Stereopopulation Control. 9. Rate and Equilibrium Enhancement in the Lactonization of (o-Hydroxyphenyl)acetic Acids[1a]

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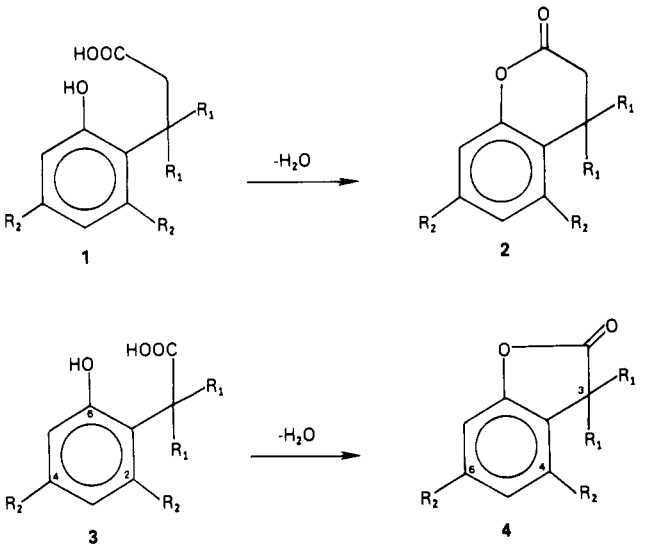
Received September 9, 1982

The kinetics of lactonization of (2,4-dimethyl-6-hydroxyphenyl)dimethylacetic acid have been investigated over the pH range 2.2–11.8 in unbuffered aqueous solution (30 °C, 20% dioxane). Concurrent catalysis by both forms of imidazole buffer has also been demonstrated. The rate constant for specific acid catalysis of lactonization (17.8 M^{-1} s^{-1}) is 2×10^7 times as great as that for the parent compound, (o-hydroxyphenyl)acetic acid; a comparable enhancement factor is found for specific base catalysis. The equilibrium content of lactone is >99% at all pH values below 10.5; in more alkaline media, phenol ionization stabilizes the dianion form of the phenolic acid. The introduction of methyl groups (α-, α-, and 2-positions) is equally effective in enhancing formation of the five-membered fused lactone as in the case of the analogous six-membered lactone.

Several earlier reports on *stereopopulation control* have dealt with the effects of multiple substitution on the cyclization of (o-hydroxyphenyl)propionic acids (1) to their six-membered lactones (2,[1b-d] Scheme I). It was shown that the progressive introduction of moderately large substituents (e.g., methyl groups) into the positions indicated leads, ultimately, to rather large enhancements in both equilibrium and rate constants for cyclization. Thus, in water–dioxane (4:1) the equilibrium content of lactone **2d** is 99.99% compared to ca. 0.8% for **2a**, and $k_{H_3O^+}$ for **1d** is 4×10^5 as great as for **1a**.[1d] Since we have found the steric component of (log) $k_{H_3O^+}$ to be a linear function of the van der Waals radius of R_2,[1c] we feel that these enhancements are due, primarily, to progressive elevation of the ground-state free energy content of the phenolic acid; this elevation, in turn, may result from (a) increases in the populations of conformers close in geometry to that of the transition state for cyclization and/or (b) steric destabilization of the phenolic acids due to overcrowding.[2]

In the course of these studies, we considered the consequences of shortening the carboxyl side chain of **1** by one carbon atom (**3**), anticipating that the additional strain involved in formation of the five-membered fused lactone **4** might be compensated by the entropic advantage of a side chain with reduced rotational modes.[3] We also hoped to use this simpler system to learn more about rotational barriers and conformational preferences in these series. Major obstacles in synthesis had delayed an investigation of the system **3** ⇌ **4**; these obstacles, however, were eventually overcome, and certain aspects of the study have now been completed.

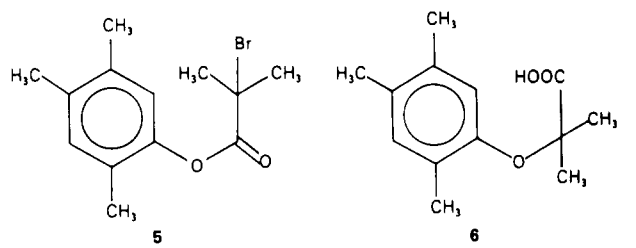
Scheme I[a]



[a] a, $R_1 = R_2 = H$; b, $R_1 = H$, $R_2 = CH_3$; c, $R_1 = CH_3$, $R_2 = H$; d, $R_1 = R_2 = CH_3$.

Results

Synthetic Methods. We anticipated that, because of the difficulties inherent in the synthesis of *o-tert*-butyltoluenes and similarly crowded systems,[4] the synthesis of **3d** or **4d** might not be achieved by classical routes. For example, benzilic acid reacts with phenol, thermally[5] or in the presence of Lewis acids,[6] to give 3,3-diphenyl-2-(3*H*)-benzofuranone (**4**; R_1 = Ph, R_2 = H) in low yield; yet, we could not obtain **4d** by analogous condensation of 3,5-dimethylphenol with 2-hydroxyisobutyric acid, 2-bromoisobutyric acid, or methacrylic acid under a variety of Friedel–Crafts conditions, nor did the phenolic ester **5**[7]



show any tendency to cyclize. While 2-phenoxyisobutyric acid undergoes a light-catalyzed rearrangement to 2-(o-hydroxyphenyl)isobutyric acid,[8] irradiation of 2-(2,4,5-

(1) (a) For paper 8 of this series, see: Hillery, P. S.; Cohen, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 2760. (b) Milstien, S.; Cohen, L. A. *Ibid* **1972**, *94*, 9158. (c) King, M. M.; Cohen, L. A. *Ibid.* **1983**, *105*, 2752. (d) Caswell, M.; Schmir, G. L. *Ibid.* **1980**, *102*, 4815.

(2) (a) Danforth C.; Nicholson, A. W.; James, J. C.; Loudon, G. M *J. Am. Chem. Soc*, **1976**, *98*, 4275. (b) Winans, R. E.; Wilcox, C. F., Jr. *Ibid.* **1976**, *98*, 4281.

(3) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; Chapter 7. Dreiding models suggest significant strain in **4** relative to **2**.

(4) E.g.: (a) Brown, H. C.; Nelson, K. L. *J. Am. Chem. Soc.* **1953**, *75*, 24. (b) Brown, H. C.; Domash, L. *Ibid.* **1956**, *78*, 5384. (c) Rickborn, B.; May, D. A.; Thelen, A. A. *J. Org. Chem.* **1964**, *29*, 91. (d) Unpublished results in this laboratory.

