

## Stereopopulation Control. II. Rate Enhancement of Intramolecular Nucleophilic Displacement

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**Abstract:** Rate data have been obtained for the formation of chromans from a variety of 3-(*o*-hydroxyphenyl)-1-propanol monoesters, ranging from mesylate to acetate in leaving ability. For a series involving an invariant leaving group, appropriate alkyl substitution in both aromatic ring and side chain produces rate-enhancement factors of almost  $10^6$ . The intramolecular nucleophilic substitution reaction exhibits no preliminary ionization of the leaving group nor sensitivity to buffer catalysis. Both the phenolate ion and the phenol participate as nucleophiles, the specific rate constant for the former ( $k_{\text{PhO}^-}$ ) exceeding that for the latter ( $k_{\text{PhOH}}$ ) by  $10^4$ – $10^6$ . In the most favorable case studied (**3f**, X = SO<sub>2</sub>CH<sub>3</sub>),  $k_{\text{PhO}^-} = 2 \times 10^6 \text{ sec}^{-1}$ . The half-life of this compound (30°, 40% dioxane) is 5 sec at pH 7 and 0.8 sec at pH 8. The rate-enhancement effect is attributed to a unique interlocking of methyl groups, which produces partial conformational freezing of the side chain and increases greatly the population of the conformer most closely resembling the transition state. A close correlation is observed between  $\log k_{\text{PhO}^-}$  and the  $\text{p}K_a$  of the conjugate acid of the leaving group, followed over a range of 6.5 units in  $\log k_{\text{PhO}^-}$  and 6.6 units in  $\text{p}K_a$ . Activation parameters show little variation in  $\Delta S^\ddagger$  (–5 to –10 eu), the rate-enhancement effect appearing primarily in the  $\Delta H^\ddagger$  term.

In the preceding paper of this series,<sup>1</sup> there was described the marked effect of severe van der Waals repulsion (one mode of stereopopulation control) on the rates of lactonization of a series of substituted *o*-hydroxyhydrocinnamic acids. As part of an extended program on the effects of stereopopulation control on rates, mechanisms, and equilibria, we have investigated a reaction type of greater mechanistic simplicity than lactonization, that of intramolecular nucleophilic displacement. In this study, the spatial orientation and the degree of conformational freedom of the carbon atom carrying the leaving group are varied, as well as the nature of the leaving group itself.

While intramolecular nucleophilic attack by phenolate ion has been used, on occasion, to prepare chromans,<sup>2</sup> we are unaware of any quantitative studies in this area. Indeed, few mechanistic studies of the more fundamental bimolecular alkylation of phenolate ion have been reported.<sup>3</sup> The intent, in the cases cited, was to determine the influence of ring substituents on rate and, despite the variety of alkylating agents used, resulted in a remarkable narrow range of  $\rho$  values, –0.9 to –1.1. Since our study was devoted, primarily, to an examination of the dependence of rate on conformational factors, little attention was given to the electronic effects of ring substituents. On the other hand, the very large rate constants observed for the more reactive compounds permitted kinetic comparisons to be made for a wide range of leaving groups, without simultaneous alteration in geometry or mechanism.

At the outset, certain differences between the mechanisms of nucleophilic displacement and of lactonization

should be emphasized: (1) in the displacement reaction, product is formed *via* a single transition state, without the incursion of true intermediates; (2) in many cases, nucleophilic displacement is essentially irreversible; (3) the displacement reaction is insensitive to buffer catalysis; (4) tolerance in the angle of approach to the transition state in nucleophilic displacement is considerably narrower than that required for carbonyl reactions.<sup>4</sup> These differences find expression in comparisons of conformational rate-enhancement effects for the two reaction types.

In this investigation, a series of hydrocoumarins (**1**) was reduced by lithium aluminum hydride to the corresponding 3-(*o*-hydroxyphenyl)-1-propanols (**2**). Selective esterification of the primary alcohol group in **2** provided the monoester **3**.<sup>5</sup> A variety of such monoesters were converted into the corresponding chromans (**4**) in media ranging from pH 6 buffer to 0.3 *N* alkali. The effect of variation in the extent of ring and side-chain substitution, as well as in the nature of the leaving group (X), was determined by comparison of the specific rate constants for the conversion of **3** to **4**.

### Experimental Section<sup>6</sup>

**Lactones 1c, 1d, and 1f** were prepared according to the published procedure.<sup>1,7</sup> 4,4,7,8-Tetramethylhydrocoumarin (**1e**) was prepared in the same way from 2,3-dimethylphenol and methyl 3-methylcrotonate, product bp 97–99° (0.2 mm).

*Anal.* Calcd for C<sub>13</sub>H<sub>16</sub>O<sub>2</sub>: C, 76.44; H, 7.90. Found: C, 76.57; H, 8.14.

**7,8-Dimethylhydrocoumarin (1b).** 7,8-Dimethylcoumarin was prepared by condensation of 2,3-dimethylphenol with malic acid,

(4) T. C. Bruice, A. Brown, and D. O. Harris, *Proc. Nat. Acad. Sci., U. S.*, **68**, 658 (1971).

(5) For the sake of clarity and consistency, the chroman numbering system (as in **1** and **4**) has been retained for the open-chain compounds (**2** and **3**).

(6) All analyses were performed by the Analytical Services Section of this laboratory, under the direction of Dr. W. C. Alford. For all compounds, the results of combustion analysis were well within the limits of acceptable error. Melting points and boiling points are uncorrected.

(7) (a) S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, **92**, 4377 (1970); (b) J. Colonge, E. LeSech, and R. Marey, *Bull. Soc. Chim. Fr.*, 776 (1957).

(1) Paper I: S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, **94**, 9158 (1972); see also S. Milstien and L. A. Cohen, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1143 (1970).

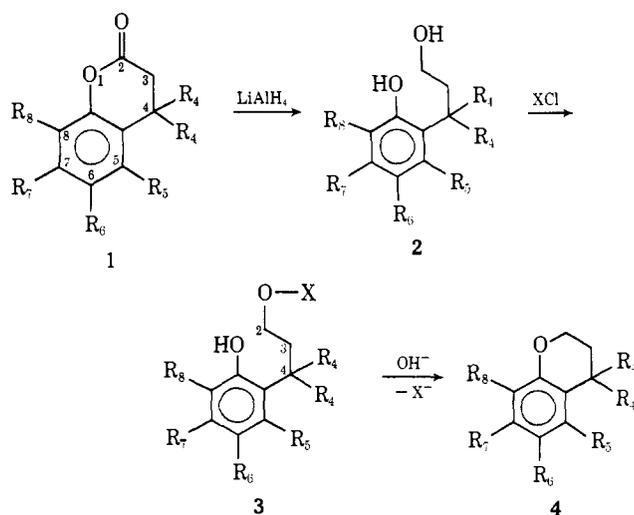
(2) S. Wawzonek in "Heterocyclic Compounds," Vol. 2, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1951, Chapter 11.

(3) D. R. Boyd and E. R. Marle, *J. Chem. Soc.*, 105, 2117 (1914); L. J. Goldsworthy, *ibid.*, 1254 (1926); A. Fischer, S. V. Sheat, and J. Vaughan, *ibid.*, 1892 (1965); R. A. Benkeser, C. E. DeBoer, R. E. Robinson, and D. M. Suave, *J. Amer. Chem. Soc.*, **78**, 682 (1956); Y. Ogata and Y. Ishikawa, *Science (Tokyo)*, **19**, 185 (1949); *Chem. Abstr.*, **45**, 5122 (1951).

