Cyclizations involving Oxyanions as Nucleophiles towards the Carbamate Linkage in the Rate-determining Step

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The rate of hydrolysis of phenyl *N*-(*o*-carboxyphenyl)carbamate (4) is rapid (k_{obs} = 1·0 × 10^{-3} s^{-1}) and pH independent over a wide range (5 < pH < 11) in 4:1 water–dioxan at 25°. The ultimate products of hydrolysis are anthranilic acid and phenol but it is demonstrated that initial cyclization [to form isatoic anhydride (8; R = H)] occurs. A mechanism involving ready nucleophilic attack by the ionized carboxy-group is proposed based on the low-deuterium isotope solvent effect (k_{H_2O}/k_{D_2O} = 1·2) and data for the model compounds phenyl *N*-(*p*-carboxyphenyl)carbamate (5) and phenyl *N*-(*o*-ethoxycarbonylphenyl)carbamate (6). Similar criteria are also used to confirm that phenyl *N*-(*o*-hydroxyphenyl)carbamate (11; R = H) cyclizes to benzoxazolinone by the same mechanism, involving in this case the ionized phenoxy-group as an internal nucleophile. Both cyclizations are markedly dependent on the nature of the leaving group [*e.g.* the Hammett ρ = +2·0 for the cyclization of aryl *N*-(*o*-carboxyphenyl)carbamates to isatoic anhydride], contrasting with the bimolecular reaction of hydroxide ion with carbamates which is relatively independent of the nature of the leaving group. This is rationalized in terms of a different rate-determining step for the intramolecular reactions possibly involving breakdown of a tetrahedral intermediate. The effect of substituents in the *N*-aryl ring of the phenol (11; R = H) was also examined and it was shown that the rate of cyclization was very sensitive to the positioning of the substituent relative to the nucleophilic and carbamate groups. Thus a nitro-group can either enhance the rate of cyclization (when *para* to the carbamate group) or reduce it (when *para* to the hydroxy-group); the rate difference between the two phenyl *N*-(2-hydroxynitrophenyl)carbamates is 800-fold.

INTRAMOLECULAR reactions have been studied intensively in an attempt to understand the mechanism of enzymic catalysis. This is because of the close analogy between an intramolecular reaction and an enzyme catalysed reaction which involves adsorption of the substrate and then proceeds through an enzyme–substrate complex.[1] The various groups which occur on amino-acid side chains (*e.g.* carboxy, hydroxy, imidazolyl, amino) have been examined as intramolecular catalysts in this context.[2] Several proteolytic enzymes such as pepsin have a carboxy-group located at the active site and various modes of involvement of the carboxy-group, as a general acid or base or as a nucleophile, have been proposed. In model systems using simple esters and acetals as substrates it has been demonstrated that a suitably positioned carboxy-group can show each of these types of catalytic activity.[3,4]

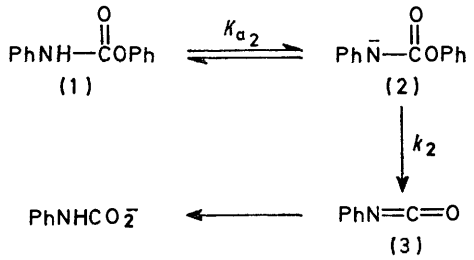
We have recently examined the role of the amide [5] and amino-groups [6] as intramolecular catalysts in the hydrolysis of carbamates where the nucleophile does not participate in the rate-limiting step. We now report on a study of the carboxy- and hydroxy-groups and show that these groups when properly positioned can greatly enhance the rate of hydrolysis of the carbamate linkage.

RESULTS AND DISCUSSION

It has previously been reported that the hydrolysis of simple carbamates with good leaving groups proceeds in basic solution by an elimination–addition (*E*1cB) mechanism (Scheme 1).[6,7] Thus the rate of hydrolysis of phenyl *N*-phenylcarbamate (1) to aniline and phenol is proportional to pH in the region 10—13·7.[6] Hydrolysis of carbamates by direct H_2O or HO^- attack on the carbamate ($B_{AC}2$ mechanism) proceeds considerably more slowly (up to 10^8-fold) and occurs only when the more ready elimination pathway is blocked by disubstitution.[8] At low [HO^-] (below say, pH 8) (1) is

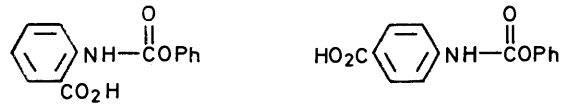
[1] T. C. Bruice and S. J. Benkovic, 'Bio-organic Mechanisms,' Benjamin, New York, 1966, ch. 1.
[2] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969.
[3] A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, 1967, **89**, 4853.
[4] B. Capon, M. C. Smith, E. Anderson, R. H. Dahm, and G. H. Sankey, *J. Chem. Soc.* (*B*), 1969, 1038; B. Capon, 'Intramolecular Catalysis' in 'Essays in Chemistry,' Academic Press, London, 1972, **3**, 127.
[5] A. F. Hegarty, L. N. Frost, and J. H. Coy, *J. Org. Chem.*, 1974, **39**, 1089.
[6] A. F. Hegarty and L. N. Frost, *J.C.S. Perkin II*, 1973, 1719.
[7] A. Williams, *J.C.S. Perkin II*, 1972, 808.
[8] L. W. Dittert and T. Higuchi, *J. Pharm. Sci.*, 1963, **52**, 852.

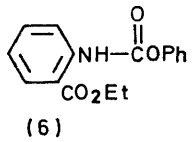
essentially stable; water catalysed hydrolysis of the neutral carbamate does occur but this is very slow at 25°.[9]



SCHEME 1

We have found [10] that phenyl *N*-(*o*-carboxyphenyl)-carbamate (4) reacts rapidly in the pH region 4—14, as judged by the rate of phenol release. The ultimate products of hydrolysis of (4) are phenol, carbon dioxide,





and anthranilic acid. The observed rates of phenol release from (4), measured in 4 : 1 water–dioxan at 25°, are summarized in Figure 1.

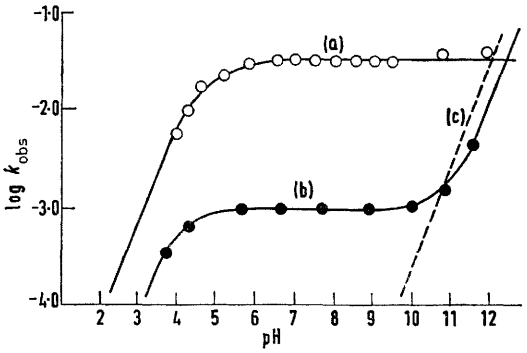


FIGURE 1 Plot of log k_{obs} measured in 4 : 1 water–dioxan at 25° (μ = 1·0; KCl) against pH for (a) phenyl *N*-(*o*-carboxyphenyl)-*N*-methylcarbamate; (b) phenyl *N*-(*o*-carboxyphenyl)-carbamate (4); and (c) phenyl *N*-(*p*-carboxyphenyl)carbamate (5)

It is seen that there is a large 'plateau' region wherein the observed rate is independent of pH. In acidic solution (pH <4) k_{obs} decreases as the acidity of the medium is increased. The rate enhancement caused by the presence of the *o*-carboxy-group is substantial since it can be calculated that at pH 4, (4) reacts 10^6 times faster than (1).

