The Kinetics of Nitrilimine Formation in Base-catalysed Hydrolysis of Hydrazonyl Halides

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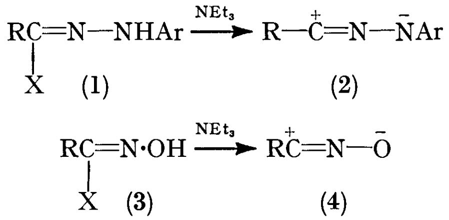
The formation of 1,3-dipolar ion and carbonium ion intermediates in the solvolysis of hydrazonyl halides is competitive, and the major reaction pathway followed depends on the pH of the medium. The kinetics of hydrolysis of alkyl- and aryl-substituted hydrazonyl bromides to hydrazides has been studied in 70% dioxan at 25° as a function of pH. At high $[H^+]$, the pH-independent reaction was identified as unimolecular dissociation to form a carbonium ion intermediate. At higher pH, the base-catalysed process was loss of bromide ion from the hydrazonyl bromide anion to give a 1,3-dipolar ion. Electron-donating substituents, attached either to the hydrazonyl carbon atom or the hydrazone nitrogen atom, aid carbonium ion formation. On the other hand, opposing effects are operative in 1,3-dipolar ion formation, which is favoured by electron-withdrawing substituents attached to the nitrogen atom and by electron-donating substituents attached to the carbon atom. With a strongly withdrawing aromatic *N*-substituent [*e.g.* $2,4\text{-}(NO_2)_2\cdot C_6H_3$] the base-catalysed pathway is dominant even at pH 3. With poorer leaving groups than bromide ion (such as ethoxide or phenoxide) the hydrazonyl anion is relatively stable, but with leaving groups (such as NO_2^- and N_3^-) of intermediate leaving ability the rate of elimination from the anion could be measured. The pH–rate profile of α-nitro-*N*-(*p*-nitrophenyl)benzaldehyde hydrazone (leaving group NO_2^-) was studied, giving k_1 (rate of decomposition of the anion) = $1{\cdot}35 \times 10^{-2}\ s^{-1}$ and K_a (acidity of the α-nitro-hydrazone) = 10^{-10}.

THE intermediacy of 1,3-dipolar ions in a wide variety of cycloadditions has been established.[1] Two of the most widely studied dipoles are the nitrilimine (2) and the nitrile oxide (4). Both are highly reactive and are usually used *in situ*. Typical reaction conditions involve treating the hydrazonyl halide (1) or α-halogeno-oxime (3) with a base (usually triethylamine) in benzene. The intermediates (2) and (4) may then dimerise or react with a dipolarophile, *e.g.* an alkene, giving rise to pyrazolines or oxazolines. The mechanism of the trapping reaction has been the subject of much recent controversy.[2] The factors which are involved in the dehydrohalogenation are little understood, however, and form the subject of this investigation.[3] The cycloaddition is normally very rapid so that under some conditions the first step, *i.e.* dehydrohalogenation, may become rate-determining for the overall process.



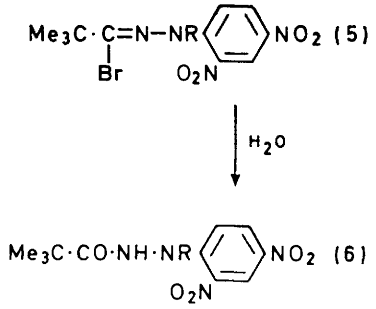
$$\underset{\displaystyle X}{RC}{=}N{-}NHAr \xrightarrow{NEt_3} R{-}\overset{+}{C}{=}N{-}\overset{-}{N}Ar$$

(1) (2)

$$\underset{\displaystyle X}{RC}{=}N{\cdot}OH \xrightarrow{NEt_3} R\overset{+}{C}{=}N{-}\overset{-}{O}$$

(3) (4)

In unbuffered dioxan–water (4 : 1 v/v) the hydrolysis of *N*-(2,4-dinitrophenyl)-2,2-dimethylpropionohydrazonyl bromide (5; R = H) to the corresponding hydrazide (6; R = H) is relatively slow ($k_{obs} = 1{\cdot}18 \times 10^{-4}\ s^{-1}$) at 75°. With an excess of sodium acetate as buffer, however, the release of bromide ion was so rapid, even at 25°, that hydrolysis was essentially complete by the time the first kinetic measurement was taken (30 s). A similar effect was noted in the presence of sodium azide. Relatively small rate enhancements have been noted in the solvolysis of hydrazonyl bromides



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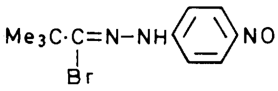
[1] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 565.