**Table I.** Diols (**2**) and Their Monoesters (**3**)

Compd	X (in <b>3</b> )	Yield, %	Mp or bp (mm), °C	Compd	X (in <b>3</b> )	Yield, %	Mp, °C
<b>2a</b>		78	124–125 (0.4) <sup>a</sup>	<b>3e</b>	COCH <sub>2</sub> Cl	72	45–47 <sup>b</sup>
<b>2b</b>		79	72–73.5 <sup>b</sup>	<b>3f</b>	COCH <sub>2</sub> Cl	87	94–96 <sup>b</sup>
<b>2c</b>		64	82–83 <sup>b</sup>	<b>3f</b>	COCH <sub>2</sub> Br	71	90–92 <sup>b</sup>
<b>2d</b>		63	110–111 <sup>b,c</sup>	<b>3f</b>	COCHCl <sub>2</sub>	74	35–36 <sup>d</sup>
<b>2e</b>		74	69–71 <sup>b</sup>	<b>3f</b>	COCCl <sub>3</sub>	83	81–82 <sup>d</sup>
<b>2f</b>		87	78–80 <sup>b</sup>	<b>3c</b>	PO(OEt) <sub>2</sub>	50	44–46 <sup>b</sup>
<b>2g</b>		84	100–102 <sup>b</sup>	<b>3e</b>	PO(OEt) <sub>2</sub>	65	80.5–82 <sup>e</sup>
<b>2h</b>		86	95–96 <sup>b</sup>	<b>3f</b>	PO(OEt) <sub>2</sub>	44	54–56 <sup>e</sup>
<b>3a</b>	COCH <sub>3</sub>	64	116–117 (0.2)	<b>3a</b>	SO <sub>2</sub> CH <sub>3</sub>	95	<i>f</i>
<b>3c</b>	COCH <sub>3</sub>	62	40–42 <sup>b</sup>	<b>3b</b>	SO <sub>2</sub> CH <sub>3</sub>	97	85–87 <sup>b</sup>
<b>3d</b>	COCH <sub>3</sub>	71	129–130 (0.3)	<b>3c</b>	SO <sub>2</sub> CH <sub>3</sub>	84	99–101 <sup>b</sup>
<b>3f</b>	COCH <sub>3</sub>	82	66–68 <sup>b</sup>	<b>3d</b>	SO <sub>2</sub> CH <sub>3</sub>	92	69–71 <sup>e</sup>
<b>3g</b>	COCH <sub>3</sub>	72	57–58.5 <sup>b</sup>	<b>3e</b>	SO <sub>2</sub> CH <sub>3</sub>	89	53–55 <sup>e</sup>
<b>3h</b>	COCH <sub>3</sub>	66	65–67 <sup>b</sup>				

<sup>a</sup> Lit. bp 176–178° (12 mm): J. Lockett and W. F. Short, *J. Chem. Soc.*, 787 (1939). <sup>b</sup> Recrystallized from acetone–hexane. <sup>c</sup> Lit.<sup>7b</sup> mp 111°. <sup>d</sup> Recrystallized from hexane. <sup>e</sup> Recrystallized from ether–hexane. <sup>f</sup> An oil which decomposed on distillation; purification for analysis and kinetics was achieved by preparative tlc on silica gel (ethyl acetate–hexane 2:3).



- a**, R<sub>4</sub> = R<sub>5</sub> = R<sub>6</sub> = R<sub>7</sub> = R<sub>8</sub> = H  
**b**, R<sub>4</sub> = R<sub>5</sub> = R<sub>6</sub> = H; R<sub>7</sub> = R<sub>8</sub> = CH<sub>3</sub>  
**c**, R<sub>4</sub> = R<sub>6</sub> = H; R<sub>5</sub> = R<sub>7</sub> = R<sub>8</sub> = CH<sub>3</sub>  
**d**, R<sub>5</sub> = R<sub>6</sub> = R<sub>7</sub> = R<sub>8</sub> = H; R<sub>4</sub> = CH<sub>3</sub>  
**e**, R<sub>5</sub> = R<sub>6</sub> = H; R<sub>4</sub> = R<sub>7</sub> = R<sub>8</sub> = CH<sub>3</sub>  
**f**, R<sub>6</sub> = H; R<sub>4</sub> = R<sub>5</sub> = R<sub>7</sub> = R<sub>8</sub> = CH<sub>3</sub>  
**g**, R<sub>6</sub> = Cl; R<sub>4</sub> = R<sub>5</sub> = R<sub>7</sub> = R<sub>8</sub> = CH<sub>3</sub>  
**h**, R<sub>6</sub> = PhCH<sub>2</sub>O; R<sub>4</sub> = R<sub>5</sub> = R<sub>7</sub> = R<sub>8</sub> = CH<sub>3</sub>

according to the method of Clayton,<sup>8</sup> except that water was removed by azeotropic distillation of the solvent (toluene). The product, obtained in 52% yield, was crystallized from benzene–hexane, mp 119–121°.

*Anal.* Calcd for C<sub>11</sub>H<sub>10</sub>O<sub>2</sub>: C, 75.84; H, 5.79. Found: C, 75.72; H, 5.85.

The unsaturated lactone was saponified and the phenolic acid was hydrogenated as described for 5,7,8-trimethylcoumarin.<sup>1</sup> The resulting *o*-hydroxyhydrocinnamic acid was recycled by azeotropic distillation of its solution in benzene containing a catalytic amount of sulfuric acid. The product, obtained in 85% yield, was crystallized from acetone–hexane, mp 50–52°.

*Anal.* Calcd for C<sub>11</sub>H<sub>12</sub>O<sub>2</sub>: C, 74.97; H, 6.87. Found: C, 74.91; H, 6.73.

**6-Chloro-4,4,5,7,8-pentamethylhydrocoumarin (1g).** To a solution of 5.0 g (23 mmol) of **1f** in 150 ml of acetonitrile, containing 5 ml of water and a catalytic amount of sulfuric acid, was added a solution of 4.0 g (30 mmol) of *N*-chlorosuccinimide in 25 ml of acetonitrile. The reaction mixture was stirred at ambient temperature for 20 hr and then diluted with water. The mixture was extracted with several portions of ether, and the combined extracts were washed with water and saturated NaCl solution and dried (MgSO<sub>4</sub>). Removal of the solvent and crystallization of the residue (acetone–hexane)

afforded 3.69 g (64%) of **1g**, mp 96–97°. The structure was supported by spectral data.

*Anal.* Calcd for C<sub>14</sub>H<sub>17</sub>O<sub>2</sub>Cl: C, 66.53; H, 6.78. Found: C, 66.46; H, 6.60.

**6-Benzyloxy-4,4,5,7,8-pentamethylhydrocoumarin (1h).** To a solution of 2.34 g (10 mmol) of 6-hydroxy-4,4,5,7,8-pentamethylhydrocoumarin<sup>1</sup> in 75 ml of anhydrous acetone were added 1.65 g (12 mmol) of benzyl chloride and 1.52 g (12 mmol) of anhydrous potassium carbonate. The reaction mixture was heated at reflux for 48 hr with vigorous stirring, cooled, and filtered. Concentration of the filtrate gave a semisolid product which, after crystallization (benzene–hexane), afforded 86% of **1h**, mp 135–137°.

*Anal.* Calcd for C<sub>21</sub>H<sub>24</sub>O<sub>3</sub>: C, 77.75; H, 7.46. Found: C, 77.81; H, 7.60.

**3-(2'-Hydroxy-3',4',6'-trimethylphenyl)-3,3-dimethyl-1-propanol (2f).** A solution of the lactone **1f** in anhydrous tetrahydrofuran was reduced with lithium aluminum hydride in the usual manner, 1 hr reflux being sufficient to effect complete reduction. The diol was obtained in 87% yield by crystallization from acetone–hexane, mp 78–80°.

The same procedure was used for reduction of the remaining lactones; yields and physical data are given in Table I.<sup>9</sup>

**3f** (X = COCCl<sub>3</sub>). To a solution of 0.50 g (2.25 mmol) of **2f** in 5 ml of dried pyridine was added, at 0°, 0.55 g (3.0 mmol) of trichloroacetyl chloride. The reaction mixture was maintained at 0° for 0.5–1 hr and diluted with water. The mixture was extracted with several portions of ether and the combined extracts were washed successively with water, 5% hydrochloric acid, and saturated NaCl solution and dried (MgSO<sub>4</sub>). Removal of solvent and crystallization of the residue (hexane) afforded 83% of **3f** (X = COCCl<sub>3</sub>), mp 81–82°.

In a similar manner, monoesters of **2f** and of several other diols were prepared by acylation with acetic anhydride, chloroacetic anhydride, dichloroacetic anhydride, and bromoacetyl bromide. Physical constants for these monoesters are given in Table I. That acylation had occurred on the side-chain hydroxyl was demonstrable, in each case, by observation of a change in the nmr chemical shift of the methylene protons at C-2, and by the fact that the ultraviolet spectrum showed the expected displacement of the phenolic absorption in alkaline medium.

Phosphorylation was effected in a similar manner, by use of equivalent amounts of diethyl chlorophosphate. The diethyl phosphates of **2c**, **2e**, and **2f** were solids (Table I); that of **2f** was purified by preparative tlc on silica gel (ethyl acetate–hexane 1:1) prior to crystallization. The esters of **2a**, **2b**, and **2d** were colorless liquids which could not be distilled without decomposition. Samples were purified by preparative tlc; identity and homogeneity were established by ir, uv, nmr, and mass spectroscopy.

(9) Elemental analyses for these compounds will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JACS-72-9166. Remit check or money order for \$3.00 for photocopy or \$2.00 for microfiche.

(8) This procedure is a modification of that described by A. Clayton, *J. Chem. Soc.*, 93, 2016 (1908).

