a 12- by 24-inch round chromatographic jar and the floor of the jar was flooded with the equilibrated aqueous phase. The required number of buffered sheets were placed in the jar and the jar tightly covered for 16 hours. The samples were applied to the pre-marked sheets by means of a pipet inserted through a hole in the rotatable cover. The developing solvent (butanol–chloroform) was added and the development carried out over a 4- to 5-hour period. After development, the sheets were removed from the jar, air-dried in the dark, and inspected by light and under ultraviolet radiation before and after exposure to ammonia.

System 2.—All operations were carried out at 25 ± 0.5°. Ethyl acetate was equilibrated by shaking with an equal volume of McEIvain's *p*H 4.5 buffer. The chromatographic sheets were dipped in the aqueous phase and dried. The solvent and aqueous phases were placed separately in the bottom of a 12 by 24 inch jar as described for system 1. Up to four buffered sheets were placed in the jar and allowed to equilibrate with the solvent atmosphere for 16 hours. After this paper pre-equilibration, the samples were spotted onto pre-marked locations across the tops of the sheets by means of a pipet inserted through a small hole in the rotatable lid of the jar. The ethyl acetate phase was then added to the top trough to begin development; about 4 hours development time was required for solvent travel of 18 inches.

System 3.—All operations were carried out at 25 ± 0.5°. One liter of butanol was equilibrated with 150 ml. of aqueous 0.3 *M* NaH_2PO_4 which had been adjusted to *p*H 3.0 with 85% phosphoric acid. The chromatographic sheets were dipped in the aqueous phase and dried. The chromatographic jar was arranged for descending development and the bottom of the jar was flooded with butanol-saturated water. Dry sheets were spotted with sufficient sample to contain 10 to 25 mcg. of tetracycline derivative. These sheets were then placed in the jar and pre-equilibrated with the jar atmosphere for 60 min. The butanol phase was used for development, about 16 hours being required for 18-inch flow. After development, the sheets were removed and examined as described above.

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Imidazole Catalysis. VII. The Dependence of Imidazole Catalysis of Ester Hydrolysis on the Nature of the Acyl Group[1]

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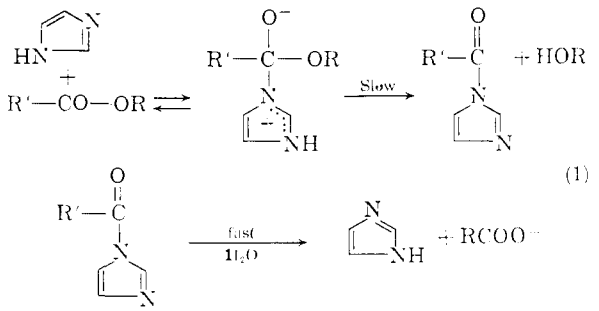
A new synthesis of 4-(2′-hydroxyphenyl)-imidazole (IV) is described. A number of substituted O-benzoyl esters of IV have been prepared and their solvolysis with intramolecular imidazolyl participation (30°) studied. From the Hammett *ρ*-constant it is concluded that the rate of imidazole catalyzed hydrolysis of substituted phenol esters is equally sensitive to the electronic nature of the ester carbonyl group and the leaving tendency of the phenoxide ion. Several aliphatic esters of 4-(2′-hydroxyethyl)-imidazole were also prepared and their rates of solvolysis with intramolecular imidazolyl participation as well as by specific base catalysis have been determined (78°). The results of this study indicate that the imidazolyl group, though many powers of 10 a weaker base than alkoxide, is capable of displacing the latter to bring about the catalysis of the hydrolysis of aliphatic esters in intramolecular processes. The values of the various rate constants for hydrolysis of the aliphatic esters are discussed in terms of inductive and electrostatic effects.

Introduction

In previous studies the nucleophilic catalysis of ester hydrolysis by imidazoles has been shown to be quite sensitive to the leaving tendency of the -OR group.