[2] R. Huisgen, *J. Org. Chem.*, 1968, **33**, 2291; R. A. Firestone, *ibid.*, p. 2285; S. Morrocchi, A. Ricca, and A. Zanarotti, *Tetrahedron Letters*, 1969, 3329; 1970, 3215; S. Beltrame, P. Sartinana, and C. Vintani, *J. Chem. Soc.* (*B*), 1971, 814.

[3] Preliminary communication, A. F. Hegarty, M. P. Cashman, and F. L. Scott, *Chem. Comm.*, 1971, 684.

(due to a primary salt effect),[4] but the dramatic increase in rate with acetate (or azide) is incompatible with a simple ionisation (carbonium ion formation) mechanism. The acetate and azide are either (*a*) acting as nucleophiles for the direct displacement of bromide ion (an S_N2-type displacement) or (*b*) increasing the pH of the previously unbuffered solution to such an extent that a strongly base-catalysed process becomes the dominant mode of hydrolysis. The following observations support the latter explanation.

The solvolysis of *N*-(*p*-nitrophenyl)-2,2-dimethylpropionohydrazonyl bromide (7) was investigated over



(7)

a range of pH values in 70% dioxan at 25° ($\mu = 0{\cdot}10$M, KNO_3) with a pH-stat to maintain the pH and follow the course of the reaction (see Table 1), thus obviating the need for buffer dilutions. The ' pH ' values quoted are the apparent values obtained directly in 70% dioxan (with a glass electrode standardised in aqueous solution) without further correction. Over the pH range 3·0—4·5 the hydrolysis rates are almost identical but as the pH is raised above 5·0 there is a large increase in the rate of hydrolysis. Above pH *ca.* 7 the rate of hydrolysis of (7) was too rapid to be measured by this method. At higher pH values the log of the observed rate constant (k_{obs}) is proportional to the pH of the medium (see Figure 1).

TABLE 1

Observed pseudo-first-order rate constants (s^{-1}) for the hydrolysis of *N*-(*p*-nitrophenyl)-2,2-dimethylpropionohydrazonyl bromide (7) in 70% dioxan at 25°

pH	3·0	3·5	4·0	4·5	5·0	5·5	5·95	6·42
10^3k_{obs}	3·10	3·02	2·84	4·04	6·02	8·44	19·8	38·0

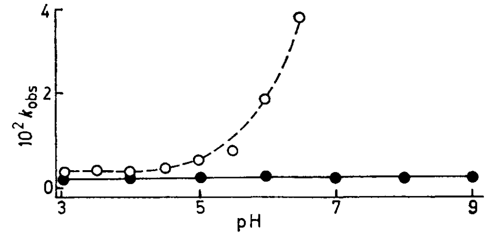
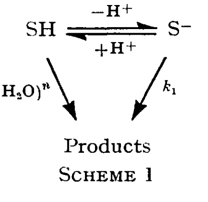


FIGURE 1 Plot of log k_{obs} *vs.* pH for the hydrolysis of (a) the hydrazonyl bromide (7) (open circles) and (b) the hydrazonyl bromide (5; R = Me) (closed circles) in 70% dioxan at 25°

These results can be accommodated by the kinetic Scheme 1 (SH and S^- refer to the neutral and ionised forms of the substrate). From this Scheme the relationship of the microscopic rate constants (k_0,k_1) to k_{obs} is obtained [equation (1)]; a_H is the activity of hydrogen ion and $K_a = [S^-]a_H/[SH]$. If $K_a \ll a_H$, then equation (1) reduces to equation (2), which is consistent with the observed kinetic results. In Figure 1, the solid line has been drawn using the values of k_0 and k_1K_a ($2{\cdot}8 \times 10^{-3}$ and $2{\cdot}0 \times 10^{-8}$ s^{-1}, respectively) which best fit the kinetic data. Since the reaction was studied at pH values much less than the pK_a of SH, it is not possible from these data to separate the constants k_1 and K_a.

