was converted to the soluble potassium salt by swirling in 24 ml. of 10% ethanolic potassium hydroxide solution. The clear yellowish solution was diluted with a 100 ml. of ethanol and 250 ml. of water, then cooled with stirring in a Dry Ice–methanol bath to approximately $-12°$. The solution was then acidified with a 1:3 sulfuric acid–ethanol solution to a Congo Red end point. The resulting colorless solid precipitate was filtered and transferred at once to 500 ml. of a buffer solution prepared in the following ratio: 100 ml. of 95% ethanol, 7.5 g. (0.055 mole) of sodium acetate (trihydrate), and 0.5 ml. of glacial acetic acid. The mixture was allowed to stand for approximately 20 min. after which time it was diluted with 1 l. of water. The resulting milky suspension was extracted with ether and the ethereal extract washed twice with a saturated sodium bicarbonate solution and once with water. The ethereal extract was dried over calcium sulfate, the ether evaporated, and the product recrystallized from *n*-hexane.

***trans*- and *cis*-2-(Substituted Phenyl)cyclohexylamines.**—These compounds were prepared by the stereospecific reduction of the corresponding nitro compounds according to the method of Kornblum, Gurowitz, Larson, and Hardies.[13] An example of this method is given below. The analysis and physical constants of the products appear in Table III.

***trans*-2-*p*-Tolylcyclohexylamine.**—Twenty-five grams of finely powdered, hydrogen-reduced iron was washed with 5% hydrochloric acid, the acid decanted, and the powder rinsed twice with glacial acetic acid. The iron powder was then slurried with 150 ml. of glacial acetic acid and the slurry transferred to a 1-l. three-neck flask. Fifteen grams (0.068 mole) of *trans*-2-*p*-tolylnitrocyclohexane (I) dissolved in 50 ml. of hot glacial acetic acid was added, with stirring, to the glacial acetic acid–iron powder mixture. The reaction mixture was refluxed for 3 hr., cooled, and filtered with suction through a Celite pad. The filtrate was made basic to pH of about 10 by slow addition of 30% sodium hydroxide solution with stirring and cooling. The mixture was exhaustively extracted with ether, dried over calcium sulfate, the ether evaporated, and the product distilled under reduced pressure.

Hydrochloride Salts.—The various salts were prepared by bubbling hydrogen chloride gas into a solution of the particular amine in hexane. The salt was filtered and recrystallized from an appropriate solvent.

The n.m.r. of all the nitrocyclohexanes were determined in a carbon tetrachloride solution containing 1% tetramethylsilane (100 mg. of compound in 0.5 ml. of solution).

The n.m.r. of all the cyclohexylamines were determined at the same concentrations but tetrachloroethylene was used as the solvent.

The melting points were determined with a Kofler micro hot state.

Rates of Saponification of Some Halogen-Substituted Ethyl Phenoxyacetates[1]

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The rates of hydrolysis by sodium hydroxide in 87.5 weight per cent aqueous ethanol have been measured at 0 and 30° of ethyl phenoxyacetate and the 2- and 4-fluoro, chloro, bromo, and iodo and the 2,4-difluoro, dichloro, dibromo, and diodo substituted esters and found to be surprisingly rapid, ranging between 0.043 and 0.115 at 0° and 0.51 and 1.39 at 30° in the second-order rate constant. The Hammett equation was not followed although the rate constants at 0° for the 4-halo esters gave a rough fit to σ°. The rate parameters were calculated and a linear enthalpy-entropy of activation relationship was shown to exist. A re-interpretation of Leffler's equation[10] has been made, and of the requirements for adherence to the Hammett relationship.

The chemistry of the halogen-substituted phenoxyacetic acids has become of interest because of the problem of finding a correlation between the plant growth or biological activity and the chemical properties.[2] A halogen in the 4-position, specially fluorine or chlorine, seems to be necessary for any appreciable activity which is enhanced by further substitution in the 2-position. We wish to report the results of a study of the saponification of a series of halogen-substituted ethyl phenoxyacetates in 87.5 weight per cent aqueous ethanol.

Rate constants were calculated from the usual second-order rate expression. Except for some instances at 0° when the initial point fell below the straight line in a plot of $\log (x + c)/x$ *vs.* time, or at 30° when the initial point fell above the plotted line, the reaction rates were straightforward. In Table I the results are given along with the values of the rate parameters calculated in the usual way. The rates turned out to be rather fast with log A factors comparable to those for the basic hydrolysis of ethyl benzoates in 85% ethanol[3] and activation energies comparable to aliphatic ester hydrolysis.[3] Substitution of halogen increase the rate in every instance. Since the phenoxy group possesses an $-I$ effect, and since the halogens all have an $-I$ effect greater than an $+M$ effect, the increases were as expected.