(1)

Thus, for the bimolecular catalysis of the hydrolysis of *m*- and *p*-substituted phenyl acetates the *ρ* for imidazole,[1a] 4-hydroxymethyl imidazole[1b] and histidine[1b] are between 1.7 and 1.9 whereas the *ρ* for hydroxide ion catalysis is but 1.0.[1a,3] Also though imidazole is capable of displacing aliphatic thiol from acyl thiols both bimolecularly[4] and intramolecularly,[1f] the displacement of alkoxide in the bimolecular process has never been observed and occurs only with difficulty in the more efficient intramolecular displacement reaction .[1e] These results have been rationalized on the basis of a competition between the attacking base and the potential leaving group for elimination from the tetrahedral intermediate. It has been suggested that the group which departs most readily is the one whose conjugate acid possesses the lowest pK_a (quantitatively applicable in a given series of like substituents, as *e.g.* in the case of substituted phenoxides, but grossly so in general).[1a,5]

To obtain a clearer picture of the transition state barriers in imidazole catalyzed ester hydrolysis, it was considered desirable to obtain information on the sensitivity of the rate constants to alterations of the electronic properties of the ester carbonyl group. The assessment of this factor along with some observations on the influence of electrostatic charge on the intramolecular catalysis of aliphatic ester hydrolysis is reported in this paper.

(1) For previous papers in this series see: (a) T. C. Bruice and G. L. Schmir, THIS JOURNAL, **79**, 1663 (1957); (b) *ibid.*, **80**, 148 (1958), (c) G. L. Schmir and T. C. Bruice, *ibid.*, **80**, 1173 (1958); (d) T. C. Bruice and R. Lapinski, *ibid.*, **80**, 2265 (1958); (e) T. C. Bruice and J. M. Sturtevant, *ibid.*, **81**, 2860 (1959); (f) T. C. Bruice, *ibid.*, **81**, 5444 (1959).

(2) (a) Postdoctoral Research Fellow, Department of Physiological Chemistry, The Johns Hopkins School of Medicine. (b) Inquiries concerning this paper should be addressed to this author.

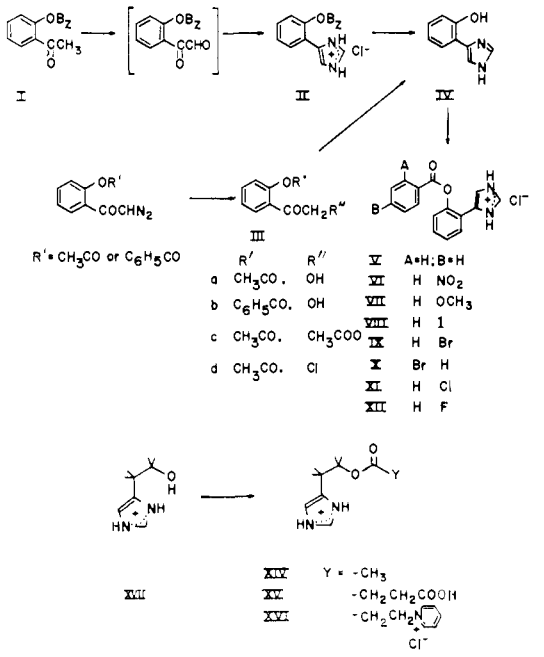
(3) T. C. Bruice and M. F. Mayahi, THIS JOURNAL, **82**, 3067 (1960).

(4) M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1652, 1656 (1957).

(5) K. B. Wiberg, *ibid.*, **77**, 2519 (1955).

For determining the importance of the electronic character of the ester carbonyl group in the aforementioned reaction, a study of *m*- and *p*-substituted benzoate esters appeared to be the most logical choice. For this purpose phenyl benzoates were employed in which the leaving phenoxy group was substituted with the catalytic imidazolyl function. Esters of this type (V to XII) were expected from previous experience to undergo hydrolysis with anchimeric participation of the imidazolyl group. To assess electrostatic charge effects on the intramolecular imidazolyl catalysis of aliphatic ester hydrolysis compounds XIV to XVI were studied.

