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(38) Rate constants are measured from Figure 1 of ref 8.
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(49) Optical rotations were taken with a Perkin-Elmer Model 141 spectropolarimeter, using a jacketed cell, $l = 1$ dm.
(50) E. F. J. Duynstee and E. Grunwald, *J. Amer. Chem. Soc.*, **81**, 4540 (1959).
(51) This was the best of several analyses. Ir ($CHCl_3$) demonstrated the absence of R_3NH^+ stretching at ~3.8 μ.
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The Question of Amide Group Participation in Carbamate Hydrolysis

A. F. Hegarty,* L. N. Frost, and J. H. Coy

Chemistry Department, University College, Cork, Ireland

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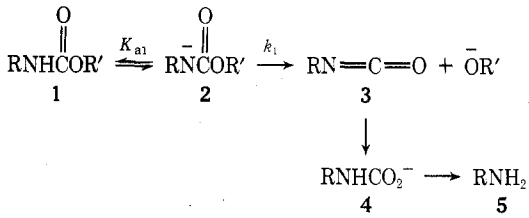
Phenyl *N*-(*o*-carbamoylphenyl)carbamate is cyclized to 2,4(1*H*,3*H*)-quinazolinedione in the presence of basic catalysis. A mechanism suggested involving rate-determining E1cB type elimination of phenoxide ion followed by trapping of the isocyanate intermediate by the amide group is consistent with data for model compounds. Phenyl *N*-methyl-*N*-(*o*-carbamoylphenyl)carbamate also cyclizes, but at a much slower rate (since the elimination–addition pathway is blocked); in this case the amide anion participates in the expulsion of phenoxide ion. When the amide group is attached to the leaving phenoxide ion as in salicylanilide carbamate, large rate enhancements are observed in hydroxide-catalyzed hydrolysis, but these may be explained in terms of the electronic effect of the substituent, rather than by participation. No evidence was found for appreciable carbamate group tautomerism.

Although simple carbamates, such as urethanes (**1**, R^1 = Et) are hydrolyzed only with difficulty even in highly alkaline solution,[1] carbamates with good leaving groups (such as phenyl carbamates, **1**, R^1 = Ph) may undergo rapid base-catalyzed cleavage. This has been interpreted in terms of the existence of a facile elimination–addition pathway for hydrolysis with the intermediate formation of the isocyanate **3** (Scheme I).[2,3] The isocyanate **3** has been shown to lie on the reaction pathway, since it can be trapped by both internal and external nucleophiles;[4] the addition of amine nucleophiles was shown to result in appreciable urea formation (by reaction of **3** with the amine after the rate-determining step) without changing the rate of disappearance of the starting carbamate **1**.

The elimination–addition pathway is so attractive that some nucleophilic groups, even when approximated to the reactive group (for example, **1**, R = *o*-$NH_2C_6H_4$), preferentially react *via* this mechanism, rather than directly attacking the carbamate center. In contrast, the ionized carboxy (**1**, R = *o*-carboxyphenyl)[5] and hydroxy (**1**, R = *o*-hydroxyphenyl)[6] groups have been shown to form cyclic products (isatoic anhydride and benzoxazinone, respectively) by direct nucleophilic attack on the carbamate. Because of the duality of behavior shown by these diverse

Scheme I



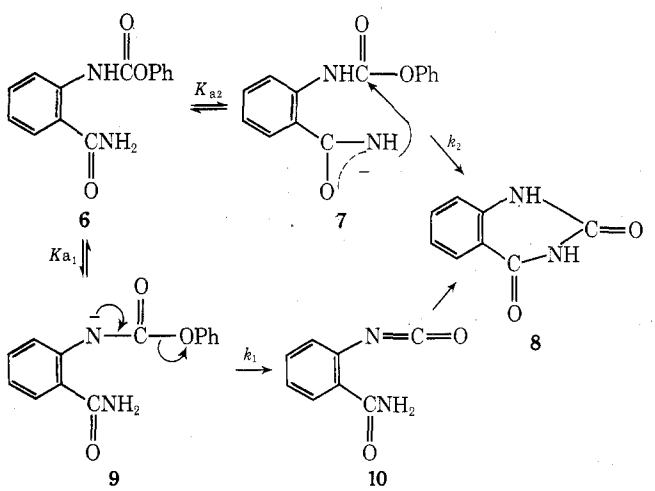
nucleophiles it is to be expected that certain groups will be borderline in this respect, participating in some instances in the rate-determining step, while in other cases merely trapping the isocyanate intermediate. We present evidence that the amide group acts in this way and show that the hydrolysis of salicylanilide carbamates may proceed through carbamate hydrolysis, contrary to a recent report.[7]