Since the basic hydrolysis of ethyl benzoates in 87.83% ethanol follows the Hammett equation[4] with $\rho = 2.498$; of ethyl phenylacetates[5] with

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(2) See for example, R. L. Weintraub, J. W. Brown, and J. A. Thorne, *J. Ag. Food Chem.*, **2**, 996 (1954); R. F. Brown and E. F. Claflin, *J. Am. Chem. Soc.*, **80**, 5960 (1958); A. M. Johnston, *J. Chem. Soc.*, 2335 (1961).

(3) E. A. Moelwyn-Hughes, "Kinetics of Reactions in Solution," Clarendon Press, Oxford, 1947, pp. 141, 149.

(4) L. P. Hammett, *J. Am. Chem. Soc.*, **59**, 96 (1937); K. Kindler, *Ann.*, **450**, 1 (1926); **452**, 90 (1927); **464**, 278 (1928); and *Ber.*, **69B**, 2792 (1936).

(5) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953), reaction number 53.

TABLE I

RATE CONSTANTS AND PARAMETERS[a] FOR THE SAPONIFICATION OF SOME HALOGEN-SUBSTITUTED ETHYL PHENOXYACETATES

Subst.	k_1, l./mole-sec.		E_a, kcal.	log A	ΔH_{25}^*,[b] kcal.	$-\Delta S_{25}^*$, e.u.
	0°	30°				
None	0.043 ± 0.003	0.51 ± 0.02	13.67 ± 0.72	9.571 ± 0.536	13.08	16.73 ± 2.45
	.043 ± .005	.52 ± .02				
	Av. .043 ± .004	.57 ± .01				
		Av. .52 ± .02				
2-F	.075 ± .003	.83 ± .05	13.11 ± .62	9.370 ± .473	12.52	17.65 ± 2.16
	.077 ± .005	.83 ± .06				
	Av. .076 ± .004	.86 ± .02				
		.79 ± .04				
		Av. .83 ± .04				
4-F	.069 ± .005	.72 ± .02	12.71 ± .38	9.020 ± .286	12.12	19.25 ± 1.31
	.071 ± .002	.72 ± .03				
	.073 ± .001	Av. .72 ± .02				
	Av. .071 ± .003					
2,4-diF	.107 ± .003	1.01 ± .01	12.21 ± .31	8.806 ± .233	11.62	20.23 ± 1.07
	.112 ± .002					
	.109 ± .006					
	Av. .109 ± .004					
2-Cl	.065 ± .002	0.78 ± .03	13.72 ± .38	9.783 ± .290	13.12	15.76 ± 1.33
	.063 ± .002					
	.063 ± .002					
	Av. .064 ± .002					
4-Cl	.081 ± .004	.88 ± .03	13.08 ± .39	9.373 ± .297	12.49	17.63 ± 1.36
	.080 ± .002					
	.082 ± .002					
	Av. .081 ± .003					
2,4-diCl	.114 ± .006	1.39 ± .06	13.67 ± .62	9.998 ± .477	13.08	14.77 ± 2.18
	.115 ± .003	1.34 ± .15				
	Av. .115 ± .004	1.44 ± .10				
		Av. 1.39 ± .10				
2-Br	.057 ± .004	0.69 ± .03	13.74 ± .52	9.756 ± .393	13.15	15.88 ± 1.80
	.058 ± .003	.74 ± .03				
	Av. .058 ± .003	Av. .71 ± .03				
4-Br	.075 ± .003	.87 ± .02	13.37 ± .35	9.577 ± .263	12.78	16.70 ± 1.20
	.076 ± .004					
	Av. .076 ± .003					
2,4-diBr	.104 ± .004	1.11 ± .04	12.94 ± .36	9.369 ± .272	12.35	17.65 ± 1.24
	.101 ± .001	1.09 ± .03				
	.103 ± .004	Av. 1.10 ± .03				
	.108 ± .006					
	.102 ± .004					
	Av. .104 ± .004					
2-I	.070 ± .002	0.64 ± .01	11.88 ± .34	8.349 ± .259	11.28	22.32 ± 1.19
	.069 ± .002	.59 ± .03				
	Av. .070 ± .002	.61 ± .01				
		Av. .61 ± .02				
4-I	.083 ± .001	.76 ± .02	12.29 ± .34	8.752 ± .261	11.70	20.47 ± 1.19
	.085 ± .002	.80 ± .03				
	.081 ± .003	Av. .78 ± .03				
	Av. .083 ± .002					
2,4-diI	.128 ± .005	1.30 ± .12	12.71 ± .70	9.284 ± .542	12.12	18.04 ± 2.48

[a] The tabulated values are carried to more places than are necessary to express the precision in order to use the values in Fig. 1 and for use in calculation of fit in the linear enthalpy-entropy relationship. [b] The uncertainties are the same as for the corresponding E_a.