The preparation of 4-(2′-hydroxyphenyl)-imidazole (IV), required for the syntheses of esters V to XII, has been described by Weidenhagen and Herrmann.[6] However, in view of the laborious procedure involved and the low yields obtained by these workers, we were prompted to investigate



other routes for the preparation of IV. Initial attempts to carry hydroxy ketones IIIa and IIIb, acetoxy ketone IIIc and the chloro ketone IIId, (themselves obtained *via* the corresponding diazo ketones) through the Weidenhagen synthesis, did not result in the formation of (IV). However, *o*-benzyloxyacetophenone (I) prepared according to the general procedure described by Priestley[7] was smoothly oxidized with selenium dioxide to the corresponding glyoxal, which could be employed in the Weidenhagen reaction to give 4-(2′-benzyloxyphenyl)-imidazole (II). Debenzylation of II by treatment with 16% HBr in glacial acetic acid, followed by neutralization, gave the free base (IV) in an over-all yield of 40%. The esters V to XII were obtained in varying yields by fusing freshly prepared samples of the corresponding benzoyl chlorides with IV, for reaction times required to display a negative test with ferric chloride. The ester XV was prepared by treatment of succinic anhydride with hydroxyethyl imidazole XVII; while XVI could be obtained in low yields (10%) by warming a paste made from XVII and pyridiniumpropionate dichloride for 3 hours.

(6) R. Weidenhagen and R. Herrmann, *Ber.*, **68**, 1953 (1935).
(7) H. M. Priestley and E. Moness, *J. Org. Chem.*, **5**, 355 (1940).

Experimental

o-**Benzyloxyacetophenone** (I).—To a solution of 0.5 mole of sodium ethoxide (11.5 g. Na) in 250 ml. of absolute ethanol was added 68.0 g. (0.5 mole) of *o*-hydroxyacetophenone, followed by 68 ml. (75 g., 0.6 mole) of benzyl chloride. The reaction mixture was refluxed for 5 hr. and the ethanol removed under reduced pressure after filtration of the precipitated NaCl. The residual oil of I was crystallized from petroleum ether (30–60° b.p.), the crystalline material collected and washed with additional solvent. In this manner 67 g. of a colorless crystalline product was obtained, m.p. 40°. On concentration of the mother liquor an additional 10 g. (total yield 68%) of the material of same purity was obtained.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.64; H, 6.22. Found: C, 79.60; H, 6.14.

4-(2′-Hydroxyphenyl)-imidazole (IV).—To a solution of SeO_2 (6 g., 0.054 mole) in dioxane (25 ml.) and water (5 ml.) was added 11.3 g. (0.05 mole) of I dissolved in 25 ml. of dioxane. The mixture was refluxed with constant stirring for 5 hr. and the Se metal removed by filtration and washed with additional dioxane. The combined filtrates and washings were concentrated under reduced pressure to give the glyoxal as a red oil. Most of the red colloidal Se was removed by passing an absolute ethanolic solution of the oil through a 20 cm. column of carboxymethyl cellulose to give an almost colorless solution. The eluate from the column was made up to 300 ml. with additional absolute ethanol and added to a solution of cupric acetate (19.2 g., 0.096 mole), 28% ammonium hydroxide (80 ml., 1.18 mole) and 36% formalin (15 ml., 0.18 mole). After standing for 48 hr. at room temperature the reaction mixture was warmed on a steam-bath for 2 hr. To the clear blue solution there was then added 300 ml. of water and 40 ml. of 28% ammonium hydroxide solution. After 1.5 hr. additional heating on the steam-bath a copious precipitate of dark green crystals was formed. After cooling, the cuprous complex was collected and washed with water until the filtrate was neutral to litmus. The wet salt was then suspended in 200 ml. of water, the suspension made acidic to congo red by addition of HCl and saturated with H_2S for 2 hr. on the steam-bath. The precipitated copper sulfide was removed by filtration and the filtrate concentrated to give II as an almost colorless product. A small amount of II was recrystallized several times from a chloroform ether mixture (charcoal) yielding colorless crystals, m.p. 165.5–166.5°.