Table II. Chromans (4)

Compd	Yield, %	Bp (mm) or mp, °C	Compd	Yield, %	Bp (mm) or mp, °C
4a	85	101-103 (20) <sup>a</sup>	4e	87	72-74 (0.4)
4b	87	69-70 (0.4) <sup>b</sup>	4f	82	82-83 (0.3)
4c	71	56-57 <sup>c,d</sup>	4g	80	66-69 <sup>d</sup>
4d	74	44-45 (0.3) <sup>e</sup>	4h	75	47-49 <sup>d</sup>

<sup>a</sup> Lit. bp 98-99° (18 mm): R. E. Rindfusz, *J. Amer. Chem. Soc.*, **41**, 668 (1919). <sup>b</sup> Lit. bp 120-121° (2 mm): O. Dann, G. Volz, and O. Huber, *Justus Liebigs Ann. Chem.*, **587**, 16 (1954). <sup>c</sup> Lit. mp 53°: footnote b. <sup>d</sup> Recrystallized from hexane. <sup>e</sup> Lit.<sup>7b</sup> bp 93° (10 mm).

The diols (except for 2f) were converted into their monomesylates by a procedure identical with that for phosphorylation and acylation.

**3f** (X = SO<sub>2</sub>CH<sub>3</sub>). Since the mesylate of 2f was found to cyclize rapidly at room temperature, solutions in acetonitrile were freshly prepared prior to each kinetic run and stored at -5°. To 13.2 mg (0.06 mmol) of 2f in 25 μl of anhydrous pyridine was added, at -5°, 7.2 mg (0.06 mmol) of methanesulfonyl chloride. The reaction mixture was maintained at -5° for 15 min, at which point 1.0 ml of chilled acetonitrile was added. The mesylate solution was stored at this temperature and generally could be kept for 2-3 hr without significant change. Kinetic measurements were performed by adding 15 μl of the stock solution to 2 ml of buffer (final concentration 3.0 × 10<sup>-4</sup> M). No pH change was noted in any of the buffers following addition of the mesylate solution.

Evidence for extensive conversion of the diol to monomesylate under these reaction conditions was obtained by performing the reaction in pyridine-d<sub>6</sub> in an nmr sample tube, and following the shift of the C-2 methylene signal (triplet) from δ 3.85 (diol) to 4.31 (mesylate).

**7,8-Dimethylchroman (4b)**. To a solution of 3.0 g (11.6 mmol) of 3b (X = SO<sub>2</sub>CH<sub>3</sub>) in 25 ml of dioxane was added 25 ml of 1 N sodium hydroxide. The mixture was stirred for 2 hr at ambient temperature, diluted with water, and extracted with several portions of ether. The combined extracts were washed with water and saturated NaCl solution and dried (MgSO<sub>4</sub>). Removal of solvent and distillation of the residual oil afforded 87% of 4b, bp 59-60° (0.4 mm).

Chroman (4a) and 5,7,8-trimethylchroman (4c) were prepared in a similar manner from the mesylates of 2a and 2c. Physical data are given in Table II.<sup>9</sup>

**4,4,7,8-Tetramethylchroman (4e)**. To 2.10 g (10 mmol) of 2e was added 1.0 g of 85% phosphoric acid. The reaction mixture was heated at 135-145° for 30 min, cooled, diluted with water, and extracted with several portions of ether. The combined extracts were washed with water and saturated NaCl solution and dried (MgSO<sub>4</sub>). Removal of solvent and distillation afforded 87% of the chroman, bp 72-74° (0.4 mm).

The same method was used to prepare 4,4-dimethylchroman (4d) from 2d.

**4,4,5,7,8-Pentamethylchroman (4f)**. To a solution of 0.76 g (0.02 mol) of sodium borohydride in 50 ml of anhydrous diglyme was added dropwise, at ice-bath temperature, a solution of 2.20 g (0.01 mol) of 1f in 50 ml of anhydrous tetrahydrofuran, to which had been added 42.0 g (0.3 mol) of redistilled boron trifluoride etherate.<sup>10</sup> The reaction mixture was stirred at 0-10° for 45 min and then heated at reflux for 3 hr. The excess hydride was decomposed by dropwise addition of 5% hydrochloric acid. The mixture was extracted with several portions of ether and the combined extracts were washed successively with 5% hydrochloric acid, water, and saturated NaCl solution and dried (MgSO<sub>4</sub>). Removal of solvent and distillation afforded 1.65 g (82%) of 4f, bp 82-83° (0.3 mm).

The same method was used to prepare 4g and 4h from 1g and 1h, respectively. Physical data are given in Table II.

**Kinetic Measurements.** Buffers were prepared from commercial reagent grade materials, using deionized, distilled water and purified dioxane.<sup>11</sup> All solutions contained 40% (by volume) of dioxane and were maintained at ionic strengths of 0.3 M with KCl. The pH of each solution was measured on a Model TTT-1c Radiometer pH meter, equipped with scale expander. In selected cases,

the pH was measured before and after kinetic runs; in no case was a pH change of greater than 0.02 unit detected. Variation of buffer pH with temperature was determined by direct measurement. Over the range 25-45°, sodium carbonate-bicarbonate buffer decreased 0.06-0.07 pH unit for each 5° increase in temperature; Tris buffer decreased 0.14 pH unit per 5° increment. Solutions of sodium hydroxide were prepared in the same solvent mixture (μ = 0.3 M KCl); the base concentration was determined, for each dilution, by titration with standardized hydrochloric acid. Fresh solutions of sodium hydroxide were prepared after 2 weeks of storage.

The rates of cyclization were measured spectrophotometrically by following the increase in absorbance at 270-290 nm, using a Model 15 Cary recording spectrophotometer, equipped with scale expander and automatic sample-changing accessory. The absorption maxima of phenol and chroman were generally quite similar in shape and wavelength, the extinction coefficient of the chroman exceeding that of the phenol by 25-35%. Constant temperature was maintained by circulation of water from a Haake KT41 constant-temperature bath through the sample holder and walls of the spectrophotometer cell compartment. The temperature in the cell compartment was monitored continuously with a Yellow Springs Tele-thermometer, whose output was displayed on a 6-in. recorder. Except for kinetic runs used to obtain activation parameters, all measurements were made at 30 ± 0.05°.

The cyclization reaction was initiated by addition of 25-50 μl of a 2.0 × 10<sup>-2</sup> M solution of the phenol in dioxane to 2.0 ml of a previously equilibrated solution of buffer (or alkali) in the cuvette. For each run, the increase in optical density was recorded continuously until no further change was observed. Except for those cyclizations involving carboxylic ester leaving groups, final spectra duplicated those of equivalent solutions of the chromans. Upon completion of a run, 5 N sodium hydroxide was added to the cuvette to ionize any remaining phenol. The absence of any spectral changes in the presence of strong alkali served to confirm that cyclization had proceeded to completion. From three to six values of *k*<sub>obsd</sub> were obtained for each compound at 5-7 pH values. Values of *k*<sub>obsd</sub> for all compounds were found to be independent of buffer concentration (0.05-0.5 M) in the several buffers cited, even at neutral pH. Pseudo-first-order rate constants were calculated on a General Electric 265 computer, using a program designed to calculate a least-squares evaluation of a plot of ln (A<sub>inf</sub> - A<sub>0</sub>)/(A<sub>inf</sub> - A<sub>t</sub>) vs. time. The correlation coefficients were usually greater than 0.9995. The specific rate constants (*k*<sub>PhO<sup>-</sup></sub>, *k*<sub>PhOH</sub>) were obtained by least-squares calculation of the slopes and intercepts of plots of *k*<sub>obsd</sub> vs. *f*<sub>PhO<sup>-</sup></sub> (the mole fraction of phenolate ion), except for the few cases in which the phenol was completely ionized. In all such calculations, standard deviations were within ±1%. Activation parameters were obtained by computer analysis of plots of log *k*<sub>PhO<sup>-</sup></sub> vs. 1/*T* (°K).

**Corrections for Alkaline Hydrolysis.** Cyclizations of some diol monocarboxylic esters required pH values sufficiently high to cause varying degrees of bimolecular hydrolysis to the parent diols. Since the hydrolyses occurred under pseudo-first-order conditions, corrections were made as for competitive first-order processes.<sup>12</sup> Upon completion of a run, a 0.5-ml sample of the reaction mixture was diluted with 3.5 ml of 1 N sodium hydroxide and the uv spectrum compared with that of the diol, in the same medium and at the same concentration as that of the initial monoester. The ratio of concentrations of the final products, diol/chroman, was calculated as A<sub>FB</sub>/(A<sub>diol</sub> - A<sub>FB</sub>) = *R*. The true *k*<sub>obsd</sub> for cyclization = *k*<sub>obsd<sup>app</sup></sub>/(1 + *R*).

**pK<sub>a</sub> Measurements.** Phenolic pK<sub>a</sub> values were determined spectrophotometrically in 40% dioxane (μ = 0.3 M), by use of pub-

(10) This procedure is based on a method previously applied to saturated esters and lactones: G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, **27**, 2127 (1962).

