Hydroxy-group Participation in Ester Hydrolysis

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Aryl esters of 4-hydroxybutyric acid, 5-hydroxyvaleric acid, 2-hydroxyphenylacetic acid, and 3-(2-hydroxyphenyl)-propionic acid are lactonised in reactions whose rates are proportional to 10^{pH-pK_w}. The anchimeric assistance corresponds to rate enhancements of 10^3—10^6 over the rates of hydrolysis of analogous esters without the hydroxy-groups. The reaction of phenyl 4-hydroxybutyrate shows buffer catalysis, possibly general base catalysis, in acetate and phosphate buffers. The esters of 4-hydroxybutyric acid and 5-hydroxyvaleric acid also react with participation by the hydroxy-groups in the acid-catalysed hydrolysis but those of 2-hydroxyphenylacetic acid and 3-(2-hydroxyphenyl)propionic acid do not. The rate of hydrolysis of phenyl 4-hydroxybutyrate increases more rapidly with acid concentration than that of phenyl butyrate does. The ϕ values are 0·59 and 0·99 respectively. The hydrolyses of the lactones of 2-hydroxyphenylacetic acid and 3-(2-hydroxyphenyl)propionic acid were also studied.

ALTHOUGH nucleophilic assistance by hydroxy-groups of serine residues has been suggested to occur in hydrolyses catalysed by several esterases,[1] intramolecular nucleophilic assistance by alcoholic hydroxy-groups which might be considered a model for this process has not been studied.[2] We now report an exploratory investigation of neighbouring group participation by alcoholic hydroxy-groups in the reactions of aryl esters of 4-hydroxybutyric acid and 5-hydroxyvaleric acid. These reactions are compared with those of the aryl esters of 2-hydroxyphenylacetic acid and 3-(2-hydroxyphenyl)propionic acid which involve neighbouring group participation by phenolic hydroxy-groups.

EXPERIMENTAL

2-Naphthyl 4-Hydroxybutyrate.—Dicyclohexylcarbodiimide (0·039 mol) in dry pyridine (6 ml) was added slowly to a stirred ice-cold homogeneous solution of benzyloxybutyric acid [3] (0·034 mol) and 2-naphthol (0·034 mol) in pyridine (9 ml) and the mixture was stirred for a further 2 h at 0° and overnight at room temperature. The solution was filtered and evaporated to give *2-naphthyl 4-benzyloxybutyrate* which was recrystallised three times from a little ethanol and finally from a large volume of ethanol after treatment with animal charcoal (yield 40%), m.p. 68·5—69·0° (Found: C, 78·9; H, 6·4. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·3%), δ ($CDCl_3$) 2·02 (2H, m), 2·68 (2H, t), 3·52 (2H, t), 4·45 (2H, s), and 7—8 (12H, m). The mass spectrum shows no parent ion (*m/e* 320) but only fragments at *m/e* 234, 177, 144, 115, and 91.

2-Naphthyl 4-benzyloxybutyrate (4 g, 0·0125 mol), dissolved in ethyl acetate (40 ml), was stirred with 10% palladium on charcoal (0·6 g) in an atmosphere of hydrogen for 12 h. The solution was dried with sodium sulphate, filtered, and evaporated under reduced pressure to give an off-white product which was dissolved in anhydrous ether (6 ml) and slowly cooled in a mixture of acetone and solid carbon dioxide to yield a precipitate, m.p. 51·5—55·5°. One further recrystallisation yielded *2-naphthyl 4-hydroxybutyrate*, m.p. 54·5—56·0° (Found: C, 72·5; H, 5·3. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%), δ ($CDCl_3$) 2·00 (2H, q), 2·72 (2H, t), 3·77 (2H, t), and 7—8 (7H, m), $\nu_{max.}$ (Nujol) 1730 and 3500 cm^{-1}. The mass spectrum showed no parent ion but only ions of butyrolactone (*m/e* 86) and 2-naphthol (*m/e* 144) and fragments derived from these (*m/e* 58 and 115).

2-Naphthyl 5-Hydroxyvalerate.—5-Benzyloxyvaleric acid was prepared from δ-valerolactone by a similar method to that used to prepare 4-benzyloxybutyric acid,[3] b.p. 171—175° at 1·5 mmHg, δ ($CDCl_3$) 1·6 (4H, m), 2·3 (2H, t), 3·4 (2H, t), 4·4 (2H, s), 7·25 (5H, s), and 11·7 (1H, s), $\nu_{max.}$ (Nujol) 3000, 1700br, and 730 cm^{-1}. *2-Naphthyl 5-benzyloxyvalerate* was prepared by a similar method to that used for the 4-benzyloxybutyrate except that methylene chloride was used as solvent. After filtering off the dicyclohexylurea and evaporating the solvent an oil was obtained from which more crystalline by-products were obtained by treating with a mixture of light petroleum (b.p. 60—80°) and ethyl acetate. The mixture was allowed to stand for one day and then filtered and evaporated to yield a residue which was distilled. The fraction distilling at *ca.* 200° and 0·5 mmHg was dissolved in methylene chloride, cooled to 0°, and extracted with ice-cold sodium hydroxide (0·5M) and water. The solution was dried (Na_2SO_4) and evaporated to yield an oil which was chromatographed on alumina. The *product* was finally distilled, b.p. 170—180° at 0·2 mmHg (yield 59%). G.l.c. analysis on a 0·5% APL column at 250° showed only one component having a retention time of 3·94 min (Found: C, 79·0; H, 6·6. $C_{22}H_{22}O_3$ requires C, 79·0; H, 6·6%), δ 1·8 (4H, m), 2·6 (2H, t), 3·5 (2H, t), 4·5 (2H, t), and 7—8 (12H, m). The mass spectrum showed no parent ion (*m/e* 334) but only fragments (*m/e* 144, 115, 101, and 91).

2-Naphthyl 5-benzyloxyvalerate was hydrogenolysed using a similar method to that for the 4-benzyloxybutyrate. *2-Naphthyl 5-hydroxyvalerate* was obtained as a solid which was recrystallised from a mixture of light petroleum (b.p. 40—60°) and diethyl ether, m.p. 45·0—46·0° (Found: C, 73·5; H, 6·5. $C_{15}H_{16}O_3$ requires C, 73·75; H, 6·6%), δ ($CDCl_3$) 1·7 (4H, m), 2·65 (2H, t), 3·7 (2H, t), and 7—8 (7H, m). No signal for the hydroxy-proton could be discerned in the n.m.r. spectrum but the presence of a hydroxy-group was indicated by a broad band centred at 3250 cm^{-1} in the i.r. spectrum.