Anal. Calcd. for $C_{16}H_{15}N_3OCl$: C, 67.01; H, 5.27; N, 9.77. Found: C, 67.24; H, 5.69; N, 9.75.

The crude preparation of II, dissolved in 25 ml. of glacial acetic acid, was debenzylated by treatment with 55 ml. of a 16% solution of HBr in glacial acetic acid for 2 hr. at room temperature and 3 hr. at steam-bath temperature. The reaction mixture was poured into 500 ml. of water. After shaking, the aqueous layer was separated and washed with three 50 ml. aliquots of ether. The aqueous solution was then chilled in ice and neutralized with $NaHCO_3$. The nearly colorless crystalline solid was collected, dried (4.8 g., m.p. 165–168°) and recrystallized from xylene or water (charcoal) to give nearly colorless plates (3.2 g., 40% yield), m.p. 174–175° (lit[6] m.p. 181°).

2-(4′-Imidazolyl)-phenyl Benzoates (Compounds V through XII).—The following general procedure was employed: The appropriate substituted benzoic acid (0.1 mole) was treated with oxalyl chloride (excess) at room temperature for 20 hr. Most of the excess oxalyl chloride was pumped off, the last traces being removed by repeatedly adding sufficient dry chloroform to dissolve the acid chloride and removing the solvent under vacuum. To the freshly prepared acid chloride was added 0.001 mole of IV and the mixture heated in an oil-bath to a temperature at which a homogeneous melt was formed. The reacting mixture was then heated until a sample gave a negative ferric chloride test for free phenol. To the cooled melt there was then added a large volume of dry ethyl ether. The solid ester hydrochlo-

TABLE I

Ester	R	M.p., °C.	Yield, %	Empirical formula	Anal., % Calcd.	Found	Solvent
V	Phenyl	233 d.	67	$C_{16}H_{13}O_2N_2Cl$	C 63.90	63.63	$CHCl_3$–MeOH–Et_2O
					H 4.36	4.42	
VI	*p*-Nitrophenyl	223–225 d.	87	$C_{16}H_{12}O_4N_3Cl$	C 55.59	55.49	$CHCl_3$–MeOH–Et_2O
					H 3.49	3.64	
					N 12.15	12.04	
					Cl 10.23	10.51	
VII	*p*-Methoxyphenyl	195–196	53	$C_{17}H_{14}O_3N_2Cl$	C 61.90	61.77	C_6H_6–CH Cl_3–MeOH
					H 4.28	4.54	
					Cl 10.74	10.77	
VIII	*p*-Iodophenyl	175–176	59	$C_{16}H_{12}O_2N_2ClI$	C 45.05	44.81	C_6H_6
					H 2.83	2.62	
IX	*p*-Bromophenyl	175–176	50	$C_{16}H_{12}O_2N_2ClBr$	C 50.62	50.39	C_6H_6
					H 3.18	2.96	
X	*o*-Bromophenyl	185–187 d.		$C_{16}H_{12}O_2N_1ClBr$	C 50.62	50.82	C_6H_6–MeOH
					H 3.18	3.20	
					Br 21.05	21.15	
XI	*p*-Chlorophenyl	199–200	44.5	$C_{16}H_{12}O_2N_2Cl_2$	C 57.32	57.56	C_6H_6
					H 3.61	3.66	
					Cl 21.17	20.87	
XII	*p*-Fluorophenyl	194–195	40	$C_{16}H_{12}O_2N_2ClF$	C 60.29	60.18	CHCl–MeOH
					H 3.79	3.84	
					N 8.79	8.55	

ride was then collected, washed with additional ether and recrystallized (Table I).