(11) W. Dasler and C. D. Bauer, *Ind. Eng. Chem., Anal. Ed.*, **18**, 52 (1946).

(12) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 569.

lished procedures.<sup>13a</sup> For those diols and their monoesters which were too weakly acidic to give complete phenol ionization in moderately strong alkali, the method of spectral extrapolation<sup>13</sup> was used. By means of this technique, values of  $pK_w$  in the mixed solvent system ( $\mu = 0.3 M$ ) were determined for a series of temperatures: 25°, 14.96; 30°, 14.81; 35°, 14.67; 40°, 14.53; 45°, 14.40. By comparison, an interpolated value of 14.89 at 30° was calculated from published data.<sup>14,15</sup> The  $pK_a$  values for the series of diols and their monoesters are given in Table III. For the more reactive monoesters,  $pK_a$  values were obtained by extrapolation (see Results).

Table III.  $pK_a$  Values of Diols (2) and Monoesters (3)

Compd	$-pK_a^c$			
	Diol	Acetate	Phosphate	Mesylate
2a	11.52	11.81	11.70	(11.63) <sup>b</sup>
2b	12.13	(12.49)	(12.40)	(12.31)
2c	12.22	12.58	12.49 <sup>c</sup>	(12.40)
2d	12.62	12.99	(12.90)	(12.81)
2e	12.98	(13.35)	(13.26)	(13.17)
2f	13.19	(13.56) <sup>d</sup>	(13.47)	(13.38)
2g	12.26	12.58		
2h	12.83	13.18		

<sup>a</sup> At 30°, 40% dioxane ( $\mu = 0.3 M$ ). <sup>b</sup> Values in parentheses were obtained by extrapolation from experimental data (see Results). <sup>c</sup> At 35°, 12.40; at 40°, 12.31. <sup>d</sup> Values estimated for substituted acetates:  $-\text{COCCl}_3$ , 13.45;  $-\text{COCHCl}_2$ , 13.47;  $-\text{COCH}_2\text{Cl}$ ,  $-\text{COCH}_2\text{Br}$ , 13.51.

Table IV. Specific Rate Constants for Cyclization (30°)

Compd	X	$k_{\text{PhO}^-}$ , sec <sup>-1</sup> <sup>a</sup>	$k'_{\text{PhO}^-}$ , sec <sup>-1</sup> <sup>b</sup>	$10^4 k_{\text{PhOH}}$ , sec <sup>-1</sup>
3f	COCCl <sub>3</sub>	243	59.3	2.7
3f	COCHCl <sub>2</sub>	19.7	4.70	2.0
3f	COCH <sub>2</sub> Cl	1.20	0.286	1.4
3f	COCH <sub>2</sub> Br	1.00	0.238	1.2
3f	COCH <sub>3</sub>	$6.00 \times 10^{-2}$	$1.43 \times 10^{-2}$	0.24
3g	COCH <sub>3</sub>	$9.91 \times 10^{-2}$	$3.93 \times 10^{-2}$	0.66
3h	COCH <sub>3</sub>	$4.03 \times 10^{-2}$	$1.17 \times 10^{-2}$	0.38
3a	SO <sub>2</sub> CH <sub>3</sub>	0.237	0.237	0.12
3b	SO <sub>2</sub> CH <sub>3</sub>	0.840	0.238	0.18
3c	SO <sub>2</sub> CH <sub>3</sub>	1.65	0.393	0.30
3d	SO <sub>2</sub> CH <sub>3</sub>	736	736	10
3e	SO <sub>2</sub> CH <sub>3</sub>	2480	704	11
3f	SO <sub>2</sub> CH <sub>3</sub>	$2.05 \times 10^6$	$5.0 \times 10^4$	540
3a	PO(OEt) <sub>2</sub>	$1.37 \times 10^{-4}$	$1.37 \times 10^{-4}$	~0
3b	PO(OEt) <sub>2</sub>	$4.80 \times 10^{-4}$	$1.36 \times 10^{-4}$	~0
3c	PO(OEt) <sub>2</sub>	$1.07 \times 10^{-3}$	$2.55 \times 10^{-4}$	~0
3d	PO(OEt) <sub>2</sub>	0.438	0.438	1.1
3e	PO(OEt) <sub>2</sub>	1.55	0.440	1.4
3f	PO(OEt) <sub>2</sub>	115	27.4	1.8

<sup>a</sup> Standard deviations were  $\pm 1\%$  or less; correlation coefficients were greater than 0.999. <sup>b</sup> Values of  $k_{\text{PhO}^-}$ , adjusted for electronic and ortho effects of ring substituents.

## Results

Cyclization rates followed simple first-order kinetics to completion of reaction for all compounds examined. In order to get conveniently measurable rates of reaction, the cyclizations of 3a–c (X = PO(OEt)<sub>2</sub>) were run in 0.03–0.3 M sodium hydroxide. In these media, ionization of the phenolic group was complete or very nearly complete. Since the concentration of alkali

(13) (a) L. A. Cohen and W. M. Jones, *J. Amer. Chem. Soc.*, **85**, 3397 (1963); (b) R. S. Stearns and G. W. Wheland, *ibid.*, **69**, 2025 (1947); (c) J. Hine and M. Hine, *ibid.*, **74**, 5266 (1952).

(14) (a) H. S. Harned and L. D. Fallon, *ibid.*, **61**, 2374 (1939); (b) E. M. Wooley, D. G. Hurkot, and L. G. Hepler, *J. Phys. Chem.*, **74**, 3908 (1970).

(15) Our values for  $pK_w$  in 40% dioxane ( $\mu = 0.3$ ) provide a value of  $\Delta H = 12.0$  kcal/mol, compared to  $\Delta H^\circ$  (water, 25°) = 13.3 kcal/mol: J. W. Larsen and L. G. Hepler in "Solute-Solvent Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 1.

had no significant effect on  $k_{\text{obsd}}$ , the values obtained in 0.3 M alkali were taken as  $k_{\text{PhO}^-}$ , the specific rate constant (Table IV).

Rates of cyclization for the more reactive monoesters were measured in carbonate, Tris, phosphate, or acetate buffer, as appropriate to the pH range required. No dependence on buffer concentration could be detected for any compound in these media, even at the lowest pH values. Plots of  $k_{\text{obsd}}$  vs. pH (Figure 1) show a gradual increase in rate with increasing pH, or increasing ionization of the phenol. Plots of  $k_{\text{obsd}}$  vs.  $f_{\text{PhO}^-}$  (the mole fraction of phenolate ion) were linear, obeying eq 1.<sup>16</sup> A typical series of plots is shown in Figure 2.

$$k_{\text{obsd}} = k_{\text{PhO}^-}(f_{\text{PhO}^-}) + k_{\text{PhOH}} \quad (1)$$

Values of  $k_{\text{PhO}^-}$  and of  $k_{\text{PhOH}}$  were obtained by least-squares calculation, with correlation coefficients usually exceeding 0.999 (Table IV). For some of the more reactive compounds, values of  $k_{\text{PhOH}}$  were also measured directly at pH 3; the results were in accord with those obtained by the extrapolation method of Figure 2. Except for the mesylate of 2f, the specific rate constants for the neutral phenol as nucleophile are small compared with  $k_{\text{PhO}^-}$  ( $k_{\text{PhO}^-}/k_{\text{PhOH}} = 10^4$ – $10^6$ ). Values of

$k_{\text{PhO}^-}$  were obtainable for the complete series of mesylates and phosphates. Only in the cases of 3f, 3g, and 3h was it possible, however, to effect cyclization with esters of carboxylic acids as the leaving groups (Table IV). With the carboxylic esters of the more flexible diols, saponification to the diol occurred much more rapidly than cyclization; if the pH was reduced sufficiently to minimize saponification, chroman formation became too slow to measure conveniently.<sup>17</sup> Even in the case of 3f, small amounts of carboxylic ester hydrolysis occurred competitively with cyclization (except for X = COCH<sub>3</sub>). The observed rate constants for cycliza-

(16) The complete form of eq 1 is  $k_{\text{obsd}} = k_{\text{PhO}^-}(f_{\text{PhO}^-}) + k_{\text{PhOH}}(1 - f_{\text{PhO}^-})$  or  $k_{\text{obsd}} = (k_{\text{PhO}^-} - k_{\text{PhOH}})f_{\text{PhO}^-} + k_{\text{PhOH}}$ . Accordingly,  $k_{\text{PhO}^-} = \text{slope (Figure 2)} + k_{\text{PhOH}}$ . Because of the large difference in magnitudes between  $k_{\text{PhO}^-}$  and  $k_{\text{PhOH}}$ , this correction may be ignored.

(17) Several of the acetates were observed to cyclize when purification by distillation was attempted.