Results and Discussion

When phenyl *N*-(*o*-carbamoylphenyl)carbamate (**6**) is treated in dioxane–water at pH 9, smooth cyclization takes place and the quinazolinedione **8** may be isolated in near-quantitative yield. The cyclization is base catalyzed (see Table I), a plot of log k_{obsd} *vs.* pH being linear with unit slope. At lower pH, no pH-independent (or neutral) reaction becomes apparent, while, at the highest pH values amenable to study (where the cyclization was most rapid), the cyclization rate was still proportional to [HO^-].

Two possible mechanisms of cyclization consistent with this kinetic behavior are outlined in Scheme II. The first involves the amide anion **7** as the nucleophilic group, displacing phenoxide ion to give the quinazolinedione **8** directly. Alternatively the carbamate could hydrolyze *via* the normal elimination–addition pathway (**6** → **9** → **10**), the quinazolinedione being formed after the rate-determining step. Since both the *N*-phenyl carbamate[4] and benzamide groups[8] are only weakly acidic (with pK_a values ≥ 14), the rate of cyclization (which is dependent on the concentration of the active species **7** or **9**) by the two pathways would be proportional to [HO^-] in the pH range studied (as observed).

Scheme II



A distinction between the possible cyclization pathways can be made by comparing the reactivity of substrates in which participation by the *o*-carbamoyl group is not possible. Data for phenyl *N*-phenylcarbamate (**1**, R = R^1 = Ph), which hydrolyzes according to the mechanism of Scheme I, are summarized in Table II. The observed rate of hydrolysis of this carbamate is also specific base catalyzed, and the rate constants obtained are expressed in terms of the composite constant k_1K_{a1} (or k_2K_{a2}), which is obtained by dividing the observed rate constant at any pH by the hydrogen ion concentration. By comparing the values for **6** with the unsubstituted material (**1**, R = R^1 = Ph) it is clear that **6** cyclizes 12.6-fold more rapidly than **1** (R = R^1 = Ph) hydrolyzes at each pH.

Table I
Observed First-Order Rate Constants for the Cyclization of Phenyl *N*-(*o*-Carbamoylphenyl)carbamate to 2,4(1*H*,3*H*)-Quinazolinedione[a]

pH	9.0	9.5	9.8	10.1	10.5
10^2 k_{obsd}, sec^{-1}	0.23	0.63	1.09	3.75	6.85

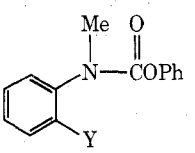
[a] In 1:4 (v/v) dioxane–water at 25° (μ = 1.0, KCl).

Table II
Summary of Rates of Hydrolysis and of Cyclization of Carbamates

Carbamate	k_1K_{a1} (or k_2K_{a2}), l. mol^{-1} sec^{-1}	Carbamate	k_1K_{a1} (or k_2K_{a2}), l. mol^{-1} sec^{-1}
1 (R = R′ = Ph)	1.9×10^{-13}	**12d**	2.0×10^{-17}
6	2.4×10^{-12}	**13**	7.9×10^{-13}
11a	7.9×10^{-14}	**14a**	7.9×10^{-12}
11b	1.7×10^{-19}	**14b**	1.1×10^{-12}
12a	2.0×10^{-11}	**14c**	1.3×10^{-9}
12b	7.9×10^{-15}	**14d**	7.9×10^{-10}
12c	4.0×10^{-14}		

