Evidence for the Formation of Nitrenium Ions in the Acid-catalysed Solvolysis of Mutagenic *N*-Acetoxy-*N*-Alkoxybenzamides

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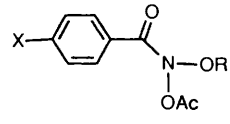
In aqueous acetonitrile, *N*-acetoxy-*N*-alkoxybenzamides undergo acid-catalysed solvolysis by the $A_{Al}1$ mechanism to give acetic acid and nitrenium ions. This is indicated by an inverse dependence of the acid-independent rate constant, k_H, upon the activity of water, a solvent kinetic isotope effect of 0.44 and positive $\Delta S^{\ddagger}$ values. In addition, relief of steric compression at the nitrogen enhances the rate of solvolysis. Hammett correlations with σ^+ substituent constants were found for the rates of solvolysis of *para*-substituted-*N*-acetoxy-*N*-butoxybenzamides and *N*-acetoxy-*N*-(*para*-substituted benzyloxy) benzamides. This fact and the low ρ-values of −1.35 and −1.56, respectively, are indicative of a strong build-up of positive charge in the transition state which has both nitrenium ion and oxonium ion character and is in accordance with computed molecular-orbital properties of *N*-alkoxynitrenium ions. Greater levels of mutagenicity have been measured for those compounds which are more readily solvolysed to nitrenium ions.

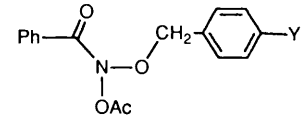
Aromatic amines are a class of compounds which are carcinogenic to humans and animals. Their biological activity is developed through metabolic activation by hepatic enzymes to ultimate carcinogens which have been variously identified as the *N*-acetoxy-*N*-arylamines (**1**), the *N*-acetoxy-*N*-arylacetamides (**2**) or their sulfate ester analogues **3** and **4**.[1,2]

Current understanding of the mode of action of these carcinogens focusses upon their ability to act as electrophiles towards DNA. Certainly, they have been found to undergo nucleophilic attack by nucleotides at nitrogen with the substitution of the acetoxy group, and both the 2-amino group (**5**) and C8 (**6**) positions of deoxyguanosine are attacked *in vivo*[3] and *in vitro*.[4] The actual mode of nucleophilic attack has, however, not yet been unequivocally established. Both Novak[5,6] and Boche[7] have recently found support for an S_N2 reaction at nitrogen while a good deal of evidence points to *N*-acetyl or *N*-sulfatooxy arylamines undergoing unimolecular solvolysis in organic–aqueous media and at physiological pHs to give arylnitrenium ions (**7**).[8,9] The lifetime of such nitrenium ions in aqueous solution is, however, predicted to be very short and greater persistence would be demanded for a significant interaction with biomolecular targets.[10]

The driving force for a unimolecular heterolysis of **1**–**4** undoubtedly resides in the resonance delocalisation of positive charge onto the aryl ring in **7**. *In vivo* formation of adducts **5** would seem to support this[3] and arylnitrenium ions usually undergo nucleophilic attack at the *ortho*- and *para*-positions.[6] A number of computational studies also indicate the substantial stabilising effect of an electron-releasing aryl substituent.[11] Our own calculations at the MNDO level are in accord with results of these workers and, in addition, point to a very similar stabilisation if a nitrenium ion is adjacent to a heteroatom bearing a lone pair (**8**).[12] Nitrogen, phosphorus, sulfur and oxygen lone pairs can overlap strongly with the vacant $2p_z$ orbital on nitrogen, the charge being shared by both atoms. These MNDO results are supported by the predictions from high-level *ab initio* calculations.[13] The acyl substituent exerts minor influence upon the stability of such nitrenium ions but, by replacing hydrogens, serves to prevent α-elimination to imines.[12]

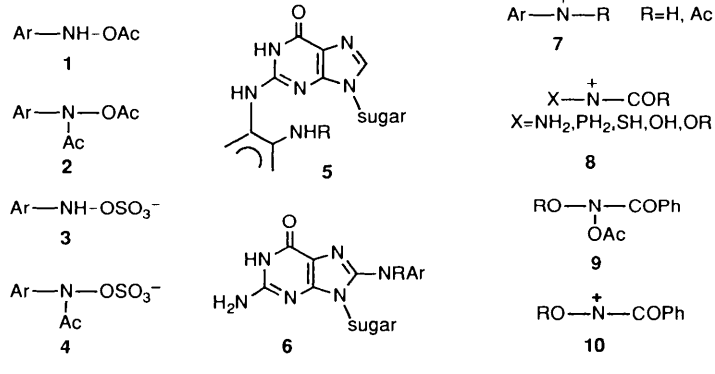


11 **a**; X = H, R = Et
b; X = H, R = Bu
c; X = H, R = Oct
d; X = H, R = Pr^i
e; X = H, R = Bu^i
f; X = OMe, R = Bu
g; X = Bu^t, R = Bu
h; X = Me, R = Bu
i; X = Ph, R = Bu
j; X = Cl, R = Bu
k; X = Br, R = Bu
l; X = NO_2, R = Bu



12 **a**; Y = H
b; Y = OMe
c; Y = PhO
d; Y = Bu^t
e; Y = Me
f; Y = Ph
g; Y = Cl
h; Y = Br
i; Y = NO_2

On the basis of the comparative abilities of aryl and alkoxyl substituents to stabilise nitrenium ions in **7** and **8** (X = OR), we recently proposed that *N*-acetoxy-*N*-alkoxy amides (**9**), like



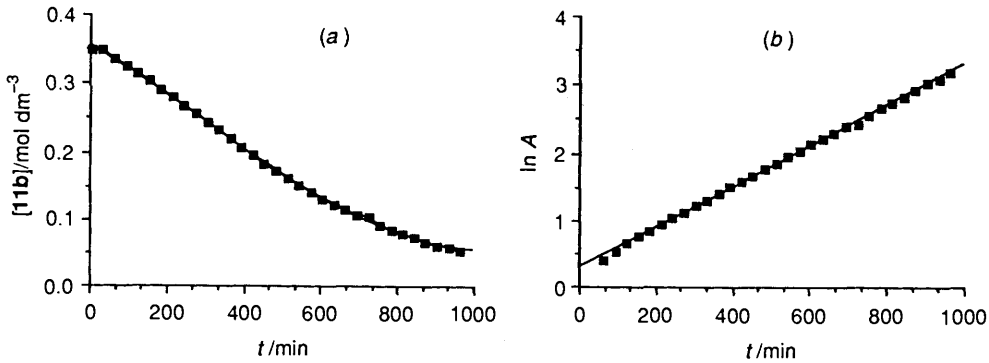


Fig. 1 (*a*) Disappearance of **11b** in CD_3CN–D_2O at 333 K. (*b*) Fit of the formation of acetic acid from **11b** to autocatalytic rate eqn. (1).

Table 1 Rate constants for solvolysis of *N*-acetoxy-*N*-alkoxybenzamides in CD_3CN–D_2O[a] at 308 K

	11				
	X	R	$k_H^{308}/10^{-2}$ dm^3 mol^{-1} s^{-1}	$k_0^{308}/10^{-5}$ s^{-1}	*r*
a	H	Et	3.82(0.22)	−1.76(2.90)	0.996
b	H	Bu	2.41(0.10)	2.31(1.30)	0.995
d	H	Pr^i	30.19(1.63)	−5.40(9.15)	0.996
e	H	Bu^i	1.91(0.15)	0.02(1.96)	0.994
f	MeO	Bu	29.56(3.04)	1.47(14.30)	0.984
h	Me	Bu	8.96(0.62)	13.40(8.50)	0.999
j	Cl	Bu	1.02(0.13)	4.24(2.58)	0.975
k	Br	Bu	1.19(0.07)	−0.43(1.50)	0.997
l	NO_2	Bu	0.245(0.02)	2.40(0.70)	0.990

[a] CD_3CN:D_2O = 3.81:1.

their aromatic analogues **2**, might exhibit biological activity. The original series of four such compounds, **11a–c** and **12a**, were indeed found to be mutagenic in *Salmonella typhurium* strains TA100 and TA98.[14] The result is made more significant by the fact that no metabolic activation was required for this activity. Compounds like **9** must be regarded as **ultimate mutagens** since current evidence points to no significant increase in the level of mutagenicity when S9 microsomal liver extract is applied in the Ames test. All chemicals in this class prepared to date have displayed mutagenicity without metabolic activation though their carcinogenicity has not yet been established.

We have recently focussed upon the solvolytic behaviour of these compounds with a view to establishing whether mutagenesis derives from **9** as a whole or whether *N*-alkoxy-*N*-benzoylnitrenium ions (**10**) are implicated.[15] This paper deals with our findings to date.

Results and Discussion

Preliminary ^{1}H NMR investigations indicated that *N*-acetoxy-*N*-butoxybenzamide (**11b**) reacted slowly in aqueous acetonitrile. Over 17 h at 333 K, however, it was found to decompose to a mixture of products and acetic acid. Monitoring the disappearance of the acetoxy methyl singlet at δ 2.08 and appearance of acetic acid δ 1.98 in a homogeneous D_2O–CD_3CN mixture at 333 K indicated a poor correlation with unimolecular or pseudo-unimolecular kinetics. Fig. 1 indicates that the data did, however, fit an integrated rate eqn. (1) for the

$$kK\sqrt{(K'[S]_0)}t = \ln\frac{(\sqrt{[S]_0} + \sqrt{[A]_t})}{(\sqrt{[S]_0} - \sqrt{[A]_t})} = \ln A \quad (1)$$

solvolysis of esters of weak carboxylic acids in which $[S]_0$ and $[A]_t$ are the initial concentration of **11b** and the concentration of acetic acid, respectively, k is the unimolecular or pseudo-unimolecular rate constant, K' is the dissociation constant of acetic acid and K is the pre-equilibrium constant for protonation of **11b** (Scheme 1 and Appendix).[16]

$$AcOH \overset{K'}{\rightleftharpoons} AcO^- + H^+$$

$$H^+ + S \overset{K}{\rightleftharpoons} SH^+$$

$$SH^+ \xrightarrow{k} \text{products} + AcOH$$

Scheme 1

$$H_3O^+ + S \overset{K}{\rightleftharpoons} SH^+ + H_2O$$

$$SH^+ \xrightarrow{k} \text{products} + AcOH$$

Scheme 2

The composite rate constant ($kK\sqrt{K'}$) at 333 K was found to be 8.58×10^{-5} dm$^{3/2}$ mol$^{1/2}$ s^{-1}. However, derivation of the first-order or pseudo-first-order rate constant, k, requires a knowledge of the dissociation constant K' for acetic acid under these conditions as well as K.

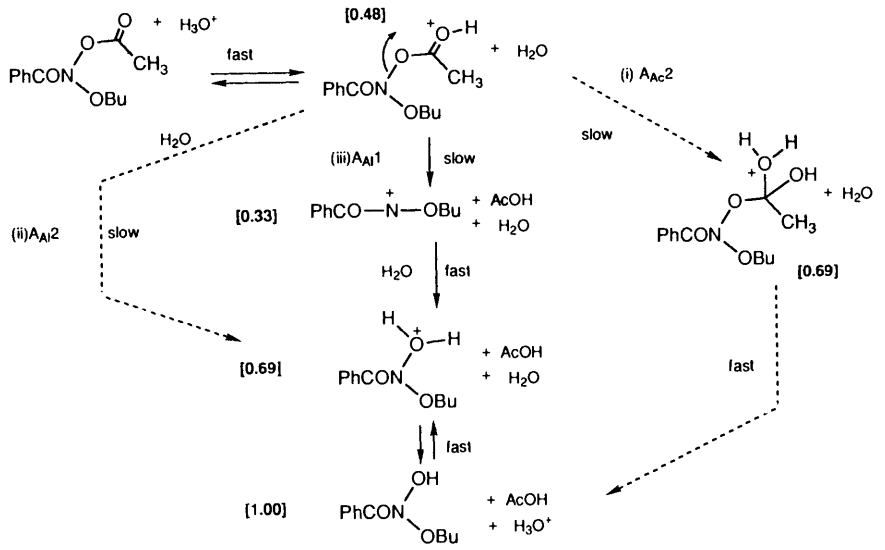
Upon addition of a solution of sulfuric acid in D_2O the reaction obeyed pseudo-unimolecular kinetics consistent with a rapid reversible protonation followed by a slow decomposition to acetic acid and products (Scheme 2). Since under these conditions water (D_2O) is in a relatively small excess compared with dilute aqueous solutions, the rate expression may best be represented by eqn. (2) where the pseudo-unimolecular rate constant $k' = kK[H_3O^+]/[H_2O] = k_H[H_3O^+]$.

$$\frac{d[S]}{dt} = \frac{d[AcOH]}{dt} = k[SH^+] = kK\frac{[S][H_3O^+]}{[H_2O]} = k'[S] \quad (2)$$

Pseudo-unimolecular rate constants k' for sulfuric acid-catalysed solvolysis of **11b** in CD_3CN–D_2O (adjusted to a constant ratio of 3.81:1 *) were found to be linearly dependent upon the acid concentration (Fig. 2) and the gradient afforded a composite rate constant k_H of $(2.41 \pm 0.10) \times 10^{-2}$ dm^3 mol^{-1} s^{-1} at 308 K. From the intercept, k_0, the rate constant for uncatalysed solvolysis, was at least three orders smaller and zero to within experimental error (Table 1). A similar linear dependence and near-zero uncatalysed rate constant was demonstrated for other substrates given in Table 1.

Scheme 3 depicts three possible hydrolysis mechanisms.[17]

* At this ratio solvents were miscible and homogeneous reaction mixtures were obtained by complete dissolution of the mutagens (typically 10–20 mg).