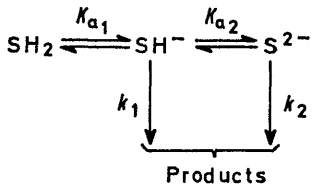
[9] T. Vontor and M. Vecera, *Coll. Czech. Chem. Comm.*, 1973, **38**, 516.

[10] Preliminary communication, L. N. Frost and A. F. Hegarty, *J.C.S. Chem. Comm.*, 1973, 82.

In basic solution (pH >10) (4) is hydrolysed by a base catalysed (presumably the normal elimination–addition or *E*1cB) pathway. The observed rate at pH 12 (which is proportional to $k_2K_{a_2}$, see Scheme 1) for (4) is *ca.* three-fold less than for the unsubstituted material (1) (Figure 1). Presumably the ionized *o*-carboxy-group decreases K_{a_2} by destabilizing formation of anion (2) on the neighbouring nitrogen atom by electrostatic repulsion.

The enhanced reactivity shown by (4) in the pH region 4—10 is only apparent when the carboxy-group is adjacent to the carbamate linkage. This can be seen from the fact that the *p*-carboxy-analogue of (4), *i.e.* (5), is hydrolysed in a manner exactly analogous to phenyl *N*-phenylcarbamate (1). In fact the observed rate at any pH for (5) is almost identical to that observed for the unsubstituted carbamate (1) which is consistent with the reported [11] σ value of *ca.* 0 for the CO_2^- group. Furthermore it is essential that the *o*-carboxy-group be capable of ionization because phenyl *N*-(*o*-ethoxycarbonylphenyl)carbamate (6) shows only *E*1cB-type reactivity and has no pH independent region in its log k_{obs} against pH profile.

The observed kinetic results for (4) can be correlated in terms of equation (1) which was derived from the empirical Scheme 2, assuming that the monoanion (SH^-)



SCHEME 2

and dianion (S^{2-}) of the substrate (4) are the reactive species. At low pH, $a_H \gg K_{a_2}$ and so equation (1) reduces

$$k_{obs} = (k_1K_{a_1}a_H + k_2K_{a_1}K_{a_2})/(K_{a_1}K_{a_2} + K_{a_1}a_H + a_H^2) \quad (1)$$

$$\text{at low pH:} \quad k_{obs} = k_1K_{a_1}/(a_H + K_{a_1}) \quad (2)$$

$$\text{at high pH:} \quad k_{obs} = k_2K_{a_2}/(a_H + K_{a_2}) \quad (3)$$

to equation (2), *i.e.* the contribution due to k_2 is negligible in this region. Equation (2) gives k_{obs} values which are pH independent at pH values > pK_{a_1}, and which decrease as the pH is decreased below pK_{a_1}. This is the behaviour shown by (4) at pH <10. At high pH (low a_H) equation (1) can be simplified to equation (3). This equation describes the observed kinetic behaviour for (4) in the pH region 11, if it is assumed that $a_H \gg K_{a_2}$.

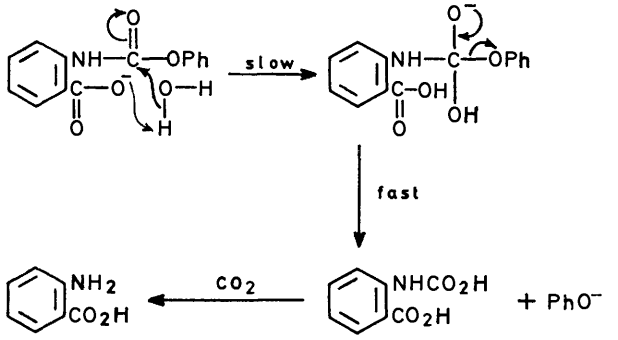
By a suitable choice of the constants k_1, K_{a_1}, and $k_2K_{a_2}$, equation (1) can be closely fitted to the observed rate constants. The line drawn from (4) in Figure 1 has been calculated from this equation using the following values: $k_1 = 1{\cdot}0 \times 10^{-3}$ s^{-1}, $K_{a_1} = 1{\cdot}06 \times 10^{-4}$, and $k_2K_{a_2} = 1{\cdot}5 \times 10^{-14}$ l mol^{-1} s^{-1}.

The pK_{a_1} value calculated from the kinetic data is

[11] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.

reasonable for the ionization of a benzoic acid derivative (pK_a of benzoic acid is 4·2).[12] We have also measured the pK_a for the ionization of methyl *N*-(*o*-carboxyphenyl)carbamate at 25° in 4 : 1 water–dioxan and obtained a value of 4·26.

Thus the data are consistent with the reactive species being the ionized substrate (9) in the pH region below pH 10·0. The decrease in the rate of phenol release at pH <4, corresponds to the conversion of (9) into the unreactive ionized species (4). These results taken together with the lack of reactivity shown by the *p*-CO_2H (5) and *o*-CO_2Et (6) compounds, show that the monoionized species (9) is responsible for the high reactivity of (4) in neutral solution.



SCHEME 3

Several possible modes of involvement by the ionized carboxy-group which are kinetically indistinguishable must be considered. One possibility is carboxy-group participation in the hydrolysis of (4) by intramolecular general base catalysis of H_2O attack by the carboxylate anion (Scheme 3).

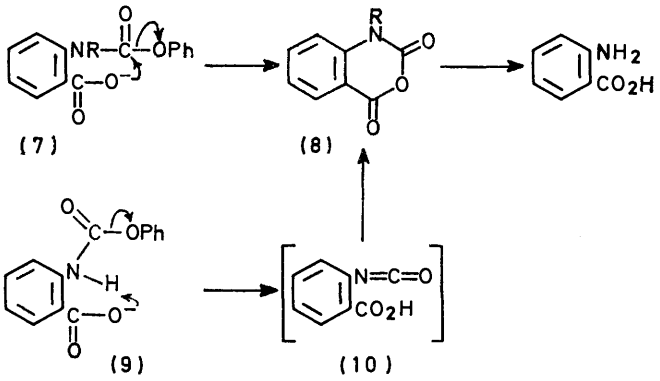
This possibility is excluded for several reasons. Thus the deuterium solvent isotope effect (measured at pH 7) for the hydrolysis of (4) is close to unity ($k_{H_2O}/k_{D_2O} = 1·2$). This low value is inconsistent with the involvement of water in the transition state. It does however bear close resemblance to the k_{H_2O}/k_{D_2O} value of 1·3 obtained by Fersht and Kirby for the intermolecularly catalysed hydrolysis of 3,5-dinitroaspirin by carboxylate anions, a process shown to involve not general base, but nucleophilic catalysis.[13] Because of the different basicities of H_2O and D_2O, the ionization constants K_{a_1} (and K_{a_2}) would be different in the two solvents. However the solvent kinetic isotope effect was measured at pH = pD = 7. At this pH, $k_{obs} = k_1$ [equation (1)] even if K_{a_1} is altered by an order of magnitude on transfer from water to deuterium oxide. This removes any uncertainty from the magnitude of the isotope effect.