2-Naphthyl 4-Methoxybutyrate.—This was prepared from 4-methoxybutyric acid in a similar way to that used for the 4-benzyloxybutyrate and was recrystallised from aqueous ethanol, m.p. 31·5—32·5° (Found: C, 73·7; H, 5·5. $C_{15}H_{16}O_3$ requires C, 73·75; H, 6·6%), δ 2·05 (2H, m), 2·70 (2H, t), 3·35 (3H, s), 3·50 (2H, t) and 7—8 (7H, m). The mass spectrum showed a parent ion of *m/e* 244, and fragment ions with 186, 144, 127, 115, 101, 69, and 58.

[1] *Cf.* K. Krisch in 'The Enzymes,' ed. P. Boyer, Academic Press, New York, 1971, 3rd edn., vol. 5, p. 43; H. C. Froede and I. B. Wilson, *ibid.*, p. 87; E. C. Webb and B. Zerner, *Biochemistry*, 1969, **8**, 2026.

[2] *Cf.* B. Capon, *Quart. Rev.*, 1964, **18**, 45; T. C. Bruice and S. J. Benkovic, 'Bio-organic Mechanisms,' Benjamin, New York, 1966, vol. 1, p. 146.

[3] D. H. Eyre, J. W. Harrison, and B. Lythgoe, *J. Chem. Soc.* (*C*), 1967, 452.

2-Naphthyl Butyrate.—This was prepared from butyryl chloride and 2-naphthol and was recrystallised from ether at −15°, m.p. 24·0—25·0° (Found: C, 78·6; H, 6·4. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%). This compound has previously been reported as an oil, b.p. 164—165° at 3·0 mmHg.[4]

Phenyl and Substituted Phenyl 4-Benzyloxybutyrates and 5-Hydroxyvalerates.—Thionyl chloride (0·03 mol) was added over *ca.* 1 h to a stirred solution of 4-benzyloxybutyric acid or 5-benzyloxyvaleric acid (0·03 mol) and the phenol (0·03 mol) in dry pyridine (10 ml) at 0° and the mixture was left for 12 h at 0°. It was then poured into water (80 ml), shaken, and the oil which formed was separated. This was shaken with more water, separated, and dissolved in ether. Pyridine was removed from the ethereal solution by shaking several times with cadmium chloride solution until no more precipitate formed. The solution was dried. the solvent evaporated, and the resultant oil was heated gently at 0·001 mmHg to distill off unchanged phenol. The oil was chromatographed [silica gel, 12% ether in light petroleum (b.p. 60—80°)] and the product was distilled in a molecular still at 0·001 mmHg. The yields were usually *ca.* 30%.

Phenyl 4-Hydroxybutyrate.—Dry hydrogen saturated with ethyl acetate was passed through a stirred solution of phenyl 4-benzyloxybutyrate (0·2 g) in dry ethyl acetate (4 ml) containing 10% palladium on charcoal (0·02 g). The reaction was complete after 2 h (t.l.c.) and the solution was filtered and evaporated. The last traces of ethyl acetate were removed by evaporation under an oil pump and the resulting oil was analysed immediately (Found: C, 66·3; H, 6·7. $C_{10}H_{12}O_3$ requires C, 66·65; H, 5·7%), δ 1·96 (2H, m), 2·65 (2H, t), 3·70 (2H, t), and 6·7—7·6 (5H, m). The i.r. spectrum showed the presence of a phenolic ester (1750 cm^{-1}) and a hydroxy-group (3400 cm^{-1}).

m-*Tolyl 4-Hydroxybutyrate.*—This was prepared in the same way as phenyl 4-hydroxybutyrate (Found: C, 68·2; H, 7·45. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%), δ 1·99 (2H, m), 2·33 (3H, s), 2·65 (2H, t), 3·75 (2H, t), and 6·5—7·5 (4H, m). The i.r. spectrum showed absorptions at 3500 (hydroxy-group) and 1750 cm^{-1} (phenolic ester).

m-*Chlorophenyl and* m-*Fluorophenyl 4-Hydroxybutyrate and 5-Hydroxyvalerate.*—These esters were not characterised but stock solutions for the kinetic experiments were prepared by reduction of the corresponding purified benzyloxy-esters in dioxan. The following is an example of the procedure adopted. Dry hydrogen saturated with dioxan was passed through a stirred solution of *m*-chlorophenyl 4-benzyloxybutyrate (60 mg) in dry dioxan (B.D.H. special for spectroscopy; 1·33 ml) containing 10% palladium on charcoal (12 mg) for 2 h when t.l.c. showed that no starting material was present. Any loss of dioxan was compensated for and the catalyst was removed by filtering through glass paper. The solution was stoppered and kept at −40° when not in use. The u.v. spectrum of the solution (10 μl) injected into water (3·0 ml) showed the absence of the phenol.

Phenyl Butyrate.—This was prepared from butyryl chloride and phenol in pyridine at 0°, b.p. 143° at 20 mmHg (Found: C, 73·2; H, 7·2. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·4%).

2-Naphthyl 2-Benzyloxyphenylacetate.—2-Benzyloxyphenylacetic acid was prepared by stirring equimolar quantities of methyl 2-hydroxyphenylacetate, sodium hydride, and benzyl chloride in dry dimethylformamide for 2 h at 0°. The mixture was diluted with water and extracted with ether. The extract was washed with water, dried, and evaporated to yield a brown oil which was chromatographed on silica gel with benzene–ether mixtures. Methyl 2-benzyloxyphenylacetate was eluted with a 1 : 1 benzene–ether mixture and was saponified to yield 2-benzyloxyphenylacetic acid which was recrystallised from carbon tetrachloride, m.p. 95·5—96·5° (lit.,[5] 96—97°) (Found: C, 74·2; H, 5·9. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%).

2-Benzyloxyphenylacetic acid (1·21 g) and 2-naphthol (0·72 g) were dissolved in a 17 : 3 (v/v) mixture of methylene chloride and ethyl acetate and cooled to −5°. Dicyclohexylcarbodi-imide (1·005 g) was added and the mixture was stirred at 0° overnight. The mixture was filtered and the precipitate was washed with cold methylene chloride. The filtrate and washings were evaporated and dissolved in a small amount of ether. This solution was kept at 0° for 20 min when more dicyclohexylurea was precipitated. It was then filtered and evaporated to yield an oil which crystallised under light petroleum and was recrystallised from di-isopropyl ether. The i.r. spectrum of this product still showed a weak peak at 1810 cm^{-1} and so it was chromatographed on deactivated alumina (20% aqueous acetic acid). The column was eluted with benzene and the first 100 ml of eluant was evaporated and the residue, *2-naphthyl 2-benzyloxyphenylacetate*, was recrystallised from ether and then di-isopropyl ether, m.p. 101—101·5°, δ ($CDCl_3$) 3·95 (2H, s), 5·1 (1H, s), and 7·4 (16H, m) (Found: C, 81·3; H, 5·5. $C_{25}H_{20}O_3$ requires C, 81·5; H, 5·5%).

