Succinamic Acids. Part II.[1] Anhydrides as Intermediates in the Aminolysis of *N*-Alkylanilic Acids in Toluene

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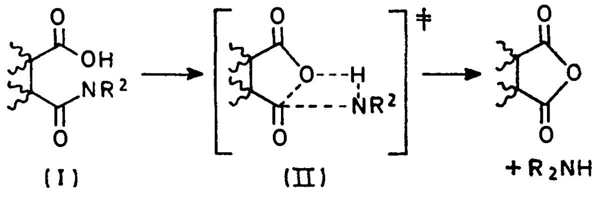
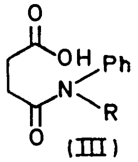
N-Alkylanilic acids are shown to undergo exchange with anilines in a reaction involving thermal dissociation of the acids to the corresponding anhydride and *N*-alkylaniline. The anhydride can be formed either by a unimolecular process or by a bimolecular, carboxylic acid-catalysed reaction.

THE ready formation of anhydrides from 1,2-dicarboxylic acids is well established. It has been postulated[2-4] that the hydrolysis of monoamides of these acids (I) also involves the formation of the anhydrides in the rate-limiting step, the main evidence for this being obtained from ^{18}O labelling experiments.[2] The reaction proceeds *via* the un-ionized acid, and the transition state suggested for the thermal dissociation of phthalamic acid involves a cyclic process in which the carboxy-group acts simultaneously as a nucleophile and as a general acid [*e.g.*, (II)]. Provided that the various bond-making and -breaking processes occur to the same extent, it would be expected that the reaction rate would be insensitive to solvent effects. Some support for this view arises from the work of Porai-Koshits,[5] who has reported that aniline displaces *N*-methylaniline from *N*-methylphthalanilic acid in ether solution during a period of weeks.



(1)

The present work shows that *N*-alkylsuccinanilic (III) and *N*-alkylphthalanilic (IV) acids undergo exchange reactions with anilines, *via* thermal dissociation into their anhydrides.



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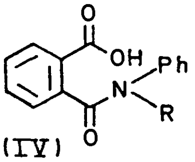

(IV)

EXPERIMENTAL

Materials.—Preparations of the succinanilic acids used have been described.[1] *N*-Ethylphthalanilic acid was prepared *in situ* by the reaction of equimolar quantities of *N*-ethylaniline and phthalic anhydride in toluene solution overnight at room temperature.

Exchange Reactions.—Solutions of *N*-alkylsuccinanilic acids (1 g) in benzene (20 ml) were heated for 6—48 h with aniline (1 g). On cooling, succinanilic acid, m.p. 144—147 °C (lit.,[6] 146 °C) precipitated. The yields obtained from *N*-methylsuccinanilic acid, *N*-ethylsuccinanilic acid, and *N*-isopropylsuccinanilic acid were 90, 92, and 85% respectively. A solution of *N*-methylphthalanilic acid (1·0 g) treated similarly gave 0·99 g of a product having m.p. 146—150 °C (when heated quickly) or 204—210° (when heated slowly). It was concluded that the original product was phthalanilic acid (m.p. 167 °C [7]) contaminated by *N*-phenylphthalimide (m.p. 207 °C [7]), derived from the acid by further dehydration.

Kinetic Procedures.—Solutions of (*a*) the aniline in toluene, and (*b*) the anilic acid and n-undecane in toluene, at the appropriate concentrations, were equilibrated at the reaction temperature. The solutions were mixed and aliquot portions were withdrawn at intervals for analysis by g.l.c. The column was 2% XF1105 on Chrom G, operating at 78 °C. Concentrations of the anilines were determined by measuring the relative areas of the aniline and n-undecane peaks, and using the determined relative response factors to obtain aniline concentrations. The initial increases in the concentration of displaced aniline were used to obtain the initial rate of formation of the aniline ($d[A_D]/dt = \nu_0$).

The formation of succinic anhydride from *N*-methylsuccinanilic acid was followed by measurements of the anhydride absorption at 1782 cm^{-1} on a Perkin-Elmer model 157 i.r. spectrometer. In order to minimize interference from overtones mesitylene was used as a solvent.

Mesitylene solutions of the acid in thin-walled glass flasks were quickly preheated to 80 °C and transferred to a 1 mm electrically heated sodium chloride cell maintained at 80 °C. The increase in absorbance at 1782 cm^{-1} was followed with time, and used to calculate the initial rate of anhydride formation, ν_a. The measured extinction coefficient of the anhydride was 46·5 l mol^{-1} for the nominal cell length of 1 mm.