A rate enhancement of this magnitude does not necessarily indicate that the amide group is acting as a nucleophile in the rate-determining step. It is expected that the electron-withdrawing amide group would enhance the reactivity of the carbamate (ρ is +0.64 for the effect of the variation of the N-aryl substituent on k_1K_{a1}).[4] Moreover, carbamates with substituents in the ortho position of the N-aryl ring have been shown to hydrolyze four- to tenfold more rapidly than the para-substituted analogs, attributable to the relief of some steric crowding in the conversion of **1** to **3**.[4] By combining the electronic and steric effect expected for the *o*-amido group, a rate enhancement of 10–20-fold relative to the unsubstituted material is predicted. The observed value of 12.6-fold is therefore well within these limits, and thus the amido group is not necessarily acting as a nucleophile in the rate-determining step.

Further support for the isocyanate pathway for **6** comes from data for the *N*-methyl carbamate **11a**. Because the nitrogen of the carbamate is disubstituted, the elimination–addition pathway (Scheme I) is blocked for this carbamate. The *N*-phenyl compound, **11b**, is hydrolyzed slowly by direct hydroxide ion attack on the carbamate linkage (with k_{obsd} = 1.7×10^{-5} l. mol^{-1} sec^{-1} at [HO^-] = 1.0 *M*, 25°).[4] The reaction of **11a** is also base catalyzed but *ca.* 5×10^5-fold faster than that of **11b** (see Figure 1). Such a large rate enhancement can only be explicable in terms of rate-determining direct attack by the amide anion on the carbamate center in **11a**. The product formed, 2-(*N*-methyl)-4(1*H*,3*H*)-quinazolinedione, supports this interpretation since alternative kinetically



11a, Y = $CONH_2$
b, Y = H
c, Y = O^-
d, Y = CO_2^-

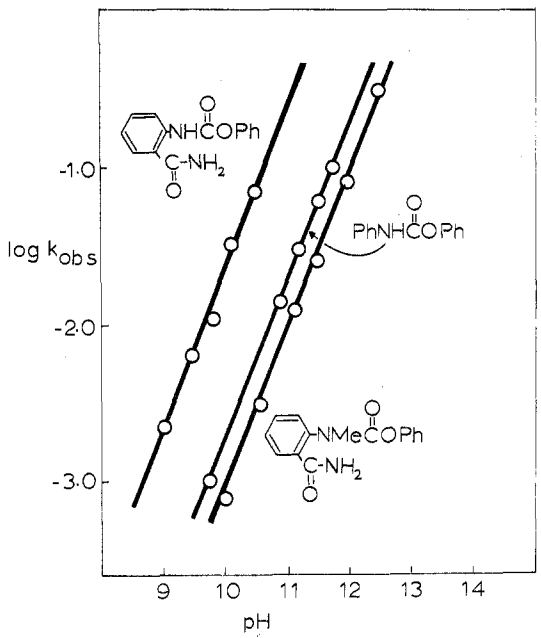


Figure 1. Plot of the logarithm of the observed rate constants (in reciprocal seconds) *vs.* pH for the cyclization of the carbamates **6** and **11** and for the hydrolysis of **1** (R = R^1 = Ph) at 25° in 4:1 water–dioxane at 25°.

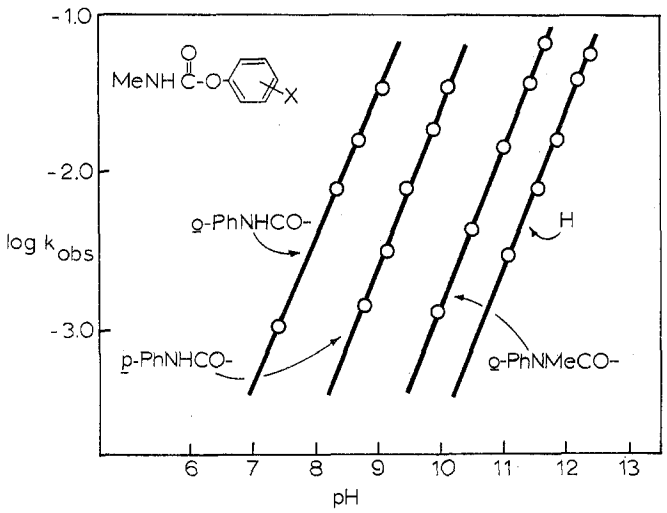


Figure 2. Plot of the logarithm of the observed rate constants (in reciprocal seconds) *vs.* pH for the hydrolysis of the aryl *N*-methylcarbamates **12a, 12b, 12c,** and **13** at 25° in 4:1 water–dioxane at 25°.