2-Naphthyl 2-Hydroxyphenylacetate.—This was prepared by passing dry hydrogen through a solution of 2-naphthyl 2-benzyloxyphenylacetate in dry ethyl acetate in which was suspended 10% palladium on charcoal. The product was recrystallised from di-isopropyl ether and hexane, m.p. 96·5—97·5°, $\nu_{max.}$ (KBr) 3410, 1730, 1345, 1155, and 750 cm^{-1} (Found: C, 78·1; H, 4·9. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·1%).

Phenyl, m-*Chlorophenyl, and* m-*Tolyl 2-Hydroxyphenylacetate.*—The corresponding benzyloxy-esters were prepared

TABLE 1

Analyses of substituted phenyl esters

	4-Benzyloxybutyrates				5-Benzyloxyvalerates			
	Found (%)		Required (%)		Found (%)		Required (%)	
Substituent	C	H	C	H	C	H	C	H
m-Me	75·8	7·15	76·0	7·1	76·8	7·50	76·5	7·4
m-Cl	67·3	5·6	67·0	5·6	68·1	6·0	68·0	6·0
m-F	70·3	6·5	70·8	5·95				
H	75·6	6·8	75·5	6·7	75·8	7·1	76·0	7·1

[4] K. Gulati, S. R. Seth, and K. Venkatraman, *J. prakt. Chem.*, 1933, **137**, 47.

[5] A. Wagner, A. N. Wilson, and K. Folkers, *J. Amer. Chem. Soc.*, 1959, **81**, 5441.

from 2-benzyloxyphenylacetic acid and the phenol in methylene chloride in the presence of dicyclohexylcarbodiimide. They were hydrogenolysed in ethyl acetate solution containing a little hydrogen chloride in the presence of palladium black. M.p.s and analyses are given in Table 2.

2-Naphthyl 3-(2-Hydroxyphenyl)propionate.—3,4-Dihydrocoumarin (7·4 g) was stirred with potassium hydroxide (8·4 g) until the solution was homogeneous. Benzyl chloride (18·9 g) in ethanol (50 ml) was added and the mixture was stirred for 1·5 h when more benzyl chloride (18·9 g) was added. After 1 h the mixture was extracted with methylene chloride and the organic layer was discarded. The aqueous layer was acidified and extracted with more methylene chloride. This extract gave a brown oil on evaporation which was chromatographed on silica gel (5% ether in benzene) to give 3-(2-benzyloxyphenyl)propionic acid as an oil, δ (CCl_4) 2·78 (4H, m), 5·0 (2H, s), 7·2 (9H, m), and 11·3 (1H, s). This was further characterised as the *cyclohexylammonium salt* which was prepared by dissolving it in ether and treating with cyclohexylamine when the salt crystallised out. It was recrystallised from di-isopropyl ether and ethanol, m.p. 152—153° (Found: C, 77·1; H, 8·9; N, 3·4. $C_{28}H_{39}NO_3$ requires C, 76·9; H, 8·9; N, 3·2%). The acid was allowed to react with 2-naphthol in methylene chloride in the presence of dicyclohexylcarbodiimide as described for 2-benzyloxyphenylacetic acid to yield *2-naphthyl 3-(2-benzyloxyphenyl)propionate*, m.p. 47·5—48·5°, δ (CCl_4) 2·96 (4H, m), 5·03 (1H, s), and 7·4 (16H, m) (Found: C, 81·4; H, 6·3. $C_{26}H_{22}O_3$ requires C, 81·65; H, 5·8%). This was hydrogenolysed with dry hydrogen in ethyl acetate solution containing a small amount of dry hydrogen chloride in the presence of palladium black to give the *hydroxy-compound*, δ ($CDCl_3$) 3·0br (4H, s) and 7·4 (11H, m) (Found: C, 79·1; H, 5·5. $C_{18}H_{16}O_3$ requires C, 78·1; H, 5·5%). This compound did not melt sharply.

2-Naphthyl 4-Hydroxyphenylacetate.—*4-Benzyloxyphenylacetic acid* was prepared from 4-hydroxyphenylacetic acid, m.p. 121—122° (Found: C, 74·4; H, 5·9. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%). This was allowed to react with 2-naphthol in methylene chloride in the presence of dicyclohexylcarbodi-imide to yield *2-naphthyl 4-benzyloxyphenylacetate*, m.p. 110° (from ethanol) (Found: C, 81·2; H, 5·45. $C_{25}H_{20}O_3$ requires C, 81·5; H, 5·5%). A solution of this in ethyl acetate was hydrogenolysed with dry hydrogen in the presence of a little dry hydrogen chloride and some palladium black to yield *2-naphthyl 4-hydroxyphenylacetate*, m.p. 132—134° (from ethyl acetate–hexane) (Found: C, 77·4; H, 5·2. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·1%).

Products.—The u.v. spectra of ' infinity solutions ' of the 2-hydroxyphenylacetates and the 3-(2-hydroxyphenyl)-propionates in buffers of pH 3·3—5·6 were always those of the corresponding lactones and phenols. Under these conditions the lactones were hydrolysed much more slowly than the esters. In acid solution phenyl 2-hydroxyphenylacetate is hydrolysed 3—4 times faster than the lactone and so it is more difficult to decide if it is an intermediate in the hydrolysis of the latter. A repeat scan of the hydrolysis of phenyl 2-hydroxyphenyl acetate ($2·5 \times 10^{-4}$M) in 2M-perchloric acid shows an isosbestic point at 247·5 nm. At this wavelength the molar extinction coefficients of acid and lactone are $1·8 \times 10^2$ and $4·8 \times 10^2$ respectively and so the absorbance would only increase 0·075 absorbance units in 1 cm cells if the ester had been converted completely into the lactone. It therefore seems unlikely that the latter would have been detected if it had been an intermediate.

A solution of phenyl 4-hydroxybutyrate (10^{-2}M; 0·5 ml) in dioxan was added to water (10 ml) at pH 7·4 in the reaction vessel of a Radiometer automatic titrator at 30°. Under these conditions the half-life for the release of phenol is about 5 min (Table 12) but only a slight consumption of alkali (*ca.* 0·025 ml of 0·01M-NaOH) was needed to maintain the pH constant over 30 min. It was therefore concluded that the other product was butyrolactone not 4-hydroxybutyric acid. A similar result was obtained with phenyl 5-hydroxyvalerate.