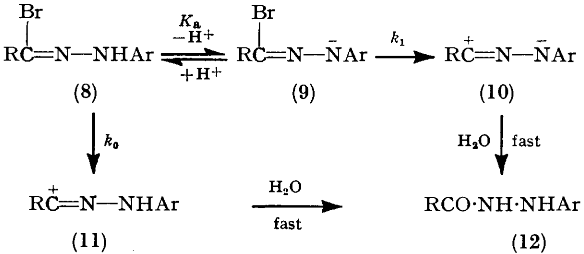


SCHEME 1

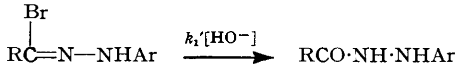
$$k_{obs} = \frac{k_0 a_H}{a_H + K_a} + \frac{k_1 K_a}{K_a + a_H} \qquad (1)$$

$$k_{obs} = k_0 + k_1 K_a/a_H \qquad (2)$$

Several kinetically equivalent mechanisms can be visualised for the hydrolysis of (7). Two of these are given in Schemes 2 and 3. In Scheme 2, k_0 represents rate-determining formation of carbonium ion (11) and the pathway represented by k_1 involves a specific base-catalysed reaction. Ionisation of the hydrazonyl bromide (8) yields the highly reactive anion (9), which rapidly loses Br^- to give the 1,3-dipolar nitrilimine (10), which is then rapidly hydrated to give the product hydrazide (12). In Scheme 3 the base-catalysed reaction involves direct attack by hydroxide ion on the hydrazonyl bromide.



SCHEME 2



SCHEME 3

The hydrolysis of *N*-(2,4-dinitrophenyl)-2,2,*N*-trimethylpropionohydrazonyl bromide (5; R = Me) was also studied over the pH range 3—9 (see Table 2). Over the entire range, k_{obs} was almost independent of pH (see Figure 1); in fact the rate of hydrolysis did not markedly increase even up to pH 11, but extraneous disappearance of HO^- with solvent or CO_2 attack was significant at this pH so that the rate constants were less reliable. It can be calculated [from equation (2)] that the unmethylated analogue (5; R = H) would hydrolyse *ca.* 10^7 times more rapidly at pH 11 than it does in the low pH plateau region (see later). Unlike the other hydrazonyl bromides studied, the *N*-methylhydrazonyl bromide (5; R = Me) does not possess an

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[4] F. L. Scott, M. P. Cashman, and A. F. Hegarty, *J. Chem. Soc.* (*B*), 1971, 1607.

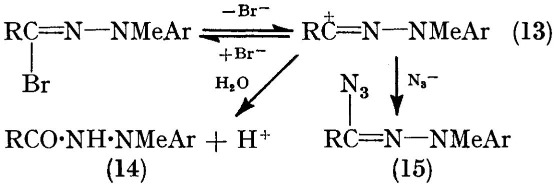
ionisable N–H group. Consequently the base-catalysed 1,3-dipolar ion pathway of Scheme 2 is not possible for this compound. The very large rate difference between the N–Me and N–H compounds at high hydroxide ion concentration renders direct attack by hydroxide ion (Scheme 3) unlikely. It follows that the term k_1K_a in equation (2) is best associated with 1,3-dipolar ion formation in Scheme 2.

TABLE 2

Observed pseudo-first-order rate constants for the solvolysis of *N*-(2,4-dinitrophenyl)-2,2,*N*-trimethylpropionohydrazonyl bromide in 70% dioxan at 25°

pH	10^4k_{obs}/s^{-1}	[KNO$_3$]/mol l^{-1}	[KBr]/mol l^{-1}
3·0	8·2	0·10	
4·0	8·8	0·10	
5·0	9·6	0·10	
6·0	10·3	0·10	
7·0	9·8	0·10	
8·0	9·8	0·10	
9·0	9·9	0·10	
8·0	9·3	0·09	0·01
8·0	6·3	0·07	0·03
8·0	4·9	0·05	0·05
8·0	2·9	0·00	0·10