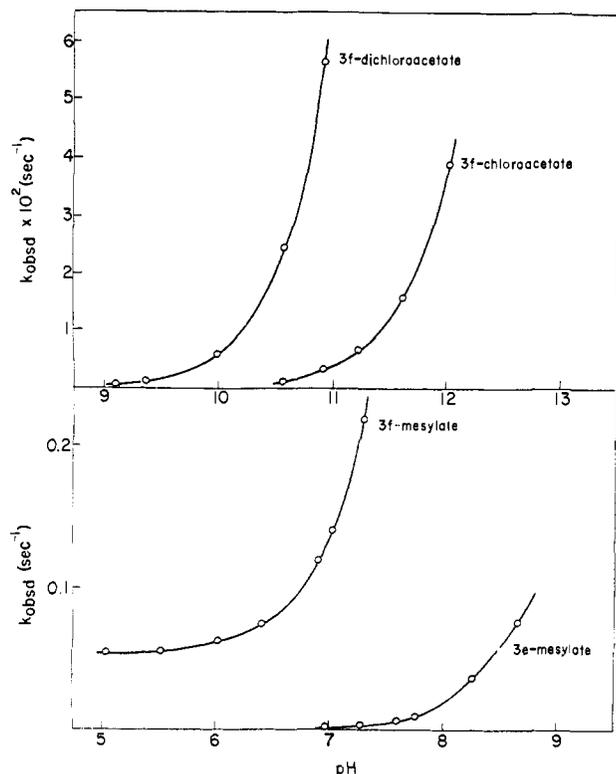


Figure 1. Typical plots of  $k_{\text{obsd}}$  vs. pH for cyclization of **3** esters ( $30^\circ$ ).

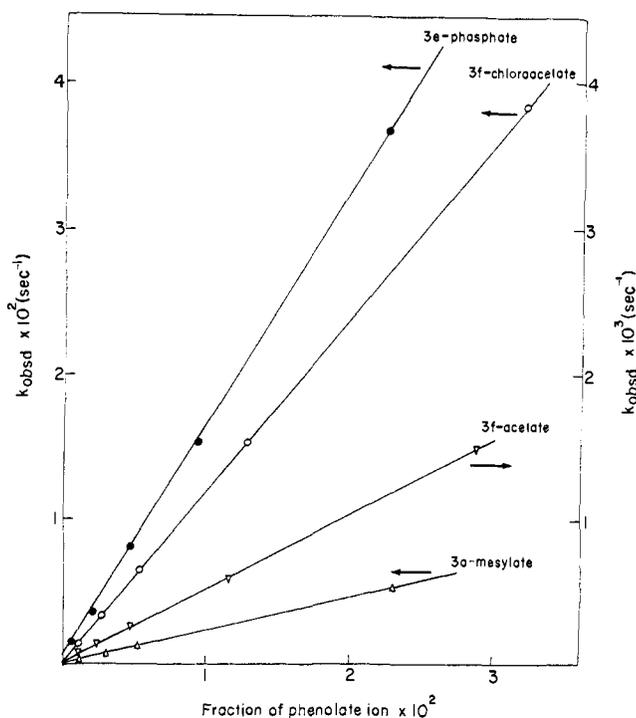


Figure 2. Typical plots of  $k_{\text{obsd}}$  vs. fraction of phenolate ion present at various pH values ( $30^\circ$ ).

tion were corrected to true rate constants from evaluation of the diol/chroman ratio present at the end of the run<sup>12</sup> (see Experimental Section).

The phenolic  $pK_a$  values, needed to calculate the fraction of phenolate ion as a function of pH, were determined spectrophotometrically for the more stable diol monoacetates and phosphates (Table III), as well

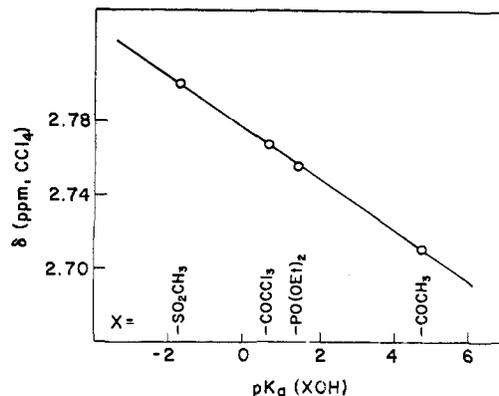


Figure 3. Variation of  $\delta$  in nmr spectrum ( $\text{CCl}_4$ , TMS = 0) for benzylic hydrogens (C-4) in **3c**, as a function of the  $pK_a$  of XOH, the conjugate acid of the leaving group.

as for the parent diols. Values for the more reactive esters were then estimated by extrapolation from the experimental data by assuming, for example, that the  $pK$  increment from **2d** to **3d** ester is applicable to **2e** and **2f**.<sup>18</sup> The variation in  $pK_a$  between acetate and phosphate was considered to be due to the difference in inductive effects of the two substituents, transmitted through the propyl side chain to the aromatic ring. The validity of this interpretation is supported by a correlation of the nmr chemical shift at the benzylic carbon (C-4) with the  $pK_a$  of the conjugate acid of X in **3c** (Figure 3). Accordingly,  $pK_a$  values for the phenolic groups in **3** containing other variants of X were interpolated from the data on phosphates and acetates vs. the  $pK_a$  values of XOH. The variation of phenolic  $pK_a$  with temperature was determined for **3c** ( $X = \text{PO}(\text{OEt})_2$ ) (Table III). Since the temperature coefficient for this compound was found to be the same as for **2c**, and since the remaining diols were found to have similar temperature coefficients,<sup>19</sup> the same increment was assumed for the four phosphates used in obtaining activation parameters.

Rates of cyclization of four monophosphates were measured at  $5^\circ$  intervals between  $25$  and  $45^\circ$ . Fractions of phenolate ion were calculated from the phenolic  $pK_a$  and buffer pH at each temperature, providing the values of  $k_{\text{PhO}^-}$  given in Table V. Plots of  $\log k_{\text{PhO}^-}$

Table V. Variation of  $k_{\text{PhO}^-}$  with Temperature ( $X = \text{PO}(\text{OEt})_2$ )<sup>a,b</sup>

Temp, $^\circ\text{C}$	<b>3a</b> $10^4 k_{\text{PhO}^-}$	<b>3c</b> $10^3 k_{\text{PhO}^-}$	<b>3d</b> $k_{\text{PhO}^-}$	<b>3f</b> $k_{\text{PhO}^-}$
25	0.73	0.61	0.29	78
30	1.37	1.07	0.44	115
35	2.49	1.84	0.66	168
40	4.45	3.14	1.04	251
45	7.81	5.20	1.53	328

<sup>a</sup> Values of  $k_{\text{PhO}^-}$  showed deviations from the mean of 1–2%, based on five to six pH values; all correlation coefficients were greater than 0.999. <sup>b</sup>  $\text{Sec}^{-1}$ .

vs.  $1/T$  were linear (Figure 4) for each of the four compounds; the activation parameters obtained from these slopes are summarized in Table VI.

(18) Even if the extrapolated  $pK_a$  values were in error by 0.2–0.3 unit, the effect on the values of  $k_{\text{PhO}^-}$  would be relatively small, and on the ultimate conclusions, negligible.

(19) To be reported in a subsequent paper.

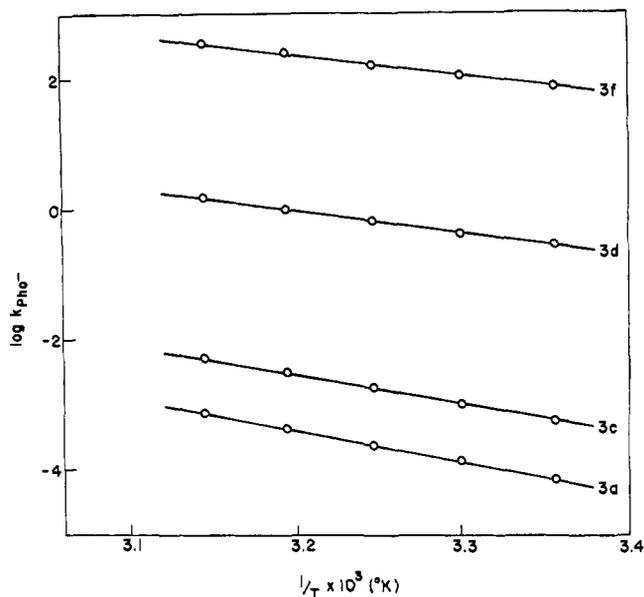


Figure 4. Plots of  $\log k_{\text{PhO}^-}$  vs.  $1/T$  ( $^{\circ}\text{K}$ ) for cyclization of **3** ( $X = \text{PO}(\text{OEt})_2$ ).