Hydrolysis of 2-hydroxyphenylacetic and 3-(2-hydroxyphenyl)propionic lactones in acid solution goes almost to completion. Thus the u.v. spectrum of 2-hydroxyphenylacetic acid was unchanged after one hour in 2M-perchloric acid at 21° under which conditions the lactone was *ca.* 50% hydrolysed. A similar result was obtained with 3-(2-hydroxyphenyl)propionic acid. Milstein and Cohen [6] reported that the equilibrium mixture of 3-(2-hydroxyphenyl)propionic acid and its lactone contained 3·6% of the acid.

TABLE 2

Properties of phenyl 2-benzyloxy- and 2-hydroxy-phenylacetates

	2-Benzyloxy-esters					2-Hydroxy-esters				
		Found (%)		Required (%)			Found (%)		Required (%)	
Substituent	M.p. (°C)	C	H	C	H	M.p. (°C)	C	H	C	H
H	88—89 [a]	79·4	5·75	79·2	5·7	78—89 [b]	73·6	5·4	73·7	5·3
m-Cl	49—40 [a]	71·6	4·8	71·5	4·9	113—114 [b]	64·0	4·3	64·0	4·2
m-Me	47·5—48 [a]	79·6	6·2	79·5	6·1	104—106 [b]	74·2	5·8	74·4	5·8

[a] Recrystallised from hexane. [b] Recrystallised from hexane-ethyl acetate.

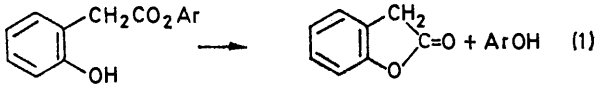
Kinetic Measurements.—These were carried out spectrophotometrically on a Cary 14 or Zeiss PMQ spectrophotometer. Analogue voltages proportional to absorbance or transmittance were fed from these instruments to Solatron data loggers which digitised them and punched them onto tape at selected time intervals using a Creed tape punch. First-order rate constants were calculated using a generalised least squares method. Activation parameters were calculated using a generalised least squares method and catalytic constants using a linear least squares method. Calculations were carried out on the Glasgow University KDF 9 computer or a Digico Micro 16P computer.

DISCUSSION

Base-catalysed Reactions.—Aryl esters of 2-hydroxyphenylacetic acid (I) are converted rapidly into the lactone in aqueous buffers of pH greater than *ca.* 3 [equation (1)]. These reactions can be studied con-

[6] S. Milstein and L. A. Cohen, *Proc. Nat. Acad. Sci. U.S.A.*, 1970, **67**, 1143.

veniently in the pH range 3·39—4·84 under which conditions k_{obs} is proportional to 10^{pH-pK_w} (Table 3). No



(I)

hydrolysis could be detected when phenyl phenylacetate was left in a buffer of pH 4 at 25° for 24 h. The ρ value for the lactonisation is 2·01. No buffer catalysis could

TABLE 3

The kinetics of lactonisation of aryl 2-hydroxyphenylacetates in aqueous buffers at 25° and *I* 0·05M

pH	*m*-Chlorophenyl [a,d] 10^3k/s^{-1}	Phenyl [a,e] 10^3k/s^{-1}	*m*-Tolyl [a,f] 10^3k/s^{-1}
4·84 [b]		48·0	35·3
4·63 [b]		29·5	21·7
4·39 [b]	92·9	18·3	12·6
4·15 [b]	57·3	10·5	7·17
3·88 [c]	32·7	5·62	4·03
3·68 [c]	21·1	3·85	2·51
3·39 [c]	10·8		

[a] Reaction followed at 225 nm. [b] Acetate buffer. [c] Formate buffer. [d] $k_2 = 3·95 \times 10^8$ l mol^{-1} s^{-1}. [e] $k_2 = 6·96 \times 10^7$ l mol^{-1} s^{-1}. [f] $k_2 = 6·08 \times 10^7$ l mol^{-1} s^{-1}.

be detected in the lactonisation of phenyl 2-hydroxyphenylacetate in acetate buffer (Table 4). The analogous intermolecular reaction, the phenolysis of phenyl acetate has been studied by Bender and Glasson [7] who reported that $k_2 = 2·79 \times 10^{-2}$ l mol^{-1} s^{-1} at 25°. If the

TABLE 4

Test for buffer catalysis in the lactonisation of 2-naphthyl 2-hydroxyphenylacetate in acetate buffers in 20% (v/v) aqueous dioxan at 25° and *I* 0·5M

[AcO$^-$]/M	pH [a]	10^3k_{obs}/s^{-1}
0·5	4·64	2·24
0·4 [b]	4·60	2·37
0·3 [b]	4·56	2·65
0·2 [b]	4·53	2·50
0·1 [b]	4·52	2·78

[a] Meter reading. [b] Ionic strength maintained constant by the addition of potassium chloride.

lactonisation is assumed to involve the form with the phenolic group ionised, the first-order constant for the reaction of the ion of phenyl 2-hydroxyphenylacetate is $6·96 \times 10^3$ s^{-1} at 25°, assuming a pK_a value of 10·0. Hence the ratio of the rate constant for the intramolecular reaction to that for the intermolecular reaction is *ca.* $2·5 \times 10^5$ mol l^{-1}.

The lactonisation of 2-naphthyl 2-hydroxyphenylacetate in 20% aqueous dioxan is also much faster than the hydrolysis of 2-naphthyl 4-hydroxyphenylacetate (Table 5). The rate constant for the latter reaction at pH* 10·06 and 25° is $2·39 \times 10^{-4}$ s^{-1}. Under these conditions the 2-hydroxy-ester lactonises very rapidly and its overall rate of hydrolysis is controlled by the rate of hydrolysis of the lactone for which k_{obs} was estimated from the results in Table 6 to be $5·4 \times 10^{-3}$ s^{-1}. Hydrolysis *via* the lactone therefore results in nucleophilic catalysis. 2-Naphthyl 3-(2-hydroxyphenyl)propionate (II; Ar = 2-naphthyl) is also converted rapidly into the corresponding lactone under the same conditions [equation (2)]. At pH* 4·79—5·56 this reaction is