Therefore a water molecule is not involved as a general base in the transition state of the intramolecularly catalysed reaction. This is not altogether unexpected since intramolecular general base catalysis usually amounts to no more than a 20-fold rate enhancement [14] (compared with $>10^6$-fold in the present instance).

Furthermore, isatoic anhydride (8; R = H) was found to be an intermediate on the reaction pathway for the hydrolysis of (4). If intramolecular general base catalysis were occurring, isatoic anhydride (8; R = H) would not be an intermediate and the product formed directly would be anthranilic acid (Scheme 3). Isatoic anhydride is itself rapidly hydrolysed to anthranilic acid in basic solution. However, below pH *ca.* 8, isatoic anhydride is relatively long-lived and the reaction of (4) is characterized by tight isosbestic points. Under these conditions the presence of isatoic anhydride on the reaction pathway can be detected both by actual isolation and comparison with an authentic sample, and by spectrophotometric determination.

At higher pH, the rate of hydrolysis of isatoic anhydride is of the same order of magnitude as the rate of cyclization of (4). The observed kinetics are consecutive in this region and the first reaction [(4) ⟶ (8; R = H)] was studied at a wavelength which was an isosbestic point for the hydrolysis of isatoic anhydride. Since isatoic anhydride has pK_a *ca.* 8·6 which is accompanied by a large spectral change,[15] repetitive scans of the u.v. spectrum were required at each pH studied between 8 and 10 to establish the position of the new isosbestic point for the further hydrolysis of (8; R = H). At pH >11, the hydrolysis of isatoic anhydride was so rapid that the hydrolysis of (4) again showed tight isosbestic points. Clearly, any mechanism for hydrolysis of (4) must therefore involve isatoic anhydride as an intermediate on the reaction pathway.

Of the remaining available mechanisms, the two most likely modes of hydrolysis (both of which would give isatoic anhydride as an intermediate) are given in Scheme 4. Both mechanisms are consistent with the



SCHEME 4

observed kinetics of cyclization of (4) (Figure 1) but the following observations lend support to the mechanism involving direct nucleophilic attack [(7) ⟶ (8)] as the correct pathway for the hydrolysis of (4).

[12] H. C. Brown, D. H. McDaniel, and L. Hafinger, ' Determination of Organic Structures by Physical Methods,' eds. E. A. Braude and F. C. Nachod, Academic Press, New York, 1955, vol. 1.

[13] A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, 1968, **90**, 5818.

[14] A. J. Kirby and G. Meyer, *J.C.S. Perkin II*, 1972, 1446.

[15] J. F. Bunnett and M. B. Naff, *J. Amer. Chem. Soc.*, 1966, **88**, 4001.

The *N*-methyl analogue of (9), *i.e.* (7; R = Me), is also hydrolysed rapidly in neutral solution. The observed rates of hydrolysis of (7; R = Me) from pH 4·0 to pH 13·0 are summarized in Figure 1. It is seen that the observed rate of hydrolysis of (7; R = Me) is virtually independent of pH above pH 5. The shape of the pH–rate profile (Figure 1) for (7; R = Me) at low pH is therefore exactly analogous to that of the unmethylated material (4). In basic solution the hydrolysis of (7; R = Me) does not increase, as expected, since the *E*1cB mode of hydrolysis is not available for this compound. The slower direct hydroxide ion attack on the carbamate would not be expected to make a significant contribution to the rate of hydrolysis of (7; R = Me) even at $[HO^-] = 1M$. The rate equation followed by (7; R = Me) is therefore equation (2); the curve in Figure 1 was drawn assuming this relationship with $k_1 = 3{\cdot}3 \times 10^{-2}$ s^{-1} and $K_{a_1} = 2{\cdot}18 \times 10^{-5}$, and this fits the observed kinetics closely, assuming that the anion (7; R = Me) is the reactive species.

In the *N*-methyl compound reaction *via* intramolecular general base catalysis [(9) ⟶ (10)] is blocked. Thus, the *o*-carboxy-group must be involved as a nucleophile in this case. Moreover it was also shown that *N*-methylisatoic anhydride (8; R = Me) was an intermediate in the hydrolysis of (7; R = Me) both by isolation when the reaction occurred at a suitable pH, and by spectrophotometric determination.

The further hydrolysis of *N*-methylisatoic anhydride (8; R = Me) to *N*-methylanthranilic acid is a simple base-catalysed process;[16] below pH *ca.* 8, the rate of cyclization of (7; R = Me) to (8; R = Me) (which is pH independent), is very much faster than the subsequent hydrolysis of (8; R = Me) and good pseudo-first-order rate constants can be obtained for the reaction of (7; R = Me).

In this pH region (below pH 8) the u.v. spectrum obtained on completion of the cyclization reaction was identical with the spectrum of an equal concentration mixture of phenol and *N*-methylisatoic anhydride (8; R = Me). As an additional check, the pH of the solution was (after the initial reaction) adjusted to pH *ca.* 9 and the rate of the further hydrolysis of *N*-methylisatoic anhydride measured. The rate constants obtained were similar to those obtained for the hydrolysis of an authentic sample of *N*-methylisatoic anhydride measured independently at the same pH.

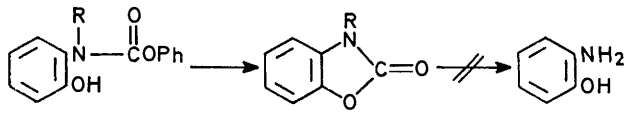
Above pH *ca.* 10·0 the hydrolysis of *N*-methylisatoic anhydride proceeds much more rapidly than the cyclization of (7; R = Me) and good pseudo-first-order rates were again obtained for the cyclization. At intermediate pH values, repetitive scans of the u.v. spectrum showed the presence of the intermediate, and the kinetics were consecutive; the k_{obs} values obtained in this pH region are therefore approximate.

[16] A. F. Hegarty and L. N. Frost, unpublished results.
[17] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1778.
[18] T. C. Bruice and R. Lapinski, *J. Amer. Chem. Soc.*, 1958, **80**, 2265.