Mono 2-(4′-Imidazolyl)-Ethyl Succinate Hydrochloride (XV).—O-Acetyl-4-(2′-hydroxyethyl) imidazole[1e] (1.54 g., 0.01 mole) was refluxed in 20 ml. of 1 *N* HCl for 24 hr. when the solvent was removed *in vacuo* and the oil dried by heating at 50°/1 mm. for 4 hr. The yellow oil of hydroxyethyl imidazole hydrochloride was then covered with 10 ml. of anhydrous toluene, 1.0 g. (0.02 mole) of succinic anhydride added and the heterogeneous mixture refluxed with stirring under anhydrous conditions for 5 hr. when the boiling toluene phase was decanted. The oil was then extracted repeatedly with boiling toluene to remove the last traces of the anhydride. The residual oil was taken up in cold methanol, ether was added until the solution became faintly turbid and the solution was decolorized by adding charcoal and filtering. To the clear, colorless filtrate there was then added a large excess of ether and the mixture cooled to 0°, whereupon the colorless oil crystallized. The colorless crystalline material was collected and recrystallized several times from chloroform–methanol by addition of ether (1.1 g., 50% yield, 107–110°). An analytical sample was prepared by recrystallizing several times from toluene–methanol mixtures by addition of ether, m.p. 112–114°.

Anal. Calcd. for $C_9H_{13}O_4N_2Cl$: C, 43.49; H, 5.27; N, 11.26; Cl, 14.50. Found: C, 43.21; H, 5.25; N, 11.39; Cl, 14.50.

4-(2′-Hydroxyethyl)-Imidazolium β,N-Pyridinium Propionate Dichloride. (XVI).—1-(2-Carboxyethyl)-pyridinium chloride[8] (1.88 g., 0.01 mole) was suspended in excess oxalyl chloride and the reaction mixture allowed to remain at room temperature for 24 hr. when the excess reagent was removed under vacuum. The residue of acid chloride (while crystalline) was added to 1.48 g. (0.01 mole) of 4-(2′-hydroxyethyl)-imidazole—as prepared previously—and the two mixed with a stirring rod to yield a thick paste. The reaction mixture was then heated on a steam-bath under anhydrous conditions for 3 hr. After cooling, the melt was extracted with absolute methanol and the product collected and washed with excess of the same solvent (0.36 g., 10%), m.p. 193–194°, with evolution of gas. An analytical sample was prepared by recrystallizing many times from ethanol–methanol (charcoal) and chloroform–methanol mixture, m.p. 208.8–209.2°.

Anal. Calcd. $C_{13}H_{17}O_2N_3Cl_2$: Cl, 22.29. Found; Cl, 22.04.

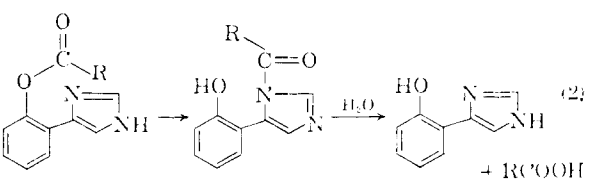
Kinetics.—The rates of solvolysis of the substituted benzoate esters of 4-(2′-hydroxyphenyl)-imidazole were followed spectrophotometrically by observing the liberation of the free phenol (295 mμ) with time. The per cent reaction was obtained from continuous variation curves of a mixture of the phenol, substituted benzoic acid and the ester. Because of the slight solubilities of the esters in water, a mixture of ethanol–water, 47.5% (*v/v*) was employed as solvent. Buffer capacity was provided by 0.1 *N* sodium acetate and the *p*H adjusted with acetic acid. A constant ionic strength of 0.65 *M* was provided by adding KCl.

The rates of hydrolysis of the esters of 4-(2′-hydroxyethyl)-imidazole were determined at 78° by following the liberation of acid in the *p*H-stat.[1e,f] For these experiments 1.0 *M* aqueous KCl was employed as solvent to prevent appreciable drifting of the ionic strength by leakage of salt solution from the bridge. The standard base employed to keep constant *p*H was also prepared in 1.0 *M* KCl.

