All other telluroxides were similarly prepared from the corresponding dibromides.

2-Methoxycyclohexyl phenyl telluroxide hydrate (4, X = OMe): a white solid, mp > 100 °C dec; IR (KBr) 3420 (s, br), 3050, 2940, 2860, 1630, 1575, 1475, 1450, 1439, 1363, 1250, 1185, 1102 (s), 1090 (sh), 1008, 1000, 929, 858, 840, 738 (s), 690 (s), 580 (s, br), 453, 115 (br) cm^{-1}; ^1H NMR (100 MHz) δ 0.8–1.9 (m, 8 H), 2.2 (br s, 1 H), 2.7–3.8 (m, 3 H), 3.32 (s, 3 H), 7.2–7.5 (m, 3 H), 7.8–8.2 (m, 2 H); ^{13}C NMR δ 23.7 (t), 25.5 (t), 26.7 (t), 31.4 (t), 55.5 (q), 77.6 (d), 79.4 (d), 128.8 (d), 130.2 (d), 132.5 (d), 133.3 (s). Anal. Calcd for $C_{13}H_{18}O_2Te \cdot H_2O$: C, 44.37; H, 5.73. Found: C, 44.80; H, 5.20.

***n*-Dodecyl phenyl telluroxide hydrate (5, R = *n*-$C_{10}H_{21}$)**: a colorless syrup; IR (neat) 3400 (br), 3075, 2945 (s), 2880 (s), 1575, 1466 (s), 1433 (s), 1374, 1304, 1180, 1095 (br s), 1035 (br s), 1020 (sh), 998, 995, 910, 735 (s), 688 (s) cm^{-1}; ^1H NMR (60 MHz) δ 0.5–1.5 (m, 23 H), 1.8–2.3 (br, 1 H), 2.5–3.7 (br, m, 3 H), 6.8–7.5 (m, 3 H), 7.5–8.4 (m, 2 H). Anal. Calcd for $C_{18}H_{30}OTe \cdot H_2O$: C, 52.98; H, 7.90. Found: C, 52.42; H, 7.65.

2-Methoxy-2-phenylethyl phenyl telluroxide hydrate (6, R = Ph): a colorless solid, mp 82–84 °C; IR (KBr) 3350 (br), 3070, 2940, 1574, 1490, 1473, 1452, 1434, 1395, 1355, 1305 (br), 1222, 1133, 1095 (s), 1020, 998, 935, 840, 760, 737 (s), 700 (s), 690 cm^{-1}; ^1H NMR (60 MHz) δ 2.65–3.7 (m, 4 H), 3.17 (s, 3 H), 4.80 (t, 1 H), 7.0–7.55 (m, 8 H), 7.9–8.3 (m, 2 H). Anal. Calcd for $C_{15}H_{16}O_2Te \cdot H_2O$: C, 48.18; H, 4.85. Found: C, 48.53; H, 4.61.

2-Methoxydecyl phenyl telluroxide hydrate (6, R = *n*-C_8H_{17}): a colorless syrup: IR (neat) 3400 (br), 3060, 2940 (s), 2870 (s), 1465, 1432, 1370, 1095 (br, s), 736, 688 cm^{-1}; ^1H NMR (60 MHz) δ 0.65–1.6 (m, 17 H), 2.5–4.0 (m, 5 H), 3.25 (s, 3 H), 7.0–7.4 (m, 3 H), 7.7–8.0 (m, 2 H). Anal. Calcd for $C_{17}H_{28}O_2Te \cdot H_2O$: C, 49.80; H, 7.37. Found: C, 49.58; H, 7.46.

Thermal Fragmentation of Alkyl Phenyl Telluroxide Hydrate (Condition d). Pyrolysis of **6** (R = Ph) (0.89 g, 2.5 mmol) was carried out by using Kugelrohr distillation apparatus at 200–240 °C (20 torr) to afford 0.188 g (1.40 mmol, 56%) of α-methoxystyrene as an oil: ^1H NMR (60 MHz) δ 3.64 (s, 3 H), 4.11 (d, 1 H; J = 2.8 Hz), 4.55 (d, 1 H, J = 2.8 Hz), 7.15 (m, 3 H), 7.42 (m, 2 H).

Pyrolysis of **4** (X = OMe) and **6** (R = *n*-C_8H_{17}) was similarly carried out to give 3-methoxycyclohexene [^1H NMR (60 MHz) δ 1.3–2.2 (m, 6 H), 3.34 (s, 3 H), 3.72 (m, 1 H), 5.74 (m, 2 H)] and 2-methoxy-1-decene [^1H NMR (60 MHz) δ 0.85 (t, 3 H), 1.0–1.6 (m, 12 H), 1.9–2.2 (m, 2 H), 3.50 (s, 3 H), 3.83 (s, 2 H); ^{13}C NMR δ 54.6 (q, OCH_3), 79.9 (t, $=CH_2$), 164.6 (s, $=C(OMe)$)], respectively.

In the case of **4** (X = H) pyrolysis was carried out at 200–220 °C (760 torr), and the distillate was dissolved in hexane and analyzed by GLC.

Acknowledgment. We are grateful to Professor Masaya Okano of Kyoto University for his encouragement throughout the work and also to Dr. Hiroshi Fujimoto of Kyoto University for his helpful discussion. We thank reviewers' valuable suggestions on the reaction mechanism.

Registry No. 1 (R = C_6H_{13}), 84988-02-3; **1** (R = C_8H_{17}), 84988-03-4; **1** (R = $C_{12}H_{25}$), 83486-08-2; **3** (X = OH), 84988-18-1; **3** (X = H), 84988-17-0; **3** (X = OMe), 82486-31-5; **4** (X = H), 84988-04-5; **4** (X = OMe), 82486-30-4; **5** (R = $C_{10}H_{21}$), 84988-08-9; **6** (R = Ph), 84988-15-8; **6** (R = C_8H_{17}), 84988-16-9; **7**, 84988-05-6; **8**, 84988-06-7; **9**, 84988-07-8; **10**, 84988-09-0; **11**, 84988-10-3; **12**, 84988-11-4; **13**, 84988-12-5; **14**, 84988-13-6; **15**, 84988-14-7; 5-methoxy-3-octene, 55668-15-0; 3-methoxy-1-cycloheptene, 31059-39-9; 3-methoxy-1-cyclooctene, 26819-54-5; 5-hydroxy-3-octene, 58856-11-4; 2-cyclohepten-1-ol, 4096-38-2; 2-cycloocten-1-ol, 3212-75-7; 2-methoxy-1-decene, 54123-72-7; 2-bromooctane, 557-35-7; 2-bromodecane, 39563-53-6; 2-bromotetradecane, 74036-95-6; bromocyclohexane, 108-85-0; bromocycloheptane, 2404-35-5; bromocyclooctane, 1556-09-8; bromocyclododecane, 7795-35-9; 1-bromododecane, 143-15-7; *trans*-4-octene, 14850-23-8; cycloheptene, 628-92-2; cyclooctene, 931-88-4; *trans*-4-octene oxide, 1689-70-9; cycloheptene oxide, 286-45-3; cyclooctene oxide, 286-62-4; cyclohexene, 110-83-8; styrene, 100-42-5; 1-decene, 872-05-9; 1-octene, 111-66-0; *trans*-2-octene, 13389-42-9; *cis*-2-octene, 7642-04-8; 2-octanol, 123-96-6; 2-octanone, 111-13-7; *cis*-2-decene, 20348-51-0; *trans*-2-decene, 20063-97-2; 2-decanol, 1120-06-5; 2-decanone, 693-54-9; 1-tetradecene, 1120-36-1; 2-tetradecene, 1652-97-7; 2-tetradecanone, 2345-27-9; 2-tetradecanol, 4706-81-4; cyclohexanol, 108-93-0; cyclohexanone, 108-94-1; cycloheptanol, 502-41-0; cycloheptanone, 502-42-1; cyclooctanol, 696-71-9; cyclooctanone, 502-49-8; *trans*-cyclododecene, 1486-75-5; cyclododecanol, 1724-39-6; cyclododecanone, 830-13-7; 1-dodecene, 112-41-4; 1-dodecanol, 112-53-8; 3-methoxy-1-cyclohexene, 2699-13-0; α-methoxystyrene, 4747-13-1; diphenyl ditelluride, 32294-60-3; phenyltellurium tribromide, 36309-64-5.

Stereopopulation Control. 7. Rate Enhancement in the Lactonization of 3-(*o*-Hydroxyphenyl)propionic Acids: Dependence on the Size of Aromatic Ring Substituents

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Received July 22, 1982

Abstract: A series of 4,4-dimethyl-6-hydroxyhydrocoumarins was synthesized with various combinations of methyl and halogen groups at C-5 and C-7. The 5,7-difluoro compound was obtained by condensation of difluorohydroquinone with dimethylacrylic ester. Controlled chlorination of the parent phenolic lactone provided the 5- and 7-chloro isomers, in addition to the 5,7-dichloro product. On the other hand, bromination gave both the 5,7-dibromo and 7-bromo products, without trace of the 5-bromo isomer; finally, iodination gave only the 7-iodo product. These compounds were converted into 6-mesylates as protection against air oxidation of the hydroquinone system in alkaline media. The lactones were hydrolyzed in aqueous base, and the kinetics of relactonization were measured at 30 °C over a wide pH range. As previously shown for similar systems, lactonization is subject to both general acid and general base catalysis. After adjustment of the rate constants (k') for the electronic effects of ring substituents, the residual rate constants (k'') were found to increase with the size of the C-5 substituent, the value for bromine being 4800 times that for hydrogen. A plot of log k''_{cat} vs. the van der Waals radius of the substituent is linear, demonstrating the existence of a free energy continuum in the relationship between k'' for lactonization and the conformational mobility of the three-carbon side chain.

In earlier work on stereopopulation control, we had shown that the introduction of substituents (e.g., CH_3) at unique sites in **1** (Scheme I) has a strong accelerating effect on the rate constants for acid- or base-catalyzed lactonization (**2**, **3**).[1,2] Analogous

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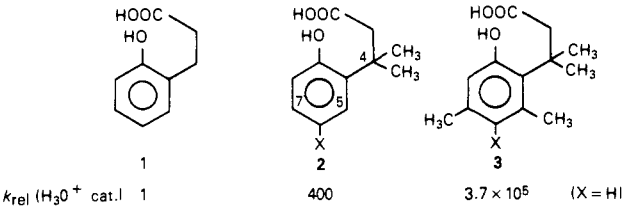
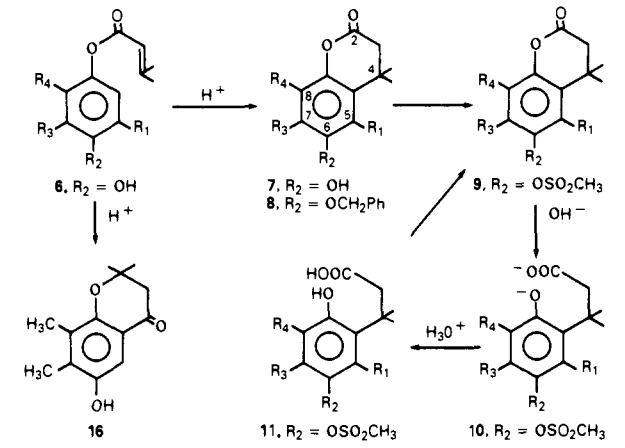
(1) (a) Milstien, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158. (b) Caswell, M.; Schmir, G. L. *Ibid.* **1980**, *102*, 4815. (c) For paper VI in this series, see Borchardt, R. T.; Cohen, L. A. *Ibid.* **1973**, *95*, 8319.