Because of the similarity in the structures and kinetic behaviour shown by (4) and its *N*-methyl analogue, it seems that both materials react *via* the same mechanistic pathway, nucleophilic attack by the ionized carboxy-group representing the first authenticated example of ready nucleophilic attack on a carbamate system.[10] The 35-fold rate enhancement for cyclization of the *N*-methyl compound (which is not unique, see below), is possibly due to steric inhibition of ground state stabilization due to resonance by the *N*-methyl group in (7; R = Me) which makes the carbamate linkage more susceptible to nucleophilic attack.

The rate enhancement caused by the presence of the *o*-CO_2^- group adjacent to the carbamate linkage can be estimated as follows. Hydroxide ion is a better nucleophile by *ca.* 7 orders of magnitude than a simple carboxylate anion such as acetate towards an acyl function, *e.g. p*-nitrophenyl acetate.[17] Since the second-order rate constant for the reaction between phenyl *N*-methyl-*N*-phenylcarbamate and HO^- is $1{\cdot}7 \times 10^{-5}$ l mol^{-1} s^{-1}, it can be estimated that the bimolecular rate of reaction of this carbamate with RCO_2^- would be *ca.* 10^7-fold less (assuming a Brønsted β coefficient of 1·0),[18] *i.e.* $1{\cdot}7 \times 10^{-12}$ l mol^{-1} s^{-1}. On this basis the rate enhancement resulting from approximating the CO_2^- group and the carbamate function can be estimated as $3{\cdot}5 \times 10^{-2}/1{\cdot}7 \times 10^{-12}$, *i.e.* 2×10^{10}-fold.

Participation by an o-*Hydroxy-group in Carbamate Hydrolysis.*—The possibility then arises that other neighbouring groups (besides carboxy) might also assist intramolecularly the hydrolysis of carbamates. A likely participant is the neighbouring oxide ion (O^-) since the same nucleophilic atom is involved as in the neighbouring carboxy-case. Moreover, Raiford and Inman[19] in studying synthetic routes to heterocyclic compounds found that the product obtained from the carbamate (11; R = H) in alkaline solution was the corresponding benzoxazolinone (12; R = H). We have made a detailed kinetic study of the reaction of (11) and analogous materials at various pH values. The results



(11) (12) (13)

SCHEME 5

obtained confirm and extend those recently reported[20] by Hutchins and Fife on the cyclization of (11; R = H).

The cyclic material (12; R = H) is formed not only in alkaline solution, but at all pH values where (11) has a measurable rate of reaction (see Figure 2 for a plot of log k_{obs} against pH, measured in 4 : 1 water–dioxan at 25°). The identification of (12) as the reaction product was unequivocal in this case since the further hydrolysis

[19] L. C. Raiford and G. O. Inman, *J. Amer. Chem. Soc.*, 1934, **56**, 1586.
[20] J. E. C. Hutchins and T. H. Fife, *J. Amer. Chem. Soc.*, 1973, **95**, 2282.

of (12; R = H) to *o*-aminophenol (13) is very slow, and both spectrophotometric estimation of (12; R = H) at the end of a kinetic run and its actual isolation were possible.

The *p*-hydroxy-isomer of (11; R = H) is hydrolysed to *p*-aminophenol and phenol in the same pH region. When log k_{obs} is plotted against pH (Figure 2), it is seen that there is also a break in the profile in much the same region as that observed for the *o*-hydroxy-isomer (11; R = H). The extent of the plateau for the *p*-hydroxy-isomer is much reduced relative to (11; R = H) and (4).

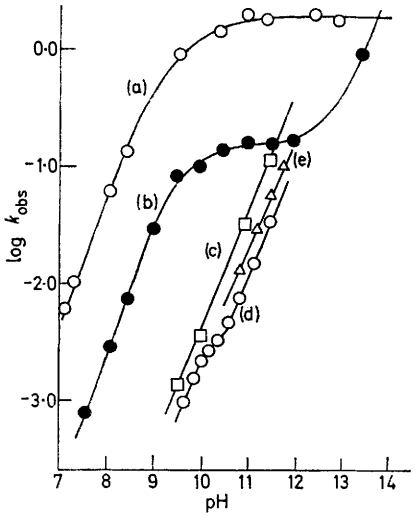
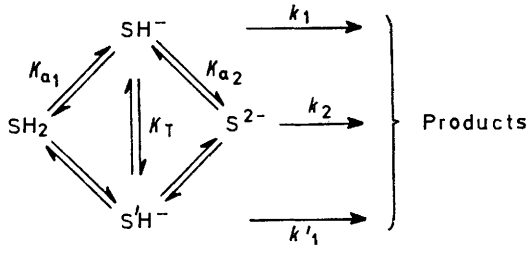


FIGURE 2 Plot of log k_{obs} against pH for the reactions of (a) phenyl *N*-(*o*-hydroxyphenyl)-*N*-methylcarbamate (11; R = Me); (b) phenyl *N*-(*o*-hydroxyphenyl)carbamate (11; R = H); (c) phenyl *N*-(*o*-methoxyphenyl)carbamate; and (d) phenyl *N*-(*p*-hydroxyphenyl)carbamate. Data for phenyl *N*-phenylcarbamate (1) (also using 4 : 1 water–dioxan as solvent at 25°) are included (e)

The rates of reaction of (11; R = H) and its *p*-hydroxy-isomer can be described in terms of the generalized Scheme 6. The equation relating the



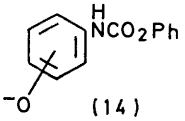
SCHEME 6

observed rate constants to the microscopic rate constants at each pH [equation (4)] is similar to that derived for the *o*-carboxycarbamate (4) with the addition of an extra term. This includes the tautomeric constant K_T which describes the relative concentration of the two possible monoanions SH^- and $S'H^-$, *i.e.* (14) and (15).

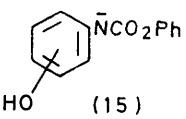
$$k_{obs} = \frac{k_1 K_{a_1} a_H + k_2 K_{a_2} + k_1' K_T K_{a_1} a_H}{a_H^2 + a_H K_{a_1} + K_{a_1} K_{a_2}} \quad (4)$$

[21] M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *J. Amer. Chem. Soc.*, 1959, **81**, 4226.

The individual constants were estimated using values in equation (4) which best fitted the observed kinetic data (Figure 2) and are summarized in the Table. It is



(14)



(15)

Calculated rate and equilibrium constants for reactions of compounds (11; R = H) and its *p*-hydroxy-isomer

	Hydroxy	
Constants	*o*	*p*
$k_1 + k_1'K_T$	$1{\cdot}58 \times 10^{-1}$	$3{\cdot}98 \times 10^{-3}$
K_{a_1}	$1{\cdot}99 \times 10^{-10}$	$1{\cdot}26 \times 10^{-10}$
$k_2K_{a_2}$	$2{\cdot}74 \times 10^{-14}$	$1{\cdot}33 \times 10^{-14}$

seen from these results that K_{a_1} is reasonable in both instances for the ionization of a *p*- or *o*-hydroxy-group. This compares with the reported pK_a values of 10·3 and 9·7 for *p*- and *o*-aminophenol respectively.[21] Also, the value of $(k_1 + k_1'K_T)$ is much larger for the *o*-hydroxy-isomer (11; R = H).