equivalent pathways (*e.g.*, assisted hydroxide ion attack at either the carbamate or amide centers) would be expected to give other products (*e.g.*, anthranilamide).

For compounds **11c** and **11d** (in which the nucleophile has been shown to participate also in the rate-determining step for cyclization of the unmethylated analogs), the presence of the *N*-methyl group actually *enhances* the rate of cyclization of the carbamate by 10–30-fold.[5,6] If this relationship also holds in the present instance, then **6** should cyclize (*via* **7**) at a rate less than one-tenth that observed for **11a.** Thus **6** actually cyclizes considerably more rapidly (at least 30 × tenfold) than expected on the basis of amide anion participation in the rate-determining step (**6** → **7** → **8**). The alternative E1cB mediated pathway (**6** → **9** → **10**) is therefore most likely operative, the *o*-amido group in **6** acting merely as an internal nucleophile to trap the isocyanate **10** which is formed in the rate-determining step. As shown above, the observed rate of cyclization of **6** is consistent with such a mechanism.

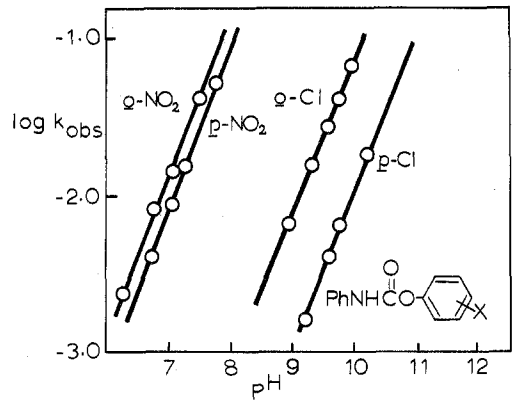
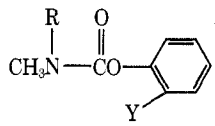


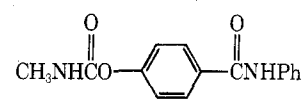
Figure 3. Plot of the logarithm of the observed rate constants (in reciprocal seconds) *vs.* pH for the hydrolysis of the *o*- and *p*-chlorophenyl and *o*- and *p*-nitrophenyl *N*-phenylcarbamates at 25° in 4:1 water–dioxane.

However, the alternative mechanism involving amide anion attack on the carbamate becomes dominant when the isocyanate pathway is blocked by N,N disubstitution.

When an *N*-phenyl carbamoyl group is attached to the ortho position in the leaving phenoxide ion (as in **12a**), a large rate enhancement (relative to the unsubstituted material **12b**) is observed (Figure 2). The products in this case are not cyclic;[7] instead methylamine and salicylanilide are formed. This does not rule out participation by the neighboring amide group either acting as a general base or as a nucleophile to give a cyclic intermediate which is itself hydrolyzed rapidly to the observed products under the conditions of the experiment. Substituents in the leaving group have a very large effect (ρ = −3.2) on the rate of E1cB carbamate hydrolysis[2,3] and the rates of hydrolysis (expressed as k_1K_{a1} values) are correlated by σ^- for the substituents. Thus we have found that the para-substituted isomer **13** is hydrolyzed 100-fold more rapidly than the unsubstituted material **12b.** This is explicable in terms of the electron-withdrawing effect of the *p*-phenyl carbamoyl group (σ^- value for $CONH_2$ is +0.62,[9] giving a calculated rate difference also of *ca.* 100).



