Neighbouring Carboxy-group Catalysis of Ring Opening of 3,1-Benzoxazin-4-ones

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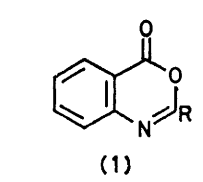
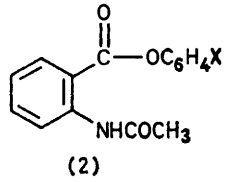
Efficient intramolecular catalysis of the hydrolysis of 2-methyl-3,1-benzoxazin-4-ones to *N*-acetylanthranilic acids by a neighbouring carboxy-group [as in (6)] is demonstrated. The 8-carboxy-compound (6) reacts 250-fold faster than the 6-carboxy-isomer (7) at pH 6. A mechanism involving the 8-carboxy-group as an internal general acid catalyst is proposed. The 5-carboxy-isomer (9) does not show enhanced reactivity but, consistent with attack of the nucleophile at the 4-position of the benzoxazinone, hydroxide ion catalysed hydrolysis is actually depressed by the presence of the CO_2^- group in this position. The anhydride (13) (formed by reaction of 3-aminophthalic acid with acetic anhydride) is hydrolysed directly (by H_2O or HO^- attack) at pH < 10; however at pH > 10 a preliminary rearrangement of the anhydride (13) to the benzoxazine (9) occurs.

3,1-BENZOXAZIN-4-ONES (1) have been detected as intermediates resulting from intramolecular attack by an amide oxygen atom on an ester or amide carbonyl group; for example (1; R = CH_3) is an intermediate [1] in the hydrolysis of aryl *N*-acetylanthranilates (2) in accordance with earlier suggestions.[2,3] In an analogous



(1)



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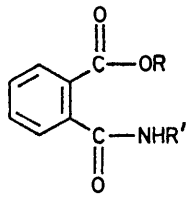

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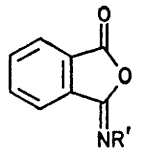

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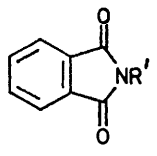


(5)

manner, isoimides (4), are possible intermediates in the hydrolysis of (3) but this may be obscured by a ready rearrangement to the imide (5).[4-6]

The hydrolysis of 2-methyl-3,1-benzoxazin-4-one (1; R = CH_3), is specific acid and base catalysed, and proceeds slowly in neutral solution. At physiological pH therefore, amide group participation in ester or amide group hydrolysis may not be overall catalytic, giving a stable benzoxazinone. This report investigates the role of appropriately placed intramolecular carboxy-groups in providing enhanced rates of hydrolysis of (1) in neutral solution.

RESULTS AND DISCUSSION

The hydrolyses of benzoxazines (6)—(9) were followed spectrophotometrically in the absence of buffer species (or extrapolated to zero buffer concentration in some cases) in water at 25° (μ 0.1M; KCl). Initial repetitive scans of the hydrolysing species indicated that reaction was clearly of first order in all cases as judged from the observation of well defined isosbestic points (Table 1, Figure 1). The spectra of solutions after complete

TABLE 1

Spectral data for substituted 2-methyl-3,1-benzoxazin-4-ones

Compound	λ_{max}/nm	λ_i/nm [a]	λ_k/nm [b]
(6)	314	291	325
(7)	317	307	325
(8)	316.5	282.5, 291.5	325
(9)	*ca.* 320		325, 300

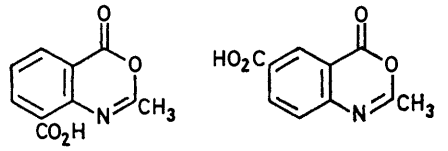
[a] λ_i = Isosbestic wavelength. [b] λ_k = Wavelength used in kinetic studies.