Scheme I



Scheme II

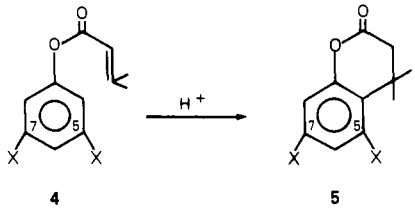


a, $R_1 = R_3 = R_4 = H$
b, $R_1 = R_4 = H$; $R_3 = CH_3$
c, $R_4 = H$; $R_1 = R_3 = CH_3$
d, $R_3 = H$; $R_1 = R_4 = CH_3$
e, $R_1 = H$; $R_3 = R_4 = CH_3$
f, $R_1 = R_3 = R_4 = CH_3$
g, $R_4 = H$; $R_1 = R_3 = F$
h, $R_4 = H$; $R_1 = R_3 = Cl$
i, $R_1 = R_4 = H$; $R_3 = Cl$
j, $R_3 = R_4 = H$; $R_1 = Cl$
k, $R_4 = H$; $R_1 = R_3 = Br$
l, $R_1 = R_4 = H$; $R_3 = Br$
m, $R_1 = R_4 = H$; $R_3 = I$
n, $R_4 = H$; $R_1 = R_3 = I$
o, $R_1 = I$; $R_3 = R_4 = CH_3$
p, $R_1 = R_4 = CH_3$; $R_3 = Br$
q, $R_1 = Br$; $R_3 = R_4 = CH_3$
r, $R_4 = H$; $R_3 = CH_3$; $R_1 = Br$

enhancements have been demonstrated for other ring-forming reactions.[3] Since the replacement of the C-5 hydrogen[4] in the phenolic ring of **2** by a methyl group (**3**) leads to an increase in k_{cat} of almost 10^3, a more thorough investigation of the role of the ring substituent seemed indicated. In particular, we wished to evaluate the importance of the size of the C-5 substituent and to search for a quantitative relationship between size and the rate constant for lactonization. In this report, we describe the results of such a study using the halogen series (as well as hydrogen and methyl) to achieve variation in the size of the C-5 substituent.

Results

Synthesis. We had observed previously[5] that the critical cyclization step (**4** → **5**) for the synthesis of the lactones[6] failed if the aromatic ring bore strongly electronegative substituents. Thus,



the 3,3-dimethylacrylate ester of 4-nitrophenol failed to cyclize under a variety of Friedel–Crafts conditions; however, the corresponding esters of 4-fluoro- and 4-chlorophenol did cyclize to lactones, and we hoped to achieve similar results with the esters of 3,5-dihalophenols. 3,5-Difluorophenol was obtained in 40% yield by a one-step alkaline hydrolysis of commercial 1,3,5-trifluorobenzene. Cyclization of its dimethylacrylic ester (**4**, X = F), under a variety of conditions, gave only trace amounts of the lactone (**5**, X = F), and it seemed likely that results would be even less promising with X = Cl or Br. Fortunately, the deactivating effect of the fluorine atoms was overcome by the presence of the second hydroxyl group of a hydroquinone system. 2,6-Difluorohydroquinone was obtained by persulfate oxidation of 2,6- or 3,5-difluorophenol. Attempts to prepare the dimethylacrylate ester (**6g**) of the hydroquinone (Scheme II) led, invariably, to the bis ester; however, direct condensation of the difluorohydroquinone with methyl 3,3-dimethylacrylate gave **7g** in 40–45% yield. An alternative approach, the direct fluorination of **7a** with xenon difluoride,[7] gave a complex mixture containing mainly a monofluoro lactone, together with **7g** and oxidation products. On the other hand, direct chlorination or bromination of **7a** occurred without difficulty[3b] to give **7h** and **7k**, respectively.

Chlorination of **7a**, either with *N*-chlorosuccinimide in acetic acid or with sulfuryl chloride in chloroform, produced a mixture containing **7h** and the isomeric monochloro lactones **7i** and **7j**. With either reagent, monochlorination occurred to about the same extent at C-5 and at C-7, despite the apparent difference in steric environment.[8] Structural assignments for **7i** and **7j** were based on the different effects of the halogen on the δ values of the benzene ring protons and on those of the *gem*-dimethyl group (Table I).

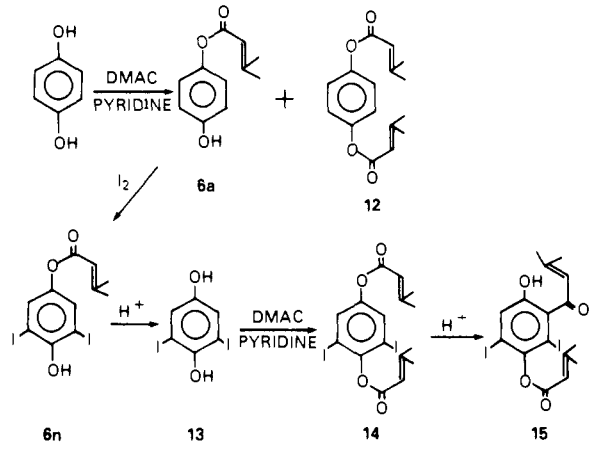
Direct bromination of **7a** with *N*-bromosuccinimide in acetic acid provided **7k** in good yield; even with low ratios of reagent,

Table I. ^1H δ Values for C-4 *gem*-Dimethyl Groups in Lactones **7**[a]

compd	$R_1 = H$	compd	$R_1 \neq H$
7a	1.34	7c	1.45
7b	1.30	7d	1.44
7e	1.28	7f	1.44
7i	1.35	7g	1.44[b]
7l	1.33	7h	1.58
7m	1.35	7j	1.57
		7k	1.60
		7p	1.45
		7q	1.53
		7r	1.55

[a] All spectra measured in $CDCl_3$. [b] Doublet, $J = 2.2$ Hz.

Scheme III



DMAC = 3,3-DIMETHYLACRYLOYL CHLORIDE

(2) The relative rate shown in Scheme I for **3** has been reduced significantly from the value reported in ref 1a; see ref 1b and Discussion section of the present paper.

(3) (a) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9166. (b) *Ibid.* **1972**, *94*, 9175. (c) See following papers in this series.

(4) For the sake of consistency and clarity, we have used the chroman (lactone) numbering system (**7**) for the phenolic acids (**1–3**, **10**, **11**).

(5) Milstein, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1970**, *92*, 4377.

(6) Many of the lactone syntheses involve the acid-catalyzed condensation of the phenol with methyl 3,3-dimethylacrylate; the phenolic ester (**4**) is a presumed intermediate, generated by transesterification.

(7) Anand, S. P.; Quaterman, L. A.; Hyman, H. H.; Migliorese, K. G.; Filler, R. *J. Org. Chem.* **1975**, *40*, 807.

(8) Halogenation with *N*-chlorosuccinimide in 1,2-dichloroethane proceeded much more slowly, giving 18% **7j**, 62% **7i**, and no **7h**.

Table II. Kinetics of Lactonization of Phenolic Acids (11)[a]

compd	$\Sigma\sigma$[b]	$k'_{H_3O^+}$	$k''_{H_3O^+}$[c]	k''_{rel}[d]	k'_{ImH^+}	k'_{Im}	$10^{-4}\cdot k'_{OH^-}$	$10^{-5}\cdot k''_{OH^-}$	k'_{H_2O}[e]	k''_{H_2O}	pK_1[f]	pK_2[f]	λ[g]
11a	0	0.0039	0.0039	1					6.0×10^{-6}	6.0×10^{-6}	5.74	11.18	276
11c	−0.15	10.8	6.09	1560					1.4×10^{-2}	1.2×10^{-2}	(5.76)	(11.59)	290
11f[h]	−0.31	37.0	5.39	1382	0.45	13.6	112	2.0	4.0×10^{-2}	1.3×10^{-2}	(5.76)	(12.01)	290
11g	0.63	0.0138	0.153	39					1.0×10^{-4}	2.2×10^{-4}	(5.69)	9.70	272
11h[i]	0.74	0.503	8.46	2169	0.015	0.564	2.3	2.5	9.0×10^{-3}	2.3×10^{-2}	(5.70)	(9.30)	295
11k	0.74	1.11	18.78	4815	0.030	1.02	4.0	4.3	1.9×10^{-2}	4.8×10^{-2}	(5.70)	(9.34)	297
ρ		−1.66					−1.39		−0.55				

[a] Units of M^{-1} s^{-1}; at 30 °C in water–dioxane (4:1, v/v), μ = 0.3 M NaCl. [b] See Table III and text. [c] Values of k'' were calculated from k', $\Sigma\sigma$, and ρ. [d] For H_3O^+ catalysis. [e] Units of s^{-1}. [f] Values in parentheses were estimated from Hammett plots (see Experimental Section). [g] Wavelengths (nm) at which lactonization rates were followed. [h] Values of k''_{cat} include division by 2.1 to adjust for rate acceleration due to the buttressing effect of the 8-methyl group (see ref 1a). [i] $k'_{AcOH} = 2.75 \times 10^{-2}$ and $k'_{AcO^-} = 3.80 \times 10^{-2}$ M^{-1} s^{-1}.

a monobrominated product could not be detected. On the other hand, the monobromo lactone **7l** was readily obtained when the reaction was performed in chloroform or methanol solution, and this product was easily converted into **7k** by further bromination. In contrast to the results with chlorination, however, the C-5 isomer of **7l** was not detected.

Ultimately, steric crowding at C-5 may become a limiting factor, since iodination of **7a** (under a variety of conditions) produced only the 7-iodo derivative (**7m**). Iodination of the benzyl ether of **7a** (**8a**) did provide a diiodo derivative, but NMR and mass spectra suggested that one of the iodine atoms had entered the benzene ring of the benzyl group. Compound **6n**, obtained by direct iodination of the dimethylacrylate ester of hydroquinone (**6a**), was subjected to Friedel–Crafts cyclization, but 2,6-diiodohydroquinone (**13**) was the only product obtained (Scheme III). When the cyclization was attempted with the diester **14**, a Fries rearrangement occurred to give **15**. In the hope of creating a more favorable electronic environment for cyclization, we explored a synthetic sequence involving only one iodine substituent. Repeated efforts to iodinate 2,3-dimethylhydroquinone resulted only in oxidation to the quinone;[9] on the other hand, the monoester **6e** could be iodinated to **6o**, but attempted cyclization of **6o** resulted in rapid loss of iodine.