Result and Discussion

The observed rates of solvolysis ($k_{obsd.}$) of the benzoate esters of IV at various *p*H values are recorded in Table I. To obtain the rate constant for full participation (k_1) of the non-protonated imidazolyl group the values of $k_{obsd.}$ were plotted *vs.* *p*H and the points fitted to the best theoretical curve for the dissociation of a monobasic acid. The values of k_1 and $K'_{app.}$ are recorded in Table II. The *p*H profile of the solvolysis constants for the *p*-nitro ester along with the theoretical dissociation curve is presented in Fig. 1.

A comparison of the k_1 value for the benzoate ester of IV to that found for the acetyl derivative[1e] (2.1×10^{-3} min.$^{-1}$ at 30° in 28.5% ethanol–water, *v/v*) indicates that the latter ester undergoes solvolysis with participation four times as readily as the benzoate ester. It may be noted that the pK'_{app} of



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the imidazolyl group of the benzoate esters, though varying only slightly within the series, is characterized by a value lower than that for the acetyl

(8) A. Kirpal and B. Wojnar, *Ber.*, **71B**, 1261 (1938).

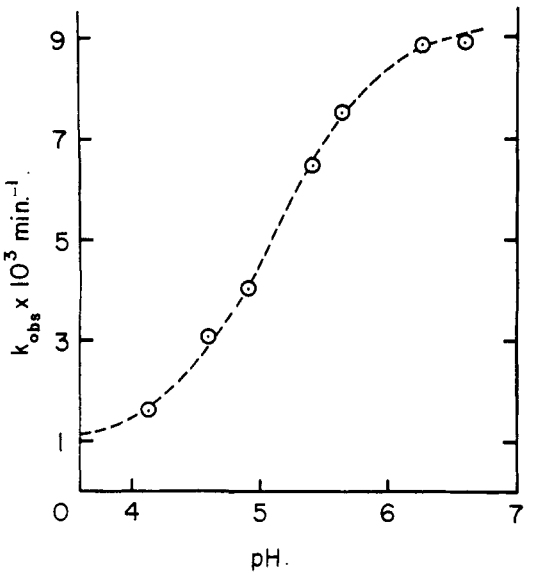

Fig. 1.—The pH dependence of the solvolysis of the p-nitrobenzoyl ester of 2-(4′-imidazolyl)-phenol. (T = 30°; μ = 0.65 M; solvent = 50–50 dioxane–water v/v.)

ester; *ca.*, 5.15 *vs.* 5.55. This difference, which is consistent with the greater electron attracting power of the benzoyl group, should decrease the rates of hydrolysis of the benzoate esters from values they would have achieved had the pK_a's in the two

TABLE II

KINETIC DATA FOR THE PARTICIPATION OF IMIDAZOLYL GROUP IN THE HYDROLYSIS OF 2-(4′-IMIDAZOLYL)-PHENYL BENZOATES

(47.5% Ethanol-water (v./v.); μ = 0.65; temp., 30°)

Substituent	pH	$k_{obsd.}$, min.$^{-1}$ × 10^5	$pK'_{app.}$	k_1, min.$^{-1}$ × 10^5
p-OCH_3	4.46	2.28		
	4.90	3.11		
	5.24	6.96		
	6.00	9.90		
	6.51	11.50	5.22	12
o-Br	4.44	6.24		
	5.00	13.98		
	5.20	15.78		
	5.44	19.44		
	5.94	23.04		
	6.40	25.32	5.12	24
H	4.12	6.66		
	4.65	13.6		
	5.16	34.7		
	5.65	43.0		
	6.66	53.4	5.02	51.6
p-Br	4.39	13.08		
	4.83	22.56		
	5.15	34.92		
	5.91	63.3		
	6.37	73.2	5.26	75
p-NO_2	4.13	160.8		
	4.60	307.2		
	4.91	403.8		
	5.41	648.0		
	5.65	753.6		
	6.27	885.0		
	6.60	888.0	5.10	820