12a, R = H; Y = CONHPh
b, R = Y = H
c, R = H; Y = CON(Me)Ph
d, R = Me; Y = CONHPh



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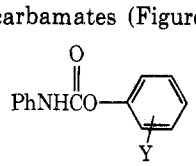
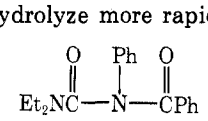
The ortho isomer **12a** is actually hydrolyzed 25-fold more rapidly than the para isomer **13** (to give methylamine and *p*-hydroxybenzanilide) (Table II). The more rapid hydrolysis of the ortho isomer appears to be general, since we have found that the *o*-nitro (**14c**) and *o*-chloro (**14a**) carbamates (Figure 3) hydrolyze more rapidly (sev-



14a, Y = *o*-Cl
b, Y = *p*-Cl
c, Y = *o*-NO_2
d, Y = *p*-NO_2



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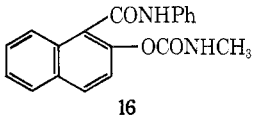
enfold in the case of the *o*-chloro group) than the para-substituted analogs (see Table II). The rate enhancement is, however, small (60%) in the case of the *o*-nitro isomer. This most likely arises since the *p*-nitro group is strongly

electron withdrawing by resonance (as shown by the use of a σ^- value to correlate data for the *p*-nitro-substituted compound).[3] To achieve this, the nitro group must become coplanar with the aromatic ring. This coplanarity, essential for optimum reactivity, is not possible in the *o*-nitro isomer owing to the adjacent carbamate group. When the *o*-amide group is disubstituted (as in **12c**) the rate of hydrolysis is actually 25-fold slower than that of the para-substituted material **13** (see Table II). The slow reaction of the methylated compound **12c** can be attributed to steric inhibition of resonance stabilization during reaction; the presence of the *N*-methyl group forces the carbamoyl group out of the plane of the phenyl ring of the leaving group (this is clear from molecular models), thus reducing its electron-withdrawing ability.

When the carbamate nitrogen is disubstituted, as in **12d**, then the E1cB pathway is blocked and the carbamate hydrolyzes very slowly (see Table II); the observed rate of hydrolysis is just that expected for direct HO^- attack on the carbamate linkage.[4,10] This contrasts with the behavior shown by compound **11a**, in which the amide group most likely participates. The possibility therefore arises that the slow rate of hydrolysis measured for **12d** at high pH was actually the subsequent reaction of a material formed rapidly by initial amide anion participation in **12d**. This is a viable possibility since the *N*-acylurea **15**, which is analogous to *N,N*-dimethyl-*N'*phenyl-*N'*-(*o*-hydroxybenzoyl)urea, is hydrolyzed at a rate (k_{obsd} = 3.7 × 10^{-4} sec^{-1} at HO^- = 1.0 *M*) comparable to that observed for **12d**. To investigate this, we have carefully examined the ultraviolet spectrum of **12d** in the pH region 7–11 and have found no evidence for reaction. Moreover, when **12d** does react at pH >11, repetitive scans of the ultraviolet region show tight isosbestic points, showing the absence of relatively stable intermediates.

Several alternative modes of catalyzed hydrolysis of **12a** have previously been suggested,[7] with in each case the carbamate moiety being converted to a nucleophilic group. The reactivity of **12a**, like that of **6**, can, however, be explained without the intervention of neighboring-group participation. Because of the large sensitivity to substituent effects shown in the leaving group in the elimination–addition pathway, even a small change in the effective σ value of a substituent (by N-methylation of the amide group, for example) would bring about a marked change in reactivity. It is likely that a similar effect might explain the observed[7] low reactivity of the carbamate **16**; the interactions between the peri hydrogen and the neighboring phenylcarbamoyl group force the latter to adopt a conformation out of the plane of the aromatic rings.