For kinetic studies of phenolic acid cyclization, the lactone **7** must be opened in moderately strong base; in such a medium, however, the hydroquinone system undergoes rapid oxidation despite efforts to exclude oxygen.[1a] Reductive removal of the 6-hydroxyl function was not considered, since other work[10] had shown that bulky ortho substituents block the formation of the requisite intermediate (e.g., tetrazole), and since halogen would probably be lost during reduction. Benzyl ether protection at C-6 (**8a**, **8f**,[3a] **8g**) was ineffective in preventing quinone formation in alkaline solution; on the other hand, the monomesylates **10**, which result from alkaline hydrolysis of series **9**, proved to be stable long enough for the kinetics of relactonization to be measured.

It is generally assumed that halogenation of phenols will be directed exclusively to the ortho and para positions, and this assumption provided the initial basis for structural assignments to **7h**–l. Furthermore, we have acquired ample evidence that a substituent at C-5 produces a significant downfield shift in the δ value for the *gem*-dimethyl group at C-4 in **7** and in various noncyclic counterparts.[11,12] Thus, a halogen atom (or other group) can be assigned to C-5 with reasonable certainty (Table I). On the other hand, several reports[13] have described the occurrence of slow meta-halogenation of phenolic systems, and it seemed desirable to provide additional support for our structural assignments. The methylated lactones **7b–e** were prepared by the usual condensation of the appropriate hydroquinones with methyl 3,3-dimethylacrylate;[5] in the synthesis of **7e**, a Fries rearrangement product (**16**) was also obtained in low yield.[14] Upon reaction with *N*-bromosuccinimide, **7d** and **7e** gave the expected products **7p** and **7q**, respectively. The 5-bromo substituent in **7q** had the usual downfield displacement effect on the δ value for the *gem*-dimethyl group. Bromination of **7b** gave a single monobromo derivative in which the δ value for the *gem*-dimethyl group was again shifted downfield. Thus, bromination of **7b** occurs at C-5 (ortho to the phenolic group) to form the supposedly crowded system (**7r**) in preference to an 8-bromo derivative, despite the availability of electronic assistance by the 7-methyl group; on the other hand, attempted iodination of **7b** (or of **7e**) gave only a mixture of monomeric and dimeric oxidation products. Finally, attempted bromination of **7c**, in which substitution must occur meta to the phenolic group, gave no bromo derivative but a similar set of oxidation products.

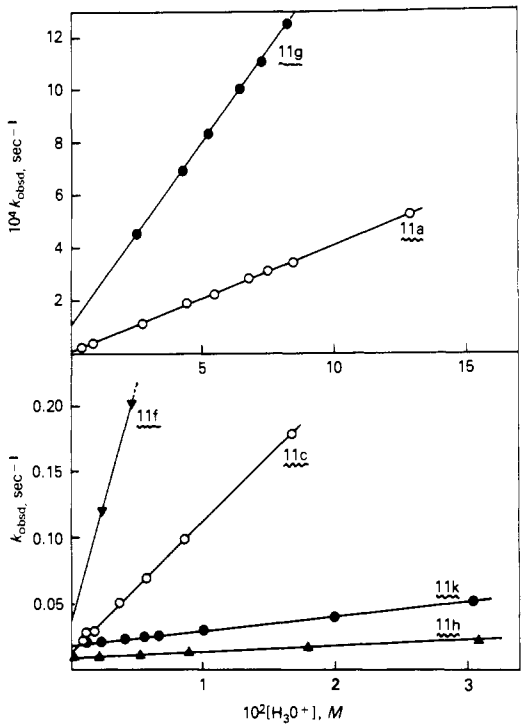


Figure 1. Acid-catalyzed lactonization of phenolic acids (**11**), according to eq 1; at pH values <3, $k_{obsd} = k'_{obsd}$. A linear plot was obtained for **11f**, at least as far as 0.01 M HCl (additional points not shown).

Kinetic Studies. Rates of lactonization of the phenolic acids (**11**) were measured, at 30 °C, in both hydrochloric acid and buffer systems containing 20% dioxane (μ = 0.3 M NaCl). All the cyclizations followed pseudo-first-order kinetics essentially to

(9) Cf. Cressman, H. W. J.; Thirtle, J. R. *J. Org. Chem.* **1966**, *31*, 1279.
(10) Hillery, P.; Cohen, L. A., following paper in this issue.
(11) Quantitative studies on the "van der Waals deshielding" effect are in progress.
(12) Günther, H. "NMR Spectroscopy"; Wiley: New York, 1973; pp 86, 373.
(13) (a) de la Mare, P. B. D.; Hannan, B. N. G. *J. Chem. Soc., Chem. Commun.* **1970**, 156. (b) Brittain, J. M.; de la Mare, P. B. D.; Isaacs, N. S.; McIntyre, P. D. *J. Chem. Soc., Perkin Trans. 2* **1979**, 933. (c) Brittain, J. M.; de la Mare, P. B. D.; Newman, P. A. *Tetrahedron Lett.* **1980**, 4111.
(14) Fries rearrangement byproducts of lactonization have also been observed in the condensation of methyl 3,3-dimethylacrylate with *m*-cresol and with 3,5-dimethylphenol (unpublished observations).

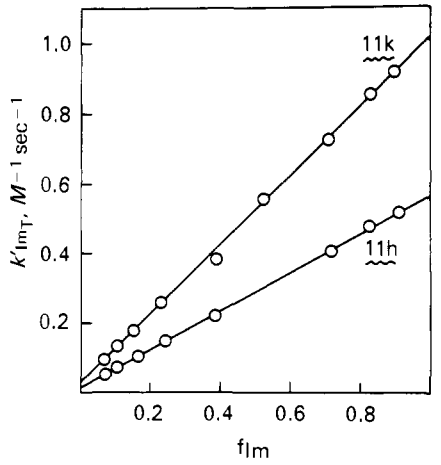


Figure 2. Plots of k'_{Im_T} (slopes of buffer dilution plots) vs. f_{Im}, the fraction of imidazole free base in the buffer at various pH values (eq 3).

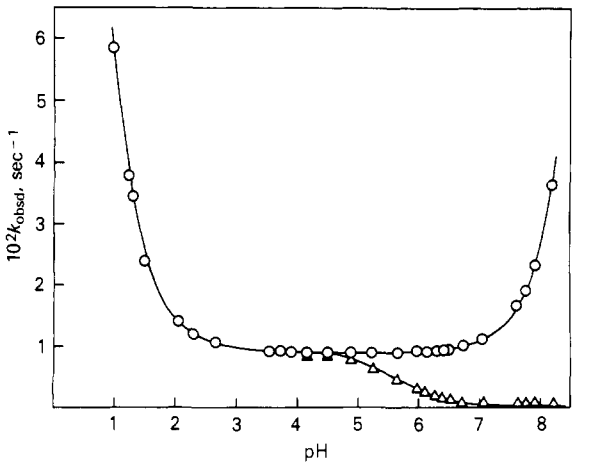


Figure 3. Variations of k_{obsd} and k'_{obsd} with pH for lactonization of **11h**: pH 1–4, k_{obsd} (=k'_{obsd}); pH 4–8 (△), k_0; (○) k'_0. The solid line shows the theoretical pH–rate profile for **11h**, calculated according to eq 4a. The theoretical line for k_0 was calculated as (k'_0) (fraction of neutral **11h**).

completion of reaction ($r > 0.9999$). Infinity spectra were almost identical with those of equivalent concentrations of the pure lactones, indicating the absence of any significant concentration of phenolic acid at equilibrium. Values of k_{obsd} were divided by f_{RCOOH} and (where necessary) by f_{PhOH} to provide k'_{obsd}, which practice is based on the consideration that only the neutral species is kinetically active.[1,5] Since carboxyl ionization is insignificant in the low pH ranges (pH <3), adjustments for f_{RCOOH} were unnecessary and $k'_{obsd} = k_{obsd}$. Plots of k'_{obsd} vs. $[H_3O^+]$ were linear (Figure 1) and obeyed the simple rate law of eq 1. Values of

$$k'_{obsd} = k'_{H_3O^+}[H_3O^+] + k'_{H_2O} \quad (1)$$

$k'_{H_3O^+}$ and k'_{H_2O} were obtained by least-squares analysis ($r > 0.998$) and are summarized in Table II.

Rates of lactonization in acetate buffer were measured for **11h** and, in imidazole buffer (0.05–0.3 M), for **11f**, **11h**, and **11k**. Buffer dilution plots were linear and obeyed eq 2, in which $[B_T]$

$$k'_{obsd} = k'_{B_T}[B_T] + k'_0 \quad (2)$$

is the total buffer concentration. Several runs were extended to 1 M buffer without evidence of curvature. Typical secondary plots of k'_{B_T} vs. mole fraction of buffer base are shown in Figure 2; the slopes follow eq 3, in which f_B is the mole fraction of buffer base

$$k'_{B_T} = k'_{BH}(f_{BH}) + k'_B(f_B) \quad (3)$$

(imidazole) and f_{BH}, that of buffer acid present at a given pH value. Thus, the y intercept at $f_B = 0$ represents k'_{BH} and that at $f_B = 1$ provides k'_B; the values obtained are summarized in Table II.

The overall pH dependence of rate constants (eq 4a) for

$$k'_0 = k'_{H_3O^+}[H_3O]^+ + k'_{OH^-}[OH^-] + k'_{H_2O} \quad (4a)$$

$$\log (k'_0 - k'_{H_2O}) = \log k'_{OH^-} + \log [OH^-] \quad (4b)$$

buffer-independent lactonization of **11h** is shown in Figure 3, together with a comparison of values of k_0 and k'_0 for the higher pH region. The contributions of the acid-catalyzed reaction to k'_0 above pH 6 are very small and can be ignored. The values of k'_{H_2O} derived from kinetics at low pH were used to evaluate k'_{OH^-} according to eq 4b; the resulting plots were linear (slope $\simeq$ 1) and provided the values of k'_{OH^-} given in Table II.

Discussion

In our earlier studies of the kinetics of lactonization in series **3**,[1a] rates were measured for reactions in imidazole buffer media at pH 7–8. The buffer-catalyzed reactions were already so fast at pH 7 that, without the use of stop-flow equipment, it seemed unlikely that reliable data could be obtained at lower pH values. Accordingly, values of $k'_{H_3O^+}$ were estimated by curve-fitting to the small values of k'_0 derived by extrapolation of buffer dilution plots. In the present studies with series **11**, we found that k'_{obsd} did not increase with acidity as rapidly as we had projected and that rates of lactonization could be measured even at pH 1–2. Thus, the rather large differences between the *measured* values for series **11** and the *estimated* values for series **3** cast considerable doubt on the validity of the latter data. At the same time, Caswell and Schmir[1b] had occasion to reinvestigate one member of series **3** and advised us that we had apparently overestimated the value of $k'_{H_3O^+}$ for this compound by a considerable factor. We have now confirmed the results of Caswell and Schmir, both by standard UV and stop-flow measurements, and have used their revised values as the basis for the rate-enhancement factors of Scheme I. The results for **11** (Table II) are consistent in magnitude with the new values for series **3**.

