**, 4049-38-1; phloroglucinol monocinnamate, 28867-41-0; phloroglucinol (diacetate), 25528-21-6; 3-methoxy-4-methoxymethyleneoxycinnamic acid, 25528-22-7.

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A New Preparation of Coumarans

JOSEPH C. MARTINI, NORMAN W. FRANKE, AND GARY M. SINGERMAN

Gulf Research and Development Company, Pittsburgh, Pennsylvania 15230

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A new reaction for the formation of 2,2-dialkylcoumarans has been discovered. When phenols are allowed to react with 2,2-disubstituted aldehydes in the presence of an acid catalyst, 2,2-dialkylcoumarans are formed in one step.

As part of an investigation of the reaction of various aldehydes with phenol and substituted phenols, the sulfuric acid catalyzed interaction of isobutyraldehyde with phenol in refluxing toluene was observed to give a substantial amount of 2,2-dimethylcoumaran (**3**), which was identified by infrared and nuclear magnetic resonance spectral parameters, elemental analysis, and conversion of the courmaran into the reported[1] solid 5,7-dinitro derivative. In addition an authentic sample of the coumaran (**3**) was prepared from β-methylallyl phenyl ether by the method of Franko-Filipasic.[2]

A number of other aldehydes and substituted phenols were allowed to interact under these same conditions in order to establish the limitations of the method. Isobutyraldehyde reacted with *o*-cresol, *m*-cresol, *p*-cresol, 2,4-xylenol, 4-(1,1,3,3-tetramethylbutyl)phenol, and α-naphthol to give coumarans in yields of 10–62% (Table I). Likewise, 2-ethylhexanal reacted with *m*-cresol to give 2-butyl-2-ethyl-6-methylcoumaran (**6**), but under the same conditions the following aldehydes failed to yield coumarans by reaction with *m*-cresol: acetaldehyde, propionaldehyde, butanal, pentanal, 3-methylbutanal, 2-methyl-2-butenal, and 2-phenylpropionaldehyde. In our hands, the only aldehydes which have produced a coumaran by interaction with a phenol are those which have only one hydrogen atom attached to the second carbon atom of the aldehyde molecule (a 2,2-disubstituted aldehyde).

Each reaction, whether it yielded a coumaran or not, produced varying amounts of resinous materials whose infrared spectra displayed a strong phenolic hydroxyl stretching absorption near 3500 cm^{-1}. Considering the reactants and the reaction conditions, these resins probably have a Novolak-type structure.[3]

The infrared spectra of all the coumarans and of the naphthofuran prepared in this work show a strong ab-

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