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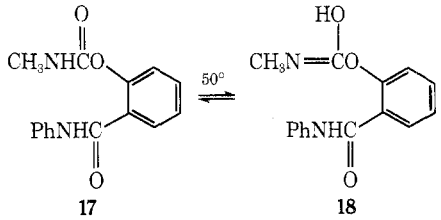
Evidence has been put forward on the basis of nmr studies to suggest that the carbonyl group of the carbamate **17** is readily tautomerizable to **18** while the anilide



17 18

carbonyl group is not.[7] The latter result is not surprising, since it has been well established[11] that simple amides exist almost exclusively (with tautomeric constants $<10^{-6}$) in that form. However, because of the structural similarities between the amide and carbamate groups (and their tautomers), it is unlikely that **18** would be sufficiently stabilized to allow nmr detection. We have therefore reexamined the nmr spectrum of **17**.

Thus the nmr spectrum of **17** in DMF-d_7 gives rise to a singlet at δ 10.00 attributable to the anilide proton and a doublet at δ 2.78 and 2.70 due to the *N*-methyl group. The aromatic ring protons and the proton on the carbamate nitrogen resonate as a multiplet between δ 7.0 and 8.0. In addition to these signals two other singlets at δ 10.50 and 3.03 have been observed by Hsi, *et al.*,[7] which were attributed to the hydroxyl proton and the *N*-methyl group of structure **18**. It was also reported that addition of D_2O to the sample removes the signal at δ 10.50 and also results in the collapse of the doublet at δ 2.78 and 2.70 to a singlet at δ 2.76, the other signals remaining unaffected. Heating the sample (to 50°) in DMF-d_7 resulted in an increase in the intensity of the peaks at δ 10.50 and 3.03 with a corresponding diminution of the *N*-methyl doublet at δ 2.78 and 2.70; this effect is reversed by cooling.

We have reexamined the nmr spectrum of **17** under the same conditions and found no trace of the peaks at δ 10.50 and 3.03 at 30° or at 50°. The doublet at δ 2.78 and 2.70 is not symmetrical at room temperature, the peak at δ 2.78 being more intense. At 50° both peaks have equal intensity and addition of D_2O results in the collapse of the doublet. A similar examination of the spectrum of phenyl *N*-methylcarbamate shows only the peaks corresponding to the expected structure (**12b**). Reports are also available of the nmr spectra of a group of *N*-methyl carbamates used as pesticides,[12] and these show no trace of substrate tautomerization. Studies on other carbamates point to partial double bond character occurring along the ethereal oxygen–carbon bond, rather than tautomerization.[13]

It is difficult, therefore, to reconcile the previously reported results for **17**. However, the anilide proton from salicylanilide, a possible hydrolysis product from **17**, does resonate at δ 10.5. Also the spectrum of neat dimethylformamide gives a doublet at δ 2.98 and 2.82 (at 34.5°). The relative intensity of the two peaks changes on heating to 50°, the peak at δ 2.98 increasing. The residual protons in DMF-d_7 give a similar effect.

Experimental Section

Materials. All inorganic compounds used were Analar grade. Dioxane was BDH Analar grade, used without further purification. Deionized water was twice distilled from alkaline potassium permanganate.

The solvent used for the kinetic experiments, 4:1 water–dioxane, was prepared by mixing four volumes of water with one volume of dioxane at 25°. The ionic strength was maintained at 1.0 by the addition of potassium chloride. The pH of the solution was maintained either by the presence of low (0.01 *M*) concentrations of pH-Stat–ultraviolet spectrophotometer, which has previously been described.[4]

Melting points were taken on a Hoover oil-bath capillary melting point apparatus and are uncorrected. Ir spectra were measured using a Perkin-Elmer Model PE257 spectrometer, the solids being examined as KBr disks. Nmr spectra were run on a Perkin-Elmer Model 20A spectrometer.

Substrates. Phenyl *N*-Methylcarbamate. Method A. To a stirred solution of phenol (0.94 g, 0.01 mol) in dry benzene (20 ml) was added a solution of methyl isocyanate (0.57 g, 0.01 mol) dissolved in benzene (5 ml). A drop of triethylamine was added and the mixture was stirred at room temperature for 20 min. On evaporation of the solvent *in vacuo*, the residue was recrystallized from diethyl ether–petroleum ether (bp 40–60°) to give the carbamate, mp 83–85°, nmr δ 7.7 (m, ArH and NH).

Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 5.96; N, 9.30. Found: C, 63.70; H, 5.40; N, 9.09.

p-**Benzanilido** *N*-**Methylcarbamate.** To a solution of *p*-hydroxybenzoic acid (2.96 g, 0.02 mol) dissolved in anhydrous THF (15 ml) was added a solution of dicyclohexylcarbodiimide (4.12 g, 0.02 mol), dissolved in anhydrous THF (20 ml) and aniline (1.86 g, 0.02 mol). The mixture was allowed to stand at 0° for 4 hr and the precipitated urea was filtered off. Evaporation of the solvent *in vacuo* gave an oil, which solidified on dissolution in ether followed by addition of petroleum ether. The solid was recrystallized from ethanol–water to yield *p*-hydroxybenzanilide, mp 198–199° (lit.[14] mp 196–197°). The anilide was converted to the carbamate using method A above, and on recrystallization from chloroform–petroleum ether had mp 176–178°.

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.6; H, 5.2; N, 10.4. Found: C, 66.60; H, 5.35; N, 10.60.

Phenyl *N*-(*o*-**Carbamoylphenyl)carbamate.** To a stirred solution of anthranilamide (2.72 g, 0.02 mol) in ether (50 ml) at ambient temperature was added a solution of phenyl chloroformate (1.56 g, 0.01 mol) in ether (20 ml). The precipitated anthranilamide hydrochloride was filtered off and the filtrate was reduced to dryness *in vacuo*. The residue was recrystallized from chloroform–petroleum ether to give phenyl *N*-(*o*-carbamoylphenyl)carbamate, mp 159–160°.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.60; H, 4.68; N, 10.91. Found: C, 65.61; H, 4.65; N, 11.02.

Phenyl *N*-**Methyl-***N*-(*o*-**carbamoylphenyl)carbamate.** To a stirred solution of *N*-methylanthranilamide (3.0 g, 0.02 mol) in THF (50 ml) was added phenyl chloroformate (1.56 g, 0.01 mol) in 5 ml of the same solvent. A drop of pyridine was added and the mixture was refluxed for 30 min. The precipitated hydrochloride of *N*-methylanthranilamide was filtered off and the filtrate was evaporated to dryness. The residue was recrystallized from chloroform–petroleum ether to give phenyl *N*-methyl-*N*-(*o*-carbamoylphenyl)carbamate, mp 146–148°.

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.18; N, 10.36. Found: C, 66.44; H, 5.11; N, 10.35.

o-**Nitrophenyl** *N*-**Phenylcarbamate.** To a stirred solution of *o*-nitrophenol (2.58 g, 0.01 mol) dissolved in 20 ml of dry benzene was added phenyl isocyanate (1.19 g, 0.01 mol) dissolved in 10 ml of the same solvent. Pyridine (0.2 ml) was added as catalyst and the mixture was refluxed for 30 min. On cooling the carbamate was precipitated by reducing the solvent *in vacuo*. Recrystallization from chloroform–pentane gave *o*-nitrophenyl *N*-phenylcarbamate, mp 127–128°.

Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.87; N, 10.85. Found: C, 60.50; H, 4.08; N, 11.05.

Similarly prepared was *o*-chlorophenyl *N*-phenylcarbamate, mp 123–125°.

Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 63.02; H, 4.04; N, 5.65. Found: C, 63.47; H, 4.05; N, 5.95.

The preparation of *p*-chlorophenyl *N*-phenylcarbamate, mp 148–150°, and *p*-nitrophenyl *N*-phenylcarbamate, mp 150–152°, has previously been described.[4]

o-Benzanilido *N*-methylcarbamate, *o*-(*N'*-methyl)benzanilido *N*-methylcarbamate, and *o*-benzanilido *N,N*-dimethylcarbamate were prepared by the method of Hsi, *et al.*,[7] and had physical properties described.