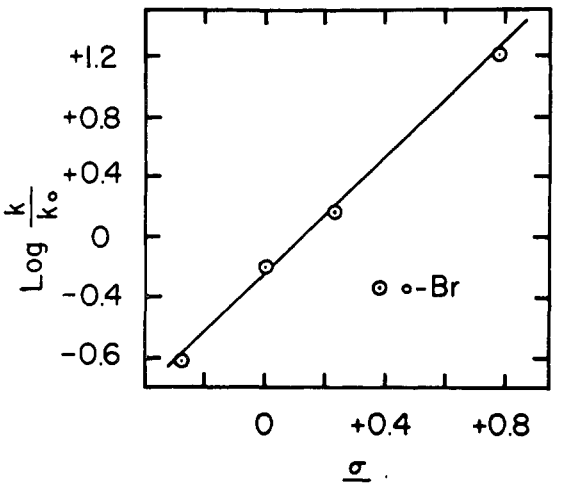

Fig. 2.—The Hammett $\rho\sigma$ plot for the solvolysis of substituted benzoyl esters of 2-(4′-imidazolyl)-phenol. (T = 30°; μ = 0.65 M; solvent = 50–50 dioxane H_2O v/v.)

series been identical. With this in mind, it may be noted that the k_1 acetate/k_1 benzoate value of 4 is comparable to that determined for the specific base catalyzed hydrolysis of acetate and benzoate esters. [k_1 CH_3COOEt/k_1 PhCOOEt = 8.6 (50°) and; k_1 CH_3COOPh/k_1 PhCOOPh = 7.6 (0°); rate constants not determined in the same solvents.][9-12]

In Fig. 2 the values of k_1 are presented in the conventional Hammett plot.[13] The value of ρ-calculated from the slope of Fig. 2 was found to be 1.67. This value compares favorably with those found for substituted phenyl acetates reacting with imidazoles (*loc. cit.* 1.9–1.7)[1a,b] in a bimolecular displacement reaction. In attempting to compare ρ-values for an intramolecular displacement reaction and the corresponding bimolecular displacement at the ester bond, it should be noted that the two may differ considerably if the steric compression in the intramolecular process lowered the activation energy for the nucleophilic attack relative to that for the partitioning of the tetrahedral intermediate (1), and thereby made the latter process the rate determining step.[1e] This however would not appear to be of concern in this study since these displacement reactions proceed slowly. In the present instance, therefore, a comparison of the ρ-value obtained for the intramolecular displacement of benzoates with that for the bimolecular displacement of substituted phenyl acetates by imidazoles should be permissible. Since the two ρ-values are numerically comparable we may conclude that the positive nature of the ester carbonyl carbon is as important in the catalysis of hydrolysis of an ester by imidazole as is the stability of the leaving group.[1a]

It has been suggested[14] that the imidazole

(9) C. K. Ingold and W. S. Nathan, *J. Chem. Soc.*, 222 (1936).
(10) H. A. Smith and H. S. Levenson, THIS JOURNAL, **61**, 1173 (1939).
(11) C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956).
(12) E. Tommila and C. N. Hinshelwood, *ibid.*, 1801 (1938).
(13) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, Ch. 7.
(14) W. P. Jencks and J. Carrinolo, *J. Biol. Chem.*, **234**, 1280 (1959).