(5) Liebig, H. V. *Chem. Ber.* **1908**, *41*, 1646.

(6) Bistrzycki, A.; Jablonski, S. V. *Helv. Chim. Acta* **1932**, *15*, 890.

(7) Prepared from the thallium phenoxide by the method of: Taylor, E. C.; McLay, G. W.; McKillop, A. *J. Am. Chem. Soc.* **1968**, *90*, 2422.

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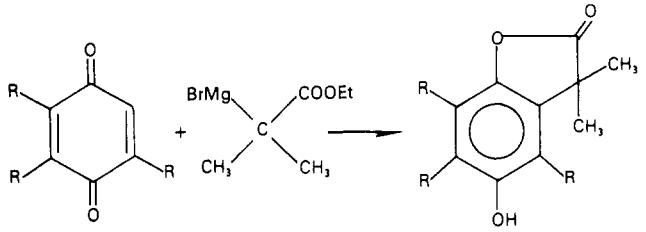
Table I. Equilibrium and Rate Constants for Lactonization (M^{-1} s^{-1})[a]

compd	% lactone at equilib	K_{eq}[b]	$k_{H_3O^+}$	k_{ImH^+}	k_{Im}	k_{OH^-}	k_{H_2O}[c]
3a	~0.5	$\sim 5 \times 10^{-3}$	8.8×10^{-7}[d]			~2.0[e]	
3b	~1.0	$\sim 1 \times 10^{-2}$	1.0×10^{-6}[d]			~2.0[e]	
3c	77	3.45	3.2×10^{-4}			67[e]	~0
3d	~100	4.2×10^{5}[f]	17.8	0.10	44.3	5.2×10^{6}	0.023
1c[g]	99.6	280	2.8×10^{-2}	1.25×10^{-6}	1.12×10^{-2}	204	1.2×10^{-5}
1d[g]	>99.9	6.5×10^{5}	26.2	2.7	14.4	2.6×10^{5}	7.5×10^{-3}

[a] At 30 °C in aqueous media containing 20% dioxane with μ = 0.3 M; all rate constants have been adjusted for f_{RCOOH} and for equilibria, where applicable. [b] Calculated as [lactone]/[acid$_T$]; activity of water taken to be 1.0. [c] In reciprocal seconds. [d] Calculated from $k_{H_3O^+}$ (hydrolysis) and K_{eq}. [e] Calculated from k_{OH^-} (hydrolysis) and K_{eq}. [f] See Experimental Section for method of calculation. [g] Data taken from ref 1b and 1d.

trimethylphenoxy)isobutyric acid (**6**), under comparable conditions, failed to produce any significant γ-lactone-containing material.[9] The desired rearrangement was finally achieved in the presence of aluminum chloride at 130 °C, but only with simultaneous migration of methyl groups on the phenolic ring. We then turned to approaches involving Reformatsky or Grignard 1,4-addition to benzoquinones.[10] Although ethyl 2-bromoisobutyrate failed to give the expected adduct (**7a**) with *p*-benzoquinone in



7a, R = H
b, R = CH_3

the presence of zinc, the corresponding Grignard reagent did form the fused lactone in low yield.[11] The same procedure was applied to trimethyl-*p*-benzoquinone, and **7b** was obtained in 7% yield. This product could not be used directly for kinetic studies because of its rapid oxidation to quinone in alkaline media, the benzyl ether of **7b** being equally unstable once the lactone ring had been opened.[12] An effort was made to remove the phenolic group of **7b** by hydrogenolysis of its 1-phenyltetrazole derivative;[13] steric hindrance by the *o*-methyl groups in **7b**, however, blocked formation of the tetrazole derivative.

Since **4c** had been prepared by direct *gem*-dialkylation of the acidic methylene group in **4a**,[14] we finally attempted the same alkylation with **4b** and, to our surprise, obtained **4d** in 23% yield. Clearly, the "trialkyl lock"[15] in this molecule is significantly less crowded than we had originally assumed. The precursor, **4b**, was prepared by reaction of cyanide ion with 2-(morpholinomethyl)-3,5-dimethylphenol to form (2,4-dimethyl-6-hydroxyphenyl)-acetonitrile, which was then hydrolyzed with acid to **3b**, and the latter was lactonized to **4b**.

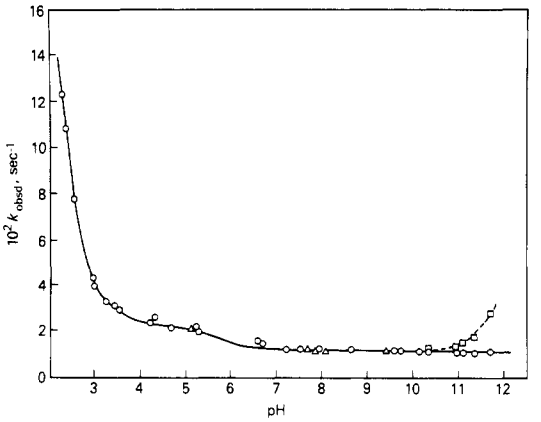


Figure 1. Plot of k_{obsd} vs. pH for lactonization of **3d** (20% dioxane, μ = 0.3 M NaCl, 30 °C): values obtained by use of pH stat (○), values obtained by extrapolation of buffer dilution plots to $[B]_{tot}$ = 0 (△), values at high pH uncorrected for equilibrium (□). The solid line shows the theoretical curve calculated from eq 1 and the data of Table I.

The phenolic acids, including **3c**, were readily obtained by alkaline ring opening of the lactones, followed by careful acidification of the salts; however, every attempt to isolate **3d** resulted only in recovery of the lactone, and kinetic studies were performed with stock solutions of **3d** in strong base.

Equilibria. Solutions of **3a** or **3b** in 0.8 M hydrochloric acid (20% dioxane) showed no UV spectral change over 48 h at 30 °C;[16] in the same medium, the spectra of equivalent concentrations of **4a** or **4b** became indistinguishable from those of the phenolic acids after 12 h. In these cases, the equilibrium content of lactone is evidently below the level of spectral measurement, and the values given in Table I have been taken as maximum estimates to be used only for purposes of comparison. Compound **3c** is converted extensively to lactone (77%) in the acid medium, while the lactonization of **3d** was found to be at least 99% complete. The UV spectrum and equilibrium content of **4d** remained unchanged up to ca. pH 10 and began to shift in more alkaline media only as phenol ionization became significant. Analysis of the dependence of K_{app} on pH provided a value of K_{eq} = [**4d**]/[**3d**] = 4.2×10^5 (see Experimental Section).