Scheme 3

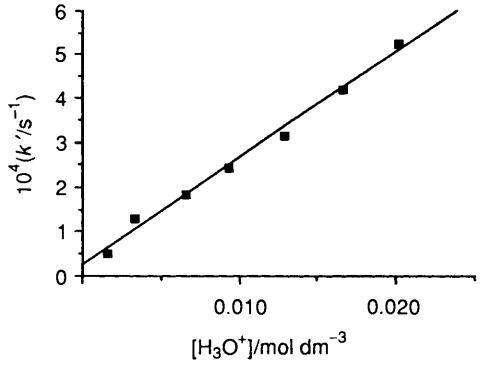


Fig. 2 Dependence of k' on acid concentration for the solvolysis of **11b** in CD_3CN–D_2O at 308 K

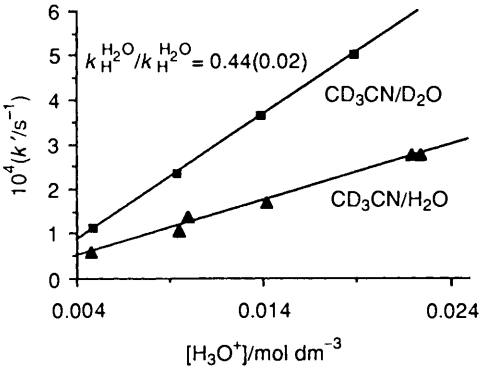


Fig. 4 Dependence of k' on acid concentration for solvolysis of **11b** in CD_3CN–D_2O and CD_3CN–H_2O at 308 K

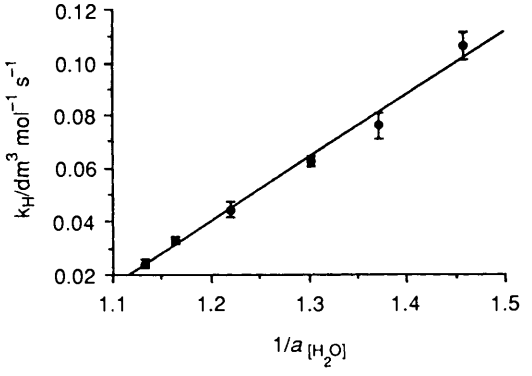


Fig. 3 Dependence of k_H for **11b** upon the inverse of the activity of water in acetonitrile at 308 K

The first (pathway i) is normal acid-catalysed ester hydrolysis in which attack of solvent (H_2O) upon the protonated intermediate is rate determining. The second (pathway ii) is the disfavoured $A_{Al}2$ process which would involve displacement of acetic acid through nucleophilic attack by a water molecule at nitrogen. Pathway iii, the $A_{Al}1$ mechanism, is typically found for the acid-catalysed hydrolysis of tertiary alkyl esters.[18]

Rate eqn. (2) indicates that k_H should be inversely proportional to the activity of water for solvolysis by the $A_{Al}1$ mechanism and independent of it if the bimolecular processes (pathways i and ii) pertain. Fig. 3 illustrates that, for **11b**, acid-independent rate constants at different volume fractions of D_2O in CD_3CN, k_H, were linearly dependent upon the inverse of a_{D_2O} in CD_3CN as determined from the corresponding activities of H_2O in CH_3CN.[19] This is in accord with the $A_{Al}1$ mechanism (path iii, Scheme 3).

Further evidence was obtained from a solvent kinetic isotope study. The theoretical kinetic isotope effects for intermediates in the three reaction pathways as derived from fractionation factors are indicated in parentheses in Scheme 3.[20] For the $A_{Al}1$ mechanism (path iii) a solvent KIE of between 0.48 and 0.33 is predicted while both bimolecular processes (pathways i and ii) would have greater values of between 0.48 and 0.69. Acid-catalysed hydrolysis of ethylene oxide derivatives and acetals which follow an A1 mechanism display KIEs of $\leqslant$0.5 while normal acid-catalysed ester hydrolyses ($A_{Ac}2$ mechanism) have values between 0.6 and 0.7.[21]

From rates of the solvolysis of **11b** at different sulfuric acid concentrations in D_2O–CD_3CN and H_2O–CD_3CN (Fig. 4), the observed solvent KIE was found to be 0.44 ($\pm$0.02). The transition state for solvolysis must therefore lie along pathway iii between the protonated ester and nitrenium ion. Fractionation factors and solvent kinetic isotope effects are not expected to differ greatly in aqueous–organic mixtures.[22]

Acid-independent rate constants, k_H, were determined over the temperature range 298–338 K for the *N*-acetoxy-*N*-alkoxybenzamides (**11a**, **b**, **d** and **e**) and Arrhenius data are given in Table 2.* The activation energies are in the region of

* Errors in Tables 2, 3 and 5 are based upon the standard deviations in the slope and intercept. Temperatures were accurate to within 0.7 K. Weighted least-squares fits taking into account all experimental inaccuracies gave smaller errors in the slope and intercept.

Table 2 Arrhenius and rate data for the acid-catalysed solvolysis of *N*-acetoxy-*N*-alkoxybenzamides (**11a, b, d** and **e**)[a]

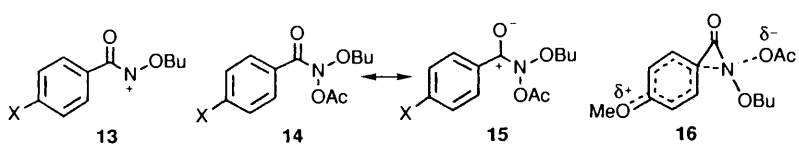
	11						
	X	R	ln *A*	E_a/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	$k_H^{308}/10^{-2}$ dm^3 mol^{-1} s^{-1} [b]	*r*
a	H	Et	41.46(0.43)	114.6(1.2)	91.5(1.0)	3.72	0.996
b	H	Bu	42.02(1.15)	116.9(2.9)	96.1(9.1)	2.60	0.998
d	H	Pr^i	45.73(2.02)	119.9(5.3)	127.0(5.6)	33.50	0.995
e	H	Bu^i	41.27(0.29)	115.8(0.8)	89.9(0.7)	1.92	0.994

[a] $CD_3CN:D_2O$ 3.81:1. [b] From Arrhenius data at 308 K.

Table 3 Arrhenius and rate data for the acid-catalysed solvolysis of *para*-substituted *N*-acetoxy-*N*-butoxybenzamides (**11b, f–l**)[a]

	11						
	X	R	ln *A*	E_a/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	$k_H^{308}/10^{-2}$ dm^3 mol^{-1} s^{-1} [b]	*r*
b	Bu	H	42.02(1.09)	116.9(2.9)	96.1(9.1)	2.600	0.998
f	Bu	MeO	43.05(1.29)	113.0(3.4)	104.7(10.7)	33.860	1.000
g	Bu	Bu^t	44.56(1.23)	121.6(3.2)	117.2(10.2)	5.337	0.999
h	Bu	Me	44.01(0.13)	120.0(0.7)	112.7(2.2)	5.875	1.000
i	Bu	Ph	44.92(1.06)	123.3(2.8)	120.6(8.8)	3.899	0.999
j	Bu	Cl	39.05(2.37)	110.8(6.3)	71.4(19.7)	1.452	0.995
k	Bu	Br	39.96(0.63)	113.2(1.7)	79.0(5.2)	1.455	1.000
l	Bu	NO_2	31.25(0.78)	95.3(2.1)	6.6(6.5)	0.252	0.999

[a] $CD_3CN:D_2O$ 3.81:1. [b] From Arrhenius data at 308 K.



those cited for the acid-catalysed hydrolysis of tertiary alkyl, diphenylmethyl and α-methylallyl esters namely *ca.* 120 kJ mol^{-1}.[18] The entropies of activation are, however, much more positive than the ester values (*ca.* 40 J K^{-1} mol^{-1}) and accord with much looser and later transition states with substantial alkoxynitrenium-ion character. At 308 K, the isopropoxy compound **11d** reacts about an order of magnitude faster than **11a, b** and **e**. A higher E_a and a substantially larger $\Delta S^{\ddagger}$ are consistent with additional relief of steric compression in the transition state involving the unimolecular heterolysis of the N–O bond. By contrast, the isobutoxy compound (**11e**), in which the branching is one methylene removed from the oxygen atom has similar parameters to straight chain substrates (**11a** and **b**).

The inverse dependence of solvolysis rates upon a_{H_2O}, the solvent kinetic isotope effect and the Arrhenius activation data are all in accordance with acid-catalysed solvolysis by the $A_{Al}1$ mechanism (pathway iii) in Scheme 3. In particular, the activation data for (**11a, b, d** and **e**) indicate a transition state with substantial alkoxynitrenium-ion character. *para*-Substituents on the benzoyl ring in **11** also exert a significant influence upon the rates of solvolysis. Electron-donating groups cause an increase in the rate while the converse is indicated for electron-withdrawing substituents (Table 3). At 308 K **11f** reacts about 13 times faster than the unsubstituted mutagen **11b** and 135 times faster than the *para*-nitro derivative **111**.

Reversible protonation of **11** is, in principle, possible at both carbonyl oxygens, at the acetoxy and alkoxy ether oxygens and at nitrogen. While according to AM1 calculations, protonation at the amide carbonyl leads to a marginally more stable intermediate, only pre-equilibrium protonation at the acetoxy group can lead to ester hydrolysis and nitrenium ion formation.* The effect of *para*-substituents upon this pre-equilibrium step is therefore likely to be negligible considering their remoteness from the site of protonation and their electronic influence must rather impact upon the rate-determining N–O bond heterolysis step leading to **13**.

Using Arrhenius-derived rate constants at 308 K (Table 3) an excellent fit was obtained with Hammett σ^+ substituent constants yielding a ρ-value of −1.4 (Fig. 5). While σ^+ correlations are expected where there is direct conjugative interaction between the aryl substituent and the positively charged centre,[23] the fit in this case is consistent with a significant build up of localised positive charge on nitrogen in the rate-determining step. The small negative Hammett ρ-value is appropriate for nitrenium ion formation β to the aromatic ring and rate enhancement by electron-releasing substituents can best be ascribed to a diminution of positive charge at the amide carbonyl carbon, *i.e.* the contribution of **15** to the hybrid **14** ⟷ **15** is offset by the electron-donating substituents, thereby facilitating the development of positive charge at nitrogen. A similar correlation (σ^+, ρ = −0.74) has been reported for the acid-catalysed decomposition of ω-diazoacetophenones in which carbenium-ion character is also developed α to the carbonyl.[24]

The Arrhenius parameters for this series of compounds show the usual trend expected for a unimolecular heteroylsis in the rate-determining step. Electron-releasing groups (negative σ^+) have much more positive $\Delta S^{\ddagger}$ indicative of a looser transition state together with a higher E_a as a consequence of the greater degree of N–O bond stretching.[25] The *para*-nitro substrate (**11l**) reacts through a much tighter transition state ($\Delta S^{\ddagger}$ positive but only 6.6 J K^{-1} mol^{-1}) without a commensurate drop in E_a.

* AM1 ΔH_f for *N*-acetoxy-*N*-methoxybenzamide protonated at nitrogen, acetoxy carbonyl and amide carbonyl are 127.85, 122.91 and 116.94 kcal mol^{-1}, respectively. Protonation at the methoxy and acetoxy ether oxygens were much less favourable processes and did not yield stable intermediates.

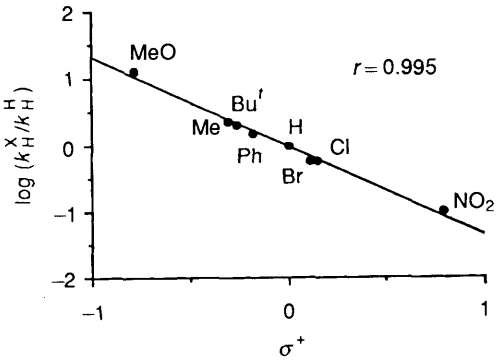


Fig. 5 Hammett correlation for the acid-catalysed solvolysis of *N*-acetoxy-*N*-butoxybenzamides **11b**, **f–l** at 308 K

The *para*-methoxy group in **11f** results in a more organised transition state than those found with other activating substituents (**11g–i**), however, this reaction is also driven by a lower E_a. The tighter transition state could, in part, be due to the planarity requirements for conjugative interaction with the carbonyl however, by analogy with the decomposition of the ω-diazoacetophenones,[24] a resonance interaction in the transition state such as that in **16** would also account for these activation parameters. With the exception of **11f** all the substrates in this series exhibit an isokinetic relationship (ln A = 0.5E_a − 16.5; r = 0.998). The deviation (of 3 ln A units) from this relationship by the *para*-methoxy substrate would appear to confirm a different mechanism of activation.*

Although electron-donating *para*-substituents result in more facile heterolytic cleavage of the N–O bond, the major factor facilitating this process is the mesomeric stabilisation of developing positive charge by the adjacent oxygen atom. MNDO and *ab initio* calculations predict that in the gas phase, the charge deficiency in alkoxynitrenium ions is shared by both nitrogen and oxygen.[12,13] The LUMO is essentially N–O π* with coefficients of 0.8 and 0.55 on N and O, respectively. AM1-optimised geometries of *N*-benzoyl-*N*-methoxynitrenium ion (**17**) and *N*-acetoxy-*N*-methoxybenzamide (**18**) are illustrated with selected bond lengths and bond angles in Fig. 6. The N–O π-bond character for the nitrenium ion **17** is 0.89 and results in a bond length of 1.199 Å which is typical of pure N–O double bonds.[26] C2, N3, O4 and C5 are coplanar to optimise N2p_z–O2p_z overlap. In contrast, the nitrogen in *N*-acetoxy-*N*-methoxybenzamide is pyramidal.

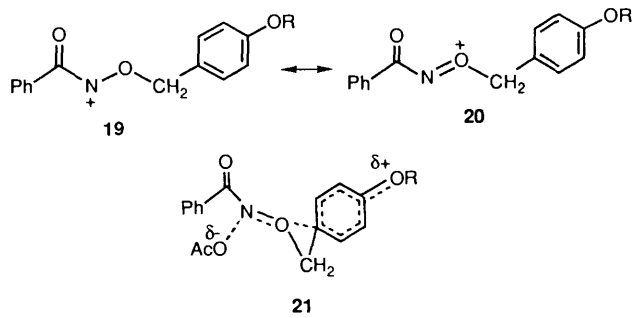
Group charges for the *N*-methoxy-*N*-benzoylnitrenium ion **17** are given in Table 4. While a charge of +0.37 resides on the benzoyl substituent, the methoxy substituents bears +0.48 of the total charge. For *N*-acetoxy-*N*-methoxybenzamide (**18**) the methoxy substituent has a charge of only −0.013. In unimolecular heterolyses to form alkoxynitrenium ions, it is reasonable therefore to expect that different alkoxy substituents on nitrogen should also exert a substantial electronic influence.