Table VI. Activation Parameters for **3** ( $X = \text{PO}(\text{OEt})_2$ )

Compd	$E_a$ , <sup>a</sup> kcal/mol	$\Delta H^\ddagger$ , kcal/mol	$\Delta S^\ddagger$ , <sup>b</sup> eu	$\Delta F^\ddagger$ , kcal/mol
<b>3a</b>	22.3	21.7	-4.6	23.1
<b>3c</b>	20.2	19.6	-7.3	21.9
<b>3d</b>	15.8	15.2	-9.9	18.2
<b>3f</b>	13.7	13.1	-5.8	15.8

<sup>a</sup> All correlation coefficients were greater than 0.999. <sup>b</sup> Calculated at  $30^{\circ}$ .

For compound **3f**, a sufficient number of variations in  $X$  had been examined to consider the possibility of a correlation between rate of cyclization and leaving ability. The results of a plot of  $\log k_{\text{PhO}^-}$  vs.  $pK_a$  of the conjugate acid of  $X$  are shown in Figure 5. The  $pK_a$  value for methanesulfonic acid ( $-1.86$ ) was based on ionization data in water, as determined by Raman spectroscopy;<sup>20a</sup> that for diethylphosphoric acid ( $1.39$ ) has been measured directly;<sup>20b</sup> the others are commonly accepted values.<sup>21</sup> The slope of the regression line of Figure 5 is  $-1.02 \pm 0.06$ , with a correlation coefficient of 0.992. Since the monocarboxylic esters of less alkylated diols were too slow to cyclize in competition with bimolecular hydrolysis, similar plots could not be constructed for these compounds (see Discussion).

The values of  $k_{\text{PhO}^-}$  represent a composite of electronic, buttressing, and conformational effects. Adjustments for the first two effects were made by following the procedure used for the phenolic acids:<sup>1</sup>  $\sigma_o(\text{CH}_3) = -0.15$ ;  $\sigma_m(\text{CH}_3) = -0.076$ ;  $\rho = -1.0$ ; steric rate-enhancement factor for C-8 methyl = 2.1. This value of  $\rho$  is the mean of values obtained from studies of bimolecular alkylations of phenolate ions<sup>3</sup> and, as indicated by these earlier studies, may be considered almost independent of the nature of the leaving group.

(20) (a) J. H. R. Clarke and L. A. Woodward, *Trans. Faraday Soc.*, **62**, 2226 (1966); (b) W. D. Kumler and J. J. Eiler, *J. Amer. Chem. Soc.*, **65**, 2356 (1943).

(21) (a) W. P. Jencks and J. Regenstein in "Handbook of Biochemistry," H. A. Sober, Ed., The Chemical Rubber Co., Cleveland, Ohio, 1968, p J-159; (b) S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, **36**, 1205 (1971).

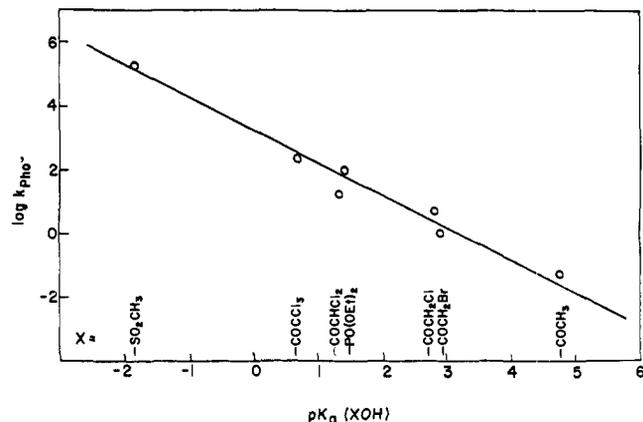


Figure 5. Correlation of  $\log k_{\text{PhO}^-}$  (for **3f**) with  $pK_a$  of the conjugate acid of the leaving group.

The steric rate-enhancement factor is viewed as an accelerating effect of the C-8 methyl on cyclization, due to buttressing on the phenolate ion or steric inhibition of ion solvation; the factor 2.1 was derived as that necessary to equate the values of  $k_{\text{PhO}^-}$  for **3a** and **3b**, following adjustment for normal electronic effects. Values of  $k_{\text{PhO}^-}$  were adjusted for a buttressing effect of the C-8 methyl and for the electronic effects of all ring substituents except that of the propyl side chain. The adjusted rate constants,  $k'_{\text{PhO}^-}$ , are given in column 4 of Table IV.

Since the methyl groups at C-5 and C-7 force the benzyloxy group at C-6 (in **3h**) out of coplanarity with the benzene ring, the resonance contribution of this substituent is diminished or negated. A modified  $\sigma$  value ( $+0.08$ )<sup>22</sup> was estimated by interpolation, using the  $pK_a$  values of the acetates of **3f** and **3g** and their  $\sigma$  constants: **3f**,  $pK_a = 13.56$ ,  $\sigma = 0$ ; **3g**,  $pK_a = 12.58$ ,  $\sigma = 0.22$ ; **3h**,  $pK_a = 13.18$ ,  $\sigma = 0.08$ . These  $pK_a$  values provide a  $\rho$  value for phenol ionization in the **3f** series (40% dioxane) of  $-4.4$ , a quite reasonable value.<sup>23</sup> When the value of  $k_{\text{PhO}^-}$  for **3h** ( $X = \text{COCH}_3$ ) is adjusted for electronic effects, reasonable agreement with  $k'_{\text{PhO}^-}$  for **3f** ( $X = \text{COCH}_3$ ) is obtained. On the other hand, a similar adjustment for **3g** provides a  $k'_{\text{PhO}^-}$  value three times that for **3f**. It would appear that the somewhat bulky halogen atom at C-6 can exert a buttressing effect on the C-5 methyl group, thereby effecting a small steric rate enhancement. A similar phenomenon was observed in the case of the *o*-hydroxypentamethylhydrocinnamic acid containing a C-6 nitro group.<sup>1</sup> Since the values of  $k_{\text{PhOH}}$  have only limited reliability, no effort was made to apply electronic corrections to them.

## Discussion

**Synthetic Methods.** Reaction of the various diols with acetic anhydride at elevated temperatures led to the formation of diacetates, except in the case of the hindered phenol, **2f**.<sup>24</sup> Acylation at room temperature, using brief reaction times, produced mainly the side-

(22) A  $\sigma$  value of  $+0.04$  has been estimated for the sterically inhibited methoxy group: R. W. Taft, Jr., and H. D. Evans, *J. Chem. Phys.*, **27**, 1427 (1957).

(23) For 2,6-di-*tert*-butylphenols in 50% ethanol, a  $\rho$  value of  $-4.62$  has been obtained: L. A. Cohen and W. M. Jones, *J. Amer. Chem. Soc.*, **85**, 3397 (1963).

(24) Even in the case of **3f**, acetylation with acetic anhydride-sulfuric acid (trace), at  $25^{\circ}$ , produced a diacetate.

chain monoacetate, the extent of diacylation decreasing with increase in steric hindrance at the phenol. No selective monoacylation at the phenolic site was observed; nor did significant reaction at the phenolic site occur when acylations, phosphorylations, or sulfonations were performed in pyridine as solvent, even with the least hindered phenol, **2a**. This fortunate circumstance may be due to steric hindrance to association of the phenol with the bulky acylpyridinium species.

Three separate methods were used for synthesis of reference samples of the chromans. (1) Cyclization of the diol in the presence of hot, 85% phosphoric acid<sup>7b</sup> was successful with **2d** and **2e**. Under the same conditions, **2f** underwent dealkylation to 2,3,5-trimethylphenol. Cyclizations of **2a-c** in phosphoric acid could not be effected. (2) Reduction of each lactone with lithium aluminum hydride led to the corresponding diol exclusively. On the other hand, reduction of **1f**, **1g**, or **1h** with sodium borohydride in the presence of boron trifluoride provided the desired cyclic ether. This procedure has been used successfully for the conversion of certain aliphatic esters to ethers,<sup>10</sup> but has not previously been applied to phenolic esters. Presumably, an intermediate lactol is converted, by boron trifluoride, into an oxocarbenium ion, which undergoes further reduction to the ether. Hemiacetal equilibria involving phenols are significantly less favorable than those involving alcohols; consequently, the success of this reaction may require the maintenance of the lactol structure by strong conformational restriction and may account for its failure with **1a** or **1d**. Alternatively, the unique behavior of **1f-h** may reflect a difference in conformation of the lactol ring (from that of **1a** or **1d**), such that the oxocarbenium ion can achieve better resonance stabilization. A similar postulate was invoked<sup>1</sup> to explain special sensitivity to acid-catalyzed breakdown of a tetrahedral intermediate analogous to the lactol resulting from **1f**. (3) Ethers **4a-c** were readily obtained by cyclization of the corresponding mesylates in strong alkali. Although this last method is applicable to the entire series, it requires the preparation of both diol and mesylate as intermediates.