TABLE 5

The kinetics of lactonisation of 2-naphthyl 2-hydroxyphenylacetate and 2-naphthyl 3-(2-hydroxyphenyl)-propionate in 20% (v/v) aqueous dioxan at 25° and *I* 0·05M

pH *	2-Naphthyl 2-hydroxyphenyl acetate [a,d] 10^4k/s^{-1}	2-Naphthyl 3-(2-hydroxyphenyl)-propionate [a] 10^4k/s^{-1}
5·56 [b]	192	41·4
5·33 [b]	124	22·4
5·08 [b]	71·1	11·9
4·79 [b]	37·4	6·97
4·47 [b]	18·1	
4·14 [c]	8·26	
3·93 [c]	5·34	
3·70 [c]	3·28	

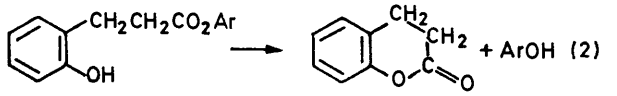
[a] Reaction followed at 329 nm. [b] Acetate buffer. [c] Formate buffer. [d] The rate constant for the hydrolysis of 2-naphthyl 4-hydroxyphenylacetate is $2·39 \times 10^{-4}$ s^{-1} in a borate buffer of pH* 10·06 at 25° (*I* 0·05M). No reaction was observed with this compound after 8 h at pH* 5·08 and 25°.

TABLE 6

The kinetics of hydrolysis of 2-hydroxyphenylacetic acid lactone and 3-(2-hydroxyphenyl)propionic acid lactone in alkaline buffers in 20% (v/v) aqueous dioxan at 25° and *I* 0·05M [a]

pH*	2-Hydroxyphenyl-acetic acid lactone [b] 10^4k/s^{-1}	3-(2-Hydroxyphenyl)-propionic acid lactone [c] 10^4k/s^{-1}
9·00 [d]	5·17	4·83
9·32 [d]	9·43	9·31
9·66 [d]	17·5	17·5 [f]
10·47 [d]	67·9	65·0 [g]
10·90 [e]	150	135
11·01 [e]	305	269

[a] The lactones were generated from the corresponding 2-naphthyl esters which lactonise very rapidly under the reaction conditions. [b] Followed at 274·5 nm. [c] Followed at 274 nm. [d] Borate buffer. [e] Carbonate buffer. [f] With [borate] = 0·025M and [NaCl] = 0·025M, $k_{obs} = 14·7 \times 10^{-4}$ s^{-1} at pH 9·66. [g] With [borate] = 0·25M and [NaCl] = 0·025M, $k_{obs} = 56·0 \times 10^{-4}$ s^{-1} at pH 10·47.



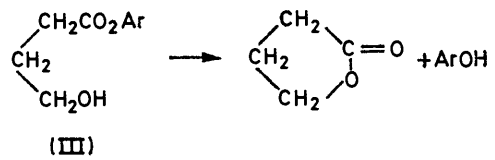
(II)

ca. 5 times slower than lactonisation of 2-naphthyl 2-hydroxyphenylacetate. This may be because the phenolic group of the hydroxyphenylacetate ester is a stronger acid than that of the hydroxyphenylpropionate which causes there to be a higher concentration of the reactive ionised form present, or because reaction of the ionised form *via* a five-membered ring is faster than *via* a six-membered ring. We think that the latter is probably the most important factor since it seems unlikely that the ratio of the pK_a values of the two compounds would be as large as 5. Also any difference in

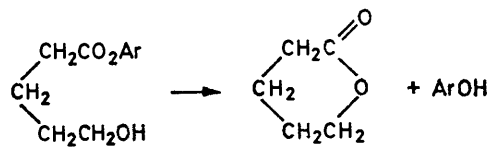
[7] M. L. Bender and W. A. Glasson, *J. Amer. Chem. Soc.*, 1959, **81**, 1590.

pK_a values would be partly counterbalanced by a difference in the nucleophilicites of the phenolate ions.

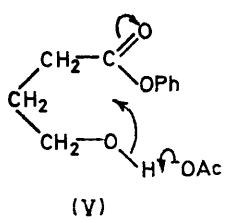
In the pH range 6·49—8·65 the rate of lactonisation of phenyl 4-hydroxybutyrate (III; Ar = Ph) is proportional to 10^{Ph-pK_w} and the second-order constant is $5·42 \times 10^3$ l mol^{-1} s^{-1} at 29·98° which is *ca.* 3000 times greater than that for the hydrolysis of phenyl acetate ($k_{OH} = 1·37$ l mol^{-1} s^{-1} at 25°).[8a] The lactonisation of phenyl 5-hydroxyvalerate (IV; Ar = Ph) also occurs rapidly under these conditions but 10—20 times more slowly than that of phenyl 4-hydroxybutyrate. Reaction *via* a five-membered ring is therefore again faster than *via* a six-membered one.



(III)



(IV)



(V)

TABLE 7

The kinetics of hydrolysis of phenyl 4-hydroxybutyrate in phosphate buffers at 30·0° (*I* 0·20M)

10^2[Na_2HPO_4]/M	pH	10^5k_{obs}/s^{-1}	pOH	10^7a_{OH}	$10^8\Delta a_{OH}$	$10^5\Delta a_{OH}k_{OH}$	10^5k_{corr}/s^{-1}	10^5k_{calc}/s^{-1}
6·05	7·30	193, 192	6·53	2·95	3·2	18·2	175, 176	175·5
4·84	7·29	186, 185	6·54	2·88	2·5	14·2	172, 171	171
3·63	7·27	176, 178	6·56	2·75	2·2	11·6	164, 166	167
2·42	7·26	168, 168	6·57	2·69	0·6	3·3	165, 165	162
1·21	7·25	156, 158	6·58	2·63	0	0	156, 158	158

pK_w Was taken to be 13·83 (R. A. Robinson and R. H. Stokes, 'Electrolyte Solutions,' Butterworths, London, 1965, p. 544); k_{OH} was calculated from the intercept of the plot of k_{obs} against [Na_2HPO_4] ($1·5 \times 10^{-3}$ s^{-1}) and a_{OH} ($2·6 \times 10^{-7}$M) to be $5·7 \times 10^3$ l mol^{-1} s^{-1}; k_{corr} was plotted against [Na_2HPO_4] to yield $k(HPO_4^{2-}) = 3·59 \times 10^{-3}$ l mol^{-1} s^{-1} (*s* 9·5%) and intercept = $1·54 \times 10^{-3}$ s^{-1} (*s* 0·89%), *r* 0·97.