To test this hypothesis we have synthesised a series of *N*-acetoxy-*N*-benzyloxybenzamides (**12a–i**) which also undergo unimolecular acid-catalysed decomposition to acetic acid and the corresponding *N*-benzyloxynitrenium ion. Table 5 gives Arrhenius activation data and rate constants for these solvolyses. In accordance with the computational data, *para* electron-supplying substituents clearly accelerate the solvolysis while the opposite is true for electron-withdrawing groups. Rate data at 308 K give a good Hammett correlation with σ^+ values yielding a ρ-value of −1.59 (Fig. 7). This correlation is consistent with a transition state which, in addition to nitrenium-ion character (**19**), is also substantially oxonium ion (**20**). Surprisingly, the *para*-methoxy and phenoxy groups are strongly activating without an obvious resonance conduit to the oxonium–nitrenium centres and resonance may be possible through non-classical structures such as **21**. The lower than expected $\Delta S^‡$ for **12b** and particularly for **12c** are consistent with tighter transition states demanded by **21**. As was found in the benzoyl series, both the *para*-methoxy- and *para*-phenoxybenzyloxy substrates deviated by *ca.* 4 units of ln A from the isokinetic relationship displayed by **12a**, **d–f** (ln A = 0.54E_a − 23.0; r = 0.988).

We conclude from these studies that the transition state for unimolecular acid-catalysed solvolysis of *N*-acetoxy-*N*-alkoxybenzamides clearly possesses both nitrenium- and oxonium-ion character.

Table 4 Group charges from AM1 calculations

Group	17	18
N	0.1451	−0.0164
CO	0.1314	0.0616
C_6H_5	0.2422	0.0554
OMe	0.4813	−0.0134
OAc	—	−0.0873



Solvolysis Products.—Apart from the formation of acetic acid, the products from acid-catalysed solvolysis of **11b** in CD_3CN–D_2O were butyraldehyde (**24**), butanol (**25**), butyl benzoate (**26**), benzohydroxamic acid (**27**) and benzoic acid (**28**). NMR Analysis of the formation of **24–26** over time indicated their parallel formation in concert with the disappearance of starting material (Fig. 8). Furthermore, butyraldehyde (**24**) and benzohydroxamic acid (**27**) were generally present in similar quantities.

Scheme 4 outlines possible mechanisms for the formation of these products. The fate of the *N*-butoxy-*N*-benzoylnitrenium ion (**22**) is most probably interception by water to give **23** which can deprotonate to *N*-butoxybenzohydroxamic acid (**29**). Acid-catalysis could lead to the formation of butanol (**25**) (in a fashion similar to the acid-catalysed hydrolysis of hemiacetals) and the benzoylnitroso compound **30** which could be the source of benzoic acid (**28**).[27] Alternatively elimination of the benzohydroxamic acid would yield butyraldehyde (**24**). Direct elimination of benzoylnitrene from **22** is unlikely to be the source of butyraldehyde since no Curtius- or Lossen-type

* An alternative suggestion put forward by a referee is that this σ^+ correlation is relevant to pre-equilibrium protonation at the amide carbonyl which precedes an entrophically favourable proton transfer to the acetoxy carbonyl. We contend that the substituent effects for the protonation and the deprotonation-transfer steps would cancel. Furthermore proton transfer would involve an entropically unfavourable seven-membered ring. The magnitude of the solvent kinetic isotope effect and Arrhenius activation data are also incompatible with a rate determining protonation at the amide carbonyl.

Table 5 Arrhenius and rate data for the acid-catalysed solvolysis of *N*-acetoxy-*O*-(*p*-substituted benzyl) benzohydroxamates (**12a–i**)[a]

	12 Y	ln *A*	E_a/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	$k_H^{308}/10^{-2}$ dm^3 mol^{-1} s^{-1} [b]	*r*
a	H	45.01(1.32)	128.0(3.5)	121.0(11.0)	0.499	0.999
b	MeO	44.50(2.60)	118.8(6.9)	116.7(21.7)	14.870	0.993
c	PhO	38.19(2.80)	106.6(7.2)	64.3(23.3)	3.160	0.999
d	Bu^t	43.82(0.94)	122.5(2.5)	111.1(7.8)	1.821	1.000
e	Me	47.06(0.71)	130.4(1.9)	138.0(5.9)	2.062	1.000
f	Ph	42.99(0.78)	122.2(2.1)	104.2(6.5)	0.876	1.000
g	Cl	41.89(1.26)	122.5(3.3)	95.0(10.5)	0.265	0.999
h	Br	40.01(0.45)	117.9(1.2)	79.4(3.7)	0.239	1.000
i	NO_2	34.43(1.09)	107.3(2.9)	33.0(9.1)	0.057	0.998

[a] $CD_3CN:D_2O$ 3.81:1. [b] From Arrhenius data at 308 K.

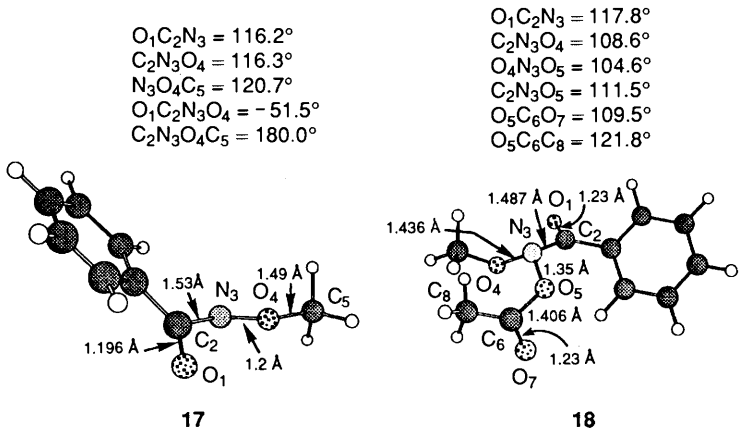


Fig. 6 AM1-optimised geometries for *N*-benzoyl-*N*-methoxynitrenium ion (**17**) and *N*-acetoxy-*N*-methoxybenzamide (**18**)

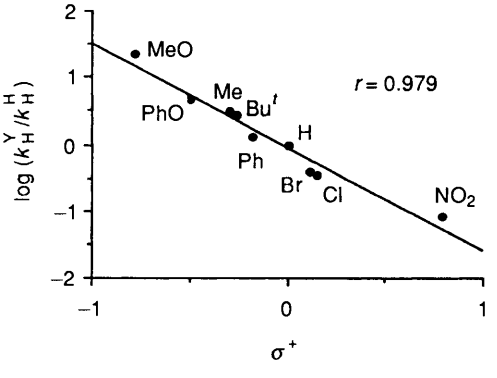


Fig. 7 Hammett correlation for the acid-catalysed solvolysis of *N*-acetoxy-*N*-benzyloxybenzamides (**12a–i**) at 308 K

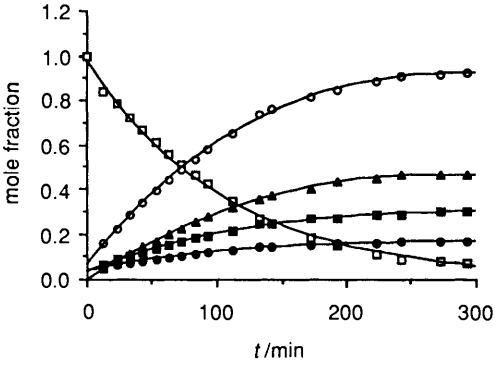
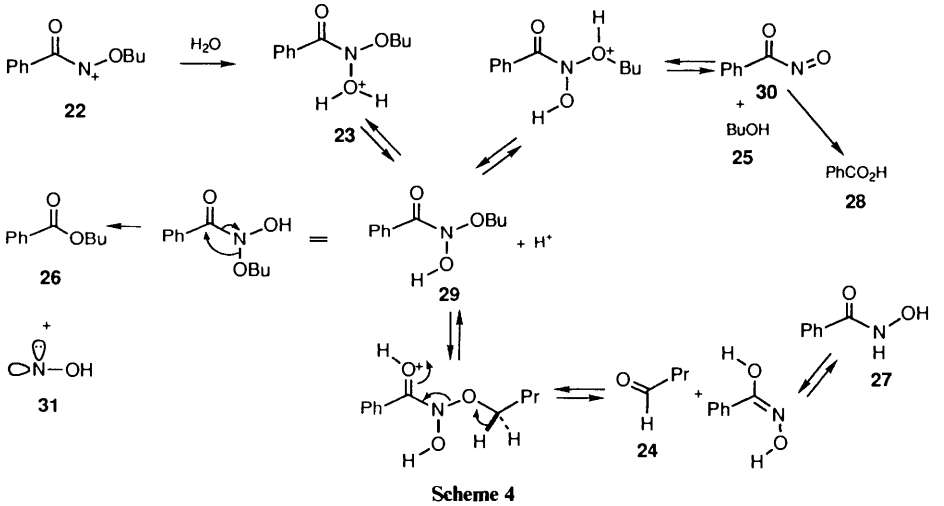
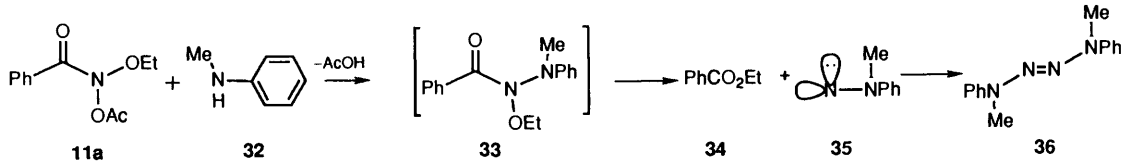


Fig. 8 Formation of butyraldehyde (▲), butyl benzoate (●) and butanol (■) from the acid-catalysed solvolysis of **11b** (□) at 308 K; ○, all products



Scheme 4



Scheme 5

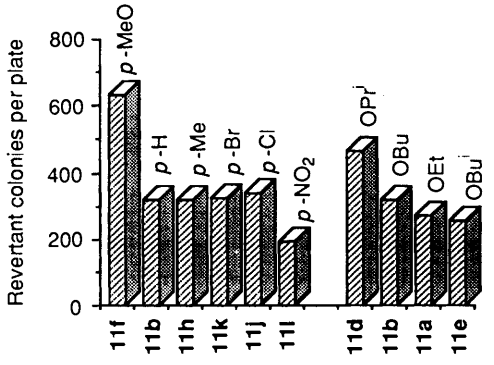


Fig. 9 Mutagenicities in Salmonella TA100 at 1 μmol per plate

rearrangement to aniline was detected in this reaction.[28] Inspection of the product distribution through the series (**11f–l**) clearly indicated that aldehyde formation was promoted by electron-releasing *para*-substituents and especially so by a *p*-methoxy group (**11f**). Butyraldehyde was barely detectable by NMR spectroscopy when the *p*-nitro substituent was present on the benzoyl ring (**11l**). It is likely therefore that this reaction is catalysed by protonation at the carbonyl oxygen, a process that would be strongly influenced by electronic effects on the benzoyl ring.

Butyl benzoate (**26**) cannot be formed consecutively from butanol and benzoic acid or the benzoylnitroso compound **30**. We propose its formation to be through a concerted rearrangement of **29**. Although hydroxynitrene (**31**), or derivatives thereof have not been detected, its formation would be facilitated by stabilisation of the nitrene centre by the neighbouring oxygen lone pair. In support of this we have recently shown that ethyl benzoate (**34**) and diazene (**35**) are generated from the reaction of **11a** and *N*-methylaniline **32**; presumably through the intermediacy of **33**,[29] **35** dimerises to the tetrazene **36** (Scheme 5). Here too rearrangement to the ester appears favourable with formation of a nitrenium ion stabilised by a nitrogen lone pair.

Similar products were observed from acid-catalysed solvolysis of both series of substrates **11** and **12**.

Mutagenesis Studies.—The mutagensis of a number of substrates has been determined as part of a wider quantitative structure–activity study. Preliminary results indicate that nearly all variants tested to date display mutagenic activity in *Salmonella* strain TA100 both with and without metabolic activation.[30] The *N*-acetoxy group is essential for biological activity since those parent hydroxamic esters tested appear to be inactive.[14] *O*-Acylation also appears to be an important activating process in the recently discovered mutagenicity of hydroxamic acids.[31] The mutagenic activity is therefore most likely derived from displacement of this *N*-acetoxy group by DNA in either an S_N1- or S_N2-type process.

Fig. 9 illustrates relative mutagenicities in TA100 at 1 μmol per plate after deduction of background rates.* Interestingly, *N*-acetoxy-*N*-isopropoxybenzamide (**11d**), which undergoes the most facile acid-catalysed hydrolysis out of **11a**, **b**, **d**, **e**, is also the most mutagenic of the series. Similarly, *N*-acetoxy-*N*-butoxy-*p*-methoxybenzamide (**11f**) which is solvolysed most readily in the butoxy series, exhibits significantly elevated levels of spontaneous mutagenicity relative to the other substrates tested (**11b**, **h**, **j**, **k**, **l**) while *N*-acetoxy-*N*-butoxy-*p*-nitrobenzamide was much less mutagenic. While these correlations would appear to suggest some nitrenium-ion involvement and the mutagenicities of this series (**11b**, **f**, **h**, **j**, **k** and **l**) also correlate with Hammett σ^+ values ($r = 0.94$) the ρ-value is only -0.29. This fact, together with the negligible rates of uncatalysed unimolecular solvolysis, would militate against nitrenium-ion intermediacy in the mutagenic process. In addition we have recently found that the reaction of **11a** with *N*-methylaniline (Scheme 5) proceeds in a bimolecular rather than a unimolecular fashion.[29] Further tests are however required before the mode of initiation of mutagenesis can be established unequivocally.

The benzyloxy substrates **12a** and **12h**, which were found to be toxic to *Salmonella* at 1 μmol per plate, were nevertheless extremely mutagenic at this dose when activated by rat-liver enzymes (revertant colonies per plate of 1200 and 2400, respectively).

* Background reversion rates of *ca.* 100 were found in control experiments without mutagen.