The variations in each set of specific rate constants (k'_{cat}) of Table II arise from a combination of electronic and steric effects, and adjustments for the electronic effects of aromatic ring substituents must be made prior to any evaluation of steric effects. As indicated in eq 5 and 6, and as previously argued,[1a,5] we

$$A \underset{}{\overset{K}{\rightleftharpoons}} T \xrightarrow{k} \text{lactone} + H_2O \quad (5)$$

$$\text{rate} = k[T] = Kk[A] \text{ and } k'_{obsd} = Kk \quad (6)$$

consider breakdown of the tetrahedral intermediate (T) to be rate-limiting and to be influenced by aryl-ring substituents according to $\sigma^\circ\rho_k$; the steady-state concentration of T, however, will be dependent on K and on the concentration of phenolic acid (A), and K should be influenced by substituents according to $\sigma^-\rho_K$. Combination of these effects leads to eq 7, in which k'' represents

$$\log (k''/k') = \alpha\sigma^0\rho_k + \beta\sigma^-\rho_K \quad (7)$$

the hypothetical rate constant devoid of substituent electronic effects, while α and β denote the normalized fractional effects ($\alpha + \beta = 1$) of a substituent on the consecutive steps. Since ρ_k and ρ_K cannot be determined independently of each other, we must use empirical values of ρ for the overall reaction in order to calculate k''. Nor can α and β be evaluated and, since $\sigma_m^0 \simeq \sigma_m^-$ for the substituents used in this study, we have arbitrarily given α and β equal weight. Thus, eq 7 is simplified to provide eq 8

$$\log (k''/k') = (\Sigma\sigma_{av})\rho \quad (8)$$

in which $\sigma_{av} = {}^1/_2(\sigma^0 + \sigma^-)$ for each substituent. A set of ρ values for k'_{cat}, involving several general acids and bases, had been previously determined for series **2** based on σ_p^- values for **X**.[5] These ρ values have now been redetermined for series **2**, on the basis of ${}^1/_2(\sigma_p^0 + \sigma_p^-)$, giving improved correlations and slightly different slopes (Table II). The excellent fit for fluoro and nitro substituents supports our assumption that $\alpha \simeq \beta$. Plots of ρ vs. the statistically adjusted pK_a values of the catalyst acids and bases are shown in Figure 4. As argued by Cordes and Jencks,[15] there

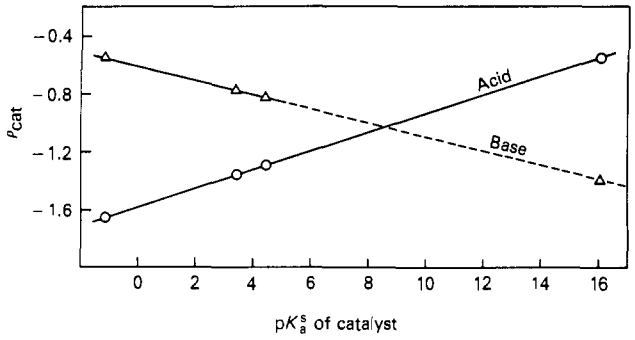


Figure 4. Plots of ρ_{cat} (for series 2) vs. pK_a^s (statistically adjusted)[38] for catalyst acids and bases. Dashed line indicates extrapolation of base plot to obtain a value for ρ_{OH^-}.

exists a theoretical basis for linear correlation in such plots; linearity is observed, at least for the limited data points available. The kinetic studies with series **2** did not provide values of k'_{OH^-} and, thus, a ρ value for hydroxide ion catalysis was lacking; an estimated value of $\rho = -1.39$ was obtained by extrapolation of the general base slope of Figure 4. The set of ρ values given in Table II was used for calculations involving eq 8; the resultant values of k''_{cat} are given in Table II. Since the 6-mesyloxy group is common to all compounds in this kinetic study, no adjustment was made for that substituent.

It is evident from the values of $k''_{H_3O^+}$ that, after adjustment for electronic effects, a sizable steric factor remains operative which is qualitatively consistent with the size of the C-5 substituent. A rate-enhancement factor of almost 5000 is realized when H-5 is replaced by bromine, and the overall trend in $k''_{H_3O^+}$ suggests the existence of a free-energy continuum. Indeed, a linear correlation was obtained (Figure 5) in a plot of log $k''_{H_3O^+}$ vs. the van der Waals radius of the substituent (r_v), based on values recommended by Bondi[16a] and Charton.[16b] The radius of the methyl group was increased slightly from Charton's minimum value of 1.715 to 1.73 Å to allow for some degree of rotational freedom; the effective radius of the 5-bromo group was reduced from Bondi's value of 1.85 to 1.81 Å, because we believe that this substituent is partially distorted in-plane or out-of-plane to accommodate a small degree of crowding. These modifications in the nonbonded radii are supported by NMR studies, which will be reported subsequently.[11] Plots of log k''_{H_2O} and of log k''_{OH^-} vs. van der Waals radii are also linear, as shown in Figure 5. The availability of such linear correlations not only will permit us to select C-5 substituents in order to achieve a desired rate of ring closure, but may also provide a kinetic method for the determination of van der Waals radii for other symmetrical functional groups. Thus, the slopes of Figure 5 lead to eq 9 and 10 for H_3O^+ and H_2O catalysis, respectively.

$$\log k''_{H_3O^+} = 6.12(r_v) - 9.79 \quad (9)$$

$$\log k''_{H_2O} = 6.64(r_v) - 13.29 \quad (10)$$

Attempts to test the validity of these relationships for other substituents are in progress.

The dependence of log k''_{cat} for lactonization (in series **11**) on the size of the C-5 substituent has been clearly demonstrated; however, the underlying cause for the rate-enhancement effect has not yet been established. Relief of steric crowding in the conversion of phenolic acid to lactone has been suggested as a major contributing factor.[17] Alternatively, or concurrently, the C-5 group may provide a barrier to the rotational flexibility of the C-4 *gem*-dimethyl groups, in turn limiting the conformational freedom of the carboxyl group and facilitating the formation of a tetrahedral intermediate. Efforts to differentiate between these interpretations (or others) are continuing.

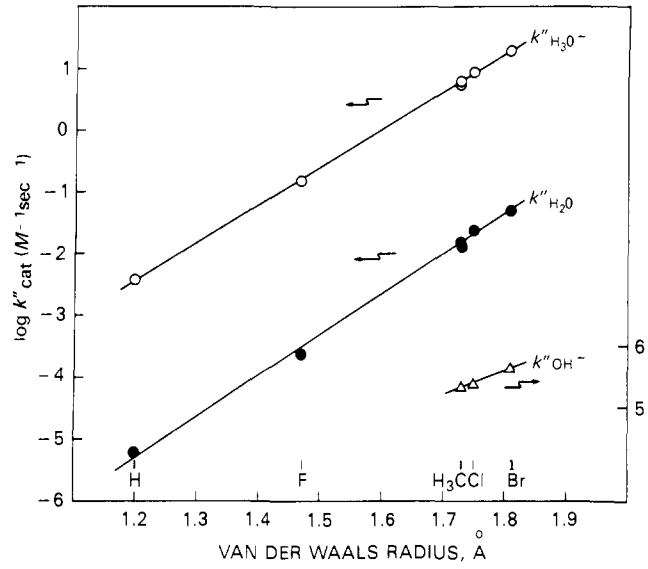


Figure 5. Plots of log k''_{cat} vs. van der Waals radii of C-5 substituents.

Experimental Section[18]

3,5-Difluorophenol. This compound had been previously prepared by mononitration of 4-acetylamino-1,3-difluorobenzene, followed by hypophosphorous acid deamination, iron reduction,[19a] and diazotization of the product.[19b] The five-step sequence provided an overall yield of 20%. The following method, involving a one-step conversion of commercial 1,3,5-trifluorobenzene, gives a 40% yield.[20] The displacement of a single fluorine atom by potassium hydroxide in Me_2SO is based on an earlier procedure for the conversion of hexafluorobenzene to pentafluorophenol with potassium hydroxide in *tert*-butyl alcohol.[21] In the case of the trifluorobenzene, however, potassium hydroxide in *tert*-butyl alcohol or in 1,2-dimethoxyethane gave only poor yields of the phenol.

A suspension of 56 g (1 mol) of potassium hydroxide pellets in 350 mL of dry Me_2SO[22] was stirred vigorously under nitrogen and was heated to 132–134 °C (oil bath) in a three-neck flask equipped with an efficient condenser. When all of the potassium hydroxide had dissolved, 26.4 g (0.2 mol) of 1,3,5-trifluorobenzene (PCR, Inc.) was added in one portion through the condenser. Heating and stirring were continued for 1 h, during which time the two-phase system became dark and a solid deposited on the walls of the flask. The reaction mixture was cooled and poured into 1000 mL of ice–water; the flask was rinsed with several portions of water. The combined solutions were saturated with sodium chloride, acidified with concentrated hydrochloric acid, and extracted with 2 × 200 and 2 × 100 mL of ether. The combined extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated to a dark oil. Distillation under reduced pressure gave a small forerun, followed by 10.1 g (40%) of the phenol, bp 65–68 °C (15 mm), mp 49.5–52.5 °C (lit.[19b] mp 55 °C). A short air condenser was used in the distillation to prevent clogging by the partially solid distillate, a hot air gun being used toward the end of the distillation to liquefy the solid condensate: ^{1}H NMR ($CDCl_3$) δ 5.55 (br, 1, OH), 6.22–6.53 (m, 3, aryl H's); ^{1}H NMR (D_2O) δ 6.46–6.60 (m, aryl H's); ^{19}F NMR (D_2O) δ −33.0 (d, d, J_{HF} = 10 Hz) relative to external CF_3COOH.

The compound was characterized further as its an α-naphthyl urethane, which was obtained by reaction with α-naphthyl isocyanate and a trace of pyridine, and was twice recrystallized from chloroform–hexane, mp 145–147 °C. Anal. ($C_{17}H_{11}F_2NO_2$) C, H, F, N.

(15) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 4319.
(16) (a) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441. (b) Charton, M. *J. Am. Chem. Soc.* **1969**, *91*, 615.
(17) Danforth, C.; Nicholson, A. W.; James, J. C.; Loudon, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 4275. Winans, R. E.; Wilcox, C. F., Jr. *Ibid.* **1976**, *98*, 4281.

(18) All combustion analyses and mass spectral measurements were performed by the Microanalytical Services and Instrumentation Section of the Laboratory of Chemistry, NIADDK, under the direction of Dr. D. F. Johnson. All reaction products were checked for homogeneity by NMR and TLC. ^{1}H NMR data are reported relative to $(CH_3)_4Si$. Melting and boiling points are uncorrected.
(19) (a) Finger, G. C.; Reed, F. H.; Finnerty, J. L. *J. Am. Chem. Soc.* **1951**, *73*, 153. (b) Finger, G. C.; Gortatowski, M. J.; Shiley, R. H.; White, R. H. *Ibid.* **1959**, *81*, 94.
(20) By use of the same procedure, *m*-difluorobenzene was converted into *m*-fluorophenol in 40% yield, bp 83–85 °C (22 mm); lit.[19b] bp 178 °C (760 mm).
(21) Birchall, J. M.; Haszeldine, R. N. *J. Chem. Soc.* **1959**, 13.
(22) Corey, E. J.; Chaykovsky, M. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 755.

Repetition of the above procedure with addition of 18-crown ether resulted in a poorer yield of the phenol. Runs at higher concentration of trifluorobenzene gave significant amounts of the intermolecular product, bis(3,5-difluorophenyl) ether.