TABLE 8

The kinetics of hydrolysis of phenyl 4-hydroxybutyrate in acetate buffers at 50·0° (*I* 0·20M)

[Acetate]/M	pH	10^5k_{obs}/s^{-1}	pOH	10^9a_{OH}	$10^9\Delta a_{OH}$	$10^5a_{OH}k_{OH}$	10^5k_{corr}/s^{-1}	10^5k_{calc}/s^{-1}
0·20	5·17	12·0, 12·0	8·09	8·13	0·54	0·57	11·4, 10·4	
0·16	5·16	11·4, 11·9	8·10	7·94	0·35	0·37	11·0, 11·5	11·3
0·12	5·14	10·9, 10·8	8·12	7·59	0	0	10·9, 10·8	10·7
0·08	5·14	10·0, 9·87	8·12	7·59	0	0	10·0, 9·87	10·0

Data treated as in Table 7 with pK_w = 13·26 and k_{OH} $1·06 \times 10^4$ l mol^{-1} s^{-1}. The values of k_{corr} for the three lowest concentrations were plotted against [Acetate] to yield $k(AcO^-) = 1·6 \times 10^{-4}$ l mol^{-1} s^{-1} (*s* 18%) and intercept = $8·7 \times 10^{-5}$ s^{-1} (*s* 4·2%), *r* 0·94.

TABLE 9

The hydrolysis of phenyl 4-hydroxybutyrate in imidazole buffers at 30·0° (*I* 0·20M)

[Imidazole]/M	pH	10^5k_{obs}/s^{-1}	pOH	10^7a_{OH}	$-10^8\Delta a_{OH}$	$-10^5\Delta a_{OH}k_{OH}$	10^5k_{corr}/s^{-1}	10^5k_{calc}/s^{-1}
0·20	7·14	292, 296	6·69	2·04	1·5	6·6	299, 303	301
0·16	7·15	254, 257	6·68	2·09	1·0	4·4	258, 261	260
0·12	7·16	218, 215	6·67	2·14	0·5	2·2	220, 217	218
0·08	7·17	175, 176	6·66	2·19	0	0	175, 176	177
0·04	7·17	137, 135	6·66	2·19	0	0	137, 135	135

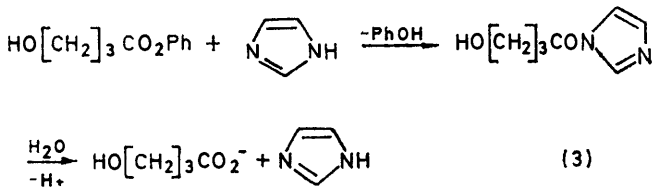
Data treated as in Table 7 with pK_w = 13·83 and $k_{OH} = 4·4 \times 10^3$ l mol^{-1} s^{-1}. The values of k_{corr} were plotted against [imidazole] to yield k(imidazole) = $1·03 \times 10^{-2}$ l mol^{-1} s^{-1} (*s* 0·93%) and intercept = $9·39 \times 10^{-4}$ s^{-1} (*s* 1·4%), *r* = 0·9996.

The reaction of phenyl 4-hydroxybutyrate was tested for catalysis by the buffer components in phosphate, acetate, and imidazole buffers. These experiments were complicated by small changes in pH with buffer concentration and the high rate of the hydroxide-catalysed reaction. The results were therefore corrected and when this was done the catalysis still appeared to be significant (see Tables 7—9). The catalytic constant for the imidazole-catalysed reaction ($k_{Im} = 1·07 \times 10^{-2}$ l mol^{-1} s^{-1} at 30° and *I* 0·20M) is very similar to that for the imidazole-catalysed hydrolysis of phenyl acetate ($k_{Im} = 8·7 \times 10^{-3}$ l mol^{-1} s^{-1} at 25° and *I* 1·0M).[9] This suggests that the imidazole acts as a nucleophilic catalysis as shown in equation (3), not as a general-base catalyst for intramolecular nucleophilic attack by the hydroxy-group. The results for the reaction of 2-naphthyl 4-hydroxybutyrate in imidazole buffers in aqueous dioxan

[8] *Cf.* E. K. Euranto in 'The Chemistry of Carboxylic Acids and Esters,' ed. S. Patai, Interscience, London, 1969 (*a*) p. 518; (*b*) p. 556.

[9] J. K. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, 1964, **86**, 837.

(Table 10) lead to a similar conclusion, as the catalytic constants for the release of 2-naphthol from the 2-naphthyl esters of butyric acid, 4-methoxybutyric acid, and



(3)

4-hydroxybutyric acid calculated from the two point plots are 1·7, 1·9, and 3·8 × 10^{-3} l mol^{-1} s^{-1} at 30°.

TABLE 10

The rate constants for the hydrolysis of some 2-naphthyl esters in imidazole buffers in 20% (v/v) aqueous dioxan at 30·0°; pH(app) = 7·20; [imidazole] = [imidazolinium chloride]

[Imidazole]/M	0·10	0·05 [a]	10^3k_{cat}
2-Naphthyl ester		$10^5k_{obs}/s^{-1}$	l mol^{-1} s^{-1}
Butyrate	13·5, 13·4	5·18, 4·79	1·7
4-Methoxybutyrate	17·2, 17·2	7·65, 7·60	1·9
4-Hydroxybutyrate	54·4, 54·1	35·5, 34·7	3·8

[a] Ionic strength made up to 0·10M with sodium chloride.

TABLE 11

The variation of the rates of hydrolysis of phenyl 4-hydroxybutyrate and phenyl butyrate with acid concentration in aqueous perchloric acid at 29·8°

$[HClO_4]$/M	Phenyl butyrate $10^5k_{obs}/s^{-1}$	Phenyl 4-hydroxybutyrate $10^5k_{obs}/s^{-1}$
1·000	6·79	121
2·000	12·6	313
2·995	19·4	623
3·947	27·4	1150
5·021	35·8	2150

The plot of the corrected rate constant for the reaction of phenyl 4-hydroxybutyrate in acetate buffers against the concentration of acetate is curved. The approximate catalytic constant is 1·6 × 10^{-4} l mol^{-1} s^{-1} at 50·0°. This is 50—100 times greater than the catalytic constant for the hydrolysis of phenyl acetate (k_{OAc} = 3·84 × 10^{-7} l mol^{-1} s^{-1} at 25°) [10] which suggests that the catalysis is associated with participation by the hydroxy-group. A possible mechanism involves general-base catalysis as symbolised by (V). The catalytic constant for phosphate, 3·59 × 10^{-3} l mol^{-1} s^{-1} at 30·0°, also appears to arise from catalysis associated with participation by the hydroxy-group since it is thirty times greater than $k(HPO_4^{2-})$ for the hydrolysis of *p*-nitrophenyl acetate at 25°, 1·23 × 10^{-4} l mol^{-1} s^{-1}.[11]