That the k_0 term [equation (2)] represents spontaneous (or water-assisted) ionisation, is supported by the following observations. The hydrolysis of (5; R = Me) was investigated at pH 8·0 in the presence of various concentrations of potassium bromide (see Table 2). Clearly increasing concentrations of bromide ion reverses the initial equilibrium (the common-ion effect [5]). The preferential trapping of the carbonium ion (13) by bromide ion rather than by water (which is present in excess) suggested that (13) might be sufficiently long-lived to permit trapping by other nucleophiles. Azide ion is a particularly attractive trapping agent since the product [the hydrazonyl azide (15)] is readily identifiable by the strong azide i.r. absorption (at 2200 cm^{-1}). Moreover at pH 8, while reaction of water with the carbonium ion (13) results in the release of 1 mol. equiv. of acid, reaction with azide ion does not; the extent of reaction with azide ion can then be gauged by recording the quantity of base required to neutralise the acid released.



The results of a trapping experiment are shown in Figure 2. While increasing the sodium azide concentration from 0·01 to 0·10M (at constant ionic strength) caused little change in the observed rate constant, the quantity of acid released progressively decreased. The percentages of azide (15) and hydrazide (14) formed (calculated from these data) are given in Table 3. Similar results were obtained when acetate was used as the trapping agent. These data support the simple ionisation mechanism (Scheme 2) resulting in the formation of a carbonium ion intermediate.[6] Previously reported kinetic data for the hydrolysis of hydrazonyl halides (which do not possess an N–Me group) in unbuffered solution also supported the ionisation mechanism;[4,7] presumably the HBr generated during the course of the solvolyses in these cases ensured that the kinetics were studied in the low pH plateau region.

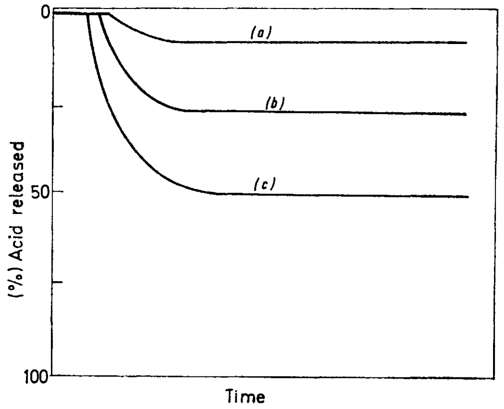


FIGURE 2 Plot of percentage acid released *vs.* time in the hydrolysis of the hydrazonyl bromide (5; R = Me) in 70% dioxan at 25° in the presence of (a) 0·10M-NaN$_3$, (b) 0·05M-NaN$_3$, and (c) 0·01M-NaN$_3$

Substituent Effects.—To investigate the effect of different substituents on the rate of formation of the 1,3-dipolar ion, pH–rate profiles for several hydrazonyl bromides (8) were determined, for representative R and Ar groups. The pH-stat technique was modified to follow the course of these reactions, the cell being placed in the sample compartment of a u.v. spectrophotometer. This permitted the pH to be kept constant while the hydrolysis was followed spectrophotometrically at a suitable wavelength.

TABLE 3

Relative amounts of hydrazonyl azide (15) and hydrazide (14) formed on hydrolysis of *N*-(2,4-dinitrophenyl)-2,2,*N*-trimethylpropionohydrazonyl bromide (5; R = Me) in 70% dioxan at pH 8 containing various concentrations of azide ion

[KNO$_3$]/ mol l^{-1}	[N$_3^-$]/ mol l^{-1}	% Azide (15)	% Hydrazide (14)
0·10	0·00		100
0·09	0·01	50	50
0·05	0·05	71	29
0·00	0·10	90	10

The results for the hydrazonyl bromides (16; R = Et, ClCH$_2$, BrCH$_2$, and Me$_3$C) are given in Table 4.

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[5] L. C. Bateman, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1940, 974.

[6] L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *J. Chem. Soc.*, 1940, 979.

[7] J. B. Aylward and F. L. Scott, *J. Chem. Soc.* (*B*), 1969, 1080; F. L. Scott and D. A. Cronin, *Tetrahedron Letters*, 1963, 715.