These results are explicable only if a different species (SH^- in one case and $S'H^-$ in the other) is providing the major reaction pathway at low pH. Thus while SH^- and $S'H^-$ can be either (14) or (15) in the case of the monoanion obtained from the *p*-hydroxycarbamate (11; R = H), the *para*-isomer as it stands is unlikely to undergo rapid spontaneous reaction. On this basis the hydrolysis of the *para*-isomer should involve the usual *E*1cB-type elimination from the carbamate itself and from the anion (14; *para*-isomer) with an ionized hydroxy-group. The difference in the reactivity of the *para*-isomer at high and low pH would thus reflect the difference in electron-donating power between the hydroxy and oxide groups. From literature data, $\Delta\sigma$ is *ca.* 0·63 (although since one of the groups is charged, its value is highly solvent dependent).[22] The difference in the rates of *E*1cB hydrolysis of neutral and mono-ionized carbamates can be estimated as 2·5-fold (using the ρ value of +0·64 already reported [6] for substituent variation in the *N*-aryl ring). This is entirely consistent with the rate difference of 2·2-fold observed in the hydrolysis rates of the *para*-isomer at high and at low pH (see Figure 2).

The rate difference calculated for the neutral and ionized forms in the case of the *ortho*-isomer (11; R = H) is much larger (*ca.* 10^3-fold) and clearly cannot be explained in terms of an electronic effect resulting from the ionized *o*-hydroxy-group. The large rate enhancement in this case is however consistent with SH^- (Scheme 6) [or (14; *ortho*-isomer)] as the reactive species since the neighbouring *o*-oxide ion could act as a neighbouring group in this case.[20]

Phenyl *N*-(*o*-methoxyphenyl)carbamate shows only normal *E*1cB reactivity; there is no break (plateau) in the pH–rate profile of this compound (Figure 2). It

[22] J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, London, 1962, 2nd edn., p. 87.

reacts a little more rapidly than phenyl *N*-phenylcarbamate (1), a phenomenon observed with all *N*-(*o*-substituted phenyl)carbamates, even when the substituent does not participate directly in hydrolysis.[6] A mechanism involving nucleophilic attack by the ionized

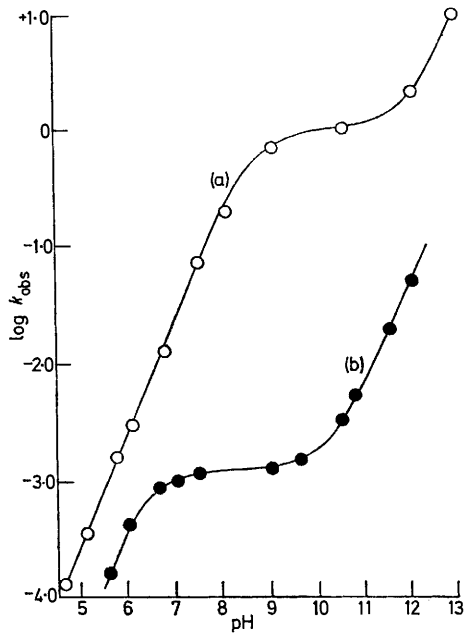


FIGURE 3 Plot of log k_{obs} against pH for the hydrolysis of (a) phenyl *N*-(2-hydroxy-5-nitrophenyl)carbamate (16) and (b) phenyl *N*-(2-hydroxy-5-nitrophenyl)carbamate (17) in 4 : 1 water–dioxan at 25° (μ = 1·0; KCl). The points are experimental and the curves were drawn with equation (4) with the following values for the constants: for (16) k_1 = 1·0 s^{-1}; pK_{a_1} = 8·6; $k_2K_{a_2}$ = 1·0 × 10^{-12}; for (17) k_1 = 1·26 × 10^{-3} s^{-1}; pK_{a_1} = 6·3; $k_2K_{a_2}$ = 6·3 × 10^{-14}

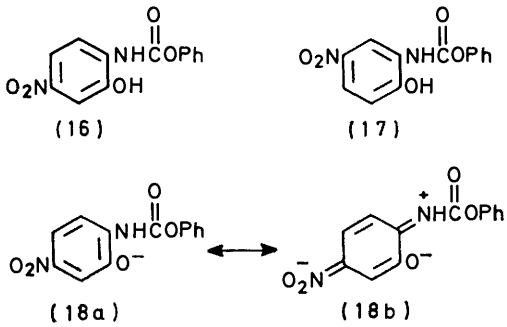
hydroxy-group on the carbamate linkage (as in the case of the *o*-carboxy-group) is indicated by the observation that the *N*-methyl analogue (11; R = Me) is smoothly cyclized to the corresponding *N*-methylbenzoxazolinone (12; R = Me) (see Figure 2).

The observed rates of cyclization of (11; R = Me) to (12; R = Me) are proportional to the fraction of the substrate in which the *o*-hydroxy-group is ionized. These rates were correlated by equation (4) and the values k_1 = 2·1 s^{-1} and pK_{a_1} = 9·75 (and $k_2 = K_T = 0$) have been used to draw the curve in Figure 2. The effective rate enhancement (relative to the bimolecular reaction between hydroxide ion and phenyl *N*-methyl-*N*-phenylcarbamate) due to the presence of the ionized *o*-hydroxy-group in (11) can be calculated as 1·2 × 10^5-fold.

Substituent Effects in the N-*Aryl Ring*.—The cyclization of two *o*-hydroxycarbamates (16) and (17) with nitro-substituents in the *N*-aryl ring was also investigated. In both cases the observed rate constants varied with pH in the same general way as observed for the unsubstituted material (see Figure 3).

It is seen that the rate of cyclization is highly dependent on the position of the nitro-group. Thus for phenyl *N*-(2-hydroxy-4-nitrophenyl)carbamate (16) the rate of cyclization of the anion (18) is greater than the anion of the unsubstituted *o*-hydroxycarbamate (11; R = H) (k_1 = 1·0 against 0·16 s^{-1}). The acidity of the hydroxy-group of (16) is also increased [pK_{a_1} 8·6 for (16) against 9·7 for (11; R = H)]. The nitro-group in (17) brings about a large decrease in the plateau rate of cyclization (k_1 = 1·26 × 10^{-3}) while the acidity of the hydroxy-group is increased still further (pK_{a_1} 6·3). These results may be rationalized as follows.