At pH 7·47 the lactonisation of the substituted phenyl 4-hydroxybutyrates (III) yields a ρ value of 1·1 and that of the substituted phenyl 5-hydroxyvalerates (IV) yields a ρ value of 1·2 (Table 12). These values are smaller than the ρ value for the hydroxide ion-catalysed reaction of substituted phenyl 2-hydroxyphenylacetates (I), 2·01 (Table 3). The latter reactions presumably involve cyclisation of the anions, but it is uncertain if the lactonisation of the 4-hydroxybutyrates and 5-hydroxyvalerates do since they show buffer catalysis which is probably general-base catalysis. Nevertheless the smaller ρ values are consistent with the nucleophile being stronger as it would be expected on the basis of Hammond's postulate that there would be less bond-forming in the transition state. This stronger nucleophile could be either the fully ionised hydroxy-group or a hydroxy-group from which the proton has been partly removed by hydroxide ion. On the assumption that the reaction of phenyl 4-hydroxybutyrate does involve the anion and that the pK_a of the hydroxy-group is the same as that of ethanol, 15·9,[12] the rate constant for its cyclisation is 5·5 × 10^5 s^{-1} at 29·8° compared to 6·96 × 10^3 s^{-1} for the cyclisation of the anion of phenyl 2-hydroxyphenylacetate at 25°. Breakdown of a tetrahedral intermediate is probably not rate limiting in the cyclisation of aryl 2-hydroxyphenylacetates since the ρ value of 2·01 is too small,[13] but this is an interesting system since a tetrahedral intermediate would have phenoxide as entering and leaving group and it is possible by introducing electron-withdrawing groups into the acid-group that breakdown of a tetrahedral intermediate could be made rate limiting.

TABLE 12

The rates of hydrolysis of substituted phenyl 4-hydroxybutyrates and 5-hydroxyvalerates

	Phenyl 4-hydroxybutyrates $10^3k_{obs}/s^{-1}$				Phenyl 5-hydroxyvalerates $10^3k_{obs}/s^{-1}$		
Substituent	H	*m*-Me	*m*-Cl	*m*-F	H	*m*-Me	*m*-Cl
1M-$HClO_4$ at 29·8°	1·21	1·20	1·10	1·09	2·58	2·73	2·30
0·1M-HCl at 49·9°	0·568	0·545	0·505	0·489	0·952	0·996	0·866
pH 7·47 at 29·8°	2·39	1·74	5·72	5·66	0·132	0·105	0·311
pH 6·02 at 49·98°	0·616	0·453	1·46	1·44	0·0610	0·462	

The pH–rate profile for the hydrolysis of phenyl 4-hydroxybutyrate is given in the Figure. This can be described satisfactorily by an equation $k_{obs} = k_{\Pi} \times 10^{-pH} + k_{OH} \times 10^{pH-pK_w} + k_{H_2O}$. The k_{H_2O} term appears to be significant as there is a substantial improvement in the fit when it is included.

Acid-catalysed Reactions.—The hydrolysis of phenyl 4-hydroxybutyrate in 1M-perchloric acid is 18 times faster than that of phenyl butyrate (Table 11) and the

[10] V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc.* (*B*), 1968, 515.

[11] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1778.

[12] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1960, **82**, 795.

[13] *Cf.* F. M. Menger and J. H. Smith, *Tetrahedron Letters*, 1970, 4163.

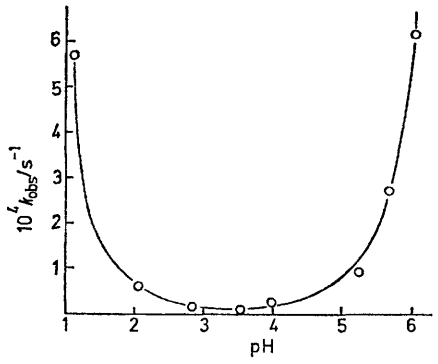
hydrolysis of phenyl 5-hydroxyvalerate is about twice as fast as that of phenyl 4-hydroxybutyrate (Table 12). These rate enhancements are similar to those found in the hydrolyses of 4-hydroxybutyramide and 5-hydroxyvaleramide [14] and presumably arise from a similar cause, intramolecular nucleophilic assistance. Reaction proceeds faster *via* a six-membered ring than *via* a five-membered ring. The factor of two is similar to that found in the acid-catalysed lactonisation of 5-hydroxyvaleric acid and 4-hydroxybutyric acid.[15] The ρ values for the reactions of substituted phenyl 4-hydroxybutyrates and substituted phenyl 5-hydroxyvalerates are −0·2 and −0·15 respectively (Table 12), which are similar to the value of −0·198 for the acid-catalysed hydrolysis of aryl acetates.[16] These small values must arise from a cancellation of a negative ρ value for protonation of the ester oxygen atom and a positive ρ value for nucleophilic attack on the resulting conjugate acid.

TABLE 13

The temperature dependence of the rate of hydrolysis of phenyl 4-hydroxybutyrate and phenyl butyrate in 1·00M-perchloric acid

Temp. (°C)	Phenyl 4-hydroxybutyrate $10^4k_{obs}/s^{-1}$	Temp. (°C)	Phenyl butyrate 10^4k_{obs} s^{-1}
20·10	4·71, 4·69		
29·97	12·2, 12·2	30·18	0·671, 0·688
40·04	29·5, 28·9	40·07	1·72, 1·66
49·97	65·9, 68·0	49·97	4·12, 3·85, 4·03
$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1} (s.d.) [a]	−18·74 (0·75)		−22·35 (1·91)
$\Delta H^{\ddagger}$/cal mol^{-1} (s.d.) [a]	16,115 (242)		16,756 (617)

[a] At 20·10 °C.