3′,5′-Difluorophenyl 3,3-Dimethylacrylate (4, X = F). To a stirred solution of 11.05 g (85 mmol) of 3,5-difluorophenol and 10.07 g (85 mmol) of 3,3-dimethylacryloyl chloride in 150 mL of dry ether was added, dropwise over 25 min, a solution of 8.58 g (85 mmol) of triethylamine in 20 mL of ether. After 10 min storage of the mixture at ambient temperature, GLC (15% Carbowax 20 M) showed all of the phenol to have been converted into ester. Triethylamine hydrochloride was removed by filtration, the solvent was evaporated in vacuo, and the residual syrup was used without further purification: NMR ($CDCl_3$) δ 1.90 and 2.18 (two d, 6, J = 1 Hz, CH_3's), 5.81 (m, 1, vinyl H), 6.63 (m, 3, aryl H's).

4,4-Dimethyl-5,7-difluorohydrocoumarin (5, X = F). Mixtures of equimolar amounts of 3,5-difluorophenol and methyl 3,3-dimethylacrylate in benzene were heated at reflux with catalytic amounts of sulfuric acid for 24–72 h.[23] In each run, the solvent was evaporated in vacuo, the residue was dissolved in ether, and the solution was washed with water, dried ($MgSO_4$), and evaporated. NMR analysis showed weak signals at the positions expected for the lactone, which did not increase with time of reflux: NMR ($CDCl_3$) δ 1.45 (d, 6, J = 2 Hz, C-4 CH_3's), 2.63 (s, 2, C-3 CH_2), 6.65 (2, m, aryl H's). No lactone was observed in the presence of boron trifluoride etherate after 3 h at ambient temperature. Attempts to cyclize **4** (X = F) with sulfuric acid or aluminum chloride led to rapid regeneration of the phenol.

2,6-Difluorohydroquinone. 2,6-Difluorophenol (bp 66 °C at 20 mm) was prepared in 59% yield by oxidation of the lithium derivative of 1,3-difluorobenzene.[24] The phenol was oxidized to the hydroquinone with potassium persulfate, according to the method previously used with 2-fluorophenol.[25] From 6.5 g (50 mmol) of the phenol, there was obtained (after chromatographic purification) 1.65 g (22%) of the hydroquinone as colorless needles from chloroform–hexane, mp 150.5–152 °C: IR (KBr) 3413 and 3257 (OH) cm^{-1}; NMR ($CDCl_3$) δ 6.5 (d, 2, J_{HF} = 10 Hz, aryl H's) and 8.28 (br s, 2, OH's). Persulfate oxidation was also applied to 3,5-difluorophenol, the hydroquinone being obtained in about the same yield. Anal. ($C_6H_4F_2O_2$) C, H, F.

5,7-Difluoro-4,4-dimethyl-6-hydroxyhydrocoumarin (7g). 2,6-Difluorohydroquinone (374 mg, 2.56 mmol) and methyl 3,3-dimethylacrylate (311 mg, 2.73 mmol) were dissolved in 15 mL of benzene, 15 drops of concentrated sulfuric acid was added slowly, and the mixture was stirred at reflux for 4 h. The reaction mixture was cooled and the solvent was removed under reduced pressure; the residual oil was dissolved in ether, the solution was washed several times with water, and the ether layer was dried ($MgSO_4$). Following evaporation of the solvent, the residual solid was chromatographed on 125 g of silica gel (eluant, 5% methanol in chloroform). The middle fractions were combined and evaporated in vacuo; the residual solid was crystallized from chloroform–hexane to give 0.24 g (41%) of **7g**, mp 158–160 °C: IR (KBr) 3333 (OH) and 1763 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.44 (d, 6, J_{HF} = 2.2 Hz, C-4 CH_3's), 2.62 (s, 2, 3-CH_2), 6.67 (two d, 1, $J_{H(8)F(7)}$ = 10 Hz, $J_{H(8)F(5)}$ = 1.8 Hz, (H-8)). Anal. ($C_{11}H_{10}F_2O_3$) C, H, F.

Intramolecular cyclization of the dimethylacryloyl ester of the hydroquinone (**6g**) could not be explored as an alternative route to **7g**, because condensation of the hydroquinone with dimethylacryloyl chloride consistently gave the bis ester.

5,7-Dichloro-4,4-dimethyl-6-hydroxyhydrocoumarin (7h) and the Isomeric Monochloro Derivatives (7i, 7j). Method A. To a solution of 0.96 g (5 mmol) of 4,4-dimethyl-6-hydroxyhydrocoumarin (**7a**)[5] in 30 mL of chloroform was added 2 mL (3.33 g, 25 mmol) of sulfuryl chloride, and the mixture was refluxed for 24 h. The yellow solution was evaporated in vacuo and the residual material was chromatographed on silica gel with benzene as eluant. The solid residue from the first fraction was crystallized from cyclohexane to give 0.40 g (30%) of **7h**, mp 131–132 °C: IR (KBr) 3413 (OH) and 1770 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.58 (s, 6, C-4 CH_3's), 2.67 (s, 2, C-3 CH_2), 6.04 (s, 1, OH), 7.12 (s, 1, H-8). Anal. ($C_{11}H_{10}Cl_2O_3$) C, H, Cl.

The second fraction was judged by NMR to be a mixture, and it was rechromatographed on silica gel (eluant, 20% ethyl acetate in hexane). The faster moving material crystallized from cyclohexane, giving 114 mg (10%) of the 5-chloro derivative (**7j**), mp 128.5–130 °C: IR (KBr) 3460 (OH) and 1789 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.56 (s, 6, C-4 CH_3's), 2.65 (s, 2, C-3 CH_2), 5.89 (s, 1, OH), 6.98 (s, 2, aryl H's). Anal. ($C_{11}H_{11}ClO_3$) C, H, Cl.

The slower moving material also crystallized from cyclohexane, giving 120 mg (11%) of the 7-chloro derivative (**7i**), mp 111–113 °C: IR (KBr) 3300 (OH) and 1742 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.35 (s, 6, C-4 CH_3's), 2.62 (s, 2, C-3 CH_2), 7.02 (s, 1, H-5), 7.10 (s, 1, H-8). Anal. ($C_{11}H_{11}ClO_3$) C, H, Cl.

Method B. A solution of 279 mg (2.1 mmol) of freshly crystallized (benzene) *N*-chlorosuccinimide in 10 mL of glacial acetic acid was added to a stirred solution of 192 mg (1 mmol) of **7a** and 0.5 g of anhydrous sodium acetate in 10 mL of acetic acid. The reaction mixture was stored at 60 °C for 6.5 h and diluted with 100 mL of water; the aqueous mixture was extracted with 3 × 25 mL of ether. The combined extracts were washed successively with water, saturated sodium bicarbonate, and saturated brine, then dried ($MgSO_4$), and evaporated in vacuo. The residual material was chromatographed on silica gel (eluant, 20% ethyl acetate in hexane). On the basis of TLC and NMR comparisons, the first fraction was found to consist of 54 mg (21%) of **7h**, the second contained 32 mg (14%) of **7j**, and the third consisted of 35 mg (15%) of **7i**.

7-Bromo-4,4-dimethyl-6-hydroxyhydrocoumarin (7l). A stirred solution of 1.526 g (8 mmol) of **7a** in 100 mL of chloroform was cooled to 0 °C and 1.424 g (8 mmol) of freshly crystallized (water) *N*-bromosuccinimide was added in portions over 15 min. The solution was stirred an additional 30 min at ambient temperature, washed with 3 × 30 mL of water, dried ($MgSO_4$), and evaporated. The residual material was crystallized from chloroform–hexane to give 1.873 g (86%) of **7l**, mp 136–137 °C: IR (KBr) 3367 (OH) and 1736 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.33 (s, 6, C-4 CH_3's), 2.62 (s, 2, C-3 CH_2), 7.03 (s, 1, H-5), 7.21 (s, 1, H-8). Anal. ($C_{11}H_{11}BrO_3$) C, H, Br.

The 7-bromo lactone (**7l**) was also detected by TLC in small-scale reactions of **7a** with NBS in dichloromethane at −50 °C, in methanol at 0 °C, and in glacial acetic acid at 0 °C. Upon further reaction with NBS in chloroform, **7l** was rapidly and cleanly converted into the dibromo lactone (**7k**).

4,4-Dimethyl-6-hydroxy-7-iodohydrocoumarin (7m). A solution of 0.90 g (4 mmol) of *N*-iodosuccinimide in 20 mL of glacial acetic acid was added dropwise over 15 min to a stirred solution of 384 mg (2 mmol) of **7a** and 0.5 g of anhydrous sodium acetate in 20 mL of acetic acid at 50 °C. The solution was stirred at 50 °C for an additional 45 min (with protection from light) and was then poured into 150 mL of water. The mixture was extracted with 3 × 25 mL of ether and the combined extracts were washed with water, 10% sodium carbonate, and saturated brine; the ether layer was dried ($MgSO_4$) and evaporated in vacuo. The residual material was chromatographed on silica gel (eluant, chloroform). Crystallization of the slower moving fraction from acetone–hexane gave 133 mg (21%) of **7m**, mp 149–150 °C: IR (KBr) 3300 (OH), 1727, 1745 (C=O) cm^{-1};[26] NMR ($CDCl_3$) δ 1.35 (s, 6, C-4 CH's), 2.63 (s, 2, C-3 CH_2), 7.08 (s, 1, H-5), 7.49 (s, 1, H-8). Anal. ($C_{11}H_{11}IO_3$) C, H, I.

Attempts at Diiodination of 7a. Diiodination of the phenolic lactone was attempted by use of the following reagents at ambient temperature: (1) I_2 + NaOAc in AcOH; (2) ICl in AcOH; (3) I_2 + KOBu^t in benzene.[27a] In each case, **7m** was the only product obtained. Iodine + *t*-BuOCl in CCl_4[27b] gave the dichloro lactone (**7h**) while *t*-BuOCl + HgI_2 in CCl_4[27c] gave a mixture of **7h** and **7m**. Oxidation to the quinone-propionic acid[3b] was observed with the following reagents: (1) I_2 + HIO_4 in AcOH;[27d] (2) I_2 + $AgOCOCF_3$ in $CHCl_3$ or AcOH;[27e] (3) I_2 + TlOAc in AcOH;[27f] (4) I_2 + $Tl(OCOCF_3)_3$ in CF_3COOH.[27g] Iodination of **8a** with the last reagent gave a product whose mass spectrum showed peaks at 535 (I_2-**8a** + 1) and 217 (iodotropylium) mass units; the NMR spectrum did not show the downfield shift for the C-4 *gem*-dimethyl group expected with C-5 substitution. In contrast, bromination of **8a** with *N*-bromoacetamide in AcOH did provide the 5,7-dibromo product (**8h**).

4′-Hydroxyphenyl 3,3-Dimethylacrylate (6a).[28] A solution of 5.93 g (50 mmol) of 3,3-dimethylacryloyl chloride in 25 mL of dry ether was added dropwise over 45 min to a stirred solution of 5.5 g (50 mmol) of hydroquinone and 3.95 g (50 mmol) of pyridine in 200 mL of dry ether. The mixture was stirred at ambient temperature for 2 h and then washed

(23) Oven-dry glassware, including a Dean-Stark trap, was used in all lactone syntheses; the small amount of water collected in the trap apparently retains a portion of the methanol formed, since yields are improved by use of a trap.