$\rho = 0.824$; and of ethyl β-phenylpropionates[6] with $\rho = 0.489$, while the corresponding acids[7] show $\rho = 1.000, 0.471, 0.212$ for ionization, it was not unreasonable to expect the Hammett equation to apply to the present data for the *para*-halogen substituents even though it is common to see the halogens lumped together because of the small differences in sigma. However, neither the data at 0° or 30° ($\Delta \log k$ *vs.* σ) fit the Hammett equation nor does a plot of $\Delta \log k$ *vs.* σ° give a good straight line[8] at 30° although at 0° a rough fit to a straight line occurred with $\rho = 1.1 \pm 0.1$. Similarly a plot of $\Delta \log k$ *vs.* $\Delta \log K_{\text{ion}}$ of phenoxyacetic acids, or the use of σ^* for the *ortho*-halogens,[8] or the use[9] of $\sigma_p{}^+$ did not lead to any correlation.

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[6] Ref. 5, reaction number 54.

[7] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 189.

[8] R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, ed., J. Wiley and Sons, Inc., New York, N. Y., 1956, p. 619. See also *J. Phys. Chem.*, **64**, 1805 (1960).

[9] H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **79**, 1913 (1957).

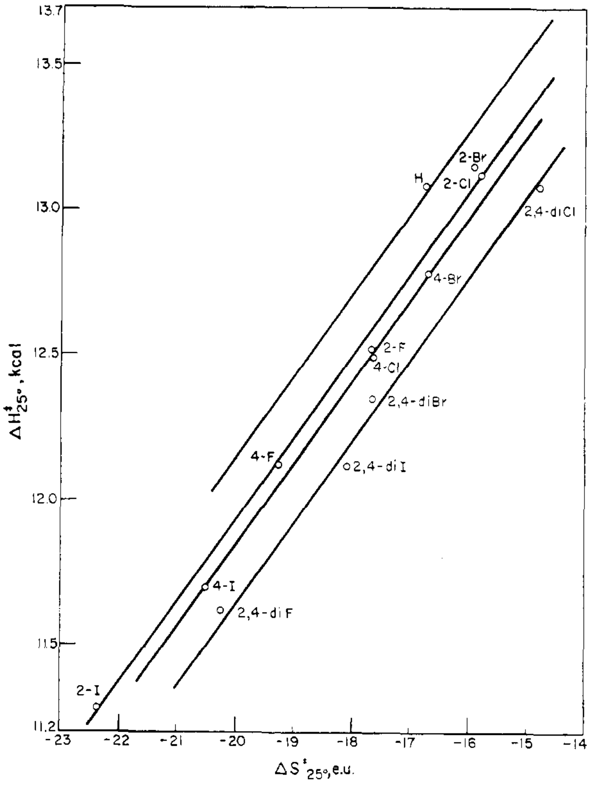

Fig. 1.—Plot of $\Delta H^*_{25°}$ against $\Delta S^*_{25°}$ for the saponification in 87.5% aqueous ethanol of ethyl phenoxyacetates with the halogen substituents indicated. The lines drawn have a slope of β_0 = 277°.

Whereas for σ_p, I > Br > Cl > F, for σ_p^+, Br > I > Cl > F, and for $\sigma°$, I = Cl > Br > F we find at 30°, Cl > Br > I > F and at 0°, I > Cl > Br > F. A plot of Δ log k for the 4-halogen substituted esters *vs.* $1/T$ shows an order of Br > Cl > F > I at temperatures above 69°, with intersections at 69, 36, 13, 5, −15°, and one other at a still lower temperature whereby the order is changed by an exchange of position. The lower limit gives I > F > Cl > Br, the inverse of the higher temperature order.