Kinetics of Lactonization. For the principal compound in this study, **3d**, the kinetics of lactonization were

(8) Kelly, D. P.; Pinhey, J. T.; Rigby, R. D. G. *Aust. J. Chem.* **1969**, *22*, 977.
(9) The phenolic acid would lactonize completely in the reaction medium.
(10) The zinc and magnesium derivatives of ethyl 2-bromoisobutyrate show a particular tendency to undergo 1,4-addition to α,β-unsaturated ketones: (a) Dubois, J. C.; Guetta, J. P.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1966**, 3008. (b) Gandolfi, C.; Doria, G.; Amendola, M.; Dradi, E. *Tetrahedron Lett.* **1970**, 3923.
(11) In the earlier studies with other series,[10] zinc was found significantly superior to magnesium.
(12) In subsequent studies in another series,[1c] we found that monosulfonates of hydroquinones are reasonably stable to oxidation in alkaline media.
(13) Musliner, W. J.; Gates, J. W. *J. Am. Chem. Soc.* **1966**, 88, 4271.
(14) (a) Elix, J. A.; Ferguson, B. A. *Aust. J. Chem.* **1973**, *26*, 1079. (b) Oude-Alink, B. A. M.; Chan, A. W. K.; Gutsche, C. D. *J. Org. Chem.* **1973**, *38*, 1993. (c) See also: Gripenberg, J.; Hase, T. *Acta Chem. Scand.* **1966**, *20*, 1561.
(15) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9175.
(16) Compound **3a** also failed to give detectable lactonization in 2 M perchloric acid: Capon, B.; McDowell, S. T.; Raftery, W. V. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1118.

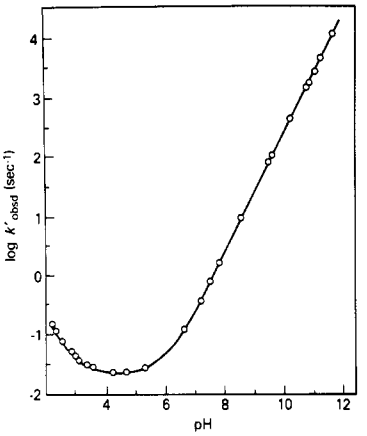


Figure 2. Plot of log k'_{obsd} vs. pH, where $k'_{obsd} = k_{obsd}/f_{AH_2}$, for lactonization of **3d**. The solid line shows the theoretical curve calculated from eq 2.

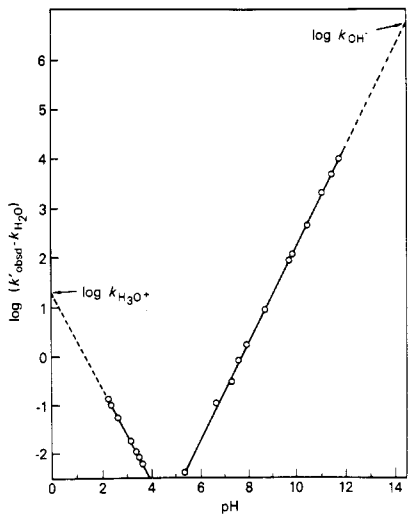


Figure 3. Plots of log ($k'_{obsd} - k_{H_2O}$) vs. pH for lactonization of **3d**. The solid lines have been fitted to slopes of ±1.

measured at 30 pH values (pH 2.2–11.8) in unbuffered media, with limited additional runs in acetate, imidazole, and borate buffers. Cyclization was found to follow first-order kinetics essentially to completion at all pH values. Infinity spectra were identical with those of **4d**, recorded under the same conditions and at the same concentration. Since the equilibrium content of **4d** is consistently >99%, kinetic data required no adjustment for equilibrium, except above pH 10, where phenol i - zatin becomes significant. The dependence of k_{obsd} on pH, in the absence of buffer, is shown in Figure 1. On the assumption of the neutral phenolic acid (AH_2) to be the *only* kinetically active species (see Discussion), k_{obsd} would include the terms in eq 1 or 2. The dependence of log

$$k_{obsd} = (k_{H_3O^+}[H_3O^+] + k_{OH^-}[OH^-] + k_{H_2O})f_{AH_2} \quad (1)$$

$$k'_{obsd} = k_{obsd}/f_{AH_2} = k_{H_3O^+}[H_3O^+] + k_{OH^-}[OH^-] + k_{H_2O} \quad (2)$$

k'_{obsd} on pH is shown in Figure 2. At the lower pH values, the term $k_{OH^-}[OH^-]$ may be ignored, and eq 2 can be simplified to eq 3 and 4. An approximate value for k_{H_2O} was

$$k'_{obsd} = k_{H_3O^+}[H_3O^+] + k_{H_2O} \quad (3)$$

$$\log (k'_{obsd} - k_{H_2O}) = \log k_{H_3O^+} - \text{pH} \quad (4)$$

obtained as the intercept of a plot of k'_{obsd} vs. $[H_3O^+]$ (see eq 3). This value was refined by successive adjustment,

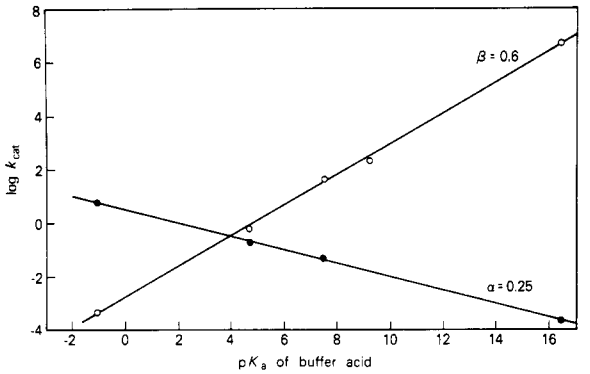


Figure 4. Brønsted plots for general-acid and general-base catalysis of lactonzation of **3d**. All data have been statistically corrected.