**Kinetics.** Rate constants for cyclization of the mesylates and phosphates were readily obtainable for all members of the series. Except for systems containing 4,4,5-trimethyl substitution (**3f-h**), cyclizations of esters with carboxylic acid leaving groups were too slow to compete with bimolecular hydrolysis. The fact that chroman formation was observed, however, during distillation of several such esters suggests that cyclization could be studied in aprotic media; such experiments are planned. Except for bimolecular hydrolysis of the carboxylic esters, the cyclization reactions gave no evidence of side reactions, such as elimination or fragmentation.

The overall spread in specific rate constants ( $k_{\text{PhO}^-}$ ) of  $10^9$  required that media ranging from pH 6 buffer to 0.3 *N* alkali be used, in order to obtain conveniently measurable rates for all the leaving groups. Values of  $k_{\text{PhOH}}$ , relative to  $k_{\text{PhO}^-}$ , were so small ( $k_{\text{PhO}^-}/k_{\text{PhOH}} = 10^4-10^6$ ) that cyclization due to the neutral phenol did not contribute significantly to the observed rates, except for the most reactive compounds, and at the lower pH values studied. Since the pentamethyl mesylate (**3f**, X = SO<sub>2</sub>CH<sub>3</sub>) cyclized so rapidly, rate data had to

be obtained at pH values at which the undissociated phenol became a significant, or even the principal, nucleophile (Table VII). At pH values below 6, the

Table VII. Contribution of Phenol Participation to  $k_{\text{obsd}}^a$

pH	$f_{\text{PhO}^-}$	$t_{1/2}$ , sec	$k_{\text{obsd}}(\text{PhOH})/$ $k_{\text{obsd}}(\text{total})$ , %
5	$4.2 \times 10^{-9}$	13	98.4
6	$4.2 \times 10^{-8}$	11	86.3
7	$4.2 \times 10^{-7}$	5	38.7
8	$4.2 \times 10^{-6}$	0.8 <sup>b</sup>	5.9
9	$4.2 \times 10^{-5}$	0.08 <sup>b</sup>	0.6

<sup>a</sup> For **3f** (X = SO<sub>2</sub>CH<sub>3</sub>). <sup>b</sup> Calculated from  $k_{\text{PhO}^-}$  and  $k_{\text{PhOH}}$ .

observed rate of cyclization for this compound was found to be pH independent, since  $k_{\text{obsd}} \cong k_{\text{PhOH}}$ .

Nucleophilic displacements are generally considered to be insensitive to catalysis by general acids or bases. Indeed, we are aware of only one example of such catalysis: the buffer-promoted cyclization of 4-chlorobutanol.<sup>25</sup> We considered the possibility of buffer base assisting in proton removal from the undissociated phenol at some stage between initial and transition state, or of buffer acid assisting the leaving group by partial proton donation. A careful search for dependence of rate on buffer concentration was fruitless for all compounds and all buffers studied. The absence of such catalysis is also supported by the linearity of plots of  $k_{\text{obsd}}$  vs.  $f_{\text{PhO}^-}$ . This linearity, as well as the constancy of the  $k_{\text{PhO}^-}/k_{\text{PhOH}}$  ratio with different leaving groups, renders competition by a solvolysis mechanism (S<sub>N</sub>1) rather unlikely.

The rate-enhancement factors achieved by conformational restriction in this series (Table VIII) follow the

Table VIII. Effect of Conformational Restriction on Relative Rates of Cyclization<sup>a</sup>

Phenolate + <i>n</i> -propyl methanesulfonate				
	3a	3c	3d	3f
$k'_{\text{PhO}^-}$ (rel)	1 <sup>b</sup>	$8.2 \times 10^{3c}$	$1.4 \times 10^{4c}$	$2.5 \times 10^{7c}$
	1	1.6	$3.1 \times 10^3$	$2.1 \times 10^6$
			1	68

<sup>a</sup> Enhancement factors are based on specific rate constants which have been corrected for electronic and ortho effects; accordingly, only that portion of the molecule contributing to conformational rate enhancement is shown. <sup>b</sup> See Discussion for source of kinetic data for this reaction. <sup>c</sup> *M*.

order previously observed in the lactonization of *o*-hydroxyhydrocinnamic acids.<sup>1</sup> Methyl-methylene interaction (**3c**) provides a small rate-enhancement effect on cyclization. Whereas the rate-enhancement effect of 4,4-dimethyl substitution (**3d**) is of comparable magnitude for the two reactions, the further introduction of a 5-methyl group is considerably less effective in the case of nucleophilic displacement than in lactonization. Since the former reaction has neither an intermediate nor a sensitivity to buffer catalysis, and has markedly

(25) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Amer. Chem. Soc.*, **87**, 1553 (1965); see also ref 12, p 169.

different and less tolerant geometrical requirements in approaching its transition state, any detailed comparison with the lactonization reaction may be unwarranted.<sup>26</sup> Space-filling models indicate the side chain of **3f** to be almost as fully locked as that of the corresponding *o*-hydroxyhydrocinnamic acid. Nmr data, on the other hand, suggest that C-2 (in **3f**) has a moderate freedom of rotation.<sup>19</sup> The modest rate-enhancement effect achieved in adding the C-5 methyl group may be due to insufficient freezing of rotation of the 2,3 bond or to the locking of this bond in an inferior orientation for backside attack. Whether further conformational modification of **3f** can produce a ground state closer in geometry to the transition state will be the subject of future investigation.

Comparison of rate constants for these intramolecular displacements with their bimolecular counterparts is severely restricted by lack of data. By combining the specific rate constant for alkaline hydrolysis of methyl methanesulfonate at 30° ( $7.04 \times 10^{-4} M^{-1} \text{sec}^{-1}$ ),<sup>27</sup> the nucleophilicity ratio  $\text{OH}^-/\text{PhO}^- = 2$ ,<sup>28</sup> and an adjustment factor for the difference in bimolecular rates between methyl-X and *n*-propyl-X of  $1/12$ ,<sup>29</sup> a rate constant of  $2.9 \times 10^{-5} M^{-1} \text{sec}^{-1}$  is obtained for the reaction between phenoxide ion and *n*-propyl methanesulfonate. A rate-enhancement factor for the intramolecular *vs.* the bimolecular displacement of  $8 \times 10^3 M$  (effective concentration) was estimated in this way.

Past efforts to correlate conformational rate-enhancement factors with either activation enthalpy or entropy have provided few clear results.<sup>30</sup> The activation parameters obtained in the present case (Table VI) follow the earlier patterns of uncertainty. On the assumption that the side chains of **3a** and **3c** are extended, while those of **3d** and **3f** are folded, as a result of conformational restriction,<sup>19</sup> we had expected to see a steady increase in values of  $\Delta S^\ddagger$ , approaching zero for **3f**. Such a gradation, due solely to loss of rotational freedom of the side chain, may in fact exist; however, this factor may be masked, and the net value of  $\Delta S^\ddagger$  distorted, by an opposing factor, the extent of solvation of the phenolate ion. For each compound, achievement of the transition state should result in the release of water molecules from the ion cage, a process endowed with positive  $\Delta S^\ddagger$ . The size of the solvent cage should decrease in the order **3a**  $\cong$  **3c** > **3d** > **3f**, the result of both ortho substitution and crowding by the folded side chain (in **3d** and **3f**). Since these two contributions to  $\Delta S^\ddagger$  vary in opposite directions, the observed values of  $\Delta S^\ddagger$  seem more plausible. It is evident from Table VI that essentially all of the rate-enhancement effect appears in the activation enthalpy change, decreasing by 8.5 kcal/mol from **3a** to **3f**.

**Leaving Ability.** In principle, the leaving abilities

(26) Considerable effort has been expended, in this laboratory and in others [J. K. Coward and W. D. Sweet, *J. Org. Chem.*, **36**, 2337 (1971); L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 2059 (1970)], to devise an effective model system for intramolecular alkyl transfer from alkylsulfonium species to nucleophiles via  $\text{S}_\text{N}2$  displacement. The failure of these efforts, to date, emphasizes the low tolerance to backside approach of a nucleophile from an angle departing even moderately from 180°.

(27) S. Hartman and R. E. Robertson, *Can. J. Chem.*, **38**, 2033 (1960).

(28) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 11.

(29) D. Segaller, *J. Chem. Soc.*, 103, 1154 (1913).

(30) T. C. Bruice in "The Enzymes," Vol. II, 3rd ed, P. D. Boyer, Ed., Academic Press, New York, N. Y., 1970, Chapter 4.