(24) Roe, A. M.; Burton, R. A.; Willey, G. L.; Baines, M. W.; Rasmussen, A. C. *J. Med. Chem.* **1968**, *11*, 814.

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(26) For studies of H-bonding in lactones, see Searles, S.; Tamres, M.; Barrow, G. M. *J. Am. Chem. Soc.* **1953**, *75*, 71.

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(28) Cf. Clark, V. M.; Eraut, M. R.; Hutchinson, D. W. *J. Chem. Soc. C* **1969**, *79*.

with 50 mL of dilute hydrochloric acid. The ether layer was dried ($MgSO_4$) and the solvent was evaporated; the residual material was chromatographed on silica gel (eluant, 25% ethyl acetate in hexane). The first fraction crystallized from hexane to give 436 mg (4%) of the bis ester **12**, mp 112–113 °C: IR (KBr) 1727 (C=O) and 1639 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.98 and 2.22 (two d, 12, J = 1 Hz, vinyl CH_3's), 5.93 (m, 2, vinyl H's), 7.15 (s, 4, aryl H's). Anal. ($C_{16}H_{18}O_4$) C, H.

The second fraction crystallized from chloroform–hexane to give 5.16 g (54%) of **6a**, mp 118–120 °C: IR (KBr) 3460 (OH), 1715 (C=O), 1645 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.96 and 2.21 (two d, 6, J = 1 Hz, vinyl CH_3's), 5.94 (m, 1, vinyl H), 6.55 (s, 1, OH), 6.76 and 6.85 (two s, 4, aryl H's). Anal. ($C_{11}H_{12}O_3$) C, H.

3′,5′-Dilodo-4′-hydroxyphenyl 3,3-Dimethylacrylate (6n). To a stirred solution of 1.92 g (10 mmol) of **6a** in 75 mL of glacial acetic acid containing 5 g of anhydrous sodium acetate was added 4.5 g (20 mmol) of *N*-iodosuccinimide in portions over 15 min. The dark solution was stirred an additional 30 min at 55–60 °C and was then poured into 150 mL of ice–water. The aqueous mixture was extracted with 3 × 75 mL of ether; the combined extracts were washed successively with water, saturated sodium bicarbonate, and saturated brine, dried ($MgSO_4$), and evaporated. The residual material was chromatographed on silica gel (eluant, 25% ethyl acetate in hexane) to give a single fraction which, upon crystallization from methanol–water, gave 1.27 g (29%) of **6n**, mp 76–78 °C: IR (KBr) 3460 (OH), 1736 (C=O), 1647 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.93 and 2.18 (two d, 6, J = 1 Hz, vinyl CH_3's), 5.58 (br s, 1, OH), 5.78 (m, 1, vinyl H), 7.36 (s, 2, aryl H's). Anal. ($C_{11}H_{10}I_2O_3$) C, H, I.

2′,6′-Diiodohydroquinone Bis(3,3-dimethylacrylate) (14). To a stirred solution of 1.00 g (3.04 mmol) of 2,6-diiodohydroquinone and 0.40 g (3.38 mmol) of dimethylacryloyl chloride in 40 mL of dry ether was added a solution of 332 mg (3.3 mmol) of triethylamine in 10 mL of dry ether, over 5 min at ambient temperature. After 2 h, TLC (silica gel, 25% ethyl acetate in hexane) indicated the presence of starting material and **14**, but not of the monoester (**6n**). An additional 392 mg (3.31 mmol) of the acid chloride and 347 mg (3.44 mmol) of triethylamine were added and stirring was continued for 30 min. The mixture was filtered and the solution evaporated to dryness. The residual material crystallized from methanol–water to give 1.25 g (78%) of **14**, mp 105–107 °C: IR (KBr) 1742 (C=O) and 1642 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.98 and 2.22 (two d, 6, J = 1 Hz, 4′-ester vinyl CH_3's), 2.03 and 2.27 (two d, 6, J = 1 Hz, 1′-ester vinyl CH_3's), 5.88 (m, 1, 4′-ester vinyl H), 6.05 (m, 1, 1′-ester vinyl H), 7.30 (s, 2, aryl H's). Anal. ($C_{16}H_{16}I_2O_4$) C, H, I.

Attempted Cyclization of 14. A solution of 100 mg of **14** in 50 mL of benzene was stirred at ambient temperature with 1 mL of concentrated sulfuric acid or with 1 mL of $BF_3{\cdot}Et_2O$. After 3 h, the starting material had disappeared; in both reactions, a new product was obtained isomeric with **14**, and giving an NMR spectrum suggestive of Fries rearrangement to the ketone **15**: NMR ($CDCl_3$) δ 1.92 and 2.16 (two d, 12, J = 1 Hz, vinyl CH_3's), 5.70 (m, 2, vinyl H's), 7.22 (s, 1, aryl H). Reaction of **14** with aluminum chloride in refluxing carbon disulfide resulted in the liberation of iodine.

6-Hydroxy-4,4,7-trimethylhydrocoumarin (7b). To a solution of 1.24 g (10 mmol) of 2-methylhydroquinone and 1.14 g (10 mmol) of methyl 3,3-dimethylacrylate in 50 mL of benzene was added 1 mL of concentrated sulfuric acid. The mixture was stirred at reflux for 3 h and, after cooling, washed with water (twice), saturated sodium bicarbonate, dilute hydrochloric acid, and saturated brine, and dried ($MgSO_4$). The solvent was removed and the residual material was chromatographed on silica gel (eluant, 5% acetone in chloroform). The middle fraction was crystallized from benzene, and the crystals were washed with hexane to give 248 mg (12%) of **7b**, mp 141.5–143 °C: IR (KBr) 3460 and 3350 (OH), 1745 and 1727 (C=O) cm^{-1};[26] NMR ($CDCl_3$) δ 1.30 (s, 6, C-4 CH_3's), 2.24 (s, 3, 7-CH_3), 2.58 (s, 2, C-3 CH_2), 5.04 (s, 1, OH), 6.68 and 6.77 (two s, 2, aryl H's). Anal. ($C_{12}H_{14}O_3$) C, H.

In efforts to improve the yield of **7b**, the condensation was repeated in 1,2-dichloroethane as solvent and in benzene with F_3CSO_2OH as catalyst; in both cases, the yields did not exceed 6%.

5-Bromo-6-hydroxy-4,4,7-trimethylhydrocoumarin (7r). To a stirred solution of 206 mg (1 mmol) of **7b** in 15 mL of glacial acetic acid was added 178 mg (1 mmol) of *N*-bromosuccinimide over 10 min. The solution was stirred at 70–80 °C for 1 h, at which time TLC (silica gel, 25% ethyl acetate in hexane) showed total absence of **7b**. The warm solution was poured into 60 mL of water and the mixture was extracted with 3 × 50 mL of ether. The combined extracts were washed successively with water, saturated sodium bicarbonate, and saturated brine and dried ($MgSO_4$). Following evaporation of the solvent, the residual material was crystallized from hexane to give 112 mg (39%)[29] of **7r**, mp 116–118 °C: IR (KBr) 3509 (OH) and 1767 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 6, C-4 CH_3's), 2.30 (s, 3, 7-CH_3), 2.65 (s, 2, C-3 CH_2), 5.82 (s, 1, OH), 6.83 (s, 1, H-8). Anal. ($C_{12}H_{13}BrO_3$) C, H, Br.

6-Hydroxy-4,4,5,8-tetramethylhydrocoumarin (7d). To a stirred solution of 1.04 g (7.5 mmol) of 2,5-dimethylhydroquinone and 0.85 g (7.5 mmol) of methyl 3,3-dimethylacrylate in 50 mL of benzene was added 1 mL of concentrated sulfuric acid. The mixture was heated at reflux for 8 h and the solvent was removed in vacuo. The residual material was dissolved in ether; the solution was washed successively with water, saturated sodium bicarbonate, and saturated brine and dried ($MgSO_4$). Following removal of solvent, the residue was chromatographed on silica gel (eluant, 20% ethyl acetate in hexane), elution being monitored by TLC. The first compound eluted was the hydroquinone monoester (**6d**), which crystallized from hexane (125 mg, 7.5%), mp 95–98 °C: IR (KBr) 3484 (OH), 1715 (C=O), 1647 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.98 and 2.23 (two d, 6, J = 1 Hz, vinyl CH_3's), 2.02 and 2.10 (two s, 6, aryl CH_3's), 5.48 (br s, 1, OH), 5.90 (m, 1, vinyl H), 6.38 and 6.65 (two s, 2, aryl H's). Anal. ($C_{13}H_{16}O_3$) C, H.

The second fraction consisted of the lactone **7d**, which crystallized from chloroform–hexane (213 mg, 13%), mp 193–194 °C: IR (KBr) 3407 and 3559 (OH), 1741 and 1757 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.44 (s, 6, C-4 CH_3's), 2.20 (s, 3, C-8 CH_3), 2.31 (s, 3, C-5 CH_3), 2.53 (s, 2, C-3 CH_2), 5.01 (s, 1, OH), 6.50 (s, 1, H-7). Anal. ($C_{13}H_{16}O_3$) C, H.

Further elution of the column provided another fraction, which consisted of the hydroquinone contaminated with lactone. The hydroquinone could be recovered on the basis of its very low solubility in hot chloroform; a small amount of impure lactone was obtained by dilution of the chloroform filtrate with hexane.

7-Bromo-6-hydroxy-4,4,5,8-tetramethylhydrocoumarin (7p). To a stirred solution of 165 mg (0.75 mmol) of **7d** in 15 mL of chloroform was added 135 mg (0.75 mmol) of *N*-bromosuccinimide in portions over 10 min. The reaction mixture was stirred at ambient temperature for 1.5 h and was then diluted with another 15 mL of chloroform. The solution was washed with 3 × 10 mL of water, dried ($MgSO_4$), and evaporated. The residual material crystallized from hexane to give 118 mg (52%) of **7p**, mp 112–114 °C: IR (KBr) 3460 (OH) and 1760 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.45 (s, 6, C-4 CH_3's), 2.36 (s, 3, C-8 CH_3), 2.40 (s, 3, C-5 CH_3), 2.54 (s, 2, C-3 CH_2), 5.54 (s, 1, OH). Anal. ($C_{13}H_{15}BrO_3$) C, H, Br.

6-Hydroxy-4,4,7,8-tetramethylhydrocoumarin (7e). 2,3-Dimethylhydroquinone[30] (552 mg, 4 mmol) and methyl 3,3-dimethylacrylate (456 mg, 4 mmol) were condensed as described for **7b**. Following workup, the dark residual material was chromatographed on silica gel (eluant, 5% acetone in chloroform). The first fraction was crystallized from cyclohexane to give 102 mg (12%) of **7e**, mp 145–147 °C: IR (KBr) 3427 (OH) and 1724 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 6, C-4 CH_3's), 2.17 and 2.22 (two s, 6, C-7 and C-8 CH_3's), 2.56 (s, 2, C-3 CH_2), 6.62 (s, 1, H-5). Anal. ($C_{13}H_{16}O_3$) C, H.