TABLE 4

Observed rate constants for the solvolysis of hydrazonyl bromides (16) in 70% dioxan at 25°

N-(2,4-Dinitrophenyl)propionohydrazonyl bromide (16; R = Et)

pH	2·0	3·0	3·9	4·45	5·0	5·51
$10^4k_{obs}/s^{-1}$	5·5	16·2	81·2	219	606	1132

Chloro-[*N*-(2,4-dinitrophenyl)]acetohydrazonyl bromide (16; R = $ClCH_2$)

pH	2·0	4·0	4·6	4·93	5·55	5·92
$10^4k_{obs}/s^{-1}$	2·0	19·6	54	119	320	1510

Bromo-[*N*-(2,4-dinitrophenyl)]acetohydrazonyl bromide (16; R = $BrCH_2$)

pH	2·3	3·2	4·0	4·56	5·0	5·49
$10^4k_{obs}/s^{-1}$	2·8	4·2	16·3	46·1	97·8	286

N-(2,4-Dinitrophenyl)-2,2-dimethylpropionohydrazonyl bromide (16; R = Me_3C)

pH	2·2	2·98	4·09	4·5	5·04	5·52
$10^4k_{obs}/s^{-1}$	9·9	11·5	48	98	228	488

The log k_{obs} *vs.* pH profiles for these four compounds are presented in Figure 3. The k_0 and k_1K_a values which best fit the kinetic data are shown in Table 5.

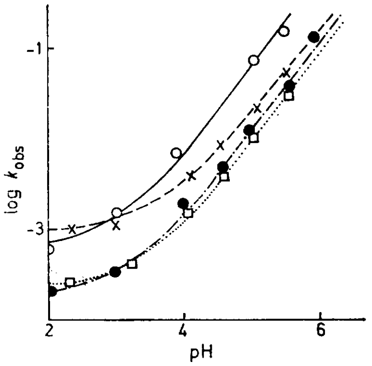


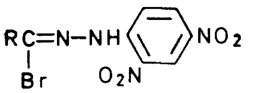
FIGURE 3 Observed log k_{obs} *vs.* pH profiles for the hydrolysis of the hydrazonyl bromides (16) in 70% dioxan at 25°: (a) (R = Et) (×); (b) (R = Me_3C) (○); (c) (R = $BrCH_2$) (□); (d) (R = $ClCH_2$) (●). The curves in each case were drawn by use of equation (2), with the values of k_0 and k_1K_a from Table 5

TABLE 5

Summary of rate and equilibrium constants obtained from pH–rate profiles for hydrolysis of hydrazonyl bromides (16) at 25° in 70% dioxan (μ = 0·10M)

R	$10^4k_0/$ s^{-1}	$10^7k_1K_a/$ s^{-1}	k_1/s^{-1}	K_a
Et	6·3	7·5	($4·7 \times 10^6$)	($1·6 \times 10^{-13}$)
$ClCH_2$	2·0	1·4		
$BrCH_2$	2·5	1·1		
Me_3C	8·0	2·1		

Further, the effect of variation of the *N*-aryl substituent was also studied. The standard substrates were *N*-(2-bromo-4-substituted phenyl)benzohydrazonyl bromides (17; X = NO_2, Br, F, and Me). The observed rate constants are presented in Table 6; the k_0 and k_1K_a values calculated to give the best fit of these data (see Figure 4) are summarised in Table 7.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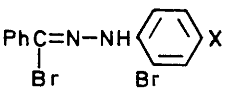
(17)

TABLE 6

Observed rate constants for the solvolysis of the hydrazonyl bromides (17) in 70% dioxan at 25°