hydrolysis corresponded exactly to those of pure samples of the open-chain substituted 2-acetylaminobenzoic acids at the same concentration. Plots of the logarithm of the observed first-order rate constants (k_{obs}) against pH for (6)—(9) are provided in Figure 2. The rate constants for the 5-carboxy-isomer (9) were obtained as detailed below. The rate profile for (1; R = CH_3) is not shown but is similar to that of (7).[2]

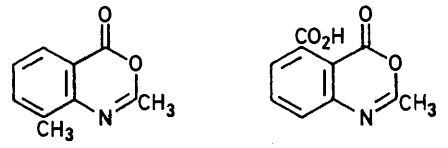
The curves drawn through the experimental points

[1] D. J. Cremin and A. F. Hegarty, *Tetrahedron*, 1977, **33**, 1823.
[2] A. Williams and G. Salvadori, *J. Chem. Soc.* (*B*), 1971, 1105.
[3] M. L. Bender, G. R. Schonbaum, and G. A. Hamilton, *J. Polymer Sci.*, 1961, **49**, 75.
[4] M. L. Ernst and G. L. Schmir, *J. Amer. Chem. Soc.*, 1966, **88**, 500.
[5] D. Y. Curtin and L. L. Miller, *J. Amer. Chem. Soc.*, 1967, **89**, 637.
[6] D. J. Cremin and A. F. Hegarty, unpublished work.

were generated from the empirical rate equations (1) for (6) and (2) for (7)—(9). The parameters yielding curves



(6) (7)



(8) (9)

of best fit to the experimental points are shown in Table 2.

$$k_{obs} = k_1 a_H + \frac{k_2 a_H}{a_H + K_{a2}} + k_2 + k_4[HO^-] \quad (1)$$

$$k_{obs} = k_1 a_H + k_3 + k_4[HO^-] \quad (2)$$

Thus, in the hydrolysis of (6) four distinct phases are evident: (i) an acid-catalysed region at low pH (below pH *ca.* 2); (ii) a sigmoid rate dependence in the pH 3—6 range; (iii) an uncatalysed (water) reaction, and (iv) hydroxide-ion catalysis at high pH. The predominant reactive species in these phases are illustrated in Scheme 1.

TABLE 2

Empirical parameters describing the rates of hydrolysis of benzoxazines (6)—(9)

Comp.	k_1/l mol^{-1} s^{-1}	k_2/s^{-1}	k_3/s^{-1}	k_4/l mol^{-1} s^{-1}
(6) [a]	178	0.220	2.51×10^{-4}	21.4
(7)	19.95		7.94×10^{-6}	56.2
(8)	89.1		1.26×10^{-5}	15.85
(9)	56.2			5.62

[a] K_{a2} for (6) = 3.55×10^{-5}.

The acid-catalysed region is attributed to water attack on the protonated species (6a). Although it is not evident from the pH–rate profile it is expected that the rate of hydrolysis would become pH-independent when the heterocyclic nitrogen is fully protonated. It was not possible to measure pK_{a1} for (6) due to the rapidity of

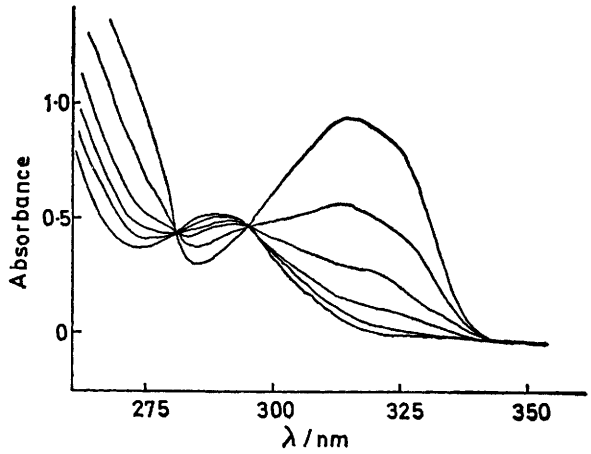


FIGURE 1 Repetitive scans of the u.v. spectrum of 2,8-dimethyl-3,1-benzoxazin-4-one (8) in water at 25° (pH 4.0). The half-life of this reaction is *ca.* 70 s