Experimental

Melting points were determined on a Reichert Microscopic Hot-Stage and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1725 × FT instrument. 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra were recorded on a Bruker AC-300P FT spectrometer. Coupling constants, *J*, are given in Hz. HPLC analyses were performed on a Waters 510 Analytical instrument using a model 481 UV absorbance detector linked to a Waters 740 data module. Mass spectral data was obtained on a Kratos MS902 spectrometer through the Mass Spectroscopy Unit of Sydney University. Microanalytical data were obtained from the Research School of Chemistry at Canberra. Ames tests were carried out in the Department of Environmental Toxicology at the National Institute of Occupational Health and Safety in Sydney. AM1 molecular orbital calculations[32] were executed on a Gould NP1 computer at the University of New England using AMPAC.[33] The precise option was used in all geometry optimisations.

Acetonitrile used was HiPerSolv, 'Far UV' grade (BDH). Ether refers to anhydrous diethyl ether stored over sodium wire. Dichloromethane (DCM) and acetone were distilled and dried over 4 Å molecular sieves. Ethyl acetate (EtOAc) and methanol (MeOH) were distilled before use. Light petroleum (LP) refers to the fraction boiling in the range 60–70 °C. Anhydrous sodium sulfate was used for drying all organic mixtures. Flash chromatography was executed on columns loaded with Kieselgel 60 (Merck). TLC was performed on aluminium sheets pre-coated with 0.2 mm of silica gel 60 F_{254} (Merck).

p-Nitrobenzyl bromide, *p*-phenoxyphenyl acetate and *para*-substituted benzoic acids were purchased from Aldrich, as was trideuterioacetonitrile (CD_3CN), 99.5%, and deuterium oxide (D_2O), 99.8%.

General Synthesis of Alkyl para-*Substituted Benzohydroxamates.*—Treatment of the appropriate *p*-substituted ethyl benzoate with hydroxylamine hydrochloride under basic conditions afforded a precipitate of potassium hydroxamate salt from MeOH after refrigeration.[34] (The esters were obtained by esterification of the appropriate *para*-substituted benzoic acid with an excess of ethanol under acidic conditions and were identified by NMR spectroscopy). Condensation of the potassium salt with the appropriate alkyl bromide, and a 10% excess of sodium carbonate in 50% aqueous MeOH provided the appropriate *para*-substituted benzohydroxamic ester in good yield.[35]

Ethyl Benzohydroxamate (General Procedure).—Potassium hydroxide (56.10 g, 1.00 mol) in boiling methanol (140 cm^3) was added to hydroxylamine hydrochloride (46.70 g, 670 mmol) in boiling methanol (240 cm^3) and the mixture was cooled in an ice bath for 5 min. Ethyl benzoate (50.00 g, 330 mmol) was added with shaking and the mixture was immediately filtered. Crystallisation upon refrigeration was complete within 48 h. Filtration, washing with ethanol and drying *in vacuo* afforded potassium benzohydroxamate (32.08 g, 55%) as white prisms and which was used without further purification. 1-Bromoethane (1.63 g, 15 mmol), potassium benzohydroxamate (1.75 g, 10 mmol) and sodium carbonate (1.2 g, 11 mmol) were stirred overnight in 50% aqueous methanol (50 cm^3) then refluxed for 2 h. Removal of MeOH *in vacuo*, acidification and extraction with DCM afforded the crude ethyl benzohydroxamate. Purification by flash column chromatography (80% $CHCl_3$–20% LP) afforded pure ethyl benzohydroxamate (1.49 g, 90%) as a white solid, m.p. 58–60 °C (Found: C, 64.6; H, 7.05; N, 7.95. $C_9H_{11}NO_2$ requires C, 65.44; H, 6.71; N, 8.48%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3243 (NH) and 1679 (CO); $\delta_H(CDCl_3)$ 1.26 (3 H, t), 4.02 (2 H, q), 7.35 (2 H, t, *m*-ArH), 7.46 (1 H, t, *o*-ArH), 7.76 (2 H, d, *p*-ArH) and 9.60 (1 H, br); $\delta_C(CDCl_3)$ 13.41 (q), 72.19 (t), 127.11 (d), 128.50 (d), 131.63 (d), 131.97 (s) and 166.50 (s).

Isopropyl benzohydroxamate. 2-Bromopropane (1.85 g, 15.0 mmol), potassium benzohydroxamate (1.75 g, 10.0 mmol) and sodium carbonate (1.17 g, 11.0 mmol) were stirred overnight in 50% aqueous methanol (50 cm^3) and refluxed for 2 h. The crude product was obtained *via* the general procedure. Purification by flash column chromatography (80% $CHCl_3$, 20% ether) afforded pure isopropyl benzohydroxamate (1.56 g, 87%) as a white solid, m.p. 83–84 °C (Found: C, 67.3; H, 7.55; N, 7.55. $C_{10}H_{13}NO_2$ requires C, 67.02; H, 7.31; N, 7.82%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3260 (NH) and 1684 (CO); $\delta_H(CDCl_3)$ 1.28 (6 H, d), 4.25 (1 H, m), 7.38 (2 H, t, *m*-ArH), 7.48 (1 H, t, *o*-ArH), 7.73 (2 H, d, *p*-ArH) and 9.11 (1 H, br); $\delta_C(CDCl_3)$ 20.50 (q), 78.15 (d), 127.09 (d), 128.53 (d), 131.79 (d), 132.17 (s) and 166.77 (s); *m/z* 179 (M^+, 18%), 137 (36), 121 (16), 105 (100), 77 (86) and 43 (48).

Butyl benzohydroxamate. 1-Bromobutane (13.93 g, 100 mmol), potassium benzohydroxamate (11.87 g, 67.0 mmol) and sodium carbonate (7.95 g, 75.0 mmol) were stirred overnight in 50% aq. methanol (300 cm^3) and refluxed for 2 h. The crude product was obtained *via* the general procedure. Purification by flash column chromatography ($CHCl_3$) afforded pure butyl benzohydroxamate (6.68 g, 52%) as an orange oil, b.p. 190 °C, 0.2 mmHg (Found: C, 68.55; H, 8.05; N, 7.5. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3225 (NH) and 1654 (CO); $\delta_H(CDCl_3)$ 0.77 (3 H, t), 1.24 (2 H, quintet), 1.50 (2 H, sextet), 3.87 (2 H, t), 7.26 (2 H, t, *m*-ArH), 7.34 (1 H, t, *p*-ArH), 7.75 (2 H, d, *o*-ArH) and 11.17 (1 H, br); $\delta_C(CDCl_3)$ 13.44 (q), 16.60 (t), 29.67 (t), 75.84 (t), 127.01 (d), 127.94 (d), 131.25 (d), 131.68 (s) and 165.65 (s).

Isobutyl benzohydroxamate. 1-Bromo-2-methylpropane (2.06 g, 15.0 mmol), potassium benzohydroxamate (1.75 g, 10.0 mmol) and sodium carbonate (1.17 g, 11.0 mmol) were stirred overnight in 50% aq. MeOH (50 cm^3) and refluxed for 2 h. The crude product was obtained *via* the general procedure. Purification by flash column chromatography (80% $CHCl_3$, 20% ether) afforded pure isobutyl benzohydroxamate (1.76 g, 91%) as a white solid, m.p. 59–60 °C (Found: C, 68.2; H, 7.5; N, 7.1. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3406 (NH) and 1684 (CO); $\delta_H(CDCl_3)$ 0.99 (6 H, d), 2.05 (1 H, m), 3.80 (2 H, d), 7.43 (2 H, t, *m*-ArH), 7.50 (1 H, t, *p*-ArH), 7.73 (2 H, d, *o*-ArH) and 8.70 (1 H, br); $\delta_C(CDCl_3)$ 19.15 (q), 27.27 (d), 83.50 (t), 127.03 (d), 128.68 (d), 131.98 (d), 132.10 (s) and 166.54 (s); *m/z* 193 (M^+, 20%), 137 (47), 121 (27), 105 (100), 77 (89), 57 (67), 43 (43) and 29 (60).

Butyl p-*bromobenzohydroxamate.* Potassium *p*-bromobenzohydroxamate was obtained as white prisms in the same manner as potassium benzohydroxamate (82%). 1-Bromobutane (17.06 g, 124.5 mmol), potassium *p*-bromobenzohydroxamate (19.09 g, 83 mmol) and sodium carbonate (10.8 g, 100 mmol) in 50% aq. MeOH (300 cm^3) were stirred at room temperature overnight and refluxed for 2 h. Work-up and recrystallisation ($CHCl_3$–LP) provided pure butyl *p*-bromobenzohydroxamate (11.5 g, 67%), m.p. 109–110 °C (Found: C, 48.7; H, 5.3; N, 5.15; Br 29.45. $C_{11}H_{14}BrNO_2$ requires C, 48.55; H, 5.19; N, 5.15; Br, 29.36%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3250 (NH) and 1696 (CO); $\delta_H(CDCl_3)$ 0.89 (3 H, t), 1.34 (2 H, sextet), 1.60 (2 H, quintet), 3.95 (2 H, t), 7.47 (2 H, d, J = 8.5, *m*-ArH), 7.63 (2 H, d) and 10.5 (1 H, br, NH); $\delta_C(CDCl_3)$ 13.74 (q), 18.91 (t), 29.96 (t), 76.48 (t), 126.48 (s), 128.77 (d), 130.67 (s), 131.62 (d) and 165.45 (s); *m/z* 271 (M^+, 45%), 262 (35), 241 (40), 228 (40), 215 (40), 199 (80) and 183 (100).

Butyl p-*chlorobenzohydroxamate.* Potassium *p*-chlorobenzohydroxamate was obtained in the same manner as potassium benzohydroxamate (60%). 1-Bromobutane (10 g, 73.0 mmol), potassium *p*-chlorobenzohydroxamate (13.5 g, 73 mmol) and sodium carbonate (10.8 g, 100 mmol) in 50% aq. MeOH (200 ml) were stirred at room temperature overnight and refluxed for 2 h. Work-up and recrystallisation ($CHCl_3$–LP) provided pure butyl *p*-chlorobenzohydroxamate (14.1 g, 85%), m.p. 95–96 °C (Found: C, 58.1; H, 6.45; N, 6.2; Cl, 15.8. $C_{11}H_{14}ClNO_2$ requires C, 58.03; H, 6.20; N, 6.15; Cl, 15.57%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3250 (NH) and 1695 (CO); $\delta_H(CDCl_3)$ 0.88 (3 H, t), 1.33 (2 H, sextet), 1.57 (2 H, quintet), 3.95 (2 H, t), 7.30 (2 H, d), 7.70 (2 H, d, J = 8.3, *o*-ArH) and 10.5 (1 H, br); $\delta_C(CDCl_3)$ 13.66 (q), 18.86 (t), 29.70 (t), 76.37 (t), 128.55 (d), 128.66 (d), 130.21 (s), 137.93 (s, *p*-ArC) and 165.29 (s); *m/z* 227 (M^+, 40%), 196 (40), 182 (45), 139 (100), 111 (65), 75 (50) and 28 (70).

Butyl p-*nitrobenzohydroxamate.* Potassium *p*-nitrobenzohydroxamate was obtained in the same manner as potassium benzohydroxamate (90%). The title compound was generated *via* the general condensation and recrystallisation procedure as pale yellow crystals (52%), m.p. 99–101 °C (Found: C, 55.0; H, 6.2; N, 11.65. $C_{11}H_{14}N_2O_4$ requires C, 55.46; H, 5.92; N, 11.76%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1695 (CO); $\delta_H(CDCl_3)$ 0.90 (3 H, t), 1.34 (2 H, sextet), 1.66 (2 H, quintet), 4.03 (2 H, t), 7.99 (2 H, d), 8.22 (2 H, d, J = 8.8) and 10.5 (1 H, br); $\delta_C(CDCl_3)$ 13.66 (q), 18.88 (t), 29.93 (t), 76.75 (t), 123.57 (d, *m*-ArC), 128.4 (d), 137.47 (s), 149.63 (s, *p*-ArC) and 164.14 (s); *m/z* 238 (M^+, 25%), 206 (30), 193 (70), 167 (40), 150 (100), 57 (55), 41 (40) and 29 (95).

Butyl p-*phenylbenzohydroxamate.* Potassium *p*-phenylbenzohydroxamate was prepared *via* the general method (20%). The title compound was generated *via* the general condensation and recrystallisation procedure as white crystals (73%), m.p. 141–142 °C (Found: C, 75.8; H, 7.3; N, 4.95. $C_{17}H_{19}NO_2$ requires C, 75.81; H, 7.11; N, 5.20%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3406 (NH) and 1684 (CO); $\delta_H(CDCl_3)$ 0.95 (3 H, t), 1.44 (2 H, m), 1.71 (2 H, m), 4.04 (2 H, t), 7.4 (3 H, m), 7.60 (4 H, m), 7.61 (2 H, d, J = 8.5, *o*-ArH) and 9.02 (1 H, br); $\delta_C(CDCl_3)$ 13.85 (q), 19.06 (t), 30.08 (t), 76.62 (t), 127.14 (d), 127.26 (d), 127.60 (dd), 128.07 (dt), 128.91 (dd), 130.67 (s), 139.83 (s, *i'*-ArC), 144.77 (s, *p*-ArC) and 166.38 (s); *m/z* 269 (M^+, 71%), 197 (43), 181 (100), 153 (77), 77 (11), 76 (15) and 29 (10).

Butyl p-tert-*butylbenzohydroxamate*. Potassium *p-tert*-butylbenzohydroxamate was obtained as white prisms in a yield of 20%. The title compound was generated *via* the general condensation and work-up procedure. Purification by flash column chromatography (15% EtOAc–85% LP) afforded pure butyl *p-tert*-butylbenzohydroxamate (1.77 g, 71%) as a clear oil, b.p. 120 °C, 0.1 mmHg (Found: C, 71.95; H, 9.5; N, 5.4. $C_{15}H_{23}NO_2$ requires C, 72.25; H, 9.30; N, 5.62%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3259 (NH) and 1679 (CO); $\delta_H(CDCl_3)$ 0.96 (3 H, t), 1.33 (9 H, s), 1.45 (2 H, m), 1.70 (2 H, m), 4.03 (2 H, t), 7.45 (2 H, d), 7.75 (2 H, d, J = 6.8, *o*-ArH) and 8.50 (1 H, br); $\delta_C(CDCl_3)$ 13.81 (q), 19.01 (t), 30.03 (t), 31.06 (q), 34.89 (s), 76.64 (t), 125.49 (d), 126.92 (d), 129.12 (s), 155.41 (s) and 166.42 (s); *m/z* 249 (M^+, 51%), 234 (33), 177 (30), 161 (74), 134 (33), 77 (19), 57 (24), 44 (41), 41 (100) and 29 (57).