Table II. Rate Constants for Lactone Hydrolysis (M^{-1} s^{-1})[a]

compd	$10^4 k_{H_3O^+}$	$10^5 k_{exch}$	k_{OH^-}[b]
4a	1.75 (1.65)[c]		440
4b	1.02		192
4c	0.96 (1.02)	1.7	20.0 (8.0)
4d	0.27[d]	1.9 (3.6)[e]	7.9[f]

[a] At 30 °C in media containing 20% dioxane. [b] In borate buffer (pH 9.5); extrapolated to zero buffer concentration. [c] Values in parentheses refer to the corresponding δ-lactones (series 2), as given in ref 1b. [d] No detectable hydrolysis; value calculated from $k_{H_3O^+}$ (lactonization) and K_{eq}. [e] Value for 2d from this work. [f] From data at pH 11–12 (aqueous base).

until a plot of log ($k'_{obsd} - k_{H_2O}$) vs. pH provided the slope of -1 required for adherence to eq 4 (Figure 3); $k_{H_3O^+}$ was then obtained as the antilogarithm of the intercept of the latter plot. Using the value for k_{H_2O} already calculated, an analogous treatment for the high-pH range provided a value for k_{OH^-}. The minimum value of log k'_{obsd} in Figure 2 almost coincides with that for log k_{H_2O}, indicating that the contributions to k'_{obsd} due to acid and base catalysis are almost negligible at pH 4.5. The specific rate constants (Table I) were then used to produce calculated summation curves for log k'_{obsd} (Figure 2) and k_{obsd} (eq 1 and Figure 1). The close agreement between the observed and calculated values (which are based on the experimental pK values of 5.80 and 12.68 for **3d**) eliminates any need to consider a multiplicity of intermediate species.[17]

Buffer Catalysis. A small number of runs were made with **3d** in buffer media, primarily in that of imidazole. Buffer dilution plots were linear over the range examined (up to 0.15 M) and provided intercept values which are included in Figures 1 and 2. Plots of $k'_{B_{total}}$ (slopes of buffer dilution plots/f_{AH_2}) vs. the fraction of buffer base provided intercept values for k_{GA} and k_{GB} (Table I).[1b] From the catalytic rate constants of Table I, approximate Brønsted slopes were evaluated for **3d** (Figure 4).

Comparison Compounds. Lactonization of **3c** occurred at a conventiently measurable rate only in moderately acidic media (pH 0–1); a plot of k_{obsd} vs. $[H_3O^+]$ was linear and provided, after equilibrium correction, the value of $k_{H_3O^+}$ given in Table I. The intercept value, k_{H_2O}, was essentially zero. For compounds **3a** and **3b**, lactone formation could not be detected in 0.8 N hydrochloric acid, and hydrolysis of the respective lactones appeared to be complete in this medium. *Maximum* values for $k_{H_3O^+}$ were

(17) (a) Garrett, E. R.; Lippold, B. C.; Mielck, J. B. *J. Pharm. Sci.* **1971**, *60*, 396. (b) Lippold, B. C.; Garrett, E. R. *Ibid.* **1971**, *60*, 1019. (c) Hershfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1973**, *95*, 7359, 8032.

estimated from the specific rate constants for acid hydrolysis of the lactones (see below) and from the assumption that the equilibrium content of lactone does not exceed 0.5% for **3a** and 1% for **3b**.[18]

Lactone Hydrolysis. Specific rate constants for both acid (0.8 M hydrochloric acid) and base (pH 9.5, borate buffer) hydrolysis of lactones **4a–d** are given in Table II. Values of k_{obsd} in 0.15 M buffer were 7–10% higher than those in 0.05 M buffer; extrapolation of the buffer dilution plots provided the values of k_{OH^-} for hydrolysis. The values of k_{OH^-} for lactonization of **3a–c** (Table I) were then calculated as $K_{eq} \times k_{OH^-}$ (hydrolysis). This treatment is permissible only if hydroxide ion is considered to function as a general base in hydrolysis, rather than as the direct nucleophile (see Discussion), and is supported by the observation of modest buffer catalysis. Since **4d** is overwhelmingly favored in its equilibrium with **3d**, the kinetics of ring opening for this lactone could not be measured directly either in the acidic or buffer medium; however, the equilibrium is markedly displaced by phenol ionization, and it was possible to follow the kinetics of ring opening of **4d** at pH 11–12. A plot of k_{obsd} (corrected for equilibrium) vs. $[OH^-]$ was linear, with $k_{OH^-} = 7.0\ M^{-1}\ s^{-1}$ and $k_{H_2O} \simeq 0$. For acid hydrolysis of **4d**, a rate constant was calculated from $k_{H_3O^+}$ (lactonization) and K_{eq}.

^{18}O Exchange. Since acid hydrolysis of **4d** could not be observed directly, the kinetics of exchange in $H_2{}^{18}O$ were determined both for **4d** and for **4c**. In 0.8 M hydrochloric acid (20% dioxane) in 24 h at 25 °C, **4d** showed 58% and **4c** 53% enrichment. Under the same conditions, **2d** showed 84% enrichement. Values of k_{ex}, based on these results, are given in Table II.

Discussion

Two types of rate and equilibrium comparison can be made with the available data: (1) the effect of alkyl substitution within the series **3** ⇌ **4**; (2) the effect of side-chain length (and lactone ring size). For series **3**, the equilibrium content of lactone increases with the degree of alkyl substitution, as was found for series **1**,[2] as well as for simple γ-butyrolactones and δ-valerolactones.[19] This gradation is attributable to the fact that bulky substituents accelerate ring closure to a greater extent than they retard opening (Tables I and II).[19a,20] The equilibrium free energies of the **3a**/**4a** and **3d**/**4d** systems different by at least 11 kcal/mol. Since there is relatively little variation in the rates of acid (6.5-fold) and alkaline (55-fold) hydrolysis of the lactones, most of this energy difference (at least 10 kcal/mol) must be attributed to structural and conformational differences in the ground states of **3a** and **3d**, assuming the tetrahedral transition states to be energetically comparable. These conclusions are quantitatively consistent with the values of $k_{H_3O^+}$ and k_{OH^-} given in Table I.

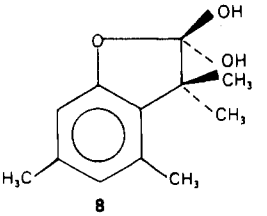
The equilibrium content of lactone is somewhat higher for **2c** than for **4c** (Table I), the six-membered lactone being favored by 1.9 kcal/mol. Since these lactones are hydrolyzed by acid at the same rate (Table II), we do not attribute this energy difference to greater fused ring strain in **4c** (although Dreiding models suggest a strain difference) but to a higher free energy content for **1c** than for **3c**; on the other hand, the values of K_{eq} for **2d** and for **4d** are essentially identical. In contrast to these results, γ-butyrolactone is favored over δ-valerolactone by 2.3 kcal/mol at equilibrium and 2,2-dimethyl-γ-butyrolactone over 3,3-dimethyl-δ-valerolactone by ca. 1.3 kcal/mol.[19a] In these simpler systems, the six-membered ring is opened much more readily than the five; while the rates of ring closure are quite similar.