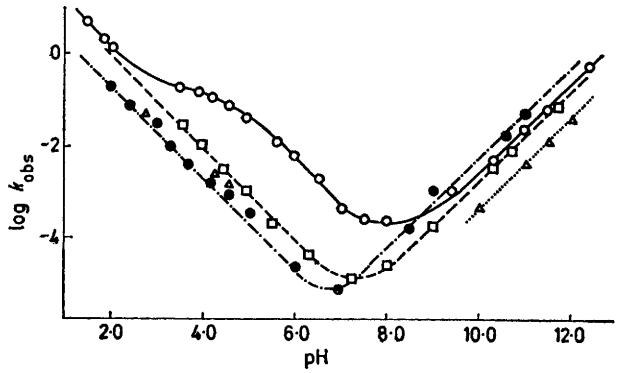
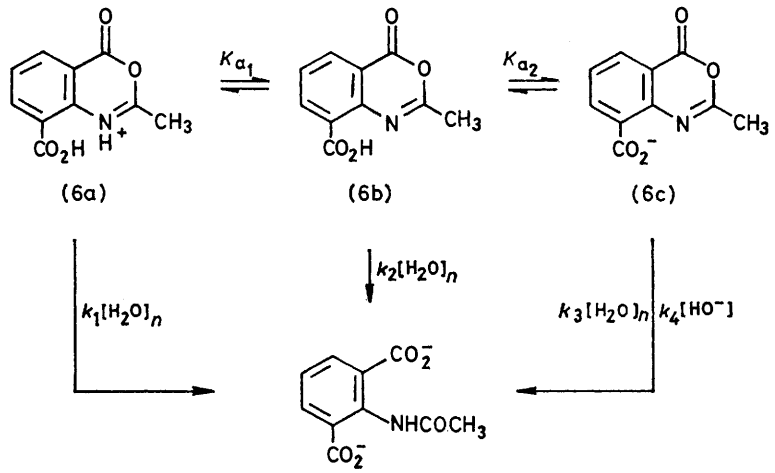


FIGURE 2 Plots of log (k_{obs}/s^{-1}) against pH for the hydrolysis of (6) (○), (7) (●), 8 (□), and (9) (△). The points are experimental and the curves generated from equations (1) and (2)

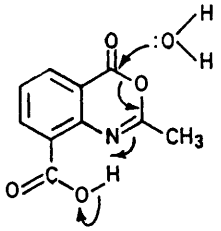


SCHEME 1

hydrolysis at low pH but preliminary investigation of (1; R = CH_3) suggests that its pK_a may be *ca.* 0. This is also expected by analogy with 2-aminobenzoxazin-4-ones (1; R = NH_2), where pK_a = 1.65.[7]

In the pH 3—6 region hydrolysis of (6) proceeds mainly through water attack on the neutral species (Scheme 1). The spectrophotometric measurement of pK_{a2} also proved difficult due to rapid hydrolysis and a small optical density change but a kinetic pK_{a2} of 4.45 was obtained. This value is indicative of some hydrogen bonding between the carboxy hydrogen in the *ortho*-position and the heterocyclic nitrogen (the pK_a of benzoic acid is 4.18).