Butyl p-*methylbenzohydroxamate*. Potassium *p*-methylbenzohydroxamate was obtained as white prisms in the same manner as potassium benzohydroxamate (54%). Butyl *p*-methylbenzohydroxamate was obtained *via* the general condensation reaction. Recrystallisation ($CHCl_3$–LP) provided pure butyl *p*-methylbenzohydroxamate (70%) (Found: C, 69.95; H, 8.0; N, 6.8. $C_{12}H_{17}NO_2$ requires C, 69.54; H, 8.27; N, 6.76%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1695 (CO) and 3250 (NH); $\delta_H(CDCl_3)$ 0.92 (3 H, t), 1.40 (2 H, sextet), 1.67 (2 H, quintet), 2.37 (3 H, s), 3.99 (2 H, t), 7.18 (2 H, d), 7.63 (2 H, d, J = 8, *o*-ArH) and 9.1 (1 H, br); $\delta_C(CDCl_3)$ 13.81 (q), 19.01 (t), 21.44 (q), 30.02 (t), 76.45 (t), 127.06 (d), 129.20 (d), 129.20 (s), 142.36 (s, *p*-ArC) and 166.44 (s); *m/z* 207 (M^+, 65%), 175 (45), 151 (30), 119 (100) and 91 (25).

Butyl p-*methoxybenzohydroxamate*. Potassium *p*-methoxybenzohydroxamate was obtained in the same manner as potassium benzohydroxamate (62%). Butyl *p*-methoxybenzohydroxamate was prepared *via* the general condensation reaction conditions. Recrystallisation ($CHCl_3$–LP) provided butyl *p*-methoxybenzohydroxamate (40%), m.p. 43–44 °C, b.p. 155 °C, 0.25 mmHg (Found: C, 63.6; H, 7.75; N, 6.15. $C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.87; N, 6.27%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1692 (CO) and 3250 (NH); $\delta_H(CDCl_3)$ 0.89 (3 H, t), 1.38 (2 H, sextet), 1.63 (2 H, quintet), 3.80 (3 H, s), 3.96 (2 H, t), 6.83 (2 H, d), 7.75 (2 H, d, J = 8.9, *o*-ArH) and 10.5 (1 H, br); $\delta_C(CDCl_3)$ 13.72 (q), 18.92 (t), 29.96 (t), 55.21 (q), 76.39 (t), 113.59 (d, *m*-ArC), 124.18 (s), 128.97 (d), 162.28 (s, *p*-ArC) and 166.12 (s); *m/z* 223 (M^+, 35%), 191 (10), 167 (10), 151 (20), 135 (100), 92 (40), 77 (45) and 28 (65).

General Synthesis of para-*Substituted Benzyl Alcohols*.—The appropriate *p*-substituted benzoic acid (or benzaldehyde) was reduced to the corresponding alcohol by treatment with $LiAlH_4$ in ether ($NaBH_4$ in ethanol–water). The mixtures were first washed with dilute acid, 10% aq. sodium carbonate, and then extracted with DCM. The appropriate alcohols were obtained in good yields and were of high purity (^1H, ^{13}C, NMR, IR, m.p.).

General Synthesis of para-*Substituted Benzyl Bromides*.—*para*-Substituted benzyl bromides (chlorides) were prepared from the appropriate alcohols by refluxing with HBr–H_2SO_4 (HCl–H_2SO_4) in ether. The mixture was washed with conc. HCl, H_2O, 10% aq. Na_2CO_3, H_2O and extracted with DCM. Concentration *in vacuo* provided the *p*-substituted benzyl bromides in good yield (>90%) and high purity (^1H, ^{13}C, NMR, IR, m.p.).

p-*Bromobenzyl bromide:* m.p. 61–62 °C (lit.,[36] 63 °C), $\delta_H(CDCl_3)$ 4.44 (2 H, s), 7.24 (2 H, d) and 7.46 (2 H, d); $\delta_C(CDCl_3)$ 32.36 (tt), 122.38 (s), 130.60 (dq), 131.68 (dd) and 136.70 (s).

p-*Chlorobenzyl bromide:* m.p. 28–30 °C (lit.,[36] 28–30 °C), $\delta_H(CDCl_3)$ 4.45 (2 H, s) and 7.32 (4 H, s); $\delta_C(CDCl_3)$ 32.34 (t), 128.91 (d), 130.30 (d), 134.20 (s) and 136.22 (s).

p-*Methylbenzyl bromide:* m.p. 32–34 °C (lit.,[36] 32–35 °C), $\delta_H(CDCl_3)$ 2.40 (3 H, s), 4.52 (2 H, s), 7.19 (2 H, d) and 7.32 (2 H, d); $\delta_C(CDCl_3)$ 21.13 (q), 33.67 (t), 128.88 (d), 129.39 (d), 134.77 (s) and 138.24 (s).

p-tert-*Butylbenzyl bromide:* $\delta_H(CDCl_3)$ 1.3 (9 H, s), 4.47 (2 H, s), 7.29 (2 H, d) and 7.34 (2 H, d); $\delta_C(CDCl_3)$ 31.22 (q), 33.55 (t), 34.57 (s), 125.69 (d), 128.71 (d), 134.71 (s) and 151.46 (s).

p-*Phenylbenzyl bromide:* m.p. 101–102.5 °C (lit.,[36] 99–101 °C), $\delta_H(CDCl_3)$ 4.72 (2 H, s), 7.46 (5 H, m) and 7.64 (4 H, m).

p-*Phenoxybenzyl bromide:* $\delta_H(CDCl_3)$ 4.49 (2 H, s), 6.93 (2 H, d), 7.00 (2 H, d), 7.12 (1 H, t) and 7.32 (4 H, m); $\delta_C(CDCl_3)$ 33.3 (t), 118.6 (d), 119.2 (d), 123.6 (d), 129.8 (d), 130.5 (d), 132.3 (s), 156.5 (s) and 157.5 (s).

p-*Methoxybenzyl chloride:* n_D^{23} = 1.5469 (lit.,[36] n_D = 1.5482); ν_{max}/cm^{-1} 1612, 1515 and 1249; $\delta_H(CDCl_3)$ 3.77 (3 H, s), 4.56 (2 H, s), 6.86 (2 H, d) and 7.30 (2 H, s); $\delta_C(CDCl_3)$ 46.27 (t), 55.28 (q), 114.11 (d), 129.88 (s), 130.03 (d) and 159.66 (s).

General Synthesis of para-*Substituted Benzylbenzohydroxamates*.—The general synthesis of hydroxamic esters from potassium hydroxamates and the appropriate benzyl bromides has been described.[35] The condensation reaction involving *p*-methoxybenzyl bromide and potassium benzohydroxamate did not provide the hydroxamic ester and hence an alternative method is described below.

Benzyl benzohydroxamate. Potassium benzohydroxamate (10.2 g, 58.5 mmol), benzyl bromide (10.0 g, 58.5 mmol) and sodium carbonate (7.8 g, 73 mmol) were stirred overnight in 50% aq. MeOH (160 cm^3) and refluxed for 2 h. Removal of MeOH *in vacuo* and acidification followed by extraction with DCM provided the crude hydroxamate. Pure benzyl benzohydroxamate (13.6 g, 93%) was obtained as white crystals upon recrystallisation ($CHCl_3$–LP), m.p. 100–102 °C (Found: C, 73.7; H, 6.0; N, 6.15. $C_{14}H_{13}NO_2$ requires C, 73.99; H, 5.77; N, 6.16%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3250 (NH) and 1678 (CO); $\delta_H(CDCl_3)$ 4.98 (2 H, s), 7.31 (5 H, m), 7.37 (2 H, t), 7.43 (1 H, t, J = 7.4, *p*-ArH) and 7.67 (2 H, d, J = 7.1, *o*-ArH); $\delta_C(CDCl_3)$ 78.02 (t), 127.08 (dt, *p'*-ArC), 128.28 (d), 128.33 (d), 128.40 (d), 129.03 (d), 131.69 (dt), 131.70 (s, *i*-ArC), 135.13 (s, *i'*-ArC) and 166.26 (s); *m/z* 227 (M^+, 40%), 210 (45), 105 (45), 91 (100), 77 (30), 51 (15) and 28 (20).

p-*Bromobenzyl benzohydroxamate*. Refluxing potassium benzohydroxamate (6.68 g, 38.2 mmol), *p*-bromobenzyl bromide (9.68 g, 38.7 mmol) and sodium carbonate (4.9 g, 46 mmol) in 50% aq. MeOH (150 cm^3) gave the title compound (4.69 g, 40%) after work-up and recrystallisation ($CHCl_3$–LP), m.p. 172–173 °C (Found: C, 54.7; H, 3.85; N, 4.4; Br, 26.09. $C_{14}H_{12}BrNO_2$ requires C, 54.92; H, 3.95; N, 4.57; Br, 26.10%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1680; $\delta_H(CDCl_3)$ 4.99 (2 H, s), 7.32 (2 H, d, J = 8.4, *m'*-ArH), 7.41 (2 H, t, J = 6.8, *m*-ArH), 7.54 (3 H, m), 7.66 (2 H, d, J = 7, *o*-ArH) and 8.57 (1 H, br); $\delta_C(CDCl_3)$ 77.46 (t), 122.83 (s, *i*-Ar), 126.67 (dt), 128.63 (dd), 130.78 (dq), 131.59 (s), 131.68 (dd), 132.09 (dt, *p*-ArC), 134.13 (s, *i'*-ArC) and 166.50 (s); *m/z* 307 (M^+, 20%), 290 (60), 169 (60), 105 (70), 90 (50), 77 (100) and 51 (80).

p-*Chlorobenzyl benzohydroxamate*. Refluxing potassium benzohydroxamate (7.66 g, 44 mmol), *p*-chlorobenzyl bromide (8.98 g, 44 mmol) and sodium carbonate (5.8 g, 55 mmol) in aq. MeOH (150 cm^3) gave the title compound (10.92 g, 95%) upon work-up and recrystallisation ($CHCl_3$–LP), m.p. 158–160 °C (Found: C, 64.15; H, 4.7; N, 5.15; Cl, 13.5. $C_{14}H_{12}ClNO_2$ requires C, 64.25; H, 4.62; N, 5.35; Cl, 13.55%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3406 (NH) and 1687 (CO); $\delta_H(CDCl_3)$ 4.99 (2 H, s), 7.36 (4 H, s), 7.4 (2 H, t, J = 7, *m*-ArH), 7.5 (1 H, t, J = 7, *p*-ArH), 7.66 (2 H, d, J = 7, *o*-ArH) and 8.62 (1 H, br); $\delta_C(CDCl_3)$ 77.55 (t), 127.01 (dt, *m*-ArC), 128.75 (dd), 128.83 (dd), 130.63 (dq, *p'*-ArC), 131.74 (s), 131.21 (dt, *p*-ArC), 133.75 (s), 134.76 (s) and 166.68 (s); *m/z* 261 (M^+, 20%), 244 (45), 139 (20), 125 (100), 105 (60), 77 (50) and 51 (25).

p-*Nitrobenzyl benzohydroxamate*. Potassium benzohydrox-

amate (4.05 g, 23.1 mmol), *p*-nitrobenzyl bromide (5.0 g, 23.1 mmol) and sodium carbonate (3.0 g, 28 mmol) provided the crude hydroxamate *via* the general procedure. Pure *p*-nitrobenzyl benzohydroxamate (5.92 g, 94% was obtained as pale yellow crystals upon recrystallisation ($CHCl_3$–LP), m.p. 174–176 °C (Found: C, 61.4; H, 4.3; N, 10.05. $C_{14}H_{12}N_2O_4$ requires C, 61.76; H, 4.44; N, 10.29%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3393 (NH) and 1691 (CO); $\delta_H(CDCl_3)$ 5.14 (2 H, s), 7.42 (2 H, t, J = 7, *m*-ArH), 7.51 (1 H, t, J = 7, *p*-ArH), 7.62 (2 H, d, J = 7, *o*-ArH), 7.65 (2 H, d, *o'*-ArH), 8.22 (2 H, d, J = 6.9, *m'*-ArH) and 8.79 (1 H, br); $\delta_C(CD_3CN)$ 77.39 (t), 124.46 (dd), 128.04 (dt), 129.58 (d), 130.86 (d), 132.91 (dt), 133.18 (s), 144.62 (s), 148.99 (s) and 166.59 (s); *m/z* 239 (M^+, 5%), 226 (90), 121 (25), 105 (100), 91 (25) and 77 (45).

p-tert-*Butylbenzyl benzohydroxamate*. Potassium benzohydroxamate (5.0 g, 28 mmol), *p-tert*-butylbenzyl bromide (3.23 g, 14.2 mmol) and sodium carbonate (2.0 g, 19 mmol) provided pure *p-tert*-butylbenzyl benzohydroxamate (2.9 g, 72%) *via* the general procedure after work-up and recrystallisation (DCM–LP), m.p. 89–93 °C (Found: C, 76.35; H, 7.7; N, 4.75. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.47; N, 4.94%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (NH) and 1685 (CO); $\delta_H(CDCl_3)$ 1.32 (9 H, s), 5.00 (2 H, s), 7.38 (6 H, m), 7.47 (1 H, t, *p*-ArH), 7.66 (2 H, d, J = 7.1, *o*-ArH) and 9.0 (1 H, br); $\delta_C(CDCl_3)$ 31.27 (q), 34.63 (s), 78.09 (t), 125.57 (dd), 126.92 (s), 127.04 (d), 128.63 (d), 128.70 (s), 129.17 (d), 131.95 (s) and 151.90 (s); *m/z* 283 (M^+, 20%), 266 (25), 147 (100), 132 (60), 117 (45), 105 (65), 91 (50) and 77 (55).