Table III. Rate Enhancement Factors in Lactonization

parameter	catalyst	compd a	compd b	compd c	compd d
$k_{rel}(3)$	H_3O^+	1	1.1	363	2×10^7
$k_{rel}(1)$	H_3O^+	1	3.2	400	3.7×10^5
$k_{rel}(3)$	OH^-	1	1.0	34	2.6×10^6
$k(1)/k(3)$	H_3O^+	80	40	88	1.5
$k(1)/k(3)$	OH^-			3	0.05

We had argued previously[2,21] that the overall kinetics for lactonization of **1c** and **1d** seem more consistent with rate-limiting breakdown of a tetrahedral intermediate than with its formation, and we considered the same mechanisms to be valid for **1a** and **1b**.[22] For the sake of comparison, these assumptions are now made for series **3**. Examination of the values of $k_{H_3O^+}$ in Table I show **3d** to cyclize at least 2×10^7 as rapidly as **3a** (Table III); this factor is ca. 50-fold greater than that obtained for series **1** (**1d**/**1a**), but the **3d**/**3a** ratio rests on the validity of the K_{eq} value taken for **4a**/**3a**. A more reliable comparison can be made by use of the values of $k_{H_3O^+}$ derived directly from lactonization kinetics: **3d**/**3c** ratio = 5.6×10^4 and **1d**/**1c** ratio $\simeq 10^3$. Enhancement in series **3** is, again, ca. 50-fold greater than for series **1**. Values of $k_{H_3O^+}$ for **3d** and **1d** are very similar, while those for **3c** and **1c** differ by a factor of 90. It is noteworthy that the ratios of K_{eq} and $k_{H_3O^+}$ are virtually identical for the binary sets. In these comparisons, no adjustments have been made for variation in the number of aryl methyl groups; such electronic adjustments, however, would have a relatively small effect on the ratios of rate constants.

Hydroxide ion catalysis (k_{OH^-}) of lactonization shows the same high degree of sensitivity to alkyl substitution as does hydronium ion catalysis (Tables I and III), and, as in the latter case, values of k_{OH^-} for **3d** and for **1d** are reasonably similar; on the other hand, the k_{OH^-} ratio for **1c**/**3c** (3) is quite smaller than the $k_{H_3O^+}$ ratio (90). We see no obvious basis for these differences in catalytic rate constants, except for a possible eclipsing effect in the tetrahedral intermediate derived from **3c** or **3d** (**8**). The rate constants



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for lactone hydrolysis and for ^{18}O exchange (Table II), however, fail to suggest any significant role for eclipsing effects in the formation of tetrahedral intermediates in series **3**, nor do rate constants for imidazole-catalyzed lactonization differ significantly in the two series.

The Brønsted β value for cyclization of **3d** (0.6) is resonably close to that for **1d** (0.5), while the α values are

(18) By use of an expanded scale on the spectrophotometer recorder, any lactone content in excess of 1% would be detectable.

(19) (a) Wheeler, O H.; Granell de Rodriguez, E. E. *J. Org. Chem.* **1964**, *29*, 1227. (b) Sebelius, H. Dissertation, University of Lund, Lund, Sweden, 1927, as quoted in: Hückel, W. "Theoretical Principles of Organic Chemistry"; Elsevier: New York, 1958; Vol. II, p 895.

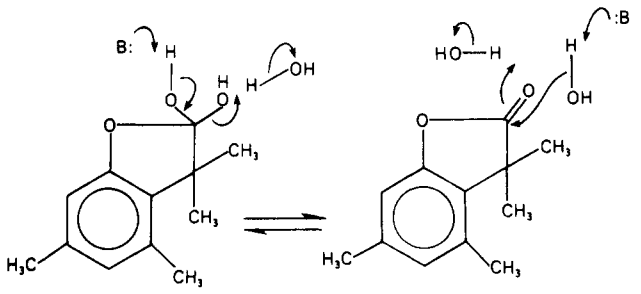
(20) Eberson, L. Welinder, H. *J. Am. Chem. Soc.* **1971**, *93*, 5821.

(21) Milstien, S. Cohen, L. A. *J. Am. Chem. Soc.* **1970**, *92*, 4377.

(22) For other evidence of rate-limiting breakdown in intramolecular systems, see: Cohen, L. A.; Takahashi, S. *J. Am. Chem. Soc.* **1973**, *95*, 443.

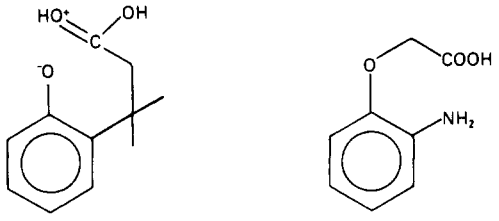
0.25 and 0.6, respectively.[1b] Although the values for **3d** are based on limited buffer data, additional measurements are not likely to increase the low α value significantly. We return to **8** and suggest that the protonated tetrahedral intermediates in series **1** and **3** (and/or the resulting carboniums ions) may have significantly different structures.

For compounds **3a–c**, values of k_{OH^-} for lactonization were calculated from k_{OH^-} for lactone hydrolysis and K_{eq}. For this calculation to be valid, hydroxide ion must be viewed as a general base in the hydrolytic process, and not as the direct nucleophile (**9a,b**). This argument is supported by the observation of mild catalysis of ring opening by borate ion and by the value of $\Delta S^{\ddagger} = -27$ eu previously obtained[21] for general-base catalysis of lactonization.



9a **9b**

In earlier studies,[2,21] the neutral phenolic acid **1**, or its kinetically equivalent form **10**, was considered to be the only significant source of lactone. In studies on the cyclization of o-hydroxycinnamic acids, Hershfield and Schmir[17c] also analyzed their kinetic data in terms of the neutral acid alone, while Garrett et al.[17a,b] considered contributions from the carboxylate ion form as well. Although there appears to be no direct experimental basis for exclusion of the second source of lactone, we offer two arguments against its consideration: (1) acetate ion shows virtually no tendency to undergo isotope exchange in alkaline $H_2{}^{18}O$;[23] (2) at pH 5, cyclization of **11** is complete within several minutes; at high pH, however, there is no significant cyclization over a 5-day period.[24a] Thus, if intramolecular addition of a nucleophile to carboxylate ion can occur at all under mild conditions, its contributions should be negligible in comparison with addition to the carboxylic acid.



10 **11**

We conclude, therefore, that both rate and equilibrium constants favor the six-membered lactone when the *gem*-dimethyl group is confronted with nonbonded hydrogen (**1c**, **3c**) but that differences between the two series disappear in the presence of an adjacent methyl group (**1d**, **3d**). At least for the latter pair, it would appear that any difference in ring strain is balanced by the entropy advantage of the shorter side chain; alternatively, there may be no significant difference in ring strain nor significant flexibility of either side chain.[25]

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(24) (a) Kirk, K. L.; Cohen, L. A., manuscript in preparation. (b) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9166.