When ΔH^* was plotted against ΔS^*, as in Fig. 1, the points suggested that three straight lines could be recognized, one for the 2-halogen, another for the 4-halogen, and a third for the 2,4-dihalogen substituted esters. A least squares fit gave slopes of 284, 277, and 270° with correlations r of 0.998, 0.997, and 0.997. If the slopes were averaged, 277°, and this slope applied to all three cases as well as to the single point representing the unsubstituted ester the intercepts came out to be 17.69, 17.48, 17.40, and 17.19 kcal. for the four lines representing the unsubstituted, the *ortho*, the *para*, and the 2,4-substituted esters. Recalculation of ΔH^* from the experimental ΔS^* values using these intercepts and the 277° slope agreed for all thirteen points with an average deviation of ±0.032 kcal! Furthermore, the differences in the intercepts were such that the difference between the unsubstituted and the *ortho* esters was 0.21 kcal., between the unsubstituted and the *para* case was 0.29 kcal., while the difference between the unsubstituted and the 2,4-substituted esters was 0.50 in exact agreement with the sum of the other two differences! Such close concordance in the intercepts as well as in the recalculation of ΔH^* suggests that enthalpies and entropies of activation are much more reliable than the average uncertainties as usually calculated would indicate.

The activation enthalpy-entropy relationship described in equation 1 is the same as that proposed

$$\Delta H^* = \Delta F_0^* - \beta_0 \Delta S^* \qquad (1)$$

by Leffler[10] except that we assign somewhat different meanings to the intercept, ΔF_0^*, and to the slope, β_0 as compared to Leffler's terms, ΔH_0^* and β. He described ΔH_0^* as "simply the intercept- . . . . it will usually have no physical meaning." On the other hand, β was termed an isokinetic temperature, the temperature at which ρ in the Hammett equation would change sign. It should be made clear that ΔH_0^* and β refer to the regression line for all points for a given reaction under given conditions and the criterion for whether or not there is an enthalpy-entropy relationship was determined by the closeness of fit. Applied to the data reported here, β = 282°, ΔH_0^* = 17.47 kcal., r = 0.966, and recalculation of ΔH^* gave an average deviation of ±0.122 kcal., still well within the experimental uncertainties. Nevertheless we prefer the separation of the data into the four distinct families of compounds and propose ΔF_0^* and β_0 as parameters, all of the compounds giving relationships having the same slope, β_0, but the families being distinguished by different ΔF_0^* values. Such values will differentiate between the subtle distinctions required for membership in a given family. As shown above, the unsubstituted ester is the sole member of one family while all the *ortho*-halogenated esters fall into a second family with a ΔF_0^* value 0.21 kcal. less than that of the unsubstituted ester. Similarly, the *para*-halogenated esters form a third family while the 2,4-dihalogenated esters form a fourth. Presumably, the *meta*-halogenated esters would form a fifth family, or perhaps fall into line with one of the four families already established, while other types of substituents may or may not form new family groups. Leffler has recognized the existence of parallel lines in several other instances but has not pushed the recognition to a consideration of the intercepts.

Substitution of equation 1 into the familiar thermodynamic relationship (2) yields equation 3

$$\Delta F^* = \Delta H^* - T\Delta S^* \qquad (2)$$

$$\Delta F^* = \Delta F_0^* + (\beta_0 - T)\Delta S^* \qquad (3)$$

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[10] J. E. Leffler, *J Org. Chem.*, **20**, 1202 (1955).

TABLE II

ETHYL PHENOXYACETATES

Comp.[a]	Yield, %	B.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. X	Found C	Found H	Found X
Parent	52	137 (19 mm.)[b]	$C_{10}H_{12}O_3$	66.6	6.7	...	66.3	6.8	...
2-F	78	101.5–101.7 (7 mm.)	$C_{10}H_{11}O_3F$	60.6	5.6	...	60.5	5.4	...
4-F	30	112.2–112.4 (12 mm.)	$C_{10}H_{11}O_3F$	60.6	5.6	...	60.7	5.6	...
2,4-diF	59	117.0–117.4 (21 mm.)	$C_{10}H_{10}O_3F_2$	56.1	4.5	...	55.8	5.1	...
2-Cl	24	162 (20 mm.)	$C_{10}H_{11}O_3Cl$	56.0	5.2	16.5	55.9	5.0	16.4
4-Cl	83	178 (24 mm.)[c]	$C_{10}H_{11}O_3Cl$	56.0	5.2	16.5	55.9	5.0	16.5
2,4-diCl	69	185.4–186 (25 mm.)[d]	$C_{10}H_{10}O_3Cl_2$	48.2	4.0	28.5	48.4	3.9	28.4
2-Br	52	153.1–153.3 (19 mm.)[e]	$C_{10}H_{11}O_3Br$	46.3	3.9	...	46.3	4.1	...
4-Br	28	173.4–173.8 (41 mm.)[f]	$C_{10}H_{11}O_3Br$	46.3	3.9	30.7	45.8	4.0	31.0
2,4-diBr	49	176.3–176.8 (15 mm.)	$C_{10}H_{10}O_3Br_2$	35.5	3.0	47.3	35.8	3.1	47.6
2-I	72	157.2–157.5 (7 mm.)	$C_{10}H_{11}O_3I$	39.2	3.6	41.5	39.1	3.8	41.5
4-I	39	164 (6 mm.)[g]	$C_{10}H_{11}O_3I$	39.2	3.6	41.5	39.3	3.8	41.5
2,4-diI	68	[h]	$C_{10}H_{10}O_3I_2$	27.8	2.3	58.8	27.9	2.4	58.6
2,4,6-triI	..	[i]	$C_{10}H_9O_3I_3$	21.5	1.6	68.2	21 6	1.9	68.2