p-*Phenylbenzyl benzohydroxamate*. Potassium benzohydroxamate (2.4 g, 13 mmol), *p*-phenylbenzyl bromide (2.4 g, 13 mmol) and sodium carbonate (3.0 g, 28 mmol) provided pure *p*-phenylbenzyl benzohydroxamate (0.62 g, 16%) after work-up and recrystallisation ($CHCl_3$–LP), m.p. 122–125 °C (Found: C, 79.05; H, 5.85; N, 4.35. $C_{20}H_{17}NO_2$ requires C, 79.19; H, 5.65; N, 4.62%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3320 (NH) and 1674 (CO); $\delta_H(CD_3COCD_3)$ 5.03 (2 H, s), 7.22 (1 H, t), 7.39 (4 H, m), 7.42 (1 H, t), 7.49 (2 H, d), 7.58 (4 H, d), 7.63 (2 H, d) and 9.62 (1 H, br); δ_C(50% $CDCl_3$–CD_3CN) 126.05 (d), 126.20 (s), 126.66 (s), 127.68 (dd), 128.03 (d), 128.94 (s), 130.62 (s), 130.92 (dt) and 164.91 (s); *m/z* 303 (M^+, 5%), 288 (55), 286 (50), 182 (65), 181 (85), 167 (100), 152 (50), 121 (40), 105 (60) and 77 (60).

p-*Tolyl benzohydroxamate*. Potassium benzohydroxamate (7.33 g, 42 mmol), *p*-tolyl bromide (7.74 g, 41.9 mmol) and sodium carbonate (5.55 g, 51.9 mmol) provided pure *p*-tolyl benzohydroxamate (5.92 g, 59%) *via* the general procedure after work-up and recrystallisation ($CHCl_3$–LP), m.p. 106–107 °C (Found: C, 74.35; H, 6.25; N, 5.55. $C_{15}H_{15}NO_2$ requires C, 74.67; H, 6.27; N, 5.80%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3200 (NH) and 1681 (CO); $\delta_H(CDCl_3)$ 2.33 (3 H, s), 4.93 (2 H, s), 7.11 (2 H, d, J = 7.8), 7.29 (2 H, d, J = 7.8), 7.34 (2 H, t, J = 7.6, *m*-ArH), 7.45 (1 H, t, J = 7.6, *p*-ArH), 7.68 (2 H, d, J = 7, *o*-ArH) and 9.62 (1 H, br); $\delta_C(CDCl_3)$ 21.09 (q), 77.96 (t), 127.07 (dt), 128.40 (dd), 129.06 (d), 129.24 (d), 131.74 (dt, *p*-ArC), 131.85 (s), 132.14 (s), 138.33 (s, *p'*-ArC) and 166.24 (s); *m/z* 272 (M^+, 55%), 150 (20), 121 (25), 105 (100), 77 (70) and 51 (40).

p-*Phenoxybenzyl benzohydroxamate*. Potassium benzohydroxamate (5.0 g, 28 mmol), *p*-phenoxybenzyl bromide (3.1 g, 12 mmol) and sodium carbonate (7.0 g, 65 mmol) provided pure *p*-phenoxybenzyl benzohydroxamate (2.42 g, 65%) after work-up and recrystallisation ($CHCl_3$–LP), m.p. 186–189 °C (Found: C, 74.95; H, 5.45; N, 4.7. $C_{20}H_{17}NO_3$ requires C, 75.22; H, 5.37; N, 4.39%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3390 (NH) and 1690 (CO); $\delta_H(CDCl_3)$ 5.00 (2 H, s), 7.00 (4 H, m), 7.13 (1 H, t, J = 6.8, *p''*-ArH), 7.43 (6 H, m), 7.43 (1 H, t, J = 7, *p*-ArH), 7.67 (2 H, d, J = 7, *o*-ArH) and 8.7 (1 H, br); $\delta_C(CDCl_3)$ 77 (t), 116.59 (dd), 119.21 (d), 123.63 (dt, *p''*-ArC), 126.66 (s), 126.98 (d), 128.69 (dd), 128.78 (s), 129.81 (dd), 131.07 (d), 131.74 (d), 132.04 (d), 156.68 (s) and 157.95 (s); *m/z* 197 (40%), 183 (100), 105 (25), 77 (40) and 51 (25).

p-*Methoxybenzyl benzohydroxamate*. Benzohydroxamic acid (1.4 g, 10 mmol), *p*-methoxybenzyl chloride (1.6 g, 10 mmol) and triethylamine (3.0 g, 30 mmol) were refluxed in $CHCl_3$ (30 cm^3) for 2 h. After being washed with 10% aq. sodium carbonate and dilute HCl, the organic layer was dried and the solvent removed *in vacuo* to afford the crude hydroxamate. Recrystallisation (EtOH–H_2O) provided pure *p*-methoxybenzyl benzohydroxamate (0.48 g, 19%), m.p. 119–121 °C (Found: C, 70.2; H, 6.05; N, 5.4. $C_{15}H_{15}NO_3$ requires C, 70.02; H, 5.88; N, 5.44%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3407 (NH) and 1684 (CO); $\delta_H(CDCl_3)$ 3.75 (3 H, s), 4.92 (2 H, s), 6.62 (2 H, d, J = 9, *m'*-ArH), 7.31 (2 H, d, J = 9, *o'*-ArH), 7.34 (2 H, t, J = 7, *m*-ArH), 7.43 (1 H, t, J = 7, *p*-ArH) and 7.68 (2 H, d, J = 7, *o*-ArH); $\delta_C(CDCl_3)$ 55.15 (q), 77.78 (t), 113.80 (d, *m'*-ArC), 127.05 (d, *o*-ArC), 127.33 (s), 128.48 (d, *m*-ArC), 130.94 (d, *o'*-ArC), 131.79 (d, *p*-ArC) and 159.83 (s); *m/z* 257 (M^+, 55%), 135 (40), 121 (100), 105 (50), 77 (60) and 51 (50).

N-*Chlorination of Hydroxamic Esters*.—*N*-Chlorination of the hydroxamates was achieved in quantitative yields by stirring with a 3 molar excess of *tert*-butyl hypochlorite in DCM or $CHCl_3$ at room temperature for 2–12 h.

Ethyl N-*Chlorobenzohydroxamate* (*General Procedure*).—A solution of ethyl benzohydroxamate (1.65 g, 10.0 mmol) and *tert*-butyl hypochlorite (3.26, 30.0 mmol) in DCM (60 cm^3) was stirred in the dark under anhydrous conditions for 3 h. The solvent and excess *tert*-butyl hypochlorite were removed under reduced pressure at 30 °C to afford ethyl *N*-chlorobenzohydroxamate (2.00 g, 100%) as a yellow oil. $\delta_H(CDCl_3)$ 1.22 (3 H, t), 4.16 (2 H, q), 7.42 (2 H, t, *m*-ArH), 7.54 (1 H, t, *p*-ArH) and 7.76 (2 H, d, *o*-ArH).

Isopropyl N-*chlorobenzohydroxamate*. $\delta_H(CDCl_3)$ 1.30 (6 H, d), 4.46 (1 H, m), 7.41 (2 H, t, *m*-ArH), 7.51 (1 H, t, *p*-ArH) and 7.77 (2 H, d, *o*-ArH).

Butyl N-*chlorobenzohydroxamate*. $\delta_H(CDCl_3)$ 0.87 (3 H, t), 1.33 (2 H, m), 1.56 (2 H, m), 4.12 (2 H, t), 7.44 (2 H, t, *m*-ArH), 7.54 (1 H, t, *p*-ArH) and 7.77 (2 H, d, *o*-ArH).

Isobutyl N-*chlorobenzohydroxamate*. $\delta_H(CDCl_3)$ 0.83 (6 H, d), 1.87 (1 H, m), 3.64 (2 H, d), 7.37 (2 H, t, *m*-ArH), 7.47 (1 H, t, *p*-ArH) and 7.74 (2 H, d, *o*-ArH).

Butyl p-*bromo*-N-*chlorobenzohydroxamate*. $\delta_H(CDCl_3)$ 0.88 (3 H, t), 1.31 (2 H, sextet), 1.59 (2 H, quintet), 4.11 (2 H, t), 7.57 (2 H, d) and 7.64 (2 H, d).

Butyl N, p-*dichlorobenzohydroxamate*. $\delta_H(CDCl_3)$ 0.87 (3 H, t), 1.31 (2 H, sextet), 1.55 (2 H, quintet), 4.11 (2 H, t), 7.39 (2 H, d) and 7.71 (2 H, d).

Butyl N-*chloro*-p-*methylbenzohydroxamate*. $\delta_H(CDCl_3)$ 0.88 (3 H, t), 1.34 (2 H, sextet), 1.58 (2 H, quintet), 2.39 (3 H, s), 4.12 (2 H, t), 7.21 (2 H, d) and 7.67 (2 H, d).

Butyl N-*chloro*-p-*nitrobenzohydroxamate*. $\delta_H(CDCl_3)$ 0.88 (3 H, t), 1.31 (2 H, sextet), 1.57 (2 H, quintet), 4.15 (2 H, t), 7.92 (2 H, d) and 8.30 (2 H, d).

Butyl N-*chloro*-p-*methoxybenzohydroxamate*. $\delta_H(CDCl_3)$ 0.89 (3 H, t), 1.31 (2 H, sextet), 1.58 (2 H, quintet), 3.64 (3 H, s), 4.12 (2 H, t), 6.92 (2 H, d) and 7.78 (2 H, d).

Butyl N-*chloro*-p-tert-*butylbenzohydroxamate*. $\delta_H(CDCl_3)$ 0.87 (3 H, t), 1.33 (9 H, s), 1.34 (2 H, sextet), 1.60 (2 H, quintet), 4.13 (2 H, t), 7.44 (2 H, d) and 7.72 (2 H, d).

Butyl N-*chloro*-p-*phenylbenzohydroxamate*. $\delta_H(CDCl_3)$ 0.89 (3 H, t), 1.34 (2 H, sextet), 1.63 (2 H, quintet), 4.16 (2 H, t), 7.40–7.47 (4 H, m), 7.61–7.68 (3 H, m) and 7.87 (2 H, d).

Benzyl N-*chlorobenzohydroxamate*. Benzyl benzohydroxamate (3.41 g, 15 mmol) and *tert*-butyl hypochlorite (4.87 g, 45 mmol) in DCM were stirred for 5 h in the dark. Removal of solvent *in vacuo* provided the title compound which was used immediately without further purification. $\delta_H(CDCl_3)$ 5.09 (2 H, s), 7.26 (2 H, m), 7.30 (3 H, m), 7.40 (2 H, t), 7.54 (1 H, t) and 7.68 (2 H, d).

p-*Bromobenzyl* N-*chlorobenzohydroxamate*. $\delta_H(CDCl_3)$ 5.03 (2 H, s), 7.11 (2 H, d), 7.41 (4 H, m), 7.52 (1 H, t) and 7.68 (2 H, d).

p-*Chlorobenzyl* N-*chlorobenzohydroxamate*. The title compound was obtained by the general chlorination procedure in $CHCl_3$. $\delta_H(CDCl_3)$ 5.04 (2 H, s), 7.17 (2 H, d), 7.26 (2 H, d), 7.40 (2 H, t), 7.54 (1 H, t) and 7.66 (2 H, d).

p-*Nitrobenzyl* N-*chlorobenzohydroxamate*. $\delta_H(CDCl_3)$ 5.21 (2 H, s), 7.44 (4 H, m), 7.54 (1 H, t), 7.70 (2 H, d) and 8.18 (2 H, d).

p-*Tolyl* N-*chlorobenzohydroxamate*. $\delta_H(CDCl_3)$ 2.35 (3 H, s), 5.06 (2 H, s), 7.15 (4 H, s), 7.41 (2 H, t), 7.54 (1 H, t) and 7.72 (2 H, d).

p-tert-*Butylbenzyl* N-*chlorobenzohydroxamate*. The title compound was obtained by the general chlorination procedure in 50% DCM–$CHCl_3$. $\delta_H(CDCl_3)$ 1.30 (9 H, s), 5.05 (2 H, s), 7.16 (2 H, d), 7.32 (2 H, d), 7.40 (2 H, t), 7.53 (1 H, t) and 7.66 (2 H, d).

p-*Phenylbenzyl* N-*chlorobenzohydroxamate*. The title compound was obtained by chlorination in 50% CH_3CN–DCM. $\delta_H(CDCl_3)$ 5.11 (2 H, s), 7.3–7.7 (12 H, m) and 8.1 (2 H, d).

p-*Phenoxybenzyl* N-*chlorobenzohydroxamate*. $\delta_H(CDCl_3)$ 5.05 (2 H, s), 6.92 (2 H, d), 7.2–7.6 (12 H, t) and 7.69 (2 H, d).

p-*Methoxybenzyl* N-*chlorobenzohydroxamate*. $\delta_H(CDCl_3)$ 3.78 (3 H, s), 5.01 (2 H, s), 6.82 (2 H, d), 7.17 (2 H, d), 7.38 (2 H, t), 7.53 (1 H, t) and 7.67 (2 H, d).

General Synthesis of Alkyl N-*Acetoxy* para-*Substituted Benzohydroxamates and* para-*Substituted Benzyl* N-*Acetoxybenzohydroxamates.—Method* 1. Acetoxylation of the *N*-chlorohydroxamate derivatives was achieved by the addition of a 0.5 molar excess of the Lewis acid silver acetate in ether at room temperature. The progress of the reaction was monitored by HPLC. Reaction times varied from 3 to 36 h. Fair to excellent yields were obtained, as determined by analytical HPLC. This method was not successful with the significantly electron-donating and -withdrawing *para*-substituents for the benzyl *N*-chlorohydroxamates. Hence an alternative method is presented.

Method 2. *p*-Substituted benzyl *N*-chlorobenzohydroxamates were stirred with 1.4 mol equivs. of anhydrous sodium acetate in dry acetone, at room temperature, for 12–72 h. The reaction was monitored by ^1H NMR spectroscopy. Suction filtration provided the *N*-acetoxy derivatives, frequently with quantitative conversion. Yields were determined by analytical HPLC analysis.