RESULTS AND DISCUSSIONS

The exchange reaction in which aniline displaces *N*-methylaniline from *N*-methylphthalanilic acid in ether at room temperature was reported by Porai-Koshits[5] in 1939. The present work supports this unexpected observation and suggests that the ready aminolysis of monoamides of 1,2-dicarboxylic acids is a general reaction. Thus the simple treatment of a series of *N*-alkylsuccinanilic acids (III) with aniline in

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[1] Part I, M. J. Gregory and M. J. Loadman, *J. Chem. Soc.* (*B*), 1971, 1862.

[2] M. L. Bender, Y. L. Chow, and F. Chloupek, *J. Amer. Chem. Soc.*, 1958, **80**, 5380.

[3] H. Morawetz and J. Schafer, *J. Amer. Chem. Soc.*, 1962, **84**, 3783.

[4] T. Higuchi, L. Eberson, and A. K. Herd, *J. Amer. Chem. Soc.*, 1966, **88**, 3805.

[5] B. A. Porai-Koshits, *Zhur. obshchei Khim.*, 1939, **7**, 604.

[6] W. H. Warren and R. A. Briggs, *Ber.*, 1931, **64**, 29.

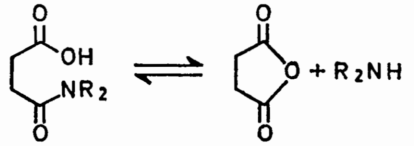
[7] M. L. Sherrill, F. L. Schaeffer, and E. P. Schoyer, *J. Amer. Chem. Soc.*, 1928, **50**, 474.

refluxing benzene overnight gave high yields of succinanilic acid. Under similar conditions a benzene solution containing equimolar amounts of *N*-methylacetanilide, acetic acid, and aniline showed no reaction after 24 h.

The reaction is therefore not simply an acid-catalysed exchange, but must presumably involve neighbouring-group participation by the carboxy-group. Such participation has been demonstrated to occur in the hydrolyses of many phthalic and succinic acid half-esters[8] and -amides, which have been postulated to form the acid anhydride as an intermediate.

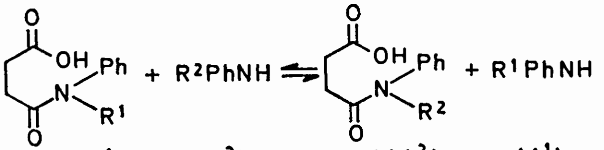
When solutions of *N*-methylsuccinanilic acid in mesitylene were heated to 80 °C, two bands at 5·34 and 5·58 μm slowly appeared in the i.r. spectrum. These two bands corresponded exactly to the anhydride stretching frequencies of succinic anhydride, suggesting that succinanilic acids undergo thermal dissociation to succinic anhydride and the corresponding aniline. This dissociation (2) provides a possible mechanism for the exchange reactions discussed.

To investigate this possibility kinetic studies of the exchange reactions and the dissociation of *N*-methylsuccinanilic acid have been carried out.



(2)

Because of the low solubility of succinanilic acid (III; R = H) in toluene it was necessary to use another secondary amine as the nucleophile. Although this prevented precipitation of the product, it introduced the added complication of an equilibrium constant for the reaction (3) of close to unity. As will be shown later, the use of the more powerfully nucleophilic secondary aliphatic amines to shift the equilibrium completely to the right, was not practicable. Therefore, the initial rates of *N*-alkylaniline formation (ν_0) were used to determine rate equations.



(3)

(AA¹) (A²) (AA²) (A¹)

It was found that in all cases the values of ν_0 obtained by use of a wide range of initial aniline (A²) concentrations were essentially constant (see, *e.g.*, Table 1). The reaction is therefore of zeroth order in the concentration of the aniline acting as a nucleophile. This is consistent with the suggested route to exchange involving the rate-limiting formation of the anhydride as an intermediate, and taken with the spectral data provides good evidence for this mechanism.

The zeroth-order dependence of the rate on amine concentration is only obeyed when the weakly basic anilines are used. When the succinanilic acids were heated with an excess of *NN*-dibutylamine in toluene no aniline could be detected in the solution. However, if a deficiency of amine is used, the aniline is liberated (Table 2). This behaviour suggests that the diethylamine is forming ion-pairs with the succinanilic acid

$$R_2NH + RCO_2H \rightleftharpoons [R_2\overset{+}{N}H_2 \cdots \overset{-}{O}_2CR] \quad (5)$$

such as in (5),[9] and that these ion pairs are inactive in forming the anhydride.

TABLE 1

Variation in the initial rate (ν_0) of *N*-ethylaniline formation from *N*-ethylsuccinanilic acid (ES) with *N*-methylaniline (MA) concentration at 80 °C in toluene solution

10^2[ES]/M	8·65	8·65	8·65	4·45	4·45
10^2[MA]/M	47·9	9·95	2·40	24·0	4·80
$10^6\nu_0$/mol l^{-1} s^{-1}	7·0	7·0	7·5	3·2	3·1

TABLE 2

Initial rates (ν_0) of displacement of *N*-ethylaniline from *N*-ethylsuccinanilic acid (ES) in the presence of diethylamine at 80 °C in toluene

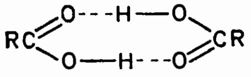
[ES] = 0·0258M

10^3 [Diethylamine]/M	0·0 *	4·9	9·8	98
$10^6\nu_0$/mol l^{-1} s^{-1}	1·8	1·8	1·5	0

* 0·122M-*N*-methylaniline.

These results indicate the need for acid catalysis of anhydride formation at some stage. To determine whether the carboxy-group of the succinanilic acids can act as both an intramolecular general-acid catalyst as well as a nucleophile it is necessary to determine the order of the reaction in the anilic acid.

It is well established that carboxylic acids in non-polar aprotic solvents do not exist as the free acids only, but form hydrogen-bonded associates. These associations complicate the kinetic rate equations considerably. The most common form of association of carboxylic acids is the formation of a cyclic dimer (V), and similar dimers appear to be the predominant species present in moderately concentrated solutions of succinanilic acids in non-polar solvents.[1] Consider first the case where the succinanilic acid forms an



(V)

inactive dimer and the monomer reacts in a unimolecular reaction to give the anhydride. The reaction can be written as (6) where D represents an inactive dimer

$$D \underset{K_{A(M)}}{\rightleftharpoons} M \xrightarrow{k_1} \text{products} \quad (6)$$

and M the monomeric succinanilic acid. Then we

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[8] T. C. Bruice and S. Benkovic, 'Bio-organic Mechanisms,' W. A. Benjamin Inc., New York, 1966, vol. 1, p. 173.

[9] D. F. DeTar and R. W. Novak, *J. Amer. Chem. Soc.*, 1970, **92**, 1361.

obtain equation (7). As $K_A = [D]/[M]^2$, we can obtain equation (8) and thence (9) where $[A_T]$ is the

$$-\mathrm{d}[AA']/\mathrm{d}t = -\mathrm{d}[M]/\mathrm{d}t = k_1[M] \tag{7}$$

$$[M] = \{(8K_A[A_T] + 1)^{\frac{1}{2}} - 1\}/4K_A \tag{8}$$

$$\left(\frac{-\mathrm{d}[M]}{\mathrm{d}t}\right)_{t \to 0} = \nu_0 = k_1\{(8K_A[A_T] + 1)^{\frac{1}{2}} - 1\}/4K_A \tag{9}$$

total concentration of acid species. In the event that $(8K_A[A_T]^{\frac{1}{2}}) \gg 1$, then we obtain equation (10) and a

$$\nu_0 = k_1[A_T]^{\frac{1}{2}}/(2K_A)^{\frac{1}{2}} \tag{10}$$

plot of ν_0 against $[A_T]^{\frac{1}{2}}$ should be linear with slope $k_1/(2K_A)^{\frac{1}{2}}$.

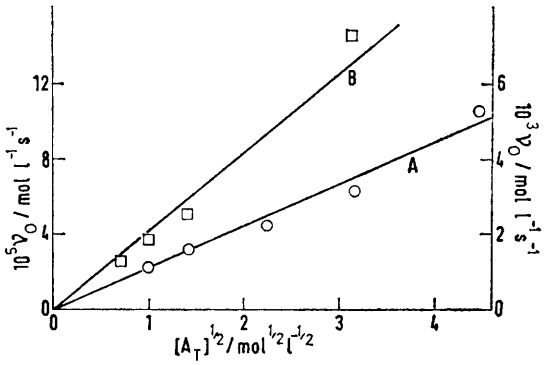
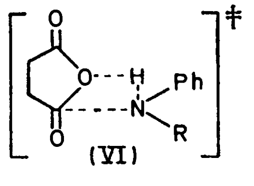


FIGURE 1 Variation in ν_0 with $[A_T]^{\frac{1}{2}}$ for exchange reactions of *N*-isopropylsuccinanilic acid (A, left-hand ordinate) and *N*-ethylphthalanilic acid (B, right hand ordinate), in toluene; A, [*N*-methylaniline] = 1·0M, 80 °C; B, [*N*-methylaniline] = 0·1M, 40 °C

It has been found that equation (10) is obeyed for the liberation of anilines for *N*-isopropylsuccinanilic acid (III; R = $\mathrm{Pr^i}$) and from *N*-ethylphthalanilic acid (IV; R = Et) (see Figure 1). Thus these two compounds form the anhydride *via* the unimolecular dissociation of the monomeric acid, the acid dimers being inactive.

The transition states (VI) for the unimolecular dissociation of these two acids are presumably similar to that suggested by Bender for the hydrolysis of phthalamic acid, in which the carboxy-group acts both as a nucleophile to the amide carbonyl functions and as an intramolecular general acid in protonating the



(VI)

amide nitrogen atom. The formation of anhydrides by such a route supports Bender's claim that hydrolysis of phthalamic acid occurs *via* the anhydride insofar as it shows that such a route is possible. The fact that the reaction occurs so readily even in toluene solution shows the transition state to be essentially non-polar, and so little increase in rate would be expected on carrying out the reaction in water. In this respect it is of interest to compare the rate data for *N*-isopropylsuccinanilic acid in toluene with that of Higuchi *et al.*[4] on the aqueous hydrolysis of succinanilic acid. At 60 °C the apparent first-order rate constant for aniline formation from succinanilic acid is *ca.* 20 times higher than that for the formation of isopropylaniline from *N*-isopropylsuccinanilic acid in 0·1M solution. The apparent activation energy for the latter process has been found to be 96 kJ mol^{-1} compared with 84 kJ mol^{-1}. In view of the complications caused by hydrogen bonding in the case of *N*-isopropylsuccinanilic acid in toluene these values are in fairly good agreement, supporting the lack of a large solvent effect for these reactions.

In contrast to *N*-isopropylsuccinanilic acid and *N*-ethylphthalanilic acid the formation of anilines from *N*-methyl- and *N*-ethyl-succinanilic acids is not a unimolecular process. For these compounds, the value of $\nu_0/[A_T]$ increased rapidly with $[A_T]$ at low concentrations, but reached an essentially constant value at higher concentrations (Figure 2). The constant value of $\nu_0/[A_T]$ at high concentrations shows the reaction to be apparently of the first order in the total acid concentration. This type of behaviour would be expected to occur if the acid were completely converted into a dimer in this region, and the dimer were the reactive species [equation (11)]. For such a reaction scheme the rate of reaction would be given by equation (12)

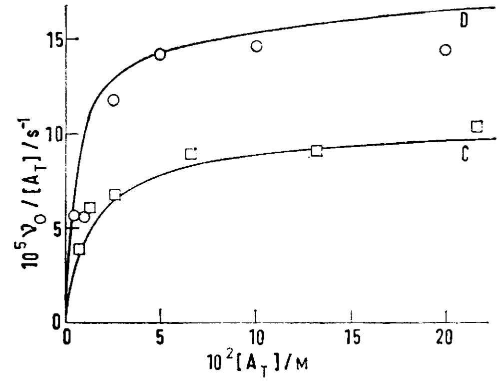


FIGURE 2 Variation in $\nu_0/[A_T]$ with *N*-ethyl- (C) and *N*-methyl- (D) succinanilic acids in toluene at 80 °C; [*N*-methylaniline] or [*N*-ethylaniline] = 0·1M. Curve C was calculated from equation (13), with K_A = 50 l mol^{-1} and k_D = 1·2 × 10^{-4} s^{-1}, and curve D was calculated with K_A = 75 l mol^{-1} and k_D = 2·0 × 10^{-4} s^{-1}

$$\mathrm{M} \underset{K_{A(M)}}{\rightleftharpoons} \mathrm{D} \xrightarrow{k_D} \text{products} \tag{11}$$

and (13).

$$\nu_0 = k_D[D] = \tfrac{1}{2}k_D([A_T] - [M]) = \tfrac{1}{2}k_D\left([A_T] - \frac{(8K_A[A_T] + 1)^{\frac{1}{2}} - 1}{4K_A}\right) \tag{12}$$

$$\nu_0/[A_T] = \tfrac{1}{2}k_D\left(1 - \frac{(8K_A[A_T] + 1)^{\frac{1}{2}} - 1}{4K_A[A_T]}\right) \tag{13}$$

It will be seen that if $[A_T]$ is very large $\nu_0/[A_T] \approx \frac{1}{2}k_D$ and as $[A_T]$ approaches zero $\nu_0/[A_T] = K_A k_D[A_T]$. By choosing appropriate values of K_A and k_D the experimental values of $\nu_0/[A_T]$ can be adequately expressed by equation (13) (Figure 2). The values of K_A used to obtain the best fit to equation (13) were 75 and 50 l mol^{-1} for *N*-methyl- and *N*-ethyl-succinanilic acids respectively. These are close to the values extrapolated from hydrogen-bonding studies on the acids in carbon tetrachloride ($K_A = 135$ and 110 l mol^{-1} respectively [1]), if allowances are made for the change of solvent. Thus, in addition to unimolecular dissociation of the monomeric acid there appears to be a mechanism for the dissociation of succinanilic acids into anhydride and aniline which involves reaction of the acid dimer. Alternatively, as the dimer concentration is proportional to the square of the concentation of monomeric acid, the equation can also be of the form (14).

$$\nu_0 = k_2[M]^2 \qquad (14)$$

This unexpected dependence of the rate of reaction on the dimeric rather than the monomeric acid concentration has been confirmed by direct measurement of the initial rates of formation of succinic anhydride from *N*-methylsuccinanilic acid in mesitylene solution at 80 °C (Table 3). It can be seen that the values of $\nu_a/[A_T]$ increase with $[A_T]$ in a manner which is very similar to the variation of $\nu_0/[A_T]$ found for the amine exchange. Further, the values of $\nu_a/[A_T]$ and $\nu_0/[A_T]$ are in fairly close agreement, allowing for the change of solvent.

These close similarities suggest strongly that succinic anhydride is an intermediate in the exchange reaction, and confirm that the dissociation is catalysed by a second molecule of the anilic acid. That this catalysis was effective for simple carboxylic acids was shown by studying the effect of added acetic acid on the exchange rates (Table 4). The addition of excess of acetic acid approximately doubles the rate of exchange, as would be expected if succinanilic acid dimers were converted into 1 : 1 succinanilic acid–acetic acid associates. It therefore seems likely that the rate equation involving the succinanilic acid dimer concentration reflects catalysis of the dissociation of one acid molecule by another molecule of the same acid.

TABLE 3

Variation in the rate of formation of succinic anhydride from *N*-methylsuccinanilic acid (MS) with concenttation of the acid at 80 °C in mesitylene

10^3[MS]/M	2·48	4·65	10·8	15·2
$10^7\nu_a$/mol l^{-1} s^{-1}	1·8	5·4	17	27
$10^5\nu_a/[MS]_0$ s^{-1}	7·2	12	16	18

TABLE 4

Variation in the rate (ν_0) of displacement of *N*-ethylaniline from *N*-ethylsuccinanilic acid [ES] by *N*-methylaniline at 80 °C in toluene in the presence of acetic acid

[ES] = 0·05M; [*N*-methylaniline] = 0·09M

[HOAc]/M	0·0	0·05	0·10	0·15
$10^6\nu_0$/mol l^{-1} s^{-1}	4·0	6·7	7·8	7·4

As a second-order reaction involving two monomeric acid molecules is likely to involve initially a hydrogen-bonded dimer, it seems probable that the reaction proceeds either *via* the major component of the dimeric species, or *via* a dimer which forms only a small fraction of the hydrogen-bonded associates. The latter case can be represented by (15), and if $K_1 \ll K_A$ the rate

$$M \underset{K_{A(M)}}{\rightleftharpoons} D_1 \underset{K_1}{\rightleftharpoons} D_2 \xrightarrow{k_D} \text{products} \qquad (15)$$

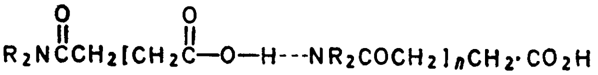
equation for the reaction would be (16) where K_A is again the association constant for the monomer forming the major dimer.

$$\nu_0/[A_T] = \tfrac{1}{2}k_D K_1\left(1 - \frac{8K_A[A_T] + 1)^{\frac{1}{2}} - 1}{4K_A[A_T]}\right) \qquad (16)$$

It is unlikely that the complexing of both the acidic site and the nucleophilic oxygen atom into a cyclic dimer (V) would enhance the rate of anhydride formation, and thus it is more likely that the reaction proceeds *via* an energetically less favourable dimer.

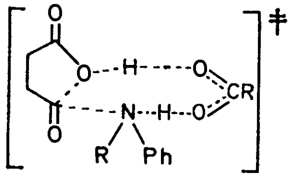
Succinamic acids are known [1,10] to form dimers and polymers in which the amide function of one acid molecule is hydrogen-bonded to the carboxy-group of another [*e.g.*, (VII)].

It is thought that such associates could be precursors to a cyclic transition state (VIII) in which the free carboxy-end-group can act as a nucleophile towards the bonded amide group. Such a mechanism would have the advantage of not involving a great deal of charge separation in the transition-state, and seems to be the most reasonable rationalization of the kinetic rate law.



$R_2N\overset{O}{\overset{\|}{C}}CH_2[CH_2\overset{O}{\overset{\|}{C}}{-}O{-}H{\cdots}NR_2COCH_2]_nCH_2{\cdot}CO_2H$

(VII)



(VIII)

The changeover from a unimolecular to a bimolecular mechanism on going from *N*-isopropyl- to *N*-ethyl-succinanilic acid is unlikely to be due to purely electronic effects, but molecular models of the likely transition states involved in the reactions show that steric interactions could be responsible for the mechanistic change. It appears that in the transition state for the bimolecular reaction there is considerable steric hindrance to protonation of the amide nitrogen by an external

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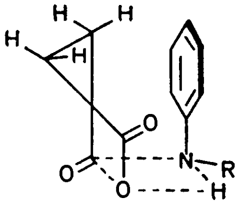
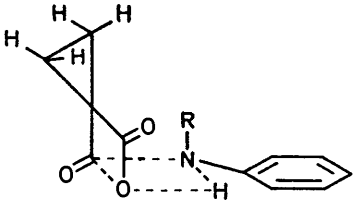
[10] N. S. Antonenko, *Zhur. obshchei Khim.*, 1965, **35**, 425.

carboxylic acid in the case of the *N*-isopropylsuccinanilic acid, but not for the *N*-methyl- or *N*-ethyl-compounds. This would slow down the bimolecular reaction of the former.

Two possible transition states (Xa and Xb) can be constructed for the unimolecular reaction. On purely steric grounds the transition state (Xa) is more favourable, but this requires the phenyl group to be out of conjugation with the amide nitrogen atom. *N*-Isopropylsuccinanilic acid can presumably achieve this state more easily than the *N*-methyl derivative as there is initially little conjugation of the phenyl group with nitrogen in the former compound. The effect of this would be to lower the free energy of activation for reaction of the former by the unimolecular route.



(Xa)



(Xb)

The net effect of the two types of steric effect described above would be to increase the rate of the unimolecular reaction and decrease the rate of the bimolecular reaction for succinanilic acids containing a bulky *N*-alkyl group. Where these steric interactions are sufficiently large a change of mechanism may even occur. For phthalanilic acids, interactions between the phenyl ring and the *N*-substituents are much smaller for the unimolecular reaction, and the *N*-phenyl group is not forced out of conjugation in the transition sate. This could account for *N*-ethylphthalanilic acid dissociating *via* a unimolecular process.

In summary then, the evidence above is most readily rationalized in terms of a concerted reaction involving simultaneous C–O bond formation and C–N bond cleavage. However, it is not possible to eliminate a process in which proton transfer from carboxy to amide nitrogen occurs in a prior equilibrium step. On the grounds that the anilic acid is detectably dissociated at the temperatures used, if a zwitterion were involved one might expect the transition state to be fairly polar, which is not the case. It seems therefore that the reaction is probably, but not indisputably, concerted.

I thank the Board of the NRPRA for permission to publish these results and Mr. M. J. R. Loadman for assistance with spectroscopic measurements.

[1/1254 *Received, 22nd July,* 1971]