[a] See ref. 16. [b] Also b.p. 250–251°, ref. 14 gives b.p. 250–251°. [c] M.p. 47.5–48°; L. Haskelberg, *J. Org. Chem.*, **12,** 426 (1947), gives b.p. 180° (22 mm.); m.p. 48°. [d] Also b.p. 132–134° (1 mm.); Haskelberg reports b.p. 128° (0.2 mm.). [e] Also b.p. 155–157° (14 mm.); K. Amoers and K. Haymann, *Ber.*, **27,** 2800 (1894) give b.p. 160–170° (16 mm.). [f] M.p. 55–57°; P. Fritzsche, *J. prakt. Chem.*, **20,** 295 (1879), gives m.p. 59°. [g] M.p. 58–59.5°. [h] M.p. 117–120°, from alcohol as first prepared, see text, pure ester, m.p. 57–58°. [i] M.p. 121°.

The latter equation displays the reason for assigning ΔF_0^* to the intercept since when $\beta_0 = T$, $\Delta F^* = \Delta F_0^*$. The term ΔF_0^* may be thought of as the intrinsic free energy of activation of a reaction of a given family of substituents. Also it may be thought of as the free energy of activation for that imaginary member of a family, a substituent which produces $\Delta S^* = 0$, remembering that then $\Delta H^* = \Delta F_0^*$. Equation 3 also shows that ΔF^* is linear in ΔS^* but is far less sensitive to ΔS^* than is ΔH^* since $(\beta_0 - T)$ will, in general, be small in comparison with β_0. Of course, one may set ΔS^* as a function of ΔH^* in which case[11] the slope becomes $1/\beta_0$ and the intercept, $-\Delta F_0^*/\beta_0$. Also, the equation[12] $\Delta H^* = a\Delta F^* + d$ has been proposed. It is easily shown that $a = \beta_0/(\beta_0 - T)$ and $d = \Delta F_0^*(1-a)$. However, since $a \to \infty$ as $T \to \beta_0$, we prefer to adhere to the form of equation 1 as first proposed by Leffler.[10]

Returning to the Hammett equation, 4, and realizing that $\sigma = \Delta \log K_a$ for the ionization of

$$\rho\sigma = \Delta \log k = -(\Delta\Delta F^*)/2.3\,RT = -[\Delta\Delta F_0^* + (\beta_0 - T)\,\Delta\Delta\,S^*]/2.3\,RT \qquad (4)$$

benzoic acids in aqueous solution at 25° (or some other standard such as is used for σ°,[8] σ^{+},[9] or σ^{*} [8]) then in order for the equation to hold, ρ must be a constant, (see 5). If the substituents belong

$$\rho = 298°\,[\Delta\Delta F_0^* + (\beta_0 - T)\,\Delta\Delta S^*]/T[\Delta\Delta F_0 + (\beta_0 - 298°)\,\Delta\Delta S]_{\text{a}} \qquad (5)$$

to the same family in both reactions, $\Delta\Delta F_0^*$ and $\Delta\Delta F_0$ become zero and $\rho = \Delta\Delta S^*/\Delta\Delta S_a$ if β_0 and β_{0a} are equal and T is the same in both numerator and denominator of (5) so that only if the ratio of entropy differences is constant will rho be constant. In the present case, in none of the families does this ratio remain constant and the Hammett relation fails. It would seem that in the choice of benzoic acid ionization for sigma, $\Delta\Delta S$ is small, and with $(\beta_0 - T)$ also small, each substituent belongs to a separate family (except perhaps the *meta* halogens) so that $\Delta\Delta F_{0a}$ is the main determinant of sigma. For substituents in different families, (5) does not simplify. But if $(\beta_0 - T)$ is small enough in both numerator and denominator then $\rho = \Delta\Delta F_0^*/\Delta\Delta F_{0a}$ and the relationship will hold.