The effect of the nitro-group is two-fold. It acts to increase the acidity of the hydroxy-group (concomitantly decreasing the nucleophilicity of the oxide ion in the conjugate base) and also increases the reactivity of the carbamate linkage by electron withdrawal. In the conjugate base (18), the nitro-group is *para* to the carbamate linkage. As shown previously [6] electron withdrawal (from the carbamate nitrogen) by resonance can then occur [(18b)] and this greatly increases the susceptibility of the carbamate carbonyl group to nucleophilic attack by decreasing the ground state stabilization of the acyl group. Also the nitro-group is *meta* to the oxide in (18) and so the effect on its nucleophilicity is merely inductive. Overall, the rate of cyclization is increased relative to the unsubstituted material (11; R = H) so that the activating effect of the nitro-group is dominant.



When the nitro-group is *para* to the hydroxy-group [as in (17)], then the nucleophilicity of the conjugate base is very much reduced by resonance electron withdrawal by the nitro-group. On the other hand, the nitro-group is *meta* to the carbamate in (17) and so activates the carbamate carbonyl much less effectively than in the case of the isomer (16). The overall result is the observed large decrease in the plateau rate of cyclization (k_1) (see Figure 3).

Using Jaffé's [23,24] four parameter Hammett equation (5), which assumes that the substituent has a dual function, acting both on the susceptibility of the carbamate ($\rho_{carbamate}$) to nucleophilic attack and on the nucleophilicity of the ionized hydroxy-group ($\rho_{hydroxy}$), it was possible to obtain estimates for both ρ values.

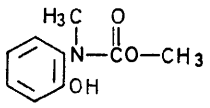
$$\log k/k_0 = \sigma_1\rho_{carbamate} + \sigma_2\rho_{hydroxy} \qquad (5)$$

The values were $\rho_{carbamate}$ +2·2 and $\rho_{hydroxy}$ −2·8, making

[23] H. H. Jaffé, *J. Amer. Chem. Soc.*, 1954, **76**, 4261.
[24] A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, 1967, **89**, 4853.

the assumption that a σ^- value is used for the nitro-group when it is *para* to either the carbamate or oxide groups. The large sensitivity to the nature of the nucleophile [the ρ value is actually larger than that reported ($+2{\cdot}36$)[25] for the protonation of phenolate anions] is consistent with a transition state (see below) involving a large degree of oxygen–carbon bond formation.

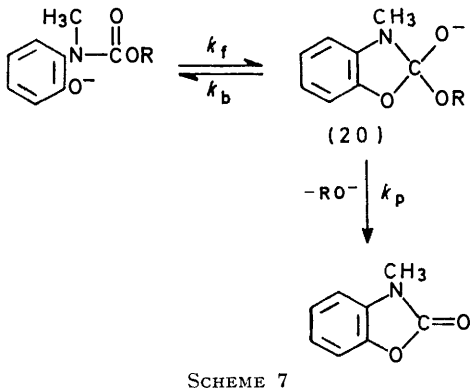
Effect of Substituents in Leaving Group.—The *o*-oxide group is such an efficient nucleophile towards the carbamate linkage that displacements of poor leaving groups are possible. Thus the methyl carbamate (19) is cyclized to *N*-methylbenzoxazolinone in basic solution. The rate of cyclization is proportional to the fraction of



(19)

the substrate in the ionized form and the observed rate constants are correlated by equation (4) with $k_1 = 7{\cdot}3 \times 10^{-4}$ s^{-1} and $pK_{a_1} = 9{\cdot}75$. Since the elimination–addition mechanism is blocked in this case, the rate constant k_1 most probably represents a mechanism in which the *o*-oxide group acts as an internal nucleophile.

It is interesting to note, by comparing the k_1 values for (11; R = Me) and (19), that the methoxy-group decreases the rate of cyclization by 2900-fold. This contrasts with the much smaller rate differences (*ca.* 3·5-fold) observed for the reactions of phenyl and methyl *N*-(*p*-nitrophenyl)carbamates.[6] A possible explanation lies in the formation of a tetrahedral intermediate (20) on the reaction pathway. The intermediate can either revert to the starting material or expel RO^- to give the product (Scheme 7).

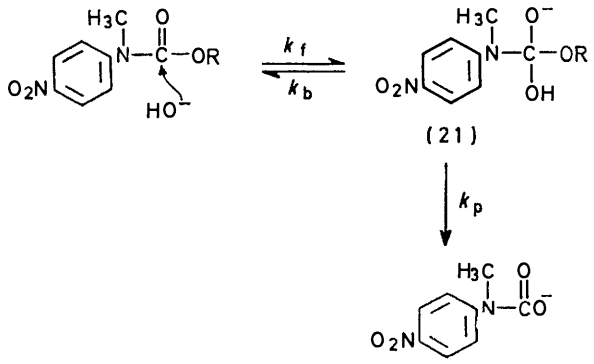


SCHEME 7

The fraction of the intermediate reverting to starting material depends on the relative magnitudes of k_p and k_b which in turn depend on the leaving group abilities of RO^- and the cyclic PhO^-. When R = Ph, the leaving abilities are approximately equal so that $k_p \sim k_b$, but when R = CH_3, $k_b \gg k_p$. In the latter instance, breakdown of the tetrahedral intermediate (k_p) could be rate determining. Since this step involves the expulsion of the RO^- group the overall reaction would show relatively high sensitivity to the nature of the leaving group. This is reflected in the large change in the observed rate of cyclization (k_1) on changing from a phenoxide to a methoxide leaving group ($\Delta\log k_1$ is 3·45 for ΔpK_a of leaving group of *ca.* 5 units).

In the bimolecular case the nucleophile is hydroxide ion. In the intermediate (21), $\bar{O}R$ or $\bar{O}H$ may be lost (Scheme 8). In this case when R = CH_3, the intermediate should have an approximately equal chance of reverting to starting material or of going on to products, while for R = Ph, $k_p \gg k_b$. Thus, formation of the intermediate (k_f) is more likely to be rate determining and thus the overall reaction shows a low sensitivity to a change in the nature of the leaving group.

Another factor which may accentuate the difference between the two systems is the magnitude of the rate constant for nucleophilic attack (k_f). The magnitude of k_f is very much increased by the approximation of the



SCHEME 8

reactive groups in the intramolecular case (see above) while k_b remains essentially unaltered. The result is that the equilibrium governing the formation of the intermediate (20) lies further to the right [than that for the formation of (21)] and this in turn also ensures that k_p becomes rate determining in the intramolecular case. This analysis does not of course prove the existence of a tetrahedral intermediate on the reaction pathway but, for convenience, the observed leaving group substituent effects are best visualized in these terms.