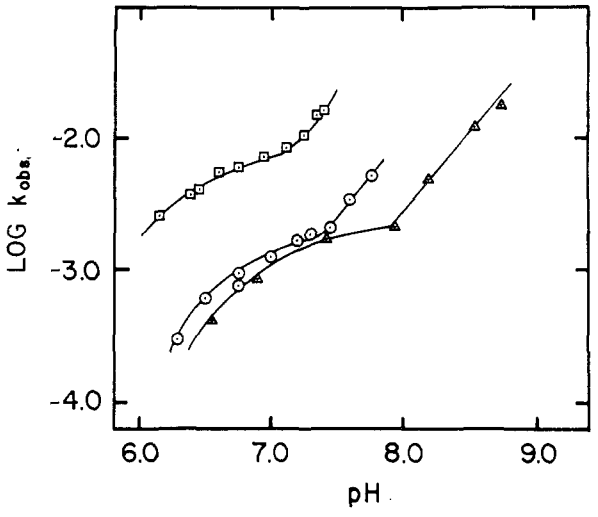

Fig. 3.—Plots of the logarithm of the solvolysis constants for three esters of 4-(2′-hydroxyethyl)-imidazole *vs.* *p*H. (T = 78°; μ 1.0 M; solvent H_2O.) The esters are: ⊡, β,*N*-pyridinium propionate: ⊙, acetate; ⧋, mono-succinate.

catalyzed hydrolysis of ethyl oxalate[15] is not a case of nucleophilic catalysis but involves general base catalysis, proceeding through the agency of OH^-, formed from H_2O *via* proton abstraction by imidazole. This suggestion arises from the observation that since imidazoles are incapable of displacing -O-alkyl from ordinary ester,[1e] the latter objective may be achieved by the mechanism of general base catalysis, with OH^- acting as the nucleophile. However, ethyl oxalate is not an ordinary aliphatic ester in that the carbomethoxy group is strongly electron attracting, having a σ^* of 2.0.[16] Since the ease of hydrolysis of an ester by imidazole would appear to depend equally on the electronic nature of the carbonyl and leaving groups, it is quite possible that imidazole could effect a direct nucleophilic displacement of -O-alkyl from ethyl oxalate.

The logarithm of the observed rates of hydrolysis of the esters of 4-(2′-hydroxyethyl)-imidazole (XV and XVI) are plotted *vs.* *p*H in Fig. 3. Also included in Fig. 3 are the hydrolytic rate constants for the O-acetyl ester (XIV) which has now been studied over a wider *p*H region than previously reported.[1e] For OH^- catalysis plots of *p*H *vs.* log $k_{obsd.}$ should be linear while for the participation of the neutral imidazolyl group one should obtain a curve reaching a plateau at full dissociation of the imidazolium ion. These features may be observed in Fig. 3. The approximate values of k_1 and $k_{OH}K_w$ for the esters are:

	$k_1 \times 10^3$ min.$^{-1}$	$k_{OH}K_w \times 10^{11}$ l. mole^{-1} min.$^{-1}$
Acetate	1.8	9.1
Succinate	2.0	3.0
β-(N-Pyridinium)-propionate	7.6	61.0

It may be noted that the alkaline hydrolysis of the succinate ester is characterized by a rate constant $^1/_3$ that for the acetate ester. The smaller constant for the succinate ester is attributed to the repulsion of OH^- by the carboxyl anion. Thus, the ratio of the rate constants for the hydrolysis of the first and second carboethoxy groups in diethyl succinate is 1:5.6 (0.05 M Na^+).[17] For solvolysis with imidazole participation the rates for the acetate and succinate esters are comparable, which is reasonable in view of the lack of charge on the imidazolyl group. In the case of the alkaline hydrolysis of the pyridinium ester the large rate enhancement is due both to the electrostatic attraction of OH^- as well as to the inductive effect of the pyridinium group. The larger rate for solvolysis with imidazolyl participation must be due to the inductive effect only. The establishment of imidazolyl participation in the hydrolysis of the succinate and β-(N-pyridinium) propionate esters as well as for the acetate ester proves that aliphatic esters can undergo hydrolysis by nucleophilic catalysis involving the imidazolyl group. These observations are of some interest insofar as an imidazolyl group of histidine has been implicated in the mode of action of several ester hydrolases.[1a,e]

Acknowledgment.—This work was supported by a grant from the Institute of Arthritic and Metabolic Diseases, National Institutes of Health.

(15) D. M. Brouwer, M. J. van der Vlugt and E. Havinga, *Proc. K. Nederl. Akad. Wetenschap.*, **60B**, 275 (1957).

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(17) R. L. Burnett and L. P. Hammett, THIS JOURNAL, **80**, 2415 (1958).