The slope, β_0, having the dimensions of temperature is not in general an isokinetic temperature since as T in the numerator of (5) is varied such that $(\beta_0 - T)$ goes from plus to zero to minus the sign of rho need not change. Only when the entire numerator changes sign will rho pass through zero and change sign.

In using (5), we have assumed that (1) and (3) apply to the ionization of benzoic acids and that β_0 is a constant applicable to all reactions. In a subsequent paper we shall explore the assumption of the view that separation into families of parallel lines of constant slope, β_0, is a characteristic of the application of the enthalpy-entropy relationship.

Nothing striking concerning biological activity correlation is apparent except that ethyl 2,4-dichlorophenoxyacetate hydrolyzed faster than any other ester studied. This was caused by the smallest entropy of activation of all the esters since equivalent or higher enthalpies of activation were displayed by the parent, the 2-chloro and the 2-bromo esters all of which lack the high biological potency of the 2,4-dichloro ester.

Experimental[13]

All of the esters were prepared by the reaction of the proper phenol with ethyl chloro- or bromoacetate in the

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(11) W. K. Wilmarth and N. Schwartz, *J. Am. Chem. Soc.*, **77**, 4543, 4551 (1955).

(12) S. Winstein and A. H. Fainberg, *ibid.*, **79**, 5937 (1957).

(13) All melting and boiling points are uncorrected. Analyses by W. Schenck and R. S. Walpole, Department of Chemistry, University of Southern California, and by Elek Micro Analytical Laboratories, Los Angeles, California.

presence of sodium ethoxide.[14] Ethyl 4-chlorophenoxyacetate and ethyl 2,4-dichlorophenoxyacetate also were obtained by direct esterification of the commercially available acids. The physical properties and analyses of the esters are listed in Table II. The presence of acidic impurities was detected in all the esters as ordinarily purified by a lowering of the saponification equivalent by 12 to 24%, and each ester was purified further by careful fractionation. In the case of ethyl 2,4-diodophenoxyacetate, even at 1 mm., decomposition sets in during distillation and purification was attempted by recrystallization. This was ineffective until a solution of the ester in petroleum hexane was allowed by accident to evaporate, and the residue was noticed to be a mixture of prisms and needles. The two forms were separated by hand and recrystallized from petroleum hexane to give needles, m.p. 121°, on the one hand and prisms, m.p. 57–58°, on the other. Analysis showed that the needles were ethyl 2,4,6-triodophenoxyacetate which originated in the dimercuration of phenol as trimercurated phenol. The prisms were ethyl 2,4-diiodophenoxyacetate. A small sample of the latter compound was hydrolyzed to give the acid, m.p. 164.0–164.5°, as compared to that reported[15], m.p. 165–167°. Except for 2-chloro-, 4-chloro-, 2,4-dichloro-, 4-bromo-, 2,4-dibromo-, and 2-iodophenol which were commercially available, the other phenols were synthesized.[16]

2-Fluoroanisole,[16] 239 g. (1.9 moles), was prepared in 36% over-all yield from *o*-anisidine by the method of English, Mead, and Niemann[17]: b.p. 64–66° (23 mm.), reported b.p. 69–70° (26 mm.).

2-Fluorophenol, 18.9 g. (0.169 mole), was prepared in 79% yield from 2-fluoroanisole by the method of Schiemann, *et al.*,[18] b.p. 53–55° (16 mm.), reported b.p. 50° (14 mm.).

4-Fluoroaniline.[16]—4-Fluoronitrobenzene, 23.6 g. (0.167 mole), was dissolved in 150 ml. of 95% alcohol, 0.3 g. of platinum oxide added, and the mixture was hydrogenated. In the first hour 42.5 lb. of hydrogen was absorbed (42.9 lb. calculated). No hydrogen was absorbed in the second hour. The solution was filtered, the solvent evaporated, and the residue distilled, b.p. 182–187°, reported[19] b.p. 187°, to give 11.2 g., 61% yield, of product.