In the case of the *o*-carboxycarbamates we found that *p*-nitrophenyl *N*-(*o*-carboxyphenyl)carbamate reacts *ca.* 10^2-fold more rapidly than (4) in the plateau region. Similarly, introduction of a much poorer leaving group causes a large rate depression. In the case of methyl *N*-(*o*-carboxyphenyl)carbamate the rate of cyclization was immeasurably low ($k_1 < 5 \times 10^{-6}$ s^{-1}) at 25°. This is consistent with a rate difference of >200-fold on changing the leaving group from phenoxy to methoxy. The effect of systematically changing the leaving group on the rate of cyclization of aryl *N*-(*o*-carboxy phenyl)-carbamates is summarized as a plot of log k_1 against σ (Figure 4). It is seen that the σ value which would bring the data for the *p*-nitro-substituent onto the line

[25] H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.

correlating the other substituents lies between a σ and a σ⁻ value; in terms of the Yukawa–Tsuno equation [26] the calculated degree of resonance interaction in the transition state (r) is 0·4. The ρ value calculated (see Figure 4) for leaving group variation is +2·0; therefore, both the sensitivity shown and the degree of resonance

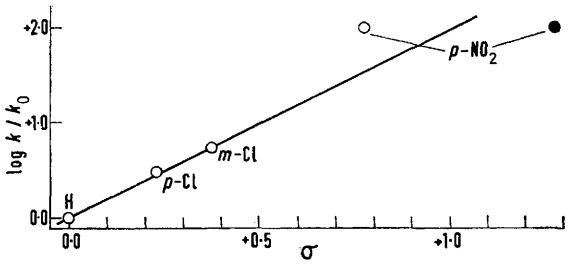
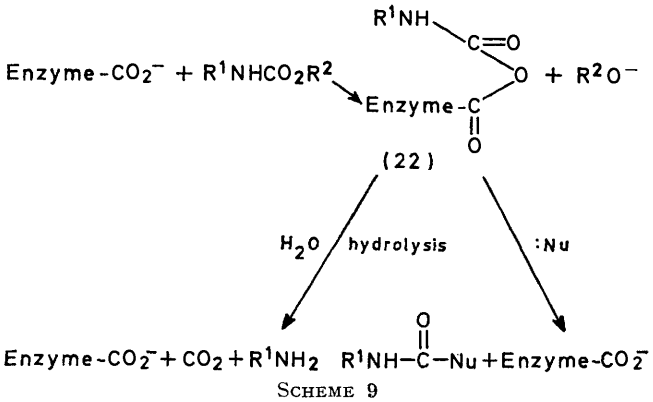


FIGURE 4 Plot of log k_1 for the cyclization of the *para*-substituted phenyl *N*-(*o*-carboxyphenyl)carbamates against the σ values of substituents. The point marked by the solid circle represents the σ⁻ value for the *p*-nitro-substituent

interaction is larger than that normally shown in simple ester hydrolysis (*e.g.* in the hydroxide catalysed aryl benzoates ρ and r are [27] +1·0 and 0·2 respectively).

The *o*-carboxycarbamate system (4) therefore provides a possible model for catalysed hydrolysis of carbamate esters. It can be seen from the results obtained that an enzyme can, by adsorption of a carbamate-like substrate onto the surface at its active site adjacent to a carboxylate function, undergo smooth reaction to give a carbamoylated enzyme intermediate (Scheme 9). The latter can either transfer the carbamoyl group to a suitable nucleophile (Nu) or assist in the overall hydrolysis of the carbamate. Isatoic anhydride, a model for the carbamoylated enzyme (22), has been shown to undergo rapid hydrolysis and reaction with amines.[15,16] The intermediate (22) which, unlike isatoic anhydride, is acyclic and possesses a very good leaving group (a substituted carboxylate ion) should undergo even more rapid hydrolysis (*via* *E*1cB-type elimination). Factors which might enhance the reactivity of the carbamate substrate are *NN*-disubstitution or the introduction of



SCHEME 9

electron-withdrawing substituents (especially those *para* to the carbamate) in the *N*-aryl ring; in both cases this appears to reduce the ground state stabilization of the carbonyl group in the carbamate linkage which consequently undergoes nucleophilic attack more readily.

EXPERIMENTAL

General.—All inorganic materials used were AnalaR grade. Dioxan was B.D.H. AnalaR grade, used without further purification. Deionized water was twice distilled from alkaline potassium permanganate.

4 : 1 (v/v) Water–dioxan at 25° was used for most kinetic experiments. 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 (0·01M) concentrations of phosphate or borate or alternatively by the use of the combined pH-stat–u.v. spectrophotometer which has been described previously.[6]

M.p.s were taken using an Electrothermal apparatus. I.r. spectra were measured using a Perkin-Elmer model PE 257 spectrometer, the solids being examined as KBr discs. N.m.r. spectra were run on a Perkin-Elmer model 20A spectrometer.

Substrates.—*Phenyl* N-(o-*carboxyphenyl*)*carbamate.* To a stirred solution of anthranilic acid (2·74 g, 0·02 mol) in ether (30 ml) was added dropwise a solution of phenyl chloroformate (1·56 g, 0·01 mol) in ether (10 ml). The hydrochloride salt of anthranilic acid which precipitated was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from chloroform–light petroleum (b.p. 40—60°) to give the *carbamate*, m.p. 171—173° (Found: C, 65·1; H, 4·65; N, 5·5. $C_{14}H_{11}NO_4$ requires C, 65·4; H, 4·3; N, 5·4%).

Phenyl N-(p-*carboxyphenyl*)*carbamate.* To a stirred solution of *p*-aminobenzoic acid (2·74 g, 0·02 mol) in dioxan (40 ml) was added a solution of phenyl chloroformate (1·56 g, 0·01 mol) in dioxan (5 ml). The hydrochloride salt of *p*-aminobenzoic acid which precipitated was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from chloroform–light petroleum (b.p. 40—60°) to yield the *carbamate*, m.p. 244—246° (Found: C, 65·7; H, 4·3; N, 5·8%).

Methyl N-(o-*carboxyphenyl*)*carbamate.* To a stirred solution of anthranilic acid (2·74 g, 0·02 mol) in anhydrous ether (40 ml) was added dropwise a solution of methyl chloroformate (0·945 g, 0·01 mol) in anhydrous ether (10 ml). The hydrochloride salt of anthranilic acid which precipitated was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized to constant m.p. from chloroform–pentane to give the *carbamate*, m.p. 173—175° (Found: C, 55·3; H, 4·9; N, 7·6. $C_9H_9NO_4$ requires C, 55·4; H, 4·6; N, 7·2%).

p-*Nitrophenyl* N-(o-*carboxyphenyl*)*carbamate.* To a stirred solution of anthranilic acid (2·74 g, 0·02 mol) in anhydrous diethyl ether (40 ml) was added *p*-nitrophenyl chloroformate (2·01 g, 0·01 mol) dissolved in anhydrous diethyl ether (15 ml). The hydrochloride salt of anthranilic acid which precipitated was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from chloroform–light petroleum (b.p. 40—60°) to give the *carbamate*, m.p. 158—160° (Found: C, 55·2; H, 3·5; N, 9·1. $C_{14}H_{10}N_2O_6$ requires C, 55·6; H, 3·3; N, 9·3%).