N-(2-Bromo-4-nitrophenyl)benzohydrazonyl bromide (17; X = NO_2)

pH	5·0	5·6	6·1	6·8	7·1
$10^4k_{obs}/s^{-1}$	28·3	58·2	119	267	499

N-(2,4-Dibromophenyl)benzohydrazonyl bromide (17; X = Br)

pH	4·0	5·95	7·1	7·43	8·15
$10^4k_{obs}/s^{-1}$	1·3	3·2	7·0	24	46

N-(2-Bromo-4-fluorophenyl)benzohydrazonyl bromide (17; X = F)

pH	4·1	5·95	6·98	7·47	8·0
$10^4k_{obs}/s^{-1}$	2·7	6·0	46	50	151

N-(2-Bromo-4-methylphenyl)benzohydrazonyl bromide (17; X = Me)

pH	4·07	4·6	6·01	7·7	8·1	8·5
$10^4k_{obs}/s^{-1}$	3·5	3·5	4·6	21	47	128

TABLE 7

Summary of rate and equilibrium constants obtained from pH profiles of *N*-(2-bromo-4-substituted phenyl)-benzohydrazonyl bromides (17) at 25° in 70% dioxan (μ = 0·10M)

Substrate	$10^4k/s^{-1}$	k_1K_a/s^{-1}	$10^5k_0/s^{-1}$ [a]
(17; X = Me)	3·55	$3·8 \times 10^{-11}$	13·9
(17; X = F)	2·7	$2·3 \times 10^{-10}$	9·7
(17; X = Br)	1·2	$5·7 \times 10^{-11}$	5·6
(17; X = NO_2)		*ca.* 10^{-8}	
(7)	28	$2·0 \times 10^{-8}$	

[a] Values from ref. 4 in unbuffered 80% dioxan at 75°.

The hydrazonyl bromide (17; X = NO_2), which had the lowest spontaneous solvolysis rate of the compounds used, was not studied at a sufficiently low pH to allow an accurate determination of k_0. Moreover the graph of log k_{obs} *vs.* pH, although linear, did not have exactly unit slope (see Figure 4). This is also true to a lesser extent for some of the other substrates studied. A rigorous treatment of this deviation was not attempted since the solvent was not pure water and therefore a

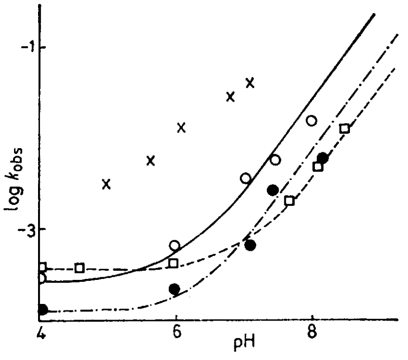

FIGURE 4 Observed log k_{obs} *vs.* pH profiles for the hydrolysis of the hydrazonyl bromides (17) in 70% dioxan at 25°: (a) (X = NO_2) (×); (b) (X = Br) (●); (c) (X = F) (○); (d) (X = Me) (□). The curves in each case were drawn by use of equation (2), with the values of k_0 and k_1K_a from Table 7

change in the measured pH by one unit might not correspond precisely to a ten-fold change in hydrogen-ion activity.

The variation of the k_0 values for spontaneous hydrolysis of hydrazonyl bromides (see Table 5) are consistent with the development of positive charge in the transition state. Thus the electron-withdrawing chloro- and bromo-methyl groups reduce the rate of solvolysis *ca.* three-fold (relative to the methyl-substituted compound). Substitution in the *N*-aryl group has a similar effect, *i.e.* carbonium ion formation is most rapid for (17) when X = Me. The k_0 values in Table 7 parallel closely those previously reported.[4] Although there are clear trends for both series of compounds (16) and (17) that electron-withdrawing substituents reduce the rate of reaction, sufficient data are not available for a rigorous Taft or Hammett treatment to be applied.

The very high reactivity shown by the hydrazonyl bromides in basic solution made direct measurement of $\text{p}K_a$ difficult. Therefore the rate of bromide ion loss from the hydrazonyl bromide anion (k_1 in Scheme 2) could not be separated from the acidity constant K_a. Increasing electron withdrawal by substituents in the hydrazonyl bromide (8) would be expected to stabilise the anion (9), thus increasing K_a. Substituents in the *N*-aryl ring would be expected to have a larger effect than those in Ar. In particular, substituents in the *ortho*- or *para*-positions in Ar which are capable of resonance stabilisation of negative charge (*e.g.* NO_2) would be expected to have a particularly large effect on K_a. Substituent effects on k_1 are more difficult to predict. However they may resemble those observed for k_0 since the reactions involved [k_0: loss of bromide ion from a neutral substrate to give a positively charged species; k_1: loss of bromide ion from an anion to give a neutral (1,3-dipolar) species] are formally similar. Thus electron-withdrawing substituents tend to decrease k_1 (*i.e.* a substituent which would increase K_a would tend to decrease k_1, reducing the overall change in the composite constant k_1K_a).