4-Fluorophenol.[16]—4-Fluoroaniline, 29.3 g. (0.264 mole), was stirred into a cold mixture of 65 ml. of water and 50 ml. of sulfuric acid. To the stirred solution was added about 100 g. of ice, and a solution of 21 g. of sodium nitrite in 40 ml. of water was dropped in while the temperature was maintained at 0–5°. After addition was complete, the mixture was stirred for 10 min., and placed in a dropping funnel and ran slowly into a solution of 135 ml. of water and 180 ml. of sulfuric acid which was being steam distilled.[20] The distillate was saturated with sodium chloride and extracted with ether. After drying the ethereal solution over magnesium sulfate, the solvent was removed and the residue distilled under reduced pressure to give 15.9 g. (0.142 mole), 54% yield of product, b.p. 77–80° (12 mm.), reported[21] b.p. 81.5° (13 mm.).

2-Fluoro-4-nitroanisole[16] was prepared by nitration of 2-fluoroanisole by the method of Elderfield, *et al.*[22] In two runs employing 3- and 6-hr. reaction time, yields of 31.0 and 39.6% of product, 42.0 g. (0.246 mole) and 53.7 g. (0.314 mole), respectively, were obtained; m.p. 102–104° from alcohol, reported m.p. 104–105°.

4-Amino-2-fluoroanisole.[16]—2-Fluoro-4-nitroanisole, 42.0 g. (0.246 mole), was suspended in 200 ml. of absolute alcohol to which was added 1 g. of chloroplatinic acid, 0.6 g. of sodium hydroxide, and about 20 g. of Raney nickel. After 26 hr. in the Parr apparatus, 64.5 lb. of hydrogen absorbed (65 lb. calculated). The solution was filtered, and the alcohol removed, leaving 30.5 g. (0.178 mole) 72.6% yield of 4-amino-2-fluoroanisole as a dark solid. Two recrystallizations from alcohol were required to give a product of m.p. 80–82° (lit.,[23] m.p. 82.6°). Reduction with stannous chloride by the method of Schiemann and Miau[23] gave a 97% yield of 4-amino-2-fluoroanisole.

2,4-Difluoroanisole,[16] 24.2 g. (0.168 mole), was prepared in 48.8% over-all yield from 4-amino-2-fluoroanisole by the method of Schiemann and Seyhan;[24] b.p. 52–54° (17 mm.), reported b.p. 52° (17 mm.).

2,4-Difluorophenol,[16] 13.4 g. (0.103 mole), was prepared in 61.3% yield from 2,4-difluoroanisole by the method of Schiemann and Seyhan,[24] b.p. 58–62° (29 mm.), reported b.p. 52–53° (19 mm.).

2-Bromophenol[16] was prepared from a solution of 50 g. of 2-bromoaniline in 400 ml. of water and 40 ml. of concentrated sulfuric acid which was cooled to below 10° and diazotized by adding a solution of 21 g. of sodium nitrite in a small quantity of water. The resulting diazonium salt solution was decomposed as described under 4-fluorophenol to give 34.5 g. (68.5%) of product b.p. 192–194°, reported[25] b.p. 190–191° (740 mm.).

4-Iodophenol.—The procedure of Dains and Eberly[26] was followed except that instead of copper bronze, copper powder, freshly washed with dilute nitric acid, and distilled water, was used. The product, 27.6 g. (0.125 mole), was obtained in 62.7% yield, m.p. 91–93° from ligroin, reported m.p. 94°.

2,4-Diacetoxymercuriphenol, 60.8 g. (0.0995 mole), was prepared by the method of Caius and Wadia[27] in 53.0% yield, m.p. 210–215°, reported, m.p. 216°.

2,4-Diiodophenol, 35.8 g. (0.103 mole), was prepared by the method of Wawzonek and Wang[28] in nearly quantitative yield, m.p. 63–67°, reported m.p. 68–70°.

The rates[29] **of basic hydrolysis** of the various halogen-substituted ethyl phenoxyacetates were measured in 87.5 weight % aqueous ethanol at 0° and 30° over an average range of 60% reaction. Excess base ranged from 10 to 100% of the concentration of the esters which ranged between 0.0017 and 0.0065 *M*. In a typical run a carefully weighed sample (approximately 0.0004 mole) of an ester was dissolved in about 85 ml. of the solvent mixture contained in a 100 ml. volumetric flask which was immersed in a thermostat held at the required temperature. To the solution was added 10 ml. of a solution of sodium hydroxide of known molarity (about 0.005 *M*) in the same solvent mixture and which had been stored in the thermostat. The mixture in the volumetric flask then was brought quickly to the mark with additional thermostated solvent, mixed by shaking, and returned to the bath. Aliquots (10 ml.) were withdrawn from time to time, quenched by the addition of a measured excess of a standardized acid, either hydrochloric or acetic, and the excess acid titrated with standard

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base. All standard solutions were referred to potassium acid phthalate as the primary standard. Since the standardizations were carried out at room temperature, and the alcoholic base for saponification was pipetted at 0°, a satisfactory correction for the increase in concentration of the solution due to contraction was made by multiplying M by $(0.806/0.785) = 1.0268$, the ratio of the densities of the solvent at the two temperatures.