The pH–rate profile for the hydrolysis of phenyl 4-hydroxybutyrate at 50·0°. The circles are experimental points and the line follows the equation $k_{obs} = k_H \times 10^{-pH} + k_{OH} \times 10^{pH-pK_w} + k_{H_2O}$ with $k_H = 6·75 \times 10^{-3}$ l mol^{-1} s^{-1}, $k_{OH} = 1·07 \times 10^4$ l mol^{-1} s^{-1}, $k_{H_2O} = 4·66 = 10^{-6}$ s^{-1}, and $pK_w = 13·2617$. The point at pH 1·10 was obtained in 0·1M-HCl and the other points in buffers with I 0·05M. The latter may contain small contributions (<10%) from buffer catalysis

The entropy of activation for the hydrolysis of phenyl butyrate in 1M-perchloric acid is *ca.* 3·5 cal K^{-1} mol^{-1} more negative than that for the hydrolysis of phenyl 4-hydroxybutyrate (Table 12). The rate of hydrolysis of phenyl 4-hydroxybutyrate increases more rapidly with acid concentration than that of phenyl butyrate does (Table 11). Thus the rate for phenyl 4-hydroxybutyrate is increased 17·5 times on going from 1 to 5M-perchloric acid whereas that for phenyl butyrate is increased 5·2 times. Presumably the effect of decreasing water activity with increasing acid concentration is less significant with the former reaction since it is the internal hydroxy-group which acts as the nucleophile. For phenyl 4-hydroxybutyrate plots of log k_{obs} *versus* H_0,[15-17] log k_{obs} *versus* log $c(H_3O^+)$,[17] log $k_{obs} + H_0$ *versus* log $a(H_2O)$,[18] and log k_{obs} − log $c(H_3O^+)$ *versus* log $a(H_2O)$ [18] are curves but the plot of log $k_{obs} + H_0$ *versus* H_0 + log $c(H_3O^+)$ [19] is a fairly good straight line with $\phi = 0·59$ (r 0·999). For the hydrolysis of phenyl butyrate $\phi = 0·99$ (r 0·98), and the smaller ϕ value for the intramolecular reaction is in accord with the change in hydration on going to the transition state being smaller.

Phenyl 2-hydroxyphenylacetate and phenyl phenylacetate are hydrolysed at similar rates in aqueous perchloric acid and so the neighbouring phenolic group does not provide appreciable anchimeric assistance for the hydrolysis of the former compound (Table 14). The hydrolysis of the lactone is probably too fast for it to be detected if it were an intermediate (see Experimental section).

TABLE 14

The kinetics of hydrolysis of phenyl 2-hydroxyphenyl acetate and phenyl phenylacetate in aqueous perchloric acid solutions at 55·0°

$[HClO_4]$/M	Phenyl 2-hydroxyphenylacetate $10^4k_{obs}/s^{-1}$	Phenyl phenylacetate $10^4k_{obs}/s^{-1}$
2·0	7·52	8·60
4·0	19·9	16·9
5·0	31·6	22·4

TABLE 15

The effect of acid concentration on the rate of hydrolysis of 2-hydroxyphenylacetic acid lactone and 3-(2-hydroxyphenyl)propionic acid lactone

$[HClO_4]$/M	2-Hydroxyphenylacetic acid lactone [a] $10^4k_{obs}/s^{-1}$ at 25°	2-Hydroxyphenylacetic acid lactone [a] $10^3k_{obs}/s^{-1}$ at 55°	3-(2-Hydroxyphenyl)-propionic acid lactone [b] $10^2k_{obs}/s^{-1}$ at 55°
1·00	1·29	1·74	3·45
2·00	2·11	2·91	5·88
3·00	2·82	4·13	8·33
4·00	3·57	5·28	
5·00	4·59	7·23	

[a] Reaction followed at 275·5 nm. [b] Reaction followed at 271·5 nm.

Lactone Hydrolysis.—The acid-catalysed hydrolysis of 2-hydroxyphenylacetic lactone is *ca.* 3·5 times faster than that of phenyl phenylacetate in 2M-perchloric acid at 55° (Tables 14 and 15) and *ca.* 3 times faster than that of

[14] L. Zürn, *Annalen*, 1960, **631**, 911.
[15] O. H. Wheeler and E. E. Granell de Rodriguez, *J. Org. Chem.*, 1964, **29**, 1227.
[16] E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1938, 1801; see H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 204.
[17] *Cf.* F. A. Long and M. A. Paul, *Chem. Rev.*, 1957, **57**, 935.
[18] J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956.
[19] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1917.

phenyl butyrate in 1M-perchloric acid (Tables 11 and 15). 3-(2-Hydroxyphenyl)propionic acid lactone is hydrolysed 20—30 times faster than 2-hydroxyphenylacetic acid lactone in perchloric acid (Tables 15 and 16). The

TABLE 16

The temperature variation of the rate of hydrolysis of 2-hydroxyphenylacetic acid lactone and 3-(2-hydroxyphenyl)propionic acid lactone in 1·00M-perchloric acid

Temp. (°C)	2-Hydroxyphenylacetic acid lactone $10^4 k_{obs}/s^{-1}$	3-(2-Hydroxyphenyl)propionic acid lactone $10^4 k_{obs}/s^{-1}$
25·0	1·293, 1·289	41·8, 42·7, 42·3, 42·5
35·0	3·37, 3·31, 3·35	89·0, 85·5, 89·1, 90·8
45·0	8·13, 8·08, 8·03, 8·01	180, 184, 187, 183
55·0	17·5, 17·5	345, 360, 356, 364
$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1} (s.d.) [a]	−23·36 (0·37)	−24·89 (0·51)
$\Delta H^{\ddagger}$/cal mol^{-1} (s.d.) [a]	15,782 (123)	13,269 (168)

[a] At 25·0 °C.

lactones are therefore hydrolysed faster than analogous esters in acidic solutions. The rate ratios are similar to those found with ethyl acetates, γ-butyrolactone, and δ-valerolactone, whose relative rates of hydrolysis in acid are 1 : 3 : 300.[9b,15]

The entropies of activation for the hydrolysis of the lactones (Table 16) are similar to that for the hydrolysis of phenyl butyrate (Table 13) but the rates of hydrolysis increase slightly less rapidly with increasing acid concentration than the rate of hydrolysis of phenyl butyrate does (Tables 11 and 15). The ϕ value for the hydrolysis of 2-hydroxyphenylacetic acid lactone is 1·1 (r 0·98). Like those of the corresponding nitro-substituted lactones,[20] the hydrolyses of 2-hydroxyphenylacetic acid lactone and 3-(2-hydroxyphenyl)propionic acid lactone occur at similar rates in alkaline buffers (Table 6). These reactions are *ca.* 20 times faster than hydrolysis of the analogous ester, 2-naphthyl 4-hydroxybenzoate, for which $k_{obs} = 2{\cdot}39 \times 10^{-4}$ s^{-1} in pH* 10·06 borate buffer in 20% (v/v) aqueous dioxan. This behaviour differs from that found with aliphatic lactones. Thus δ-valerolactone is hydrolysed 35 times faster than γ-butyrolactone in alkali and 6550 times faster than n-butyl caproate.[21]

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[2/2351 *Received*, 16*th October*, 1972]

[20] P. Tobias, J. Heidema, K. W. Lo, E. T. Kaiser, and F. J. Kezdy, *J. Amer. Chem. Soc.*, 1969, **91**, 202.
[21] R. Huisgen and M. Ott, *Tetrahedron*, 1959, **6**, 253.