These considerations do in general apply to the observed data. k_1K_a Does not vary greatly with R (see Table 5), but is somewhat lower with the electron-withdrawing substituents bromo- and chloro-methyl. If K_a remains essentially constant throughout the series (the substituent change being relatively remote from the proton removed), then the variation in k_1K_a observed would be due solely to k_1. In fact this appears to be so since the values of k_1K_a in this case parallel closely the corresponding k_0 values (see Table 5).

For substituents in the *N*-aryl ring (see Table 7), the overall effect on k_1K_a is the converse. In this case K_a is presumably the dominant term (as argued before); substituents in this ring have been shown[4] to have only a small effect ($\rho = -0{\cdot}62$) on the simple ionisation term (k_0). Therefore k_1K_a should reflect changes in K_a, *i.e.* increasing with increasing electron-withdrawing substitution. This is in general observed (see Table 7) although the increasing values of k_1K_a ($\text{Me} < \text{Br} < \text{F} \ll \text{NO}_2$) are not quite the same as the order of increasing electron withdrawal ($\text{Me} < \text{F} < \text{Br} \ll \text{NO}_2$), as judged by the σ-values of the substituents.[8] It is particularly noticeable that the only substituent capable of substantial resonance stabilisation of the anion (*p*-NO_2) causes a large increase in k_1K_a (*i.e.* in K_a).

Estimation of K_a.—Although the $\text{p}K_a$ values of the hydrazonyl bromides (8) could not be measured directly, it was possible to estimate values using the corresponding hydrazones (18) as models. The actual $\text{p}K_a$ value

$$\text{RCH=N—NHAr} \qquad (18)$$

would be lower than that of the hydrazone owing to stabilisation of the anion (9) by the electron-withdrawing bromo-group. The $\text{p}K_a$ of propionaldehyde 2,4-dinitrophenylhydrazone [18; R = Et, Ar = $2,4\text{-}(NO_2)_2\cdot C_6H_3$] was measured spectrophotometrically. A plot of optical density (see Experimental section) *vs.* pH (see Figure 5) was correlated with a theoretical curve (solid line) with $\text{p}K_a = 12{\cdot}8$.* An attempt was also made to measure $\text{p}K_a$ values of the corresponding halogeno-substituted hydrazones, but these were unstable in basic solution. Assuming the $\text{p}K_a$ of 12·8 (a maximum value) for the hydrazonyl bromide [8; R = Et, Ar = $2,4\text{-}(NO_2)_2\cdot C_6H_3$], K_a and k_1 values can be estimated (Table 5) and hence it can be calculated that $k_1/k_0 = ca.\ 8 \times 10^9$. Since k_1 is a measure of the rate of 1,3-dipolar ion (10) formation from the anion

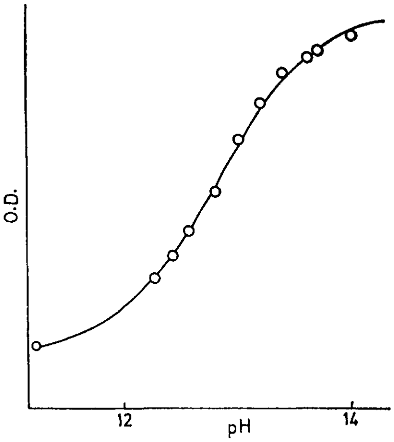

FIGURE 5 Optical density at 350 nm *vs.* pH plot for propionaldehyde 2,4-dinitrophenylhydrazone in 70% dioxan at 25°. The curve has been drawn assuming $\text{p}K_a = 12{\cdot}8$

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* Values of the $\text{p}K_a$ of benzaldehyde (and its simple derivatives) 2,4-dinitrophenylhydrazone have been previously quoted[9] as *ca.* 11.