Since the hydrolysis of (6) is significantly faster than (1; R = CH_3)[2] in the pH 3—7 region (250 times faster at pH 6) it appears likely that intramolecular general acid catalysis (10) operates, *i.e.* the presence of the neutral carboxy-group *ortho* to the heterocyclic ring nitrogen atom allows intramolecular general acid catalysis of protonation of the leaving group, increasing the susceptibility of the carbonyl group to nucleophilic attack. Attack of water on C-2, (11), is also a mechanistic possibility and ^{18}O labelling experiments have indicated that this is the favoured site of attack of water on benzoxazin-4-ones[2] and isoimides.[8] It is evident that water attack at both C-2 and -4 yield the same product. The catalysis observed by the 8-carboxy-group is similar to, but larger than that previously



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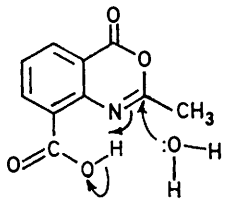

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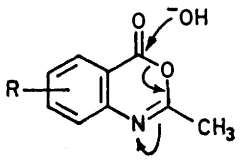


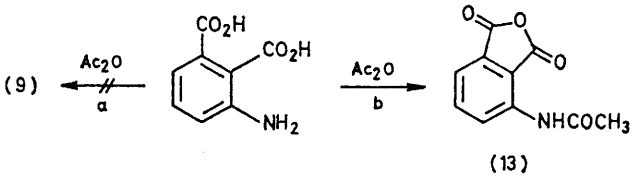
(12)

reported for the hydrolysis of 2-amino-3,1-benzoxazin-4-ones.[9]

The significant catalysis exhibited in (6) is not due to an electronic effect since (7) (with a carboxy-group in a remote but electronically similar position) hydrolyses at comparable rates to the unsubstituted benzoxazin-4-one (1) (Figure 1) in the pH 3—7 region. A steric effect due to the proximity of the carboxy-group to the heterocyclic nitrogen of (6) is unlikely since (8) shows only very moderate rate increase over the unsubstituted benzoxazin-4-one (1). This rate increase (a factor of three) exhibited by (8) is attributable to electron donation by the methyl group, enhancing the susceptibility of nitrogen to protonation.

There is general agreement[2,7,8] that attack of hydroxide ion takes place at the carbonyl group (12). Reference to Figure 1 and Table 1 indicates little variation in the base-catalysed profiles of the benzoxazines (7) and (8), consistent with a reported σ value of *ca.* 0 for a CO_2^- group.[10] However, the hydroxide catalysed hydrolysis of the 5-carboxy-substituted material (9) is depressed by a factor of four relative to the norm. This is most likely due either to a steric effect (the effective size of the CO_2^- group being increased by co-ordination with solvent molecules), or an electrostatic effect on the incoming negatively charged nucleophile.

Anhydride–Benzoxazinone Rearrangement.—The attempted synthesis of 5-carboxy-2-methyl-3,1-benzoxazin-4-one (9), yielded instead the isomeric 3-acetylaminophthalic anhydride (13) (path b of Scheme 2).



SCHEME 2

The hydrolysis of (13) was followed spectrophotometrically (at 320 nm) at constant pH in the absence of buffer species (25°; μ 0.1M; KCl). The data are presented in Table 3; the rate constants obtained were closely paralleled by those of phthalic anhydride, studied under identical conditions (measured at 300 nm). It is clear that k_{obs} is essentially constant in the pH 0—6.5 region confirming the anhydride structure. Anhydrides, like imides[4,6] (5), do not have an acid-catalysed pathway available so a rate law (3) is obeyed

$$k_{obs} = k_1 + k_2[HO^-] \qquad (3)$$

with k_1 1.0 × 10^{-2} s^{-1} and k_2 2.95 × 10^4 l mol^{-1} s^{-1} for (13). These parameters are similar to those of phthalic anhydride so the *o*-amido-group does not appear to increase the rate of hydrolysis of (13).