Experimental Section[26]

2-(2,4,5-Trimethylphenoxy)isobutyric Acid (6). A solution of 2,4,5-trimethylphenol (6.0 g, 0.044 mol) and 1,1,1-trichloro-2-methyl-2-propanol (Chloretone; 17.0 g, 0.092 mol) in 120 mL of dry acetone (4A molecular sieves) was cooled in an ice–salt bath, and 4.7 g of sodium hydroxide pellets was added.[27] The mixture was stirred for 2 h, maintaining the temperature below 35 °C with a cold water bath. A second portion of 4.7 g of sodium hydroxide was then added and, after 2 h of stirring, a third portion, for a total of 0.35 mol of alkali. Stirring was then continued for 17 h. the solvent was removed in vacuo, and a solution of the residue in 30 mL of water was acidified with 20 mL of 6 N hydrochloric acid (cold). The mixture was extracted with ether (3 × 75 mL), the combined ether layers were extracted with 5% sodium bicarbonate (3 × 30 mL), and the combined bicarbonate extracts were acidified with 6 N hydrochloric acid. This mixture was extracted with ether (3 × 75 mL), and the combined extracts were dried ($MgSO_4$) and evaporated, leaving a brownish oil. The oil was dissolved in 10% sodium bicarbonate, and the solution was filtered and acidified and, upon cooling in ice, gave 2.4 g of solid material. The solid was dissolved in hot water–methanol (3:1), and the solution was decolorized with charcoal and, upon cooling, gave 1.93 g (20%) of **6** (mp 78.5–79.5 °C) which was recrystallized from hexane: mp 79–80 °C; IR (CCl_4) 3378 (OH, free), 2915 (OH, bonded), 1770 (C=O), free), 1710 cm^{-1} (C=O, bonded);[28] NMR ($CDCl_3$) δ 1.58 (s, 6, C-2 CH_3's), 2.13 (s, 9, ring CH_3's), 6.60 and 6.87 (2 s, 2, ring H's). Anal. ($C_{13}H_{18}O_3$) C, H.

Photochemical and Thermal Rearrangement of 6. A solution of **6** in 95% ethanol was irradiated (medium-pressure mercury-arc lamp) for 4–12 h at 25 °C, with and without a Vycor filter. In each case, the starting material was consumed, and the crude product showed IR bands at 3610, 1725, and 1700 cm^{-1}, but negligible absorption at 1800 cm^{-1}, expected for a phenolic γ-lactone.

A mixture of 1.0 g of **6** and 1.5 g of anhydrous aluminum chloride was fused and maintained at 130–135 °C for 1.5 h. The melt was cooled and extracted with chloroform. Silica gel chromatography of the dried extract gave 6% of material with IR absorption at 1800 cm^{-1} and the appropriate parent ion in the mass spectrum; however, the multiplicity of methyl signals in the NMR spectrum showed that extensive ring methyl migration had occurred.

3,3-Dimethyl-5-hydroxy-2(3*H*)-benzofuranone (7a). To a suspension of magnesium turnings (1.5 g, 0.062 mol) in 35 mL of dry tetrahydrofuran was added an iodine crystal. The mixture was flushed with nitrogen and was maintained at 60 °C while several milliliters of a solution of 12.6 g (0.065 mol) of ethyl 2-bromoisobutyrate in 50 mL of tetrahydrofuran was added. When the iodine color had been discharged, the remainder of the ester solution was added dropwise over 30 min. A solution of 5.0 g (0.046 mol) of *p*-benzoquinone in 100 mL of tetrahydrofuran was then added dropwise over 3 h, while the reaction mixture was stirred and maintained at reflux. The resulting blue-black solution was refluxed an additional 2 h. The mixture was diluted with ice–water, acidified to litmus with 6 N hydrochloric acid, and extracted with ether (3 × 150 mL). The combined ether extracts were washed with saturated, aqueous sodium hydrosulfite (2 × 60 mL), dried ($MgSO_4$), and concentrated. The residual oil was applied to a silica gel column (300 g), and the column was developed with ethyl acetate–hexane (3:7), yielding 0.92 g of a solid. A solution of the solid in chloroform–hexane was decolorized with

(25) We have not attempted to obtain activation parameters for series **1** or **3**, since the multiplicity of factors which contribute to rate enhancement[2] may each involve enthalpic and entropic terms and since such data for comparable systems has provided no striking conclusions.[21,24]
(26) Microanalyses and mass spectral measurements were performed by the Microanalytical Services and Instrumentation Section of this laboratory, under the direction of Dr. D. F. Johnson. Melting points are uncorrected. The identity and homogeneity of each compound were confirmed by mass spectroscopy, NMR spectroscopy, and TLC.
(27) This procedure is a modification of that used to prepare 2-(*p*-tolyloxy)isobutyric acid: Corey, E. J.; Barcza, S.; Klotmann, G. *J. Am. Chem. Soc.* **1969**, *91*, 4782.
(28) Free and intramolecularly hydrogen-bonded forms of 2-phenoxyisobutyric acids have been demonstrated by IR analysis: Oki, M.; Hirota, H. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 119.

charcoal, and the product was recrystallized three times from the same solvent mixture to give 9% of **7a**, mp 144.5–145.5 °C (lit. mp 149–152,[29a] 139–141 °C.[29b] Additional products in the mother liquors were not investigated further. The NMR, IR, and mass spectra of **7a** were consistent with the assigned structure. One attempt to effect the same condensation with zinc (in place of magnesium) yielded no lactone-containing products.

5-Hydroxy-3,3,4,6,7-pentamethyl-2(3*H*)-benzofuranone (7b). Essentially the same procedure was used for the Grignard addition to 2,3,5-trimethyl-*p*-benzoquinone. The product was purified by silica gel chromatography (ethyl acetate–hexane, 1:4) and, after decolorization and recrystallization from ethyl acetate–hexane, gave a 7% yield of **7b**: mp 188–189 °C; IR ($CHCl_3$) 3580 (OH), 1775 cm^{-1} (lactone C=O); NMR ($CDCl_3$) δ 1.55 (6, s, C-3 CH_3's), 2.20–2.26 (9, 3 s, C-4, C-6, and C-7 CH_3's), 4.54 (OH). Anal ($C_{13}H_{16}O_3$) C, H.