The second fraction crystallized from cyclohexane to give 40 mg (4.5%) of the Fries rearrangement product (**16**), mp 188–189 °C; recrystallization from toluene–hexane gave mp 190–191.5 °C: IR (KBr) 3436 (OH) and 1669 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.43 (s, 6, C-2 CH_3's), 2.15 and 2.22 (two s, 6, C-7 and C-8 CH_3's), 2.67 (s, 2, C-3 CH_2), 5.97 (s, 1, OH), 7.24 (s, 1 H-5). Anal. ($C_{13}H_{16}O_3$) C, H.

5-Bromo-6-hydroxy-4,4,7,8-tetramethylhydrocoumarin (7q). To a chilled and stirred solution of 165 mg (0.75 mmol) of **7e** in 15 mL of chloroform was added 134 mg (0.75 mmol) of *N*-bromosuccinimide in portions over 10 min. The ice bath was removed and the solution was stirred at ambient temperature for 0.5 h. The solution was then diluted with 15 mL of chloroform and was washed with 3 × 10 mL of water and dried ($MgSO_4$); the solvent was evaporated. Crystallization of the residue from cyclohexane gave 143 mg (64%) of **7q**, mp 145–147 °C: IR (KBr) 3419 (OH) and 1744 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.53 (s, 6, C-4 CH_3's), 2.20 and 2.23 (two s, 6, C-7 and C-8 CH_3's), 2.59 (s, 2, C-3 CH_2), 5.76 (s, 1, OH). Anal. ($C_{13}H_{15}BrO_3$) C, H, Br.

6-Hydroxy-4,4,5,7-tetramethylhydrocoumarin (7c). 2,6-Dimethylhydroquinone (552 mg, 4 mmol) and methyl 3,3-dimethylacrylate (456 mg, 4 mmol) were condensed as described for **7b**. Following workup, the solid residue was chromatographed on silica gel (eluant, 5% methanol in chloroform) and the lactone was crystallized from cyclohexane (353 mg, 40%), mp 141–142 °C: IR (KBr) 3436 (OH) and 1742 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.45 (s, 6, C-4 CH_3's), 2.29 (s, 3, C-7 CH_3), 2.38 (s, 3, C-5 CH_3), 2.56 (s, 2, C-3 CH_2), 5.13 (s, 1, OH), 6.68 (s, 1, H-8).

(29) Bromination in chloroform solution gave a lower yield.

(30) This compound was obtained in 20% yield by potassium persulfate oxidation of 2,3-dimethylphenol, mp 220–224 °C, according to Aasen, A. J.; Kimland, B.; Enzell, C. R. *Acta Chem. Scand.* **1971**, *25*, 3537 (lit. mp 215–222 °C dec). Mp 221–224 °C was reported by Fields, D. L.; Miller, J. B.; Reynolds, D. D. *J. Org. Chem.* **1962**, *27*, 2749.

Anal. ($C_{13}H_{16}O_3$) C, H.

Attempted Bromination of 7c. To a solution of 22 mg (0.1 mmol) of **7c** in 3 mL of chloroform was added 17.8 mg (0.1 mmol) of *N*-bromosuccinimide. An orange color developed immediately. The solution was stirred at ambient temperature for 1.5 h, at which point TLC indicated the absence of starting material. The solution was diluted with 15 mL of chloroform, washed with 3 × 15 mL of water, dried ($MgSO_4$), and evaporated. Mass spectral analysis of the crude product showed none of the double peaks characteristic of brominated compounds. Purification by preparative TLC (silica gel, 5% acetone in chloroform) gave a band which moved faster than starting material and which, according to mass spectral analysis, contained the quinonepropionic acid (or its spirolactone)[3b] and dimeric products (which may have resulted from radical coupling at the C-7 methyl group.[31]

2′,3′-Dimethyl-4′-hydroxyphenyl 3,3-Dimethylacrylate (6e). To a stirred solution of 1.38 g (10 mmol) of 2,3-dimethylhydroquinone and 2.40 g (30 mmol) of dry pyridine in 200 mL of anhydrous ether was added, dropwise over 0.5 h, a solution of 1.19 g (1 mmol) of 3,3-dimethylacryloyl chloride in 50 mL of ether. The mixture was stirred at ambient temperature for 5 days; the solution was washed with dilute hydrochloric acid and saturated brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (eluant, 25% ethyl acetate in hexane). The middle fraction crystallized from cyclohexane to give 691 mg (31%) of **6e**, mp 128–130 °C: IR (KBr) 3484 (OH), 1718 (C=O), 1647 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.99 and 2.22 (two d, 6, J = 1 Hz, vinyl CH_3's), 2.02 and 2.09 (two s, 6, aryl CH_3's), 5.59 (s, 1, OH), 5.92 (m, 1, vinyl H), 6.39 and 6.62 (two d, 2, J = 9 Hz, aryl H's). Anal. ($C_{13}H_{16}O_3$) C, H.

The slowest fraction crystallized from ethyl acetate–hexane to give 340 mg of 2,3-dimethylhydroquinone.

2′,3′-Dimethyl-4′-hydroxy-5′-iodophenyl 3,3-Dimethylacrylate (6o). To a stirred solution of 440 mg (2 mmol) of **6e** and 202 mg (2 mmol) of triethylamine in 10 mL of methanol was added 508 mg (2 mmol) of iodine in 5 mL of methanol. The mixture was stirred at ambient temperature for 5 h and the solvent was removed in vacuo. The residual material crystallized from hexane as a mixture of **6e** and **6o**, which could not be resolved by sublimation. The mixture was chromatographed on silica gel (eluant, chloroform), and the faster moving material was crystallized from cyclohexane to give 85 mg (12%) of **6o**, mp 131–132.5 °C: IR (KBr) 3472 (OH), 1727 (C=O), 1645 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.99 and 2.22 (two d, 6, J = 1 Hz, vinyl CH_3's), 2.05 and 2.25 (two s, 6, aryl CH_3's), 5.17 (s, 1, OH), 5.92 (m, 1, vinyl H), 7.18 (s, 1, aryl H). Anal. ($C_{13}H_{15}IO_3$) C, H, I.

Attempts to cyclize **6o** to the lactone with sulfuric acid or with boron trifluoride etherate resulted in liberation of iodine. The nature of the product was not investigated further.

6-Benzyloxy-4,4-dimethylhydrocoumarin (8a). To a solution of 3.84 g (20 mmol) of **7a** and 2.84 g (22.4 mmol) of benzyl chloride in 75 mL of 2-butanone was added 3.17 g (23 mmol) of anhydrous potassium carbonate. The mixture was refluxed for 2 days, but TLC showed the presence of significant starting material. An additional 0.9 g of benzyl chloride and 1.0 g of potassium carbonate were added and reflux was continued for 2 more days. The mixture was filtered and the solvent was removed in vacuo. The residual material was crystallized from ligroin (after decolorization with charcoal) to give 4.58 g (81%) of **8a**, mp 115–116.5 °C: NMR ($CDCl_3$) δ 1.30 (s, 6, C-4 CH_3's), 2.57 (s, 2, C-3 CH_2), 5.08 (s, 2, $-OCH_2Ph$), 6.97 (m, 3, H-5, H-7, H-8), 7.45 (m, 5, $-OCH_2Ph$). Anal. ($C_{18}H_{18}O_3$) C, H.

6-Benzyloxy-4,4-dimethyl-5,7-difluorohydrocoumarin (8g). To a solution of 456 mg (2 mmol) of **7g** in 20 mL of 2-butanone were added 440 mg (3.5 mmol) of benzyl chloride and 488 mg (3.5 mmol) of anhydrous potassium carbonate. The mixture was stirred at reflux for 11 h, then filtered, and concentrated. The residual oil was chromatographed on 25 g of silica gel (eluant, chloroform). The first fractions provided a colorless oil which crystallized from isooctane to give 446 mg (70%) of the benzyl ether, mp 84–85 °C: IR (KBr) 1779 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.42 (d, 6, J_{HF} = 2.2 Hz, C-4 CH_3's), 2.58 (s, 2, 3-CH_2), 5.11 (s, 2, $-OCH_2Ph$), 6.66 (two d, 1, $J_{H(8)F(7)}$ = 10.5 Hz, $J_{H(8)F(5)}$ = 2.0 Hz), 7.38 (m, 5, $-OCH_2Ph$). Anal. ($C_{18}H_{16}F_2O_3$) C, H, F.

6-Mesylate of 7g (9g). A solution of 114 mg (0.5 mmol) of **7g** in 1 mL of dry pyridine was added to a cold, stirred solution of 0.2 mL (296 mg, 2.58 mmol) of methanesulfonyl chloride in 3 mL of dry pyridine. The reaction mixture was stirred at 0 °C for 0.5 h and at ambient temperature for 4.5 h. It was then diluted with 50 mL of water and the mixture was extracted with 3 × 20 mL of dichloromethane. The combined extracts were washed with dilute hydrochloric acid, dried ($MgSO_4$), and evaporated in vacuo. Crystallization of the residue from chloroform–hexane afforded 94 mg (61%) of **9g**, mp 94–96 °C: IR (KBr) 1788 (C=O), 1368 and 1168 (RSO_2OR') cm^{-1}; NMR ($CDCl_3$) δ 1.48 (d, 6, J_{HF} = 2.2 Hz, C-4, CH_3's), 2.66 (s, 2, C-3 CH_2), 3.32 (s, 3, $-SO_2CH_3$), 6.77 (two d, 1, $J_{H(8)F(7)}$ = 10 Hz, $J_{H(8)F(5)}$ = 2.2 Hz, H-8). Anal. ($C_{12}H_{12}F_2O_5S$) C, H, S.

6-Mesylate of 7a (9a). Mesylation of **7a** was performed according to the procedure used for **7g**. Crystallization from chloroform–hexane gave 72% of **9a**, mp 98–100.5 °C: IR (KBr) 1783 (C=O), 1364 and 1153 (RSO_2OR') cm^{-1}; NMR ($CDCl_3$) δ 1.37 (s, 6, C-4 CH_3's), 2.64 (s, 2, C-3 CH_2), 3.18 (s, 3, $-SO_2CH_3$), 7.12–7.35 (m, 3, aryl H's). Anal. ($C_{12}H_{14}O_5S$) C, H, S.

6-Mesylate of 7c (9c). Mesylation of **7c** was performed according to the procedure used for **7g**. Crystallization from cyclohexane gave 82% of **9c**, mp 127–128 °C: IR (KBr) 1786 (C=O); NMR ($CDCl_3$) δ 1.46 (s, 6, C-4 CH_3's), 2.35 (s, 3, C-7 CH_3), 2.47 (s, 3, C-5 CH_3), 2.58 (s, 2, C-3 CH_2), 3.30 (s, 3, $-SO_2CH_3$), 6.80 (s, 1, H-8). Anal. ($C_{14}H_{18}O_5S$) C, H, S.