Ethyl N-*acetoxybenzohydroxamate* **11a**. Prepared by general method 1. Purification by flash column chromatography (DCM then EtOAc) afforded pure ethyl *N*-acetoxybenzohydroxamate (1.98 g, 89%) as an orange oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1789 (CO) and 1724 (CO); $\delta_H(CDCl_3)$ 1.28 (3 H, t), 2.10 (3 H, s), 4.23 (2 H, q), 7.41 (2 H, t, *m*-ArH), 7.54 (1 H, t, *p*-ArH) and 7.77 (2 H, d, *o*-ArH); $\delta_C(CDCl_3)$ 13.50 (q), 16.78 (q), 71.26 (t), 128.23 (d), 128.98 (d), 131.70 (s), 132.66 (d), 166.18 (s) and 174.25 (s).

Isopropyl N-*acetoxybenzohydroxamate* **11d**. Prepared by general method 1. Purification by flash column chromatography (DCM then EtOAc) afforded pure isopropyl *N*-acetoxybenzohydroxamate (1.90 g, 80%) as an orange oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1788 (CO) and 1724 (CO); $\delta_H(CDCl_3)$ 1.33 (6 H, d), 2.03 (3 H, s), 4.47 (1 H, m), 7.39 (2 H, t), 7.49 (1 H, t) and 7.76 (2 H, d, *o*-ArH); $\delta_C(CDCl_3)$ 16.76 (q), 20.93 (q), 78.41 (d), 128.12 (d), 128.88 (d), 131.98 (s), 132.37 (d), 166.21 (s) and 174.68 (s).

Isobutyl N-*acetoxybenzohydroxamate* **11e**. Prepared by general procedure 1. Purification by flash column chromatography (DCM then EtOAc) afforded pure isobutyl *N*-acetoxybenzohydroxamate (1.87 g, 74%) as an orange oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1790 (CO) and 1724 (CO); $\delta_H(CDCl_3)$ 0.85 (6 H, d), 1.92 (1 H, m), 2.09 (3 H, s), 3.92 (2 H, d), 7.39 (2 H, t, *m*-ArH), 7.49 (1 H, t, *p*-ArH) and 7.75 (2 H, d, *o*-ArH); $\delta_C(CDCl_3)$ 16.65 (q), 16.95 (q), 27.17 (d), 81.75 (t), 128.14 (d), 128.91 (d), 131.69 (s), 132.62 (d), 166.05 (s) and 174.15 (s).

Butyl N-*acetoxybenzohydroxamate* **11b**. The title compound was prepared *via* general method 1 in a yield of 82%. Purification was achieved by flash chromatography (75% DCM–25% LP). This compound has been characterized previously.[14]

Butyl N-*acetoxy*-p-*bromobenzohydroxamate* **11k**. The title compound was prepared *via* general method 1 in a yield of 48%. Purification was achieved by flash chromatography (75% DCM–25% LP). $\nu_{max}(CHCl_3)/cm^{-1}$ 1791 (CH_3CO) and 1731 (ArCO); $\delta_H(CDCl_3)$ 0.90 (3 H, t), 1.35 (2 H, sextet), 1.63 (2 H, quintet), 2.12 (3 H, s, OAc), 4.16 (2 H, t), 7.58 (2 H, d, J = 8.7, *m*-ArH) and 7.64 (2 H, d); $\delta_C(CDCl_3)$ 13.58 (q), 18.59 (q), 18.83 (t), 29.86 (t), 75.31 (t), 127.54 (s), 130.43 (d), 131.47 (d), 167.94 (s) and 173.12 (s).

Butyl N-*acetoxy*-p-*chlorobenzohydroxamate* **11j**. The title compound was prepared *via* general method 2. Purification by flash chromatography (75% DCM–25% LP) provided **11j** (1.21 g, 96%) as a viscous oil that solidified upon standing. $\nu_{max}(CHCl_3)/cm^{-1}$ 1792 (CH_3CO) and 1728 (ArCO); $\delta_H(CDCl_3)$ 0.89 (3 H, t), 1.35 (2 H, sextet), 1.63 (2 H, quintet), 2.12 (3 H, s), 4.17 (2 H, t), 7.39 (2 H, d) and 7.75 (2 H, d, J = 8.6, *o*-ArH); $\delta_C(CDCl_3)$ 13.47 (q), 18.46 (q), 18.75 (t), 29.78 (t), 75.17 (t), 128.40 (d), 129.80 (s), 130.27 (d, *o*-ArC), 138.84 (s, *p*-ArC), 167.82 (s) and 172.85 (s).

Butyl N-*acetoxy*-p-*methylbenzohydroxamate* **11h**. The title compound was prepared *via* general method 1 in a yield of 68%. Purification was achieved by flash chromatography (75% DCM–25% LP). $\nu_{max}(CHCl_3)/cm^{-1}$ 1790 (CH_3CO) and 1730 (ArCO); $\delta_H(CDCl_3)$ 0.90 (3 H, t), 1.35 (2 H, sextet), 1.63 (2 H, quintet), 2.10 (3 H, s), 2.39 (3 H, s), 4.18 (2 H, t), 7.21 (2 H, d) and 7.67 (2 H, d, J = 8.2, *o*-ArH); $\delta_C(CDCl_3)$ 13.53 (q), 18.61 (q), 18.81 (t), 21.42 (q), 29.67 (t), 75.03 (t), 128.57 (s), 128.78 (d), 129.02 (d), 143.45 (s, *p*-ArC), 168.01 (s) and 173.93 (s).

Butyl N-*acetoxy*-p-*nitrobenzohydroxamate* **11l**. The title compound was prepared *via* general method 1 in a yield of 96%. $\nu_{max}(CHCl_3)/cm^{-1}$ 1794 (CH_3CO) and 1729 (ArCO); $\delta_H(CDCl_3)$ 0.90 (3 H, t), 1.32 (2 H, sextet), 1.62 (3 H, quintet), 2.13 (3 H, s), 4.16 (2 H, t), 7.91 (2 H, d) and 8.28 (2 H, d); $\delta_C(CDCl_3)$ 13.57 (q), 18.47 (q), 18.82 (t), 29.62 (t), 75.72 (t), 123.32 (d, *m*-ArC), 129.82 (d), 137.58 (s), 149.83 (s, *p*-ArC), 167.83 (s) and 172.15 (s).

Butyl N-*acetoxy*-p-*methoxybenzohydroxamate* **11f**. The title compound was prepared *via* general method 1 in a yield of 68%. Purification was achieved by flash chromatography (75% DCM–25% LP). $\nu_{max}(CHCl_3)/cm^{-1}$ 1790 (CH_3CO) and 1728 (ArCO); $\delta_H(CDCl_3)$ 0.90 (3 H, t), 1.36 (2 H, sextet), 1.64 (2 H, quintet), 2.12 (3 H, s), 3.84 (3 H, s), 4.18 (2 H, t), 6.90 (2 H, d) and 7.78 (2 H, d, J = 8.9, *o*-ArH); $\delta_C(CDCl_3)$ 13.47 (q), 18.59 (q), 18.76 (t), 29.82 (t), 55.18 (q), 74.78 (t), 113.39 (d, *m*-ArC), 123.22 (s), 131.28 (d), 163.18 (s, *p*-ArC), 168.02 (s) and 173.18 (s).

Butyl N-*acetoxy*-p-tert-*butylbenzohydroxamate* **11g**. The title compound was prepared *via* general method 2 in a yield of 52%. Purification was achieved by flash chromatography (15% EtOAc–85% LP). $\nu_{max}(CHCl_3)/cm^{-1}$ 1794 (CH_3CO), 1721 (CO); $\delta_H(CDCl_3)$ 0.90 (3 H, t), 1.32 (9 H, s), 1.33 (2 H, sextet), 1.64 (2 H, quintet), 2.12 (3 H, s), 4.19 (2 H, t), 7.43 (2 H, d) and 7.73 (2 H, d, J = 8.9, *o*-ArH); $\delta_C(CDCl_3)$ 13.57 (q), 18.72 (q), 18.85 (t), 29.93 (t), 30.92 (q), 34.96 (s), 75.11 (t), 125.12 (d), 128.54 (s), 128.97 (d), 156.45 (s, *p*-ArC), 168.08 (s) and 173.70 (s).

Butyl N-*acetoxy*-p-*phenylbenzohydroxamate* **11i**. The title compound was prepared *via* general method 2 in a yield of 82%. Purification was achieved by flash chromatography (5% EtOAc–95% LP). $\nu_{max}(CHCl_3)/cm^{-1}$ 1794 (CH_3CO), 1721 (CO); $\delta_H(CDCl_3)$ 0.91 (3 H, t), 1.33 (2 H, sextet), 1.64 (2 H, quintet), 2.14 (3 H, s), 4.21 (2 H, t), 7.39–7.47 (3 H, m), 7.66 (4 H, m) and 7.86 (2 H, d, J = 8.9, *o*-ArH); $\delta_C(CDCl_3)$ 13.71 (q), 18.83 (q), 18.97 (t), 30.03 (t), 30.89 (q), 75.36 (t), 126.66 (d), 127.21 (d),

128.25 (d), 128.94 (d), 129.67 (d), 130.24 (s), 139.71 (s), 145.53 (s), 166.24 (s) and 173 (s).

Benzyl N-*acetoxybenzohydroxamate* **12a**. The title compound was prepared *via* general method 2. Purification by flash chromatography (90% LP–10% EtOAc) provided **12a** (87%) as a viscous oil. This compound has been characterized previously.[14]

p-*Bromobenzyl* N-*acetoxybenzohydroxamate* **12h**. The title compound was prepared *via* general method 2. Purification by flash chromatography (90% LP–10% EtOAc) provided **12h** (94%). (Yield *via* method 1, 25%). $\nu_{max}(CHCl_3)/cm^{-1}$ 1791 (CH_3CO) and 1731 (CO); $\delta_H(CDCl_3)$ 2.05 (3 H, s), 5.12 (2 H, s), 7.23 (2 H, d, J = 8.3, *m'*-ArH), 7.40 (2 H, t, J = 7.1, *m*-ArH), 7.45 (2 H, d, J = 8.3, *o'*-ArH), 7.55 (1 H, t, J = 7.1, *p*-ArH) and 7.69 (2 H, d, J = 7.1, *o*-ArH); $\delta_C(CDCl_3)$ 18.56 (q), 76.54 (t), 122.66 (s, *p'*-ArC), 128.21 (dd, *o*-ArC), 128.82 (dt, *m*-ArC), 130.64 (dq, *o'*-ArC), 131.40 (s, *i*-ArC), 131.49 (dd, *m'*-ArC), 132.74 (d, *p*-ArC), 133.73 (s, *i'*-ArC), 168.02 (s, Ac) and 174.04 (s).

p-*Chlorobenzyl* N-*acetoxybenzohydroxamate* **12g**. The title compound was prepared *via* general method 2. Purification by flash chromatography (90% LP–10% EtOAc) provided **12g** (96%) as a pale yellow oil which solidified upon standing. (Yield *via* method 1, 45%). $\nu_{max}(CHCl_3)/cm^{-1}$ 1793 (CH_3CO) and 1731 (CO); $\delta_H(CDCl_3)$ 2.04 (3 H, s), 5.14 (2 H, s), 7.30 (4 H, s), 7.39 (2 H, t, J = 7.6, *m*-ArH), 7.53 (1 H, t, J = 7.6, *p*-ArH) and 7.69 (2 H, d, J = 7.6, *o*-ArH); $\delta_C(CDCl_3)$ 18.58 (q), 76.54 (t), 128.22 (dd), 128.54 (dd), 128.85 (dt), 130.41 (d), 131.45 (s), 132.76 (dt), 133.25 (s), 134.48 (s), 168.02 (s) and 174.08 (s).

p-*Nitrobenzyl* N-*acetoxybenzohydroxamate* **12i**. The title compound was prepared *via* general method 2. Purified by flash chromatography (90% LP–10% EtOAc) provided **12i** (93%) as a yellow solid. (Yield *via* method 1, 0%). $\nu_{max}(CHCl_3)/cm^{-1}$ 1793 (CH_3CO) and 1732 (CO); $\delta_H(CDCl_3)$ 2.04 (3 H, s), 5.29 (2 H, s), 7.40 (2 H, t, J = 8, *m*-ArH), 7.55 (3 H, m), 7.69 (2 H, d, J = 6.8, *m'*-ArH) and 8.18 (2 H, d, J = 6.8, *m'*-ArH); $\delta_C(CDCl_3)$ 18.66 (q), 75.98 (t), 123.60 (dd), 128.42 (d), 128.87 (d), 129.24 (d), 131.29 (s, *i*-Ar), 133.04 (dt, *p*-ArC), 142.29 (s, *i'*-ArC), 147.90 (s, *p'*-ArC), 168.18 (s) and 174.20 (s).

p-*Tolyl* N-*acetoxybenzohydroxamate* **12e**. The title compound was prepared *via* general method 2. Purification by flash chromatography (90% LP–10% EtOAc) provided **12e** (60%). (Yield *via* method 1, <5%). $\nu_{max}(CHCl_3)/cm^{-1}$ 1791 (CH_3CO) and 1729 (CO); $\delta_H(CDCl_3)$ 2.05 (3 H, s, OAc), 2.33 (3 H, s), 5.13 (2 H, s), 7.13 (2 H, d, J = 7.8, *m'*-ArH), 7.25 (2 H, d), 7.40 (2 H, t), 7.51 (1 H, t) and 7.74 (2 H, d, J = 8, *o*-ArH); $\delta_C(CDCl_3)$ 18.70 (q), 21.20 (q), 77.42 (t), 128.21 (dd), 129.05 (d), 129.12 (d), 129.25 (d), 131.59 (s), 131.65 (s), 132.68 (dt, *p*-ArC), 138.56 (s, *p'*-ArC), 168.10 (s) and 174.14 (s).

p-tert-*Butylbenzyl* N-*acetoxybenzohydroxamate* **12d**. The title compound was prepared *via* general method 2. Purification by flash chromatography (90% LP–10% EtOAc) provided **12d** (26%). $\nu_{max}(CHCl_3)/cm^{-1}$ 1790 (CH_3CO), 1725 (CO); $\delta_H(CDCl_3)$ 1.29 (9 H, s), 2.02 (3 H, s), 5.14 (2 H, t), 7.26–7.40 (6 H, m), 7.49 (1 H, t, J = 7, *p*-ArH) and 7.73 (2 H, d, J = 7, *o*-ArH); $\delta_C(CDCl_3)$ 18.49 (q), 31.11 (q), 34.44 (s), 77.17 (t), 125.25 (dd, *m'*-ArC), 128.09 (dd), 128.92 (d), 128.96 (d), 131.46 (s), 131.53 (s), 132.57 (dt, *p*-ArC), 151.62 (s, *p'*-ArC), 167.89 (s) and 173.94 (s).