4,6-Dimethyl-2(3*H*)-benzofuranone (4b). To a solution of 2-(morpholinomethyl)-3,5-dimethylphenol (40.0 g, 0.18 mol)[30] in 250 mL of dimethylformamide (dried over 5A molecular sieves) was added 23.6 g (0.36 mol) of dry, powdered potassium cyanide.[31] The mixture was heated at reflux (with exclusion of moisture) for 5 h, although TLC showed starting material to have disappeared after 2 h. The mixture was cooled, and most of the solvent was removed on a rotary evaporator (45 °C, 3 mmHg). The flask was connected to an alkali trap, 40 mL of concentrated hydrochloric acid was added slowly, and the acidified mixture was finally flushed with nitrogen for 10 min. A brown, gummy precipitate was extracted with chloroform (3 × 250 mL); the combined extracts were washed with saturated NaCl, the solvent was evaporated, and the residual dimethylformamide was removed at 45 °C (3 mmHg). An IR spectrum of the dark brown oil (44.2 g) suggested the presence of nitrile, amide, and acid functions. This material was dissolved in 250 mL of warm glacial acetic acid, 25 mL of 45% hydrobromic acid was added, and the mixture was refluxed for 48 h. The reaction mixture was cooled, and the solvents were removed, first at aspirator pressure and finally at a vacuum pump. The residue was dissolved in ethyl acetate (250 mL); the solution was filtered, and the solvent was removed to give 31.5 g of a dark brown oil, which set to a glass on storage. This material was distilled through a short-path column, the condenser being heated with steam to avoid clogging; an almost colorless liquid (4 g) distilled at 95–103 °C (bath temperature) and 0.3 mmHg. a solution of the distillate in 30 mL of hot ether was decolorized with charcoal and, upon cooling, deposited 2.5 g (8.6% overall yield) of **4b**: mp 106–107 °C;[32] IR ($CHCl_3$) 1795–1800 cm^{-1} (γ-lactone C=O); NMR ($CDCl_3$) δ 2.25 (s, 3, CH_3), 2.35 (s, 3, CH_3), 3.55 (br s, 2, CH_2), 6.8 (br, 2, aryl H's). Anal. ($C_{10}H_{10}O_2$) C, H.

3,3-Dimethyl-2(3*H*)-benzofuranone (4c). 2(3*H*)-Benzofuranone (0.40 g, 3 mmol) was alkylated with methyl iodide and potassium carbonate in dimethylformamide.[14a] The solvent was removed on a rotary evaporator with vacuum pump pressure, the residue was dissolved in chloroform, and, after filtration, the solution was concentrated to 2–3 mL. This solution was applied directly to three preparative thin-layer plates (silica gel, 2-mm thickness), and the plates were developed with ether–hexane (3:7). The most mobile material (R_f 0.64) was extracted with chloroform and provided 0.21 g (44%) of **4c** as a colorless oil: IR ($CHCl_3$) 1810 cm^{-1} (γ-lactone C=O).

3,3,4,6-Tetramethyl-2(3*H*)-benzofuranone (4d). To a solution of **4b** (0.30 g, 1.85 mmol) in 15 mL of dry dimethylformamide was added 0.45 mL of methyl iodide (7.2 mmol) and 1.5 g of anhydrous potassium carbonate (10.8 mmol). The mixture was stirred at ambient temperature for 24 h, at which time TLC showed total absence of starting material. Salts were removed by filtration, and the filtrate was concentrated on a rotary evaporator (40 °C, 3 mmHg). The residual oil was dissolved in 50 mL of chloroform, and the solution was filtered and reduced to a volume of 3 mL. This solution was applied to three preparative silica gel plates (2-mm thickness), and the plates were developed with ether–hexane (3:7). The most mobile band (R_f 0.58) was eluted with chloroform and provided 80 mg (23%) of a pale yellow oil: NMR ($CDCl_3$) δ 1.55 (s, 6, C-3 CH_3's), 2.35 (br s, 6, C-4 and C-6 CH_3's), 6.85 (br, 2, aryl H's); IR (CCl_4) 1805 cm^{-1} (γ-lactone C=O). Anal. ($C_{12}H_{14}O_2$) C, H.

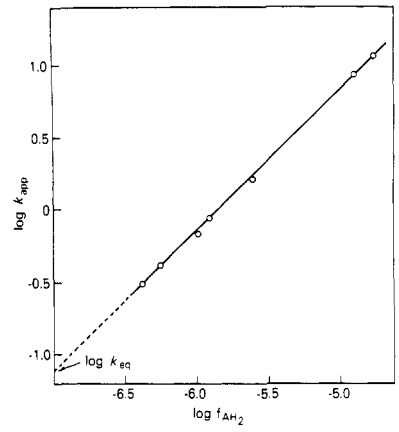

Figure 5. Plot of log K_{app} vs. log f_{AH_2} for the **3d–4d** system; the y intercept = log K_{eq}.

(2,4-Dimethyl-6-hydroxyphenyl)acetic Acid (3b). A suspension of **4b** (0.20 g, 1.2 mmol) in 25 mL of 0.1 N potassium hydroxide was heated on steam to effect solution (ca. 10 min). The pale yellow solution was cooled to 0 °C and was extracted with ether (2 × 25 mL). Ice was added to the aqueous layer, which was then made acid to litmus with concentrated hydrochloric acid and was extracted with chloroform (2 × 25 mL). The extract was dried ($MgSO_4$) and evaporated to give a solid (80 mg, 39%), which was decolorized and recrystallized from ether–petroleum ether; mp 153.5–154.5 °C.

2-(2-Hydroxyphenyl)isobutyric Acid (3c). A sample of **4c** (45 mg) was added to 10 mL of 0.1 N potassium hydroxide, and the mixture was heated with steam to effect solution (3–5 min). The solution was cooled and extracted with ether (2 × 25 mL); ice was added to the aqueous phase, which was then acidified to litmus with concentrated hydrochloric acid. The solution was extracted with chloroform (2 × 25 mL) and with ether (25 mL), and the combined extracts were dried ($MgSO_4$) and evaporated to give 38 mg of an oil, which solidified upon addition of hexane. The product was recrystallized from 5 mL of warm hexane to give 18 mg (35%) of **3c**, mp 86–88 °C.

p*K* Measurements. pK_1 values (carboxyl ionization in 20% dioxane, μ = 0.3 M NaCl, 30 °C) were calculated for **3a–c** from pH data at $^1/_4$, $^1/_2$, and $^3/_4$ neutralization. The following pK's are the averages of the three values for each compound: **3a**, 4.87 ± 0.02; **3b**, 5.03 ± 0.02; **3c**, 5.56 ± 0.01. Since **3d** could not be isolated, a pK_1 value of 5.80 was estimated by adding 0.16, the difference between the value for **3a** and **3b**, to that for **3c**, thus adjusting for the electronic effect of the ring methyl groups. Values of pK_2 (phenol ionization) were calculated from spectral data at 290–300 nm in acid, base, and buffer media: **3a**, 11.46 ± 0.03; **3b**, 11.73 ± 0.02; **3c**, 12.40 ± 0.07. This simple procedure could not be used for **3d**, since the absorbance of the undissociated phenol could not be recorded prior to significant lactonization. The compound is much more stable above pH 10, and the required absorbance value was obtained by extrapolation of a plot of A vs. $[OH^-](A_{PhO^-} - A)$, in which A is the measured absorbance at a given pH and A_{PhO^-} is the absorbance in 2.4 M alkali (complete ionization); the intercept value = A_{PhOH} while the slope = K_2/K_w.[33] This procedure gave a value of pK_2 for **3d** of 12.68. The predicted value, based on adjustment of that for **3c** for the electronic effect of the ring methyl groups, is 12.67. From literature data,[1d] pK_w (20% dioxane, μ = 0.3 M NaCl, 30 °C) was estimated to be 14.10.