6-Mesylate of 7f (9f). Mesylation of **7f** was performed according to the procedure used for **7g**. Crystallization from chloroform–hexane gave 54% of **9f**, mp 122–123 °C: IR (KBr) 1773 (C=O), 1350 and 1176 (RSO_2OR') cm^{-1}; NMR ($CDCl_3$) δ 1.45 (s, 6, C-4 CH_3's), 2.23 and 2.28 (two s, 6, C-7 and C-8 CH_3's), 2.45 (s, 3, C-5 CH_3), 2.53 (s, 2, C-3 CH_2), 3.28 (s, 3, $-SO_2CH_3$). Anal. ($C_{15}H_{20}O_5S$) C, H, S.

6-Mesylate of 7h (9h). The procedure used for the mesylation of **7g** was followed for **7h**. The product (72% yield) was crystallized from cyclohexane, mp 124–125 °C: IR (KBr) 1776 (C=O), 1353 and 1168 ($ROSO_2R'$) cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 6, C-4 CH_3's), 2.71 (s, 2, C-3 CH_2), 3.53 (s, 3, $-SO_2CH_3$), 7.35 (s, 1, H-8). Anal. ($C_{12}H_{12}Cl_2O_5S$) C, H, Cl, S.

6-Mesylate of 7k (9k). The 5,7-dibromo lactone, **7k**, was prepared in 50% yield according to the published procedure.[3b] This compound was converted into its mesylate as described above for the preparation of **9g**. The product crystallized from benzene–hexane (80% yield), mp 174–175 °C: IR (KBr) 1789 (C=O), 1364 and 1175 ($ROSO_2R'$) cm^{-1}; NMR ($CDCl_3$) δ 1.62 (s, 6, C-4 CH_3's), 2.68 (s, 2, C-3 CH_2), 3.53 (s, 3, $-SO_2CH_3$), 7.40 (s, 1, H-8). Anal. ($C_{12}H_{12}Br_2O_5S$) C, H, Br, S.

6-Mesylate of 7l (9l). Mesylation of **7l** was performed according to the procedure used for **7g**. Crystallization from chloroform–hexane afforded 184 mg (70%) of **9l** as needles, mp 155–156 °C: IR (KBr) 1766 (C=O), 1364 and 1152 ($ROSO_2R'$) cm^{-1}; NMR ($CDCl_3$) δ 1.35 (s, 6, C-4 CH_3's), 2.62 (s, 2, C-3 CH_2), 3.25 (s, 3, $-SO_2CH_3$), 7.23 and 7.28 (two s, 2, aryl H's). Anal. ($C_{12}H_{13}BrO_5S$) C, H, S.

pK_a Determinations. Potentiometric titration was used to determine pK_1 values (carboxyl ionization) in 20% dioxane–water (μ = 0.3 M NaCl) at 30 °C.[32] For **2** (X = H), pK_1 = 5.76 (lit.[1b] 5.69); **11a**, 5.74; **11l**, 5.73; a value of 5.78 (derived from kinetic analysis) was taken for **3** (X = H).[1b] A Hammett plot of these values vs. $\sum\sigma^0$ was linear, with ρ = −0.047. For the compounds used in the present study (series **11**, R_2 = $-OSO_2CH_3$), pK_1 values (Table II) were estimated by extrapolation of the Hammett plot; in view of the very small value of ρ, errors in the extrapolation would have relatively small effects on the calculated values of k'_{cal}. The majority of σ^0 values were taken from the compilation of Cohen and Takahashi;[33] for F, σ^0_o (aq) = 0.88,[34] and for CH_3SO_2O-, σ^0_m = 0.39.[35]

Phenolic pK_2 values were determined spectrophotometrically for **11a** (11.18), **11g** (9.70), and **11l** (10.10). A Hammett plot of these values vs. $\sum\sigma^-$[5,36] was linear and gave ρ = −2.53.[37] Other values in Table II were obtained by extrapolation. Literature pK values were used for imidazole, pK_1 = 7.22,[1a] and for hydroxide ion, pK_w = 14.09.[1b] Statistical adjustment of pK_a values (cf. Figure 4) was performed according to accepted procedures.[38]

Kinetic Measurements. Lactones were hydrolyzed by dilution of 0.1 M solution in dioxane with equal volumes of 0.2 M sodium hydroxide; UV spectra showed hydrolysis to be complete within 30 min in this medium. These alkaline stock solutions of series **10** were prepared just before kinetic runs and were discarded after 1 h. Rates of lactonization were measured as previously described,[1,5] following the decrease in absorption at the wavelengths given in Table II; final concentrations of phenolic acid were 4–5 × 10^{-4} M. Infinity spectra corresponded to those

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(32) For pK_a and kinetic measurements, spectral grade dioxane was filtered through a column of Fisher neutral alumina and was discarded after 1 day.

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(34) Takeuchi, Y.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3570.

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(37) For $CH_3SO_2O^-$, σ_p^- was taken equal to σ_p, 0.33: Stang, P. J.; Anderson, A. G. *J. Org. Chem.* **1976**, *41*, 781.

(38) (a) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969; p 173. (b) Bell, R. P. "Acid-Base Catalysis"; Oxford: Oxford, 1941; Chapter V.

of the lactones over the entire pH range investigated.

Registry No. 4 (X = F), 84944-93-4; **5** (X = F), 84944-94-5; **6a**, 41167-81-1; **6d**, 84944-95-6; **6e**, 84944-96-7; **6n**, 84944-97-8; **6o**, 84944-98-9; **7a**, 29423-72-1; **7b**, 84944-99-0; **7c**, 50442-68-7; **7d**, 84945-00-6; **7e**, 84945-01-7; **7f**, 40662-76-8; **7g**, 84959-63-7; **7h**, 84945-02-8; **7i**, 84945-03-9; **7j**, 84945-04-0; **7k**, 40662-32-6; **7l**, 84945-05-1; **7m**, 84945-06-2; **7p**, 84945-07-3; **7q**, 84945-08-4; **7r**, 84945-09-5; **8a**, 84945-10-8; **8g**, 84945-11-9; **9a**, 84945-12-0; **9c**, 84945-13-1; **9f**, 84945-14-2; **9g**, 84945-15-3; **9h**, 84945-16-4; **9k**, 84945-17-5; **9l**, 84945-18-6; **11a**, 84945-19-7; **11c**, 84945-20-0; **11f**, 84959-64-8; **11g**, 84945-21-1; **11h**, 84945-22-2; **11k**, 84945-23-3; **12**, 41167-82-2; **14**, 84945-24-4; **15**, 84945-25-5; **16**, 84945-26-6; 3,5-difluorophenol, 2713-34-0; 1,3,5-trifluorobenzene, 372-38-3; 3,5-difluorophenol α-naphthyl urethane derivative, 84945-27-7; 3,3-dimethylacryloyl chloride, 3350-78-5; 2,6-difluorohydroquinone, 84959-65-9; 2,6-difluorophenol, 28177-48-2; methyl 3,3-dimethylacrylate, 924-50-5; 2,6-diiodohydroquinone, 1955-21-1; 2-methylhydroquinone, 95-71-6; 2,5-dimethylhydroquinone, 615-90-7; 2,3-dimethylhydroquinone, 608-43-5; 2,6-dimethylhydroquinone, 654-42-2; hydroquinone, 123-31-9.

Stereopopulation Control. 8. Rate and Equilibrium Enhancement in the Formation of Homophthalic Anhydrides

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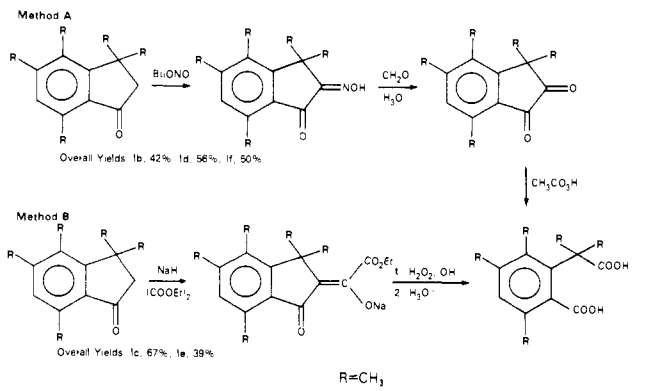
Abstract: The kinetics of cyclization of α,α,3,4,6-pentamethylhomophthalic acid have been measured in solvent acetonitrile at 28.5 °C, using as catalysts a series of acids ranging in strength from perchloric to acetic. In the presence of 0.12 M $HClO_4$, $t_{1/2}$ for acid anhydride formation = 0.3 s. For the stronger acid catalysts, k_{cycl} is a linear function of catalyst concentration; for the weak acids, however, a change in rate-limiting step is revealed by curvature in the plots of k^{tot}_{obsd} vs. [catalyst]. All the weak acids show the same limiting value, 6.45×10^{-3} min^{-1}; this value is considered to be the rate constant for uncatalyzed formation of the tetrahedral intermediate. Homoconjugate bases (HA_2^-) of the weak acids show a similar curvature in their dilution plots, and the same limiting rate constant as for weak acids. Two independent and competitive pathways for cyclization are proposed. For strong acid catalysis, an intermediate acylium ion is considered on the basis of Brønsted $\alpha = -0.79$, $k_H/k_D \simeq 1$, and acceleration of anhydride hydrolysis by methyl substituents. A value of $\Delta S^{\ddagger} = -23$ eu suggests that cyclization, rather than acylium ion formation, is rate limiting. For weak acid catalysis, $\alpha = -0.17$, $k_H/k_D = 4.3$, $\Delta S^{\ddagger} = -31$ eu, and methyl groups retard anhydride hydrolysis by electron release; for this pathway, catalyzed breakdown of a tetrahedral intermediate is considered rate limiting. The composite Brøsted plot is curved because the two pathways follow different rate laws. In contrast to rate enhancement results for phenolic lactone formation, the pentamethylhomophthalic acid is only sevenfold as reactive as α,α-dimethylhomophthalic acid. For the catalyst acids, pK(acetonitrile) is shown to be a linear function of p$K(H_2O)$ over the entire range of acids examined.

Severe restriction of conformational mobility (stereopopulation control) has been shown to enhance both rate and equilibrium constants for cyclization in intramolecularly reactive systems.[1-4] Quantitative data have already been reported for the formation of benzylic[3a] and phenolic[1,3,4] lactones, phenolic ethers,[5] and lactones resulting from carboxyl addition to double bonds.[6] In our earlier reports, we argued that stereopopulation control serves, primarily, to raise the free energy content of the starting material over that of an analogous system with greater conformational mobility. It should be possible, therefore, to utilize the potential of the energy-rich system to drive the formation of bonds which, in acylic analogues, are recognized as "high-energy."[7] Earlier studies[8] have shown, for example, that both rate and equilibrium constants for the formation of cyclic acid anhydrides (succinic, maleic, phthalic) can be enhanced by the introduction of moderately bulky substituents, suitably placed to limit some degree of rotational freedom.[9] We have now extended these studies to include the formation of homophthalic anhydrides, thiolactones,[10]

Scheme I



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(9) As we[3] and others[8] have emphasized, conformational restriction is the basis for a number of consequences, all of which may lead to enhancement phenomena.

(10) Blum, M.; Cohen, L. A., manuscript in preparation.