The Linear Enthalpy-Entropy Effect

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A limitation to the Compensation law or the linear enthalpy-entropy relationship as previously proposed by us whereby membership in a family of closely similar structure was required in order for the law to hold has been explored by consideration of data on esterification, hydrolysis, ionization, free radical, displacement, and other reactions as well as on solvent effects and salt effects. The limitation has broadened the applicability of the law and emphasized the relative invariance of the slope of the linear equation and the additivity of the differences in the intercepts. The implications of the relationship are discussed briefly.

In a previous paper[1] a restriction to the commonly accepted method[2] of correlating enthalpy of activation with entropy of activation was suggested whereby the linear relationship, equations 1 and 2,

$$\Delta H^* = \Delta F_0^* + \beta_0 \Delta S^* \qquad (1)$$

$$\Delta F^* = \Delta F_0^* + (\beta_0 - T)\Delta S^* \qquad (2)$$

was applied only to families of closely related structures, each family having a characteristic value of ΔF_0^* (the intrinsic free energy of activation).[3] Furthermore, all the families had a common slope, $\beta_0 = 277°$, for a specific reaction, as illustrated by the parameters for the saponification of the ethyl esters of halogen-substituted phenoxyacetic acids. The conditions for membership in a given family were shown to be of a subtle nature by the formation of four families, the parent ester, the 2-halogen-substituted esters, the 4-halogen-substituted esters, and the 2,4-dihalogen-substituted esters. Here we wish to report that the relationship seems to be quite general, being applicable to cases which did not fit the more general method[4] of attempting to adjust a single regression line for all substituents relating the enthalpy to the entropy for a reaction. Also, the slope, β_0, does not appear to vary very much reaction to reaction and may well be a constant or a multiple of a constant such that equations 1 and 2 may be universally applicable.

Before proceeding with an examination of the data in the literature it should be made clear that the assumption has been made that such data fit the simple Arrhenius equation, $\ln k = \ln A - (E_a/RT)$, with both $\ln A$ and E_a being independent of temperature.[5,6] A modified form of the Arrhenius equation exists which contains the added term $(C/R)\ln T$ in which C is the heat capacity at constant pressure.[7] However, this added term can only be evaluated from the curvature of the $\log k$ *vs.* $(1/T)$ plot which is seldom observed if the range and number of temperatures used is small. With the Arrhenius parameters in hand, it is also assumed that $\Delta H = E_a - RT$ and that $\Delta S = 2.303\ R\ (\log A - \log k/h - \log T - 1/2.303)$. With these provisos, it is easily shown that if E_a is plotted against $\log A$, the slope of the family line is $2.303\ R\beta_0$. For the reverse plots, ΔS *vs.* ΔH and $\log A$ *vs.* E_a the resulting slopes are the reciprocals of β_0 and $2.303\ R\beta_0$.

Although many studies have been carried out on the effects of substituents on the rates and equilibria of reactions at a given temperature, not all investigators have studied the effect of temperature variation. A far from exhaustive search of the literature showed that many results were not suitable for examination for classification into families because the variation of structure of the substituents was too drastic. On the other hand, the data from the work of Hartman and collaborators[8] as well as that from Smith and Hurley[9] for the esterification

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[3] The intrinsic free energy of activation also may be regarded as a standard state, the specification for such a standard state being that ΔS^* be zero or that the intrinsic free energy of activation be equal to the intrinsic enthalpy of activation. Because the terminology is clumsy and because no loss of clarity will be caused, the adjectival phrase "of activation" and the asterisk * will be dropped in the subsequent usage in this paper. When equilibria are considered the context for the shift to the thermodynamic entities should be clear.

[4] The general linear enthalpy-entropy effect has been noted not only for rates of homogeneous and heterogeneous reactions but also in diffusion, viscosity, electron emission, equilibria of all types, conductivity, and solvent effects, and has been called the Compensation Law.[47]

[5] Recently a tendency to report $\ln A$ or $\log A$ as $\ln pZ$ or $\log pZ$ has occurred even though the latter is a function of T as shown by $\Delta\log pZ = 0.5\ \Delta\log T$ from the collision rate theory.[6]

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