An anomalous feature of the hydrolysis of (13) was the appearance of a second measurable base-catalysed reaction in the pH 11—13 region. Table 3 indicates clearly that this could not be due to anhydride hydrolysis since this becomes very rapid above pH 8. Repetitive scans of the u.v. spectrum of (13) in water at 25° at pH 11 indicated that the intermediate species had $\lambda_{max.}$ 320 nm; a decreasing absorbance was observed during its subsequent reaction with a half-life of 155 s. The hydrolysis rates were measured at various pH values in

[7] A. F. Hegarty and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 6561.
[8] C. K. Sauers, *Tetrahedron Letters*, 1970, 1149.
[9] A. F. Hegarty, R. F. Pratt, T. Giudici, and T. C. Bruice, *J. Amer. Chem. Soc.*, 1971, **93**, 1428.
[10] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.

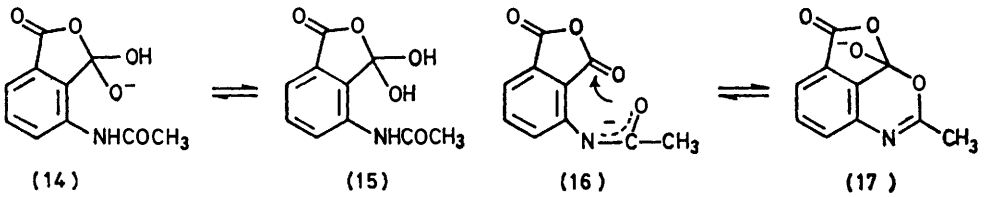
water at 25° and are included in Figure 2. Both the spectral data and hydrolysis profile are consistent with structure (9) for the intermediate [formed through rearrangement of anhydride (13)].

TABLE 3

Rate constants for the hydrolysis of 3-acetylaminophthalic anhydride (13) at 25° in water (μ 0.1M; KCl)

pH	1.0	1.5	2.0	2.8	4.0
$10^3 k_{obs}/s^{-1}$	10.0	10.3	10.0	10.5	9.5
pH	5.7	6.5	7.0	7.6	8.25
$10^3 k_{obs}/s^{-1}$	10.8	11.5	13.6	22.0	41.2

That rearrangement did take place at high pH was confirmed as follows: the benzoxazine (9) should also have an acid-catalysed hydrolysis pathway available; at pH *ca.* 10 the anhydride is highly reactive and should generate benzoxazine on dissolution, while the benzoxazine itself is relatively unreactive. Thus, addition of the anhydride (13) to a water solution at pH > 10, followed by rapid acidification of the solution to a pH range where benzoxazinones are known to undergo acid catalysed hydrolysis, was carried out. Several experiments in the pH range 1—5 confirmed the existence of a subsequent acid-catalysed hydrolysis (see Figure 2, △) comparable with that observed for other benzoxazinones.



(14) (15) (16) (17)

Thus, in the pH 0—10 region the anhydride (13) appears to hydrolyse in a straightforward manner to the corresponding phthalic acid derivative. This is clear from the well defined isosbestic points observed in repetitive scans of the u.v. spectrum from pH 0—6 and the invariant absorbances recorded on completion of reaction in the rate measurements [particularly in the pH 2.5—4.5 region where hydrolysis rates of anhydride (13) and benzoxazinone (9) are comparable]. Further confirmation that the anhydride (13) used was not contaminated by the isomeric benzoxazinone (9) was obtained from i.r. and n.m.r. data on (13).

In contrast, at high pH an initial rearrangement of anhydride to benzoxazine takes place followed by subsequent ring opening of benzoxazine. The rate of conversion of the anhydride (13) to the benzoxazine (9) which occurred at pH 10 was too fast to measure directly. However since the competing hydrolysis of the anhydride (13) (to *N*-acetyl-6-carboxyanthranilic acid) was shown to be base catalysed up to pH 8.25, the rearrangement is also most likely catalysed by HO^- (or $[HO^-]^2$). Possible mechanisms which might explain this change-over in product include: (a) formation of the intermediate (14) which can break down at low pH [*via* (15)] to give the normal hydrolysis products or *via* (14) at high pH involving neighbouring group participation by O^- on the neighbouring amide group; (b) attack by the amide anion (16) on the anhydride to give an intermediate (17) which breaks down to give the benzoxazine (9) only at high pH.