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Equilibria. For the **3c–4c** system, the same equilibrium content of lactone was determined spectrally from either starting material. Normal procedures could not be used for the **3d–4d** system. Equilibrium spectra were recorded for solutions of **4d** at pH 10–13. The equilibrium concentrations of **4d** were calculated from the previously determined absorbance values of $\mathbf{3d}^-$, $\mathbf{3d}^{2-}$, and **4d**. Values of $K_{app} = [\mathbf{4d}]/[\mathbf{3d}]_{tot}$ were then calculated for each pH. We define $K_{eq} = [\mathbf{4d}]/[\mathbf{3d}] = K_{app}/f_{AH}$, where f_{AH} is the fraction of neutral **3d** at the given pH value, and $f_{AH_2} = [H^+]^2/([H^+]^2 + K_1[H^+] + K_1K_2)$. Thus, $\log K_{app} = \log f_{AH} + \log K_{eq}$; a plot of $\log K_{app}$ vs. $\log f_{AH_2}$ was fitted to a slope of 1, and $\log K_{eq}$ was obtained as the intercept (Figure 5).

Kinetic Measurements. Kinetic measurements were performed as previously described,[2,21] in media containing 20% (by volume) of purified dioxane; acid and base concentrations are final values. All measurements were made at 30 ± 0.1 °C and at a total ionic strength of 0.3 M (NaCl). The majority of kinetic runs were made in the absence of buffer by use of a pH stat–spectrophotometer combination.[34] Rates of lactonization were followed by the increase in absorption at 240–260 nm or the decrease at 270–285 nm, and the reverse for lactone hydrolysis. Phenolic acids **3a–c** were sufficiently stable for isolation; in the case of **3d**, however, the lactone was opened in 0.08 M KOH (20% dioxane), and aliquots of this stock solution were added to appropriate buffer media or to media of the desired pH value. For the majority of runs, initial and final pH values differed by less than 0.05 unit. For calculations, final pH values were taken routinely. In kinetic runs, correlation coefficients generally exceeded 0.998, and values of k_{obsd} were usually reproducible to ±2% or better, reproducibility decreasing somewhat for the very fast reactions.

Registry No. **3a**, 614-75-5; **3b**, 86549-97-5; **3c**, 86549-98-6; **3d**, 86549-99-7; **4a**, 553-86-6; **4b**, 33901-25-6; **4c**, 13524-76-0; **4d**, 86562-99-4; **6**, 86550-00-7; **7a**, 26172-13-4; **7b**, 86563-00-0.

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Isolation, Partial Synthesis, and Structure Determination of Sterols with the Four Possible 23,24-Dimethyl-Substituted Side Chains[1]

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Received March 15, 1983

(23*R*,24*R*)- and (23*S*,24*R*)-4α,23,24-trimethyl-5α-cholestan-3β-ol, (23*R*,24*R*)- and (23*S*,24*R*)-23,24-dimethyl-5α-cholestan-3β-ol, and (23*S*,24*R*)-23,24-dimethylcholest-5-en-3β-ol were isolated from various marine organisms. Methyl substitution at C-23 and C-24 was proved by comparison of their 360-MHz ^{1}H NMR spectra with those of the hydrogenation products of dinosterol ((*E*,24*R*)-4α,23,24-trimethyl-5α-cholest-23-en-3β-ol) and synthetic 24-epidinosterol and 4-demethyl-5-dehydro-24-epidinosterol. The configuration at C-23 in the natural products was determined by chemical correlation of one of them with peridinosterol ((*E*,23*R*,24*R*)-4α,23,24-trimethyl-5α-cholest-17(20)-en-3β-ol). The configuration at C-23 of sterols with a 23,24(*S*)-dimethyl-substituted side chain was solved by X-ray analysis of the *p*-bromobenzoate of (23*R*,24*S*)-23,24-dimethyl-5α-cholestan-3β-ol.

Research on cultured unicellular marine algae has solved the problem of the origin of two cyclopropyl sterols, viz., gorgosterol (**3m**) and 23-demethylgorgosterol (**3l**), as it has been shown[2] that dinoflagellates (unicellular algae belonging to the phylum Pyrrhophyta) are primary sources of sterols with such side chains (**m,l**). Dinoflagellates are also sources of sterols with other uncommon side chains such as dinosterol[3] (**1i**) and its Δ^5,[4] $\Delta^{8(14)}$,[5,6] Δ^{14},[5] 4-demethyl[2,7] (**2i**), and 4-demethyl-5-dehydro[2] (**3i**) analogues, 24-demethyldinosterol[8,9] (**1h**) and its 4-demethyl[2] (**2h**) and 4-demethyl-5-dehydro[2,8] (**3h**) analogues, and 24-epioccelasterol[10] (**3g**). Sterols with the corresponding saturated side chains have not yet been unequivocally found in marine organisms with the exception of one claim[11] whose validity is discussed below.

We now report the partial synthesis and structure determination of sterols with the four possible 23,24-dimethyl-substituted side chains (**a–d**) and the isolation of five sterols having two of these side chains and three different nuclei.

Results and Discussion

The 360-MHz ^{1}H NMR and chromatographic mobility data of the natural products (**1a,b**, **2a,b**, and **3b**, Figure 1) discussed in this paper are listed in Table I together with their sources. The NMR data clearly show that the five naturally occurring sterols have two different side chains, **a** and **b**. In other papers[5,6] we have described how the structure of the skeleton and the site of nuclear unsaturation are deduced by NMR and mass spectra, including application of Zürcher's rules.[12] To avoid repetition, we will discuss here only the determination of the structure of the side chains by a combination of chemical and spectroscopic methods.

The NMR spectra of the 4α-methyl sterols of M_r = 430 (Table I) include six methyl doublets (one at δ 0.946 due

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[§] Buffalo Medical Foundation.

(1) Part 42 of the series "Sterols in Marine Invertebrates". For part 41 see: Bonini, C.; Cooper, C. B.; Kazlauskas, R.; Wells, R. J.; Djerassi, C. *J. Org. Chem.* **1983**, *48*, 2108.
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