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

[9] L. A. Jones and N. L. Mudler, *J. Org. Chem.*, 1962, **27**, 2356; S. Brownstein and A. E. Stillman, *J. Phys. Chem.*, 1959, **63**, 2061.

(9),* loss of bromide ion from the anion is *ca.* 10^7—10^{10} times more rapid than from the neutral substrate. It is thus clear why easy 1,3-dipolar ion formation occurs even at relatively low pH.

The pK_a values of hydrazones other than 2,4-dinitrophenylhydrazones were generally too high (*i.e.* >14) to be measured in 70% dioxan. One other value was estimated, however. In Figure 6 the optical density (at 480 nm) of the hydrazone (18; R = Et, Ar = 4-NO_2·C_6H_4) is plotted as a function of pH; the pK_a value calculated from these data is 14·2: this is not as precise as that for the dinitrophenylhydrazone since datum points could not be obtained experimentally at sufficiently high pH (Figure 6). Interpolating this pK_a as before gives a maximum estimate of k_1 for (17; X = NO_2) of 1·6 × 10^6 s^{-1}.

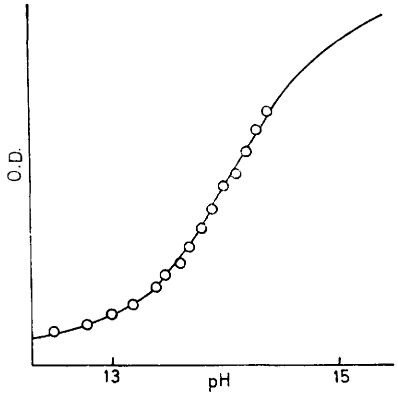
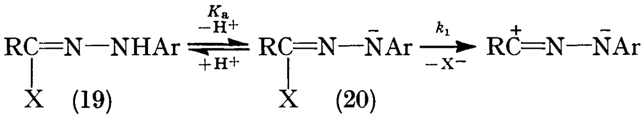


FIGURE 6 Optical density at 480 nm *vs.* pH plot for the hydrazone (18; R = Et, Ar = *p*-NO_2·C_6H_4) in 70% dioxan at 25°. The curve has been drawn assuming pK_a = 14·2

Variation of the Leaving Group.—If the hydrolysis of the hydrazonyl bromide (8) could have been followed over the entire pH range, then on the basis of equation (1) a second plateau at high pH would be expected. However, as pointed out previously, loss of bromide ion in this region is very rapid. Moreover, with the proviso that K_a be >10^{-14}, no change in R or Ar would be expected to bring k_1 within measurable range. Groups with a poorer leaving ability than bromide ion were therefore sought to reduce k_1. In fact, the rate of loss of X^- from the anion (20) was dependent on the nature of X.



$$\underset{\substack{|\\ \mathrm{X}}}{\mathrm{RC}}{=}\mathrm{N{-}NHAr}\ \underset{+\mathrm{H}^+}{\overset{K_a,\ -\mathrm{H}^+}{\rightleftharpoons}}\ \underset{\substack{|\\ \mathrm{X}}}{\mathrm{RC}}{=}\mathrm{N{-}\bar{N}Ar}\ \xrightarrow[-\mathrm{X}^-]{k_1}\ \mathrm{R\overset{+}{C}{=}N{-}\bar{N}Ar}$$

(19) (20)

(a) *Ethoxy* (X = OEt). Ethyl *N*-(2,4-dinitrophenyl)-2,2-dimethylpropionohydrazonate [19; R = Me_3C, Ar = 2,4-$(NO_2)_2$·C_6H_3, X = OEt] was chosen for study since the dinitrophenyl group facilitates anion formation at attainable pH values. The hydrazonate dissolved in 0·1M-potassium hydroxide but was recovered unchanged in quantitative yield after 24 h at 25°. In another experiment, the hydrazonate was dissolved in 70% dioxan and the pH adjusted to 13. A change in the visible spectrum characteristic of anion formation was noted, but repeated scans of the visible and u.v. regions showed no change in 24 h. Acidification of the solution yielded a spectrum similar to that of the starting hydrazonate but distinct from that of the expected hydrolysis product, the corresponding hydