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The Kinetics of the Aminolysis of Phenyl Phenoxyacetates with Benzylamine in Dioxane

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The rates of the reactions of *p*- and *m*-substituted phenyl phenoxyacetates with benzylamine in dioxane, thus forming *N*-benzylphenoxyacetamide and the corresponding phenols, were followed by the non-aqueous titration of benzylamine. The reaction satisfied the following general equation:

$$v = \{k_2'+k_3'[\text{Amine}]\}[\text{Amine}][\text{Ester}] + \{k_3''+k_4[\text{Amine}]\}[\text{Amine}][\text{Ester}]^2.$$

The reaction was a neucleophilic substitution, and the Hammett plots gave straight lines with positive ρ values. A marked enhancement in the conductivity of the reaction mixtures in 50% dioxane was observed, it increasing with the reaction time. A probable mechanism was presented which involves an ion pair of the quaternary ammonium salt type somewhat similar to that discussed in a previous paper (Y. Furuya, S. Goto, K. Itoho, I. Urasaki and A. Morita, *Tetrahedron*, **24**, 2367 (1968)).

The mechanism for the aminolysis of carboxylates has been studied by many investigators.[1a—e] In our previous paper, we suggested that a probable mechanism of the triethylenediamine-catalyzed aminolysis of phenyl *N*-phenylcarbamates with aniline in dioxane involves an ion pair of quarternary ammonium salt as an incipient intermediate. Generally, a specific catalyst is not required for usual aminolyses because the reactant amine itself acts as a catalyst.

In the present paper, it will be shown that the non-catalyzed aminolysis also involves an ion pair of the ammonium salt type.

Experimental

Materials. The phenyl phenoxyacetates were prepared by the reaction of phenoxyacetyl chloride and the corresponding phenols in the presence of a catalytic amount of tertiary amine in dry benzene, and then the reaction mixtures were recrystallized from aqueous methanol. Phenyl phenoxyacetate, mp 54—55°C (lit,[2] 56—57°C). *p*-Tolyl phenoxyacetate, mp 86—86.5°C. Found: C, 74.55; H, 6.03%. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83%. *p*-Chlorophenyl phenoxyacetate, mp 101.5—102°C. Found: C, 64.35; H, 4.46%. Calcd for $C_{14}H_{11}O_3Cl$: C, 64.01; H, 4.22%. *m*-Nitrophenyl phenoxyacetate, mp 97°C. Found: C, 61.28; H, 3.94; N, 5.21%. Calcd for $C_{14}H_{11}O_5N$: C, 61.54; H, 4.06; N, 5.13%. The *N*-benzylphenoxyacetamide used as an authentic sample was obtained by the reaction of phenoxyacetyl chloride with benzylamine; mp 82—83°C (lit,[3] 85—86°C). The benzylamine was dried over anhydrous sodium sulfate and then distilled; bp 183°C. The dioxane was purified as has been described in a previous report;[4] bp 102°C. The N/100 glacial acetic acid solution of perchloric acid was prepared with glacial acetic acid and 70% perchloric acid (special grade), and then standardized with a N/100 sym.-diphenylguanidin benzene-monochlorobenzene solution, using a tetrahydrofuran (THF) solution saturated with methyl violet as the indicator. The benzene was distilled from metal sodium; bp 80.1°C.

Reaction Product Criterion. The crystal obtained in an almost quantitative yield by the reaction of phenyl phenoxyacetate with benzylamine in dioxane did not show any melting-point depression when the product was mixed with the authentic sample of *N*-benzylphenoxyacetamide; mp and mmp 82—83°C.

The Reaction Products in 50% Aqueous Dioxane. A mixture of phenyl phenoxyacetate (0.02 mol) and benzylamine (0.02 mol) in 200 m*l* of 50% aqueous dioxane was stirred for a few hours at room temperature (*ca.* 30°C) and then allowed to stand overnight. The reaction mixture was diluted with a 200 m*l* of cold water and subsequently extracted several times with a total of 200 m*l* of ether. The ether layer was dried on anhydrous sodium sulfate overnight and then was washed with cold water. The oily matter obtained by removing the ether was recrystallized from aqueous methanol.

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[1] a) R. L. Betts and L. P. Hammett, *J. Amer. Chem. Soc.*, **59**, 1568 (1937); b) J. F. Bunnett and G. T. Davis, *ibid.*, **82**, 665 (1960); c) W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 675 (1960); d) T. C. Bruice and M. F. Mayahi, *ibid.*, **82**, 3067 (1960); e) M. F. Menger, *ibid.*, **88**, 3081 (1966), *etc.*

[2] P. S. Bataev and Z. G. Vorob'eva, *Med. Prom. SSSR*, **17**(5), 13(1963); *Chem. Abstr.*, **59**, 8652a (1963).

[3] S. Kushner, R. I. Cassell, J. Morton, II, and J. H. Williams, *J. Org. Chem.*, **16**, 1283 (1951).

[4] Y. Furuya, S. Goto, K. Itoho, I. Urasaki and A. Morita, *Tetrahedron*, **24**, 2367 (1968).

The crystal of *N*-benzylphenoxyacetamide was thus obtained; mp and mmp, 82°C; yield, 64.2%. The aqueous layer was acidified with aqueous hydrogen chloride together with the washings, and then extracted several times with a total of 250 m*l* of ether. The extract was dried on anhydrous sodium sulfate overnight. When the ether was then removed, an acidic crystalline matter, phenoxyacetic acid, was obtained; mp and mmp, 96°C; yield, 33.5%.

The Calibration Curve in the Chemical Analysis of Benzylamine. The calibration curve gave a straight line in solutions with benzylamine concentrations ranging from 1×10^{-2} to 3×10^{-1}M. It was, moreover, not influenced at all by the presence of ester, amide, and phenol.

A Typical Run for the Rate Measurement. A 7.5-m*l* portion of a 0.2M dioxane solution of benzylamine was poured into a solution of 7.5 m*l* of 0.2M phenyl phenoxyacetate in dioxane to start the reaction after both solutions had attained temperature equilibrium. Aliquots (each 1.0 m*l*) were pipetted out at appropriate time intervals, and each one was diluted with cold benzene (50 m*l*). The solution was then titrated by a N/100 perchloric acid - glacial acetic acid solution, using a solution saturated with methyl violet (0.5—1.0 m*l*) as the indicator. The values of the second-order rate constants, $k_{2\text{obs}}$, were calculated from the conversions thus obtained.

A Typical Procedure for the Conductivity Measurement. A 25-m*l* portion of a 50% aqueous dioxane solution of 1×10^{-2}M benzylamine aged at 30±0.2°C was added to a 25-m*l* portion of a 50% aqueous dioxane solution of 1×10^{-2}M phenyl phenoxyacetate; then the conductivity at 30±0.2°C was measured by means of a Yokogawa-Hewlett-Packard universal bridge 4255A (BV-Z-13C) at appropriate intervals of time.

Results and Discussion

Typical rate data of the aminolysis at 20°C are shown in Fig. 1. Here, *a*, *b*, and *x* are the initial concentrations of the amine and the ester and the consumed concentration of the amine at time *t* respectively. The kinetics follows the second-order equation. The plots of the apparent second-order rate constant *vs.* the concentration of the ester gave a straight line which does not pass through the point of origin, as is illustrated in Fig. 2. Therefore, the $k_{2\text{obs}}$ rate constant is given by the following equation:

$$k_{2\text{obs}} = k_2 + k_3[\text{Ester}] \tag{1}$$

The values of k_2 and k_3 varied with the concentration of benzylamine (Figs. 3 and 4). Hence, k_2 and k_3, the rate constants, should be expressed as follows:

$$k_2 = k_2' + k_3'[\text{Amine}] \tag{2}$$

$$k_3 = k_3'' + k_4[\text{Amine}] \tag{3}$$

The total kinetics is, therefore, given by the following equation:

$$\begin{aligned} v = {} & \{k_2' + k_3'[\text{Amine}]\}[\text{Amine}][\text{Ester}] \\ & + \{k_3''+k_4[\text{Amine}]\}[\text{Amine}][\text{Ester}]^2 \end{aligned} \tag{4}$$

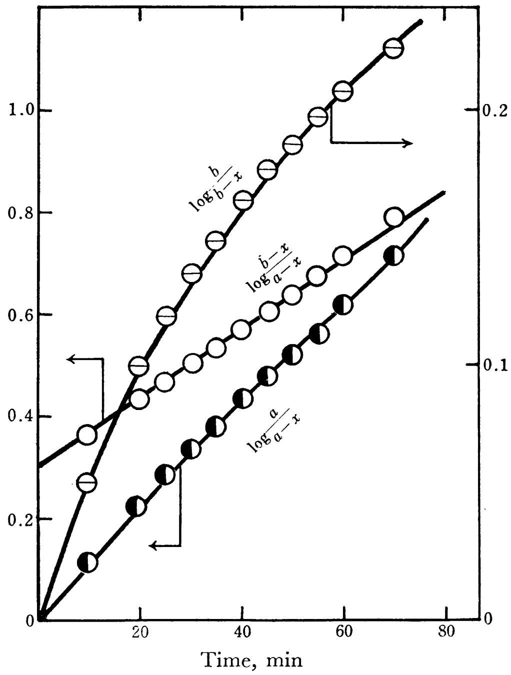


Fig. 1. Determination of reaction order of the aminolysis in dioxane at 20°C.
Concn. of phenyl phenoxyacetate: 0.20M
Concn. of benzylamine: 0.10M

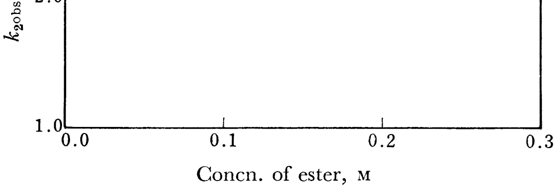


Fig. 2. The plots of $k_{2\text{obs}}$ *vs.* the concentration of the ester for the aminolysis in dioxane at 20°C.
Concn. of benzylamine: 0.10M

The values of k_2', k_3', k_3'', and k_4 are tabulated in Table 1.

The reaction was retarded by the introduction of an electron-releasing group into the phenyl group of the ester. Thus, the plots of the logarithm of k_2', k_3', k_3'', and k_4 *vs.* Hammett's σ gave straight lines with slopes of +1.13, +2.38, +2.42, and +2.45 respectively. The reaction course represented by the first term of Eq. (4) is considered to be as follows:

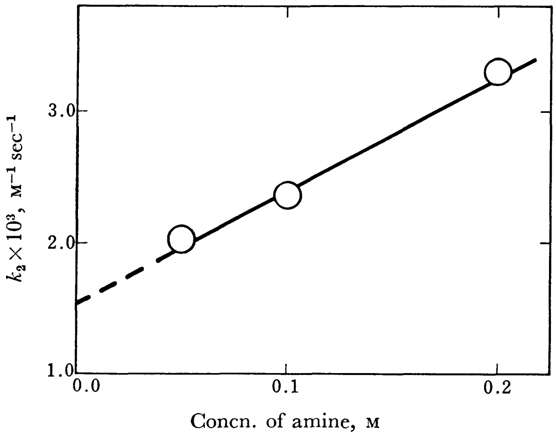


Fig. 3. The plots of k_2 *vs.* the concentration of the amine for the aminolysis in dioxane at 20°C. Concn. of phenyl phenoxyacetate: 0.05—0.25M

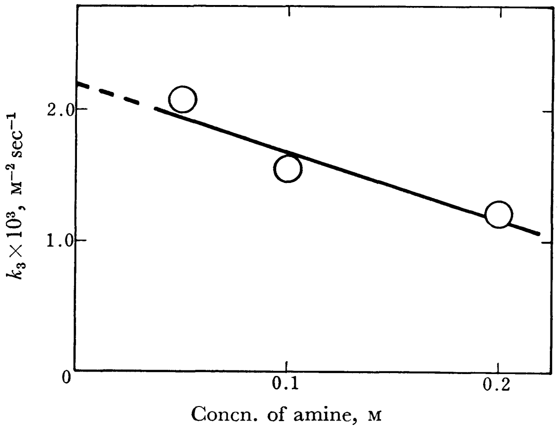


Fig. 4. The plots of k_3 *vs.* the concentration of the amine for the aminolysis in dioxane at 20°C. Concn. of phenyl phenoxyacetate: 0.05—0.25M

Table 1. The rate data for the aminolysis of phenyl phenoxyacetates with benzylamine in dioxane at 20°C
Initial concn. of the esters: 0.05—0.20 M
Initial concn. of benzylamine: 0.05—0.25 M

Esters	Rate constants			
	$k_2' \times 10^3$ M^{-1} sec^{-1}	$k_3' \times 10^3$ M^{-2} sec^{-1}	$k_3'' \times 10^3$ M^{-2} sec^{-1}	$k_4 \times 10^3$ M^{-3} sec^{-1}
p-Tolyl phenoxyacetate	0.95	6.29	0.61	6.38
Phenyl phenoxyacetate	1.53	8.55	2.20	−5.27
p-Chlorophenyl phenoxyacetate	2.65	67.0	5.70	−29.8
m-Nitrophenyl phenoxyacetate	9.65	430	91.5	−335

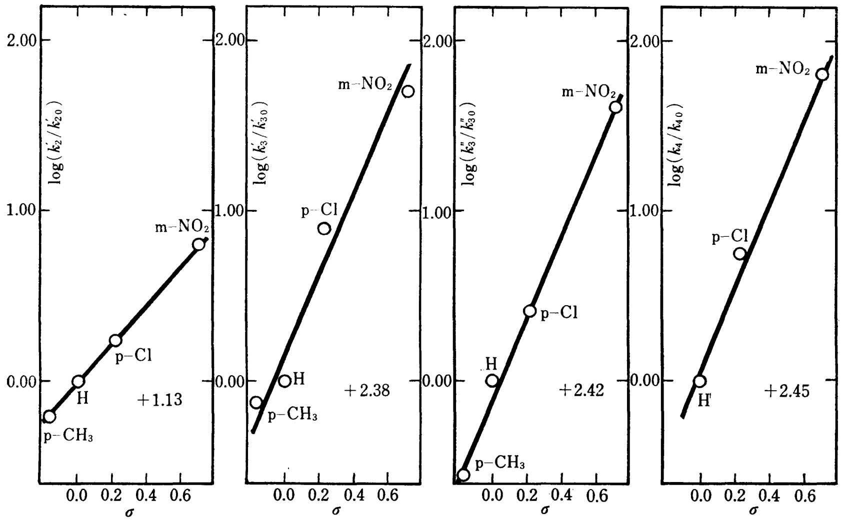
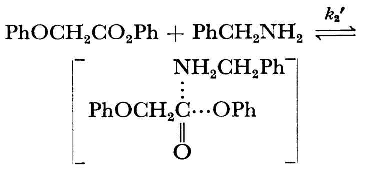


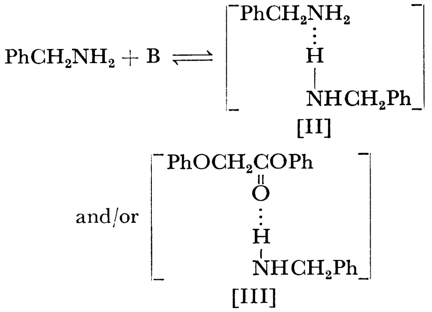
Fig. 5. Hammett's plots for k_2', k_3', k_3'' and k_4 rate constants of the aminolysis of the substituted esters at 20°C.
Initial concn. of phenyl phenoxyacetate: 0.025—0.25M
Initial concn. of benzylamine: 0.05—0.25M



$$\mathrm{PhOCH_2CO_2Ph + PhCH_2NH_2} \overset{k_2'}{\rightleftharpoons} \left[\begin{array}{c} \mathrm{NH_2CH_2Ph} \\ \vdots \\ \mathrm{PhOCH_2C\cdots OPh} \\ \| \\ \mathrm{O} \end{array}\right]$$

[I]

As the ρ values of the reaction steps expressed by the second, third, and fourth terms all have plus signs and are nearly equal to each other, the rates must be controlled by similar steps. It is apparent from the calculation of the reaction order in the rate equation, however, that the rates of the two courses expressed by the second and third terms are not controlled by Step (7), but by Steps (5) and (6) respectively.



$$\mathrm{PhCH_2NH_2 + B} \rightleftharpoons \left[\begin{array}{c} \mathrm{PhCH_2NH_2} \\ \vdots \\ \mathrm{H} \\ | \\ \mathrm{NHCH_2Ph} \end{array}\right] \text{ [II]}$$

$$\text{and/or } \left[\begin{array}{c} \mathrm{PhOCH_2COPh} \\ \| \\ \mathrm{O} \\ \vdots \\ \mathrm{H} \\ | \\ \mathrm{NHCH_2Ph} \end{array}\right] \text{ [III]}$$

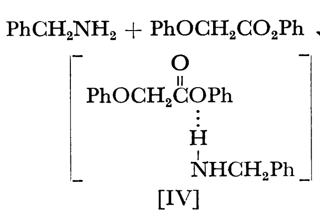
(B: Benzylamine or phenyl phenoxyacetate)

$$\mathrm{PhOCH_2CO_2Ph + II} \overset{k_3',\ -\mathrm{Amine}}{\rightleftharpoons} \mathrm{I} \qquad (5)$$

$$\mathrm{PhOCH_2CO_2Ph + III} \overset{k_3'',\ -\mathrm{Ester}}{\rightleftharpoons} \mathrm{I} \qquad (6)$$

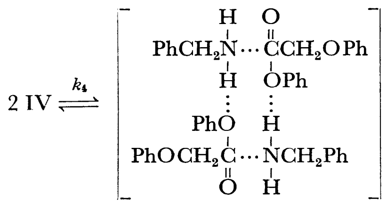
$$\mathrm{I} \longrightarrow \mathrm{Prod. + PhOH} \qquad (7)$$

As the reaction indicated by the fourth term is very small under these concentration conditions, it might be negligible in the reaction of the non-substituted ester. However, if we make bold to suggest a probable mechanism for the reaction expressed by the fourth term, it can be written as follows:



$$\mathrm{PhCH_2NH_2 + PhOCH_2CO_2Ph} \rightleftharpoons \left[\begin{array}{c} \mathrm{O} \\ \| \\ \mathrm{PhOCH_2COPh} \\ \vdots \\ \mathrm{H} \\ | \\ \mathrm{NHCH_2Ph} \end{array}\right] \qquad (8)$$

[IV]



$$2\,\mathrm{IV} \overset{k_4}{\rightleftharpoons} \left[\begin{array}{c} \mathrm{H\quad O} \\ |\quad \| \\ \mathrm{PhCH_2N\cdots CCH_2OPh} \\ |\quad | \\ \mathrm{H\quad OPh} \\ \vdots\quad \vdots \\ \mathrm{PhO\quad H} \\ |\quad | \\ \mathrm{PhOCH_2C\cdots NCH_2Ph} \\ \|\quad | \\ \mathrm{O\quad H} \end{array}\right] \qquad (9)$$

[V]

$$\mathrm{V} \longrightarrow \mathrm{Prod. + PhOH} \qquad (10)$$

$$\mathrm{V} \longrightarrow \mathrm{Ester + Amine} \qquad (11)$$

Considering the reaction order obtained by the calculation, the rate-determining step is probably Step (9). When the phenoxy group has an electron-releasing group, phenol may be easily able to leave the ring complex, V. On the other hand, each bond in the carbophenoxy group, especially the bond between the carbonyl C-atom and the phenoxy O-atom, may be strengthened by the resonance effect in the carbophenoxy group when an electron-attracting group is introduced into the phenoxy group. This may be the reason why the Hammett plot of the k_4 rate constant has a positive ρ value.

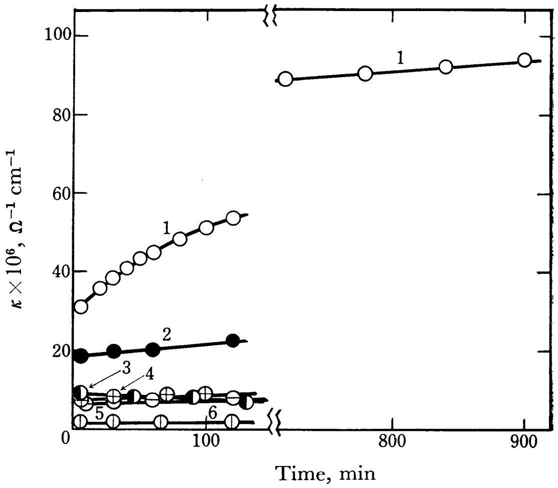


Fig. 6. Conductivity change with time for the each member and the couple of the aminolysis of phenyl phenoxyacetate with benzylamine in 50% aqueous dioxane at 30°C.
1, Concn. of the mixture of the ester and amine: each 5×10^{-3}M; 2, concn. of the mixture of the amine and phenol: each 5×10^{-3}M; 3, concn. of the mixture of the ester and amide: each 5×10^{-3}M; 4, concn. of the mixture of the amide and phenol: each 5×10^{-3}M; 5, concn. of the amine: 5×10^{-3}M; 6, concn. of the ester, amide and/or phenol: 5×10^{-3}M, respectively.

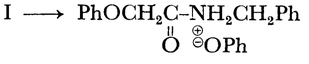
The conductivities of the [Ester+Amine], [Amine+PhOH] and [Amide+PhOH] couples are larger than the sums of the conductivities of the components, as is shown in Fig. 6 and Table 2. No initial large increase such as that in the conductivity of the [Ester+Amine] couple is observed in the conbinations of [Amine+PhOH] and [Amide+PhOH], as is shown in Fig. 6. The value of the conductivity on the heel of starting the actual reaction ($30\times10^{-6}\Omega^{-1}$cm^{-1}) is larger than the value of the sum of the ester and the amine ($10.4\times10^{-6}\Omega^{-1}$ cm^{-1}). It corresponds to the value in a 10% conversion of hydrolysis. Moreover, in the reaction in 50% aqueous dioxane at 30°C for 30 hr, the conversions of hydrolysis and aminolysis were 30 and 60% respectively. The conductivity of the model mixture, which has 30 and 60% conversions

TABLE 2. SPECIFIC CONDUCTIVITIES OF THE REACTANTS AND PRODUCTS IN 50% AQUEOUS DIOXANE AT 30 ± 0.2°C
Initial reaction concn. of each component: 5×10^{-3}M
Measurement concn.: same concentration described above

Component	Specific conductivity $10^{-6}\Omega^{-1}\mathrm{cm}^{-1}$	Couple of components	Specific[a] conductivity $10^{-6}\Omega^{-1}\mathrm{cm}^{-1}$
Ester	1.3	Ester+Amine	31.1 (10.4)[b]
Amine	9.1	Amine+Phenol	18.5 (10.6)
Amide	1.4	Amide+Phenol	7.6 (2.9)
Phenol	1.5	Amide+Ester	8.6 (2.7)

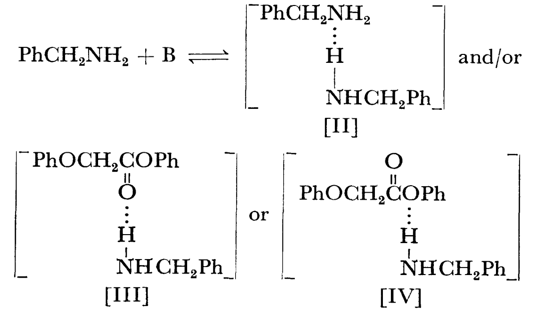
a) The values measured on the heel of mixing the components of each couple.
b) The values in parentheses are the sums of an actual value of each component constituting each couple.

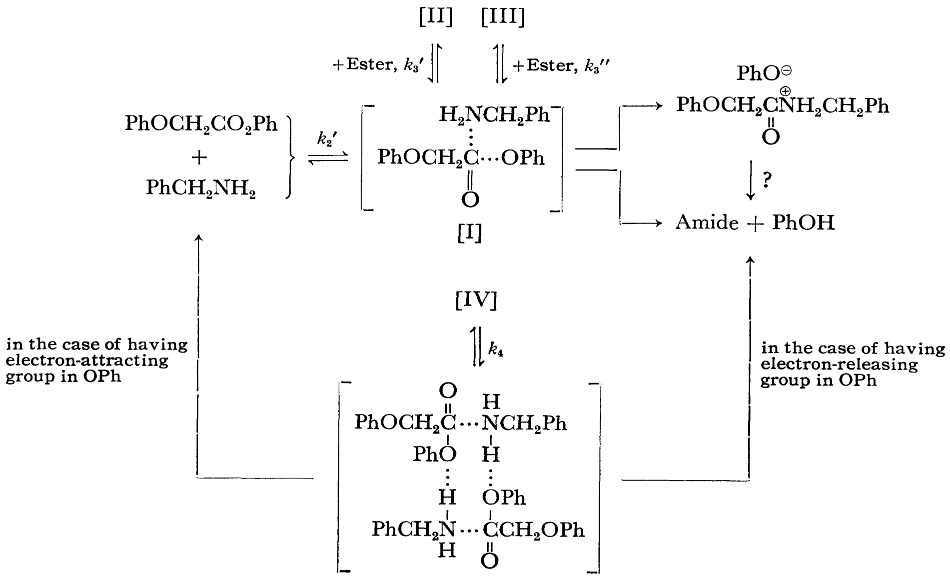
of hydrolysis and aminolysis respectively, was observed to be $69\times10^{-6}\Omega^{-1}\,\mathrm{cm}^{-1}$. This value is considerably smaller than the conductivity value ($94\times10^{-6}\Omega^{-1}\,\mathrm{cm}^{-1}$) obtained in the actual reaction at 30°C for 900 min. This suggests that another conductive matter is formed in addition to the formation of benzylammonium phenoxyacetate. It would be a quarternary ammonium salt like VI. Though the ion pair is perhaps formed, we can't decided that the salt is either an intermediate or a side reaction product. The amide formed by the reaction did not give benzylamine in either the presence or absence of phenol in dioxane at 70°C for 2 hr. From these findings, the following probable mechanism which involves I formed by the nucleophilic attack of the lone pair of the N-atom of amine on the carbonyl C-atom of the ester may be suggested:



$$\mathrm{I} \longrightarrow \underset{\overset{\|}{\mathrm{O}}}{\mathrm{PhOCH_2C}}\text{-}\overset{\oplus}{\mathrm{N}}\mathrm{H_2CH_2Ph}\;{}^{\ominus}\mathrm{OPh}$$

[VI]





(B: Benzylamine, Phenyl Phenoxyacetate)

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