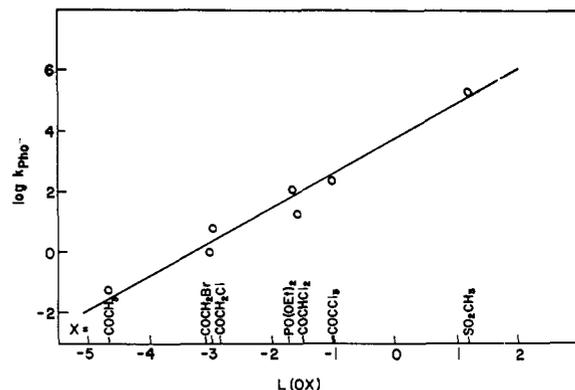


Figure 6. Correlation of  $\log k_{\text{PhO}^-}$  with  $L$ , the leaving-group parameter (Swain-Lohmann).

of a series of substituents may be expected to follow a linear free-energy relationship, particularly if the bond being broken remains uniform throughout the series. The validity of this assumption is evident from the correlation shown in Figure 5. Swain and Lohmann,<sup>31</sup> utilizing a relationship (eq 2) similar to those of the

$$\log(k_i/k_0) = \gamma L \quad (2)$$

Hammett and Brønsted equations, assigned a set of parameters ( $L$ ) to various leaving groups, based on the reaction



and the arbitrary values of  $L = 0$  for  $\text{X} = \text{Br}$  and  $\gamma = 1.000$  for this reaction. Unlike the Hammett relationship, however, only a limited correlation of  $L$  with the  $\text{p}K_\text{a}$  of  $\text{HX}$  is observed, the greatest deviations appearing with charged leaving groups. Utilizing Swain and Lohmann's values of  $L$  for three neutral substituents which involve breaking of C-O bonds, we established eq 3, from which values of  $L$  were calculated for the

$$L = -0.88\text{p}K_\text{a} - 0.49 \quad (3)$$

other leaving groups used in the present investigation. A plot of  $\log k_{\text{PhO}^-}$  *vs.*  $L$  (Figure 6) provides a regression line ( $\gamma$ ) of  $1.15 \pm 0.07$ , which is close to the assumed value of 1.00 for the bimolecular displacement reaction. The intramolecular displacement series, **3f**, provides a particularly useful means of testing eq 2, under a uniform set of conditions and for a wide variety of leaving groups. Extrapolation of Figure 5 to leaving groups poorer than acetate suggests that the half-life (at 30°) of a compound such as **3f** ( $\text{X} = \text{OPh}$ ) would be about 24 hr at full phenol ionization. Efforts to obtain rate data for such compounds are in progress.

Since it had been established that cyclization of each member of the series represented by **3** proceeds by a simple nucleophilic displacement, we wished to determine how the value of  $\gamma$  (in eq 2) for less alkylated (and less reactive) diol monoesters would compare with that for **3f**. Rate data for all the mesylates were readily obtainable. However, monocarboxylic esters of **3a-e** underwent bimolecular saponification too rapidly to permit cyclization to become a competitive reaction. In a search for leaving groups whose conjugate acids

(31) C. G. Swain and K. H. Lohmann, cited in E. R. Thornton, "Solvolysis Mechanisms," Ronald Press, New York, N. Y., 1964, p 164; K. H. Lohmann, Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1959.

were weaker than sulfonic acids, and yet relatively stable to alkaline hydrolysis as esters, we were attracted by the fact that trimethyl phosphate ( $k_2 = 1.4 \times 10^{-4} M^{-1} \text{sec}^{-1}$ ,  $25^\circ$ )<sup>32a</sup> is almost  $10^7$  times as stable to alkaline hydrolysis as is ethyl dichloroacetate ( $k_2 = 9.0 \times 10^2 M^{-1} \text{sec}^{-1}$ ,  $25^\circ$ )<sup>32b</sup> the corresponding acids having comparable  $pK_a$  values. Accordingly, the diethyl phosphates of **3a-f** were prepared and were found to cyclize readily without detectable hydrolysis. Other leaving groups meeting these special requirements are being sought. Tentative comparisons can be made by examining the ratios,  $k_{\text{PhO}^-}(\text{mesylate})/k_{\text{PhO}^-}(\text{phosphate})$  for **3a-f** (Table IX). Within the limits of error

**Table IX.** Comparisons of  $k_{\text{PhO}^-}$  Values for Mesylates (M) and Phosphates (P)

Compd	$k_{\text{PhO}^-}(\text{M})/$ $k_{\text{PhO}^-}(\text{P})$	Compd	$k_{\text{PhO}^-}(\text{M})/$ $k_{\text{PhO}^-}(\text{P})$
<b>3a</b>	1730	<b>3d</b>	1680
<b>3b</b>	1750	<b>3e</b>	1610
<b>3c</b>	1540	<b>3f</b>	1780

of the kinetic measurements, these ratios may be considered sufficiently similar to suggest that values of  $\gamma$  for **3a-e**, when obtained, will be comparable to that for **3f**.

It is clear from these studies that severe conformational restriction, in combination with secondary phenomena resulting therefrom,<sup>1</sup> can narrow significantly the gap, in terms of geometry and activation energy, between ground and transition states, thus compensating for the poor leaving abilities of various substituents. Some of the leaving groups encountered in enzyme-catalyzed displacements are also rather ineffective by chemical standards (Table X). Since there

(32) (a) F. Ramirez, B. Hansen, and N. B. Desai, *J. Amer. Chem. Soc.*, **84**, 4588 (1962); (b) W. P. Jencks and J. Carriuolo, *ibid.*, **83**, 1743 (1961).

**Table X.** Examples of Enzyme-Catalyzed Displacement Reactions<sup>a</sup>

Type of reaction	Leaving group
fluoroacetate $\rightarrow$ glycolate <sup>b</sup>	F
chloroacetate $\rightarrow$ glycolate <sup>b</sup>	Cl
epoxide + $\text{Cl}^- \rightleftharpoons$ chlorohydrin <sup>c</sup>	Cl
$\text{PhCH}_2\text{OAc} + \text{RSH} \rightarrow \text{PhCH}_2\text{SR} + \text{AcOH}^d$	AcO
allyl-OAc + RSH $\rightarrow$ allyl-SR + AcOH <sup>d</sup>	AcO
betaine + homocysteine $\rightarrow$ dimethylglycine + methionine <sup>e</sup>	$\text{R}_3\text{N}$
pyridine <sub>1</sub> + pyridinium <sub>2</sub> -R <sup>+</sup> $\rightleftharpoons$ pyridine <sub>2</sub> + pyridinium <sub>1</sub> -R <sup>+</sup> (NADase) <sup>f</sup>	Pyridine
catechol + S-adenosylmethionine $\rightarrow$ 2-methoxyphenol + adenosylhomocysteine <sup>e</sup>	$\text{R}_2\text{S}$
glucose-1-P + fructose $\rightarrow$ sucrose + P <sub>1</sub> <sup>e</sup> (sucrose phosphorylase)	P <sub>1</sub>
ribose-1-P + hypoxanthine $\rightarrow$ inosine + P <sub>1</sub> <sup>e</sup>	P <sub>1</sub>
dimethylallyl-PP + isopentenyl-PP $\rightarrow$ geranyl-PP + PP <sub>1</sub> <sup>e</sup>	PP <sub>1</sub>
thiazole + RCH <sub>2</sub> -PP $\rightarrow$ thiazole-CH <sub>2</sub> R + PP <sub>1</sub> <sup>e</sup> (thiamin biosynthesis)	PP <sub>1</sub>
$\text{PhNH}_2 + \text{RCH}_2\text{-PP} \rightarrow \text{PhNHCH}_2\text{R} + \text{PP}_1^e$ (tetrahydrofolic acid biosynthesis)	PP <sub>1</sub>
methionine + ATP $\rightarrow$ S-adenosylmethionine + PPP <sub>1</sub> <sup>e</sup>	PPP <sub>1</sub>

<sup>a</sup> Carbonium ion mechanisms have not been excluded for some of these examples. <sup>b</sup> P. Goldman and G. W. A. Milne, *J. Biol. Chem.*, **240**, 5557 (1965); P. Goldman, G. W. A. Milne, and D. B. Keister, *ibid.*, **243**, 428 (1968). <sup>c</sup> E. W. Bartnicki and C. E. Castro, *Biochemistry*, **8**, 4677 (1969). <sup>d</sup> E. Boyland and L. F. Chasseaud, *Advan. Enzymol.*, **32**, 173 (1969). <sup>e</sup> H. R. Mahler and E. R. Cordes, "Biological Chemistry," Harper and Row, New York, N. Y., 1966. <sup>f</sup> Standard biochemical abbreviations have been used in this table.

is little evidence for general acid-general base catalysis of nonenzymatic nucleophilic displacement (or even for enzymatic cases), we are led to conclude that conformational freezing of the substrate (or substrates) may be one of the principal devices employed by the enzyme to promote this type of reaction.

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