[11] M. T. Bogert and A. H. Gothelf, *J. Amer. Chem. Soc.*, 1900, **22**, 534.

EXPERIMENTAL

8-Carboxy-2-methyl-3,1-benzoxazin-4-one.—To a solution of 2-aminoisophthalic acid (1.81 g, 0.01 mol) in acetic acid (5 ml) acetic anhydride (10.2 g, 0.1 mol) was added and the mixture was refluxed for 1 h. On cooling a *precipitate* formed which was filtered and recrystallized from chloroform, m.p. 219—221°; $\nu_{max.}$ 3 100—2 500 (OH), 1 780 (cyclic C=O), 1 750 (acid C=O), and 1 650 cm^{-1} (cyclic C=N) (Found: C, 58.2; H, 3.6; N, 6.5. $C_{10}H_7NO_4$ requires C, 58.5; H, 3.4; N, 6.8%). Similarly prepared were *6-carboxy-2-methyl-3,1-benzoxazin-4-one*, recrystallized from benzene–pentane, m.p. 135—137°; $\nu_{max.}$ 3 200—2 300 (OH), 1 770 (cyclic C=O), 1 690 (acid C=O), and 1 650 cm^{-1} (cyclic C=N) (Found: C, 58.0; H, 3.45; N, 7.2. $C_{10}H_7NO_4$ requires C, 58.5; H, 3.4; N, 6.8%) and *2,8-dimethyl-3,1-benzoxazin-4-one*, recrystallized from ethanol, m.p. 132—133°; $\nu_{max.}$ 1 750 (cyclic C=O) and 1 650 cm^{-1} (cyclic C=N) (Found: C, 68.3; H, 5.4; N, 8.4. $C_{10}H_9NO_2$ requires C, 68.6; H, 5.1; N, 8.0%). 2-Methyl-3,1-benzoxazin-4-one was prepared as previously described, m.p. 76—77° (lit.,[2,11] 77—78; 79—80°).

2-Acetylaminoisophthalic Acid.—A solution of 2-aminoisophthalic acid (3.62 g, 0.02 mol) and acetic anhydride (2.04 g, 0.02 mol) in acetic acid (15 ml) was refluxed for 1 h. On cooling, the solution was added to ice–water and the precipitate obtained was recrystallized from ethanol, m.p. 216—217° (lit.,[12] 216—217°); $\nu_{max.}$ 3 330 (NH), 3 250—2 400 (OH), and 1 680 cm^{-1} (C=O) (Found: C, 53.9; H, 4.4; N, 6.55. Calc. for $C_{10}H_9NO_5$: C, 53.8; H, 4.05; N, 6.3%). Similarly prepared were *2-acetylamino-5-methylbenzoic acid*, m.p. 180—182°; $\nu_{max.}$ 3 200 (NH), 3 100—2 300 (OH), 1 690 (acid C=O), and 1 660 cm^{-1} (amide C=O) (Found: C, 61.7; H, 5.9; N, 7.2. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.25%); *2-acetylamino-3-methylbenzoic acid*, m.p. 204—205°; $\nu_{max.}$ 3 270 (NH), 3 200—2 300 (OH), 1 700 (acid C=O), and 1 670 cm^{-1} (amide C=O) (Found: C, 62.0; H, 5.8; N, 7.2. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.25%); and *N*-acetylanthranilic acid, m.p. 182—184° (lit.,[2,13] 186—186.5; 185°); $\nu_{max.}$ 3 300 (NH), 3 300—2 300 (OH), and 1 700br cm^{-1} (C=O).