2,4(1*H*,3*H*)-Quinazolinedione and 2-(*N*-methyl)-4(1*H*,3*H*)-quinazolinedione were prepared from methyl 2-ureidobenzoate and methyl 2-(*N*-methylureido)benzoate by the method of Hegarty and Bruice.[15]

N,N-**Diethyl-***N'*-**benzoyl-***N'*-**phenylurea.** *N,N*-Diethyl-*N'*-phenylformamide chloride (1.0 g) was refluxed for 16 hr with an equimolar quantity of silver benzoate (1.15 g) in dry ether. The precipitated silver chloride was filtered off and evaporation of the solvent gave the urea, mp 74–75°.

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.75; N, 9.5. Found: C, 72.90; H, 7.10; N, 9.40.

Kinetic Measurements. The kinetics of hydrolysis or cyclization of the N-aryl and N-alkyl carbamates were studied in 1:4 dioxane–water at 25° by following the change in optical density at suitable wavelengths. For those experiments measured in the presence of buffer (or those which were self-buffered at high pH) 3-ml quartz cuvettes were used, the reaction being initiated by the addition of 1 drop of a concentrated (usually 10^{-2} *M*) solution of the substrate in dioxane to the buffer solution in the cuvette. Optical density *vs.* time plots were then obtained using a Unicam Model SP800B spectrophotometer equipped with multiple thermostattable cell compartment, scale expansion accessory, and external AR25 recorder. Preliminary repetitive scans of the ultraviolet region established the suitable wavelengths at which the optical density changed in the course of the reaction; it was established that the observed rate constants were independent of the wavelength chosen to study the reaction. Some measurements were also made in the absence of added buffer species. In this case, the course of the reaction was also followed spectrophotometrically using a Cary Model 14 spectrophotometer fitted with a special cell (which has previously been described)[4] whose contents can be maintained at constant pH using a radiometer pH-Stat assembly. In all cases good pseudo-first-order rate constants were obtained to >95% reaction. The individual constants were calculated either graphically or using a weighted least-squares program using an Olivetti Underwood Programma 101 calculator. In all cases the pH values quoted were the values directly measured in 4:1 water–dioxane using a Radiometer Model PHM 26 pH meter equipped with a Metrohm EA 125U combined glass electrode. The electrode was initially standardized using Radiometer aqueous buffer solutions. The pH of the reaction solutions was measured before and after a kinetic experiment; any run which showed an excessive pH drift (±0.05 pH unit) was discarded.

The products of hydrolysis were determined in all cases by comparing the ultraviolet spectrum obtained at the completion of a kinetic experiment with the spectrum of an authentic sample of the product (or mixture of products). In most cases the products were additionally identified by actual isolation by carrying out the reaction on a larger scale than that used for the spectrophotometrically measured runs; thin layer chromatography established the identity of the products formed in each case. When one of the products (*e.g.*, the quinazolinedione **8**) had a pK_a value within measurable range, additional confirmation of its presence as a reaction product could be obtained by recording the change in the uv spectrum of the product as the pH was changed; this gave an estimate of the pK_a of the product, which could be compared with the value for an authentic sample measured under the same conditions.

Registry No.—**1** (R = R' = Ph), 4930-03-4; **6**, 50585-30-3; **11a**, 50585-31-4; **11b**, 13599-69-4; **12a**, 5591-49-1; **12b**, 1943-79-9; **12c**, 35410-16-3; **12d**, 35410-18-5; **13**, 50585-32-5; **14a**, 16400-07-0; **14b**, 16323-15-2; **14c**, 21468-56-4; **14d**, 6320-72-5; **15**, 50585-33-6; 2,4-(1*H*,3*H*)-quinazolinedione, 86-96-4; phenol, 108-95-2; methyl isocyanate, 624-83-9; *p*-hydroxybenzoic acid, 99-96-7; aniline, 62-53-3; anthranilamide, 88-68-6; phenyl chloroformate, 1885-14-9; *N*-methylanthranilamide, 4141-08-6; *o*-nitrophenol, 88-75-5; phenyl isocyanate, 103-71-9.

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