p-*Phenylbenzyl* N-*acetoxybenzohydroxamate* **12f**. The title compound was prepared *via* general method 2. Purification by flash chromatography (90% LP–10% EtOAc) provided **12f** (60%) as a viscous oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1791 (CH_3CO) and 1729 (CO); $\delta_H(CDCl_3)$ 2.03 (3 H, s), 5.20 (2 H, s), 7.4 (7 H, m), 7.51 (5 H, m) and 7.76 (2 H, d); $\delta_C(CDCl_3)$ 18.55 (q), 77.11 (t), 126.93 (dd), 127.04 (dd), 127.37 (dt), 128.16 (d), 128.67 (d), 128.91 (d), 129.54 (d), 131.49 (s), 132.66 (dq), 133.53 (s), 140.39 (s), 141.43 (s), 166.10 (s) and 174.14 (s).

p-*Phenoxybenzyl* N-*acetoxybenzohydroxamate* **12c**. The title compound was prepared *via* general method 2. Purification by flash chromatography (85% LP–15% EtOAc) provided **12c** (78%) as a very viscous oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 1795 (CH_3CO) and 1725 (CO); $\delta_H(CDCl_3)$ 2.09 (3 H, s), 5.14 (2 H, s), 6.9 (4 H, m), 7.1 (1 H, t, J = 7, *p''*-ArH), 7.2–7.4 (6 H, m), 7.53 (1 H, t, J = 7, *p*-ArH) and 7.71 (2 H, d, J = 7, *o*-ArH); $\delta_C(CDCl_3)$ 18.75 (q), 76.95 (t), 118.61 (d, *o''*-ArC), 120.27 (dd, *m'*-ArC), 128.28 (dd), 129.00 (d), 129.76 (dd), 131.09 (dq), 132.80 (d), 155.46 (s), 157.40 (s), 168.15 (s, Ac) and 174.17 (s).

p-*Methoxybenzyl* N-*acetoxybenzohydroxamate* **12b**. The title compound was prepared *via* general method 2. Purification by flash chromatography (85% LP 15% EtOAc) provided **12b** (57%). $\nu_{max}(CHCl_3)/cm^{-1}$ 1795 (CH_3CO), 1725 (CO); $\delta_H(CDCl_3)$ 2.03 (3 H, s), 3.73 (3 H, s), 5.09 (2 H, s), 6.82 (2 H, d, J = 7, *m'*-ArH), 7.26 (2 H, d, J = 7, *o'*-ArH), 7.36 (2 H, t, J = 7, *m*-ArH), 7.48 (1 H, t) and 7.69 (2 H, d); $\delta_C(CDCl_3)$ 18.45 (q), 55.94 (q), 76.95 (t), 113.60 (d, *m'*-ArC), 126.47 (s, *i'*-ArC), 128.01 (dd, *o*-ArC), 128.78 (dt, *m*-ArC), 130.77 (dq, *o'*-ArC), 131.44 (s, *p*-ArC), 132.49 (dt), 159.77 (s, *p'*-ArC), 168.15 (s) and 174.17 (s).

Kinetic Studies.—The acid-catalysed solvolysis of the substrates was monitored in the variable-temperature probe of a Bruker AC300P NMR spectrometer (298–338 K). 10–40 mg of substrate in CD_3CN (400 mm^3) was diluted with D_2O such that after addition of an appropriate volume of a solution of sulfuric acid in D_2O (typically 0.5–1.5 molar), the ratio of CD_3CN:D_2O was constant at 3.81:1. The acid solution was added to the tube, prewarmed to the temperature of the probe, and mixed into the mixture to initiate reaction just prior to insertion into the probe.

^1H NMR spectra were acquired automatically; at pre-programmed intervals peak areas for the acetoxy methyl singlet (and acetic acid) were obtained by integration. Autocatalysis was demonstrated in the absence of sulfuric acid while the inverse dependence upon the activity of water was demonstrated at CD_3CN:D_2O ratios of 400:107.5, 425:82.5, 450:57.5, 462.5:45, 470:37.5 and 475:32.5. Arrhenius studies were carried out at an appropriate fixed acid concentration to enable data collection at each temperature. A minimum of five temperatures between 298 and 338 K were used for each substrate.

Appendix

In the acid-catalysed solvolysis of esters of weak acids, if the initial concentration of ester is a and the concentration transformed at time t is x,

$$\frac{dx}{dt} = k[H^+](a - x)$$

where k is the rate constant for hydrolysis. If an initial concentration b of weak acid, produced by hydrolysis, is introduced then

$$[H^+] = \sqrt{[K(b + x)]}$$

where K is the equilibrium constant for dissociation of the acid, and

$$\frac{dx}{dt} = k\sqrt{K(a - x)}\sqrt{(b + x)}$$

To integrate, let $z = \sqrt{(b + x)}$ then $x = z^2 - b$ and $dx = 2zdz$. Thus

$$\frac{k}{2}\sqrt{K}\mathrm{d}t = \frac{\mathrm{d}z}{a+b-z^2} = \frac{\mathrm{d}z}{[\sqrt{(a+b)}+z][\sqrt{(a+b)}-z]}$$

$$= \frac{1}{2\sqrt{(a+b)}}\left(\frac{1}{\sqrt{(a+b)}+z} + \frac{1}{\sqrt{(a+b)}-z}\right)\mathrm{d}z$$

$x = 0$ initially therefore $z = \sqrt{b}$ and by integration,

$$kt\sqrt{[K(a+b)]} = \ln\frac{\sqrt{(a+b)}-\sqrt{b}}{\sqrt{(a+b)}+\sqrt{b}} \cdot \frac{\sqrt{(a+b)}+\sqrt{(b+x)}}{\sqrt{(a+b)}-\sqrt{(b+x)}}$$

If no initial acid is added, then

$$k\sqrt{(Ka)} \cdot t = \ln\frac{(\sqrt{a}+\sqrt{x})}{(\sqrt{a}-\sqrt{x})}$$

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References

1 G. M. Blackburn and B. Kellard, *Chem. Ind. (London)*, 1986, 608, 687 and 770; Y.-T. Woo, J. C. Arcos and D. Y. Lai, in *Bioactive Molecules*, ed. P. Politzer and F. J. Martin Jr., Elsevier, New York, 1988, vol. 5, 'Chemical Carcinogens', p. 1; R. C. Garner, C. N. Martin and D. B. Clayson, in *Chemical Carcinogens*, 2nd edn., ed. C. E. Searle, ACS Monograph 182, American Chemical Society, Washington, 1984, 175; B. Singer and J. T. Kusmierek, *Annu. Rev. Biochem.*, 1982, **52**, 655; E. C. Miller and J. A. Miller, *Cancer*, 1981, **47**, 2327; E. C. Miller, *Cancer Res.*, 1978, **38**, 1479; J. A. Miller, *Cancer Res.*, 1970, **30**, 559; J. L. Radomski, *Annu. Rev. Pharmacol. Toxicol.*, 1979, **19**, 129.

2 E. W. Boberg, E. C. Miller, J. A. Miller, A Poland and A. Liem, *Cancer Res.*, 1983, **43**, 5163; C.-C. Lai, E. C. Miller, J. A. Miller and A. Liem, *Carcinogenesis*, 1985, **6**, 1037; K. B. Delcos, E. C. Miller, J. A. Miller and A. Liem, *Carcinogenesis*, 1986, **7**, 277.

3 F. A. Beland and F. F. Kadlubar, *Environ. Health Perspect.*, 1985, **62**, 19; F. F. Kadlubar, J. A. Miller and E. C. Miller, *Cancer Res.*, 1978, **36**, 3628; F. A. Beland, K. L. Dooley and C. D. Jackson, *Cancer Res.*, 1982, **42**, 1348; H. Neumann, *J. Cancer Res. Clin. Oncol.*, 1986, **112**, 100.

4 C. Meier and G. Boche, *Chem. Ber.*, 1990, **123**, 1699; *Tetrahedron Lett.*, 1990, **31**, 1685, 1693; F. Bosold and G. Boche, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 63; M. Famulok and G. Boche, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 468; M. Famulok, F. Bosold and G. Boche, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 337.

5 J. S. Helmick, K. A. Martin, J. L. Heinrich and M. Novak, *J. Am. Chem. Soc.*, 1991, **113**, 3459; J. S. Helmick and M. Novak, *J. Org. Chem.*, 1991, **56**, 2925.

6 M. Novak, K. Martin and J. L. Heinrich, *J. Org. Chem.*, 1989, **54**, 5430.

7 R. Ulbrich, M. Famulok, F. Bosold and G. Boche, *Tetrahedron Lett.*, 1990, **31**, 1689; G. Boche, F. Bosold and S. Schroder, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 973.

8 M. Novak and R. K. Lagerman, *J. Org. Chem.*, 1988, **53**, 4762; M. Novak, L. H. Rovin, M. Pelecanou, J. J. Mulero and R. K. Lagerman, *J. Org. Chem.*, 1985, **52**, 2002; M. Novak and A. K. Roy, *J. Org. Chem.*, 1985, **50**, 571, 4884; M. Novak, M. Pelecanou and L. Pollack, *J. Am. Chem. Soc.*, 1986, **108**, 112; M. Novak, M. Pelecanou, A. K. Roy, A. F. Andronico, F. M. Plourde, T. M. Olefirowicz and T. J. Curtin, *J. Am. Chem. Soc.*, 1984, **106**, 5623.

9 R. V. Hoffman, A. Kumar and G. A. Buntain, *J. Am. Chem. Soc.*, 1985, **107**, 4731; P. G. Gassman and J. E. Granrud, *J. Am. Chem. Soc.*, 1984, **106**, 1498 and 2448; C. M. Scott, G. R. Underwood and R. B. Kirsch, *Tetrahedron Lett.*, 1984, **25**, 499; G. R. Underwood and R. B. Kirsch, *Tetrahedron Lett.*, 1985, **26**, 147; *J. Chem. Soc., Chem. Commun.*, 1985, 136; G. R. Underwood and R. J. Callahan, *Tetrahedron Lett.*, 1987, **28**, 5427; C. Nicolaou and G. R. Underwood, *Tetrahedron Lett.*, 1989, **30**, 1479.

10 J. C. Fishbein and R. A. McClelland, *J. Am. Chem. Soc.*, 1987, **109**, 2824.

11 G. P. Ford and P. S. Herman, *J. Mol. Struct.*, 1990, **203**, 121; G. P. Ford and J. D. Scribner, *J. Am. Chem. Soc.*, 1981, **103**, 4281; T. Ohwada and K. Shudo, *J. Am. Chem. Soc.*, 1989, **111**, 34; Y. Li, A. Abramovitch and K. N. Houk, *J. Org. Chem.*, 1989, **54**, 2911.

12 S. A. Glover and A. P. Scott, *Tetrahedron*, 1989, **45**, 1763.

13 A. P. Scott, Ph.D. Thesis, University of New England, 1991; S. A. Glover and A. P. Scott, ref. 12.

14 R. G. Gerdes, S. A. Glover, J. F. ten Have and C. A. Rowbottom, *Tetrahedron Lett.*, 1989, **30**, 2649.

15 J. J. Campbell, S. A. Glover and C. A. Rowbottom, *Tetrahedron Lett.*, 1990, **37**, 5377.

16 G. Pannetier and P. Souchay, *Chemical Kinetics*, Elsivier, London, 1967, p. 285.

17 N. S. Isaacs, *Physical Organic Chemistry*, Longman, UK, 1987, p. 474.

18 K. R. Adam, I. Lauder and V. R. Stimson, *Aust. J. Chem.*, 1962, **15**, 467.

19 H. T. French, *J. Chem. Thermodyn.*, 1987, **19**, 1158.

20 V. Gold, *Adv. Phys. Org. Chem.*, 1969, **7**, 259; N. S. Isaacs, ref. 17, p. 272.

21 J. G. Prichard and F. A. Long, *J. Am. Chem. Soc.*, 1956, **78**, 6008; N. S. Isaacs, ref. 17, p. 350.

22 V. Gold, ref. 20, p. 322.

23 Y. Okamoto and H. C. Brown, *J. Org. Chem.*, 1957, **22**, 485; *J. Am. Chem. Soc.*, 1958, **80**, 4979.

24 Y. Tsuno, T. Ibata and Y. Yukawa, *Bull. Chem. Soc. Jpn.*, 1959, **32**, 960; Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jpn.*, 1959, **32**, 965, 967.

25 N. S. Isaacs, ref. 17, p. 102 and references cited therein.

26 M. W. Schmidt, P. N. Truong and M. S. Gordon, *J. Am. Chem. Soc.*, 1987, **109**, 5217; M. W. Schmidt and M. S. Gordon, *Inorg. Chem.*, 1986, **25**, 248.

27 J. E. Rowe and A. D. Ward, *Aust. J. Chem.*, 1968, **21**, 2761.

28 D. V. Banthorpe, in *Chemistry of the Amino Group*, ed. S. Patai, Interscience, New York, 1968, p. 585; L. Bauer and O. Exner, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 376.

29 J. J. Campbell, S. A. Glover and C. A. Rowbottom, unpublished work.

30 B. Ames, J. McCann and E. Yamasaki, *Mutat. Res.*, 1975, **31**, 347.

31 M. Lee and M. Isobe, *Cancer Res.*, 1990, **50**, 4300; P. L. Skipper, S. R. Tannenbaum, W. G. Thilly, E. E. Furth and W. A. Bishop, *Cancer Res.*, 1980, **40**, 4704.

32 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.

33 M. J. S. Dewar and J. J. P. Stewart, AMPAC, *QCPE*, Program 506.

34 C. R. Hauser and W. B. Renfrow, Jr., *Org. Synth.*, Coll. Vol. II, 1963, 67.

35 J. H. Cooley, W. D. Bills and J. R. Throckmorton, *J. Org. Chem.*, 1960, **25**, 1734.

36 *CRC Handbook of Chemistry and Physics*, 67th Edition, ed. R. C. Weast, CRC Press, Boca Raton, 1987.

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