2-Aminoisophthalic acid was prepared according to the

[12] C. Cardani and F. Piozzi, *Gazzetta*, 1956, **86**, 849.
[13] A. Kaufmann, *Ber.*, 1909, **42**, 3480.

method of Ospenson,[14] m.p. 312—315° (decomp.) [lit.,[15] 319—320° (decomp)]; $\nu_{max.}$ 3 470, 3 360 (NH_2), 3 300—2 500 (OH), and 1 695 cm^{-1} (C=O).

4-Acetylaminoisophthalic Acid.—An analogous method to that of Clark and Taylor [16] was employed. To a mixture of 2-acetylamino-5-methylbenzoic acid (4.82 g, 0.025 mol) and water (200 ml), potassium permanganate (7.9 g, 0.05 mol) was added. Initially the mixture was heated gently and was subsequently refluxed for 3 h. The manganese dioxide which precipitated was filtered and the resulting yellowish solution was treated with decolourising charcoal. The solution was reheated, acidified with concentrated HCl, cooled, and a *precipitate* was obtained. This was recrystallized from ethanol–water, and had m.p. 278—290° (slow decomp.) [lit.,[12] 270—280° (decomp.)]; $\nu_{max.}$ 3 200 (NH), 3 500—2 300 (OH), 1 735 (acid C=O), 1 700 (acid C=O), and 1 665 cm^{-1} (amide C=O) (Found: C, 54.5; H, 5.4; N, 6.9. $C_{10}H_9NO_5$ requires C, 53.8; H, 5.7; N, 7.25%).

3-Acetylaminophthalic Anhydride.—A solution of 3-aminophthalic acid hydrochloride (1.0 g, 0.004 6 mol) and acetic anhydride (5.1 g, 0.05 mol) in acetic acid (7 ml) was refluxed for 2 h. On cooling, a precipitate formed which was recrystallized from chloroform–pentane, m.p. 184—186° (lit.,[17,18] 185—186°); $\nu_{max.}$ 3 360 (NH), 1 843 (cyclic C=O), 1 765 (cyclic C=O), and 1 700 cm^{-1} (amide C=O); $\delta(CDCl_3)$ 2.3 (3 H, s), 7.78 (3 H, q), and 8.95 (1 H, d).

Phthalic anhydride was B.D.H. AnalaR grade used without further purification.

Kinetic Measurements.—All kinetic experiments (except where stated) were carried out in water at 25°. Ionic strength was maintained at 0.10M by the addition of KCl (except where pH < 1.0 was employed). The water used was deionized and then twice distilled from alkaline permanganate.

The course of hydrolysis was followed spectrophotometrically with either Unicam SP 800 or Cary 14–pH stat assembly u.v. spectrophotometers. Initial repetitive scans of the u.v. region established suitable wavelengths at which an appreciable optical density change occurred during reaction; the first-order rate constants were calculated from the slopes of plots of log (O.D.$_t$—O.D.$_\infty$) against time t. The substrate was made up (usually 10^{-2}M) in pure dioxan (B.D.H. AnalaR) and reaction was initiated by adding one drop of this solution to the u.v. cell. The rates of hydrolysis were generally measured in the absence of added buffer, using the Cary 14–pH stat assembly. Where buffer species were used, extrapolation to zero buffer concentration gave the reported value of k_{obs}. A Radiometer PHM 26 pH meter (with expanded scale) and Metrohm 125U glass electrode were used in pH measurements. In all cases the pH of the solution was measured after a kinetic experiment to confirm the absence of pH drift.

For the more rapid reactions ($t_{\frac{1}{2}} < 10$ s) a Durrum–Gibson model D-110 stopped-flow spectrometer, equipped with Kel-F components was used. The apparatus had a log convertor and the resultant absorbance–time plots were recorded on a Phillips model storage oscilloscope. The absorbance–time plots were analysed in all cases to give the pseudo-first-order rate constants from the experimental infinity values, using a least squares program written for the Olivetti Underwood Programma 101 or graphically. Good pseudo-first-order rate constants were obtained in all cases to >95% reaction.

[7/844 *Received*, 16*th May*, 1977]

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