Phenyl N-(o-*ethoxycarbonylphenyl*)*carbamate.* This was prepared similarly from ethyl anthranilate and had m.p. 63—65° [from chloroform–light petroleum (b.p. 40—60°)]

[26] Y. Yukawa and Y. Tsuno, *J. Chem. Soc. Japan*, 1965, **86**, 875.

[27] Z. S. Chaw, A. Fischer, and D. A. R. Harper, *J. Chem. Soc.* (*B*), 1971, 1819.

(Found: C, 67·25; H, 5·5; N, 4·9. $C_{16}H_{15}NO_4$ requires C, 67·4; H, 5·3; N, 4·9%).

Phenyl N-(2-*carboxy*-4-*nitrophenyl*)*carbamate*. This was prepared from 4-nitroanthranilic acid (3·64 g, 0·02 mol) dissolved in chloroform (40 ml) and phenyl chloroformate (1·56 g, 0·01 mol) dissolved in chloroform (5 ml). The residue obtained as above was recrystallized several times from chloroform to give the *carbamate*, m.p. 188—192° (Found: C, 55·1; H, 3·4; N, 9·4. $C_{14}H_{10}N_2O_4$ requires C, 55·6; H, 3·3; N, 9·3%).

Similarly prepared were *phenyl* N-(2-*carboxy*-5-*nitrophenyl*)*carbamate*, m.p. 241—242° (Found: C, 55·2; H, 3·3; N, 9·7%); *phenyl* N-(2-*carboxy*-4-*chlorophenyl*)*carbamate*, m.p. >360° (Found: C, 57·7; H, 3·6; N, 5·0; Cl, 11·6. $C_{14}H_{10}ClNO_4$ requires C, 57·6; H, 3·4; N, 4·8; Cl, 12·2%); *phenyl* N-(2-*carboxy*-5-*chlorophenyl*)*carbamate*, m.p. 176—180° (Found: C, 57·7; H, 3·7; N, 5·0; Cl, 12·1%); *phenyl* N-(2-*carboxy*-5-*methylphenyl*)*carbamate*, m.p. 186—189° (Found: C, 65·6; H, 4·5; N, 5·1. $C_{15}H_{13}NO_4$ requires C, 66·4; H, 4·8; N, 5·2%).

Aryl N-(2-*carboxyphenyl*)*carbamates*. *p*-Chlorophenyl *N*-(2-carboxyphenyl)carbamate was prepared from anthranilic acid and *p*-chlorophenyl chloroformate [28] in dry tetrahydrofuran (THF). The *carbamate* had m.p. 172—175° (Found: C, 56·1; H, 3·6; N, 4·7; Cl, 12·4. $C_{14}H_{10}ClNO_4$ requires C, 57·6; H, 3·4; N, 4·85; Cl, 12·2%). Similarly prepared was m-*chlorophenyl* N-(2-*carboxyphenyl*)*carbamate*, m.p. 165—167° (Found: C, 56·9; H, 3·65; N, 4·9; Cl, 11·1%).

Methyl N-(2-*hydroxyphenyl*)-N-*methylcarbamate*. To a stirred solution of *o*-amino-*N*-methylphenol (2·46 g, 0·02 mol), prepared by the method of ref. 29, in anhydrous ether (25 ml) was added dropwise a solution of methyl chloroformate (0·95 g, 0·01 mol) in anhydrous ether (5 ml). The hydrochloride salt of *o*-amino-*N*-methylphenol which precipitated was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from chloroform–light petroleum (b.p. 40—60°) to yield the *carbamate*, m.p. 104—106° (Found: C, 59·7; H, 6·4; N, 7·7. $C_9H_{11}NO_3$ requires C, 60·0; H, 6·1; N, 7·8%).

[28] M. J. Zabik and R. D. Schuetz, *J. Org. Chem.*, 1967, **32**, 300.
[29] G. W. Anderson and F. Bell, *J. Chem. Soc.*, 1949, 2668.
[30] S. F. MacDonald and A. J. Chechak, *Canad. J. Res.*, 1948, **26B**, 432.

Similarly prepared were phenyl *N*-(2-hydroxyphenyl)-*N*-methylcarbamate, m.p. 135—137° (lit.,[20] m.p. 146°) from *o*-amino-*N*-methylphenol and phenyl chloroformate and phenyl *N*-(2-hydroxyphenyl)carbamate, m.p. 146—149° (lit.,[20] m.p. 150°) from *o*-aminophenol and phenyl chloroformate. In each case analysis and i.r. spectrum were consistent with the assigned structure.

Phenyl N-(2-*hydroxy*-5-*nitrophenyl*)*carbamate*. To a stirred solution of 2-amino-5-nitrophenol (3·08 g, 0·02 mol) in anhydrous ether (40 ml) was added dropwise a solution of phenyl chloroformate (1·56 g, 0·01 mol) in diethyl ether (5 ml). The hydrochloride of 2-amino-5-nitrophenol which precipitated after a short time was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from chloroform–light petroleum (b.p. 40—60°) to yield the *carbamate*, m.p. 216—218° (Found: C, 56·5; H, 3·85; N, 10·25. $C_{13}H_{10}N_2O_5$ requires C, 56·9; H, 3·6; N, 10·2%). *Phenyl* N-(2-*hydroxy*-4-*nitrophenyl*)-*carbamate* was similarly prepared from 2-amino-4-nitrophenol and phenyl chloroformate, m.p. 211—214° (Found: C, 56·9; H, 3·8; N, 10·2%).

Phenyl N-(4-*hydroxyphenyl*)*carbamate*. To a stirred solution of 4-aminophenol (2·18 g, 0·02 mol) in anhydrous THF (30 ml) was added dropwise a solution of phenyl chloroformate (1·56 g, 0·01 mol) in anhydrous THF (10 ml). The hydrochloride of 4-aminophenol which precipitated was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from chloroform–light petroleum (b.p. 40—60°) to yield the *carbamate*, m.p. 137—139° (Found: C, 67·9; H, 5·3; N, 6·6. $C_{13}H_{11}NO_3$ requires C, 68·1; H, 4·8; N, 6·1%).

Benzoxazolin-2-one was prepared by a known procedure [30] and was recrystallized from water, m.p. 138—140° (lit.,[31] m.p. 141—142°). *N*-Methylbenzoxazolin-2-one was prepared by treating benzoxalinone with concentrated NaOH and dimethyl sulphate according to the method of Anderson and Bell.[29] Recrystallization from ethanol–water gave crystals, m.p. 86—88° (lit.,[29] 86°).

[3/2620 *Received*, 28*th December*, 1973]

[31] T. M. Heilbron, ' Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965, 4th edn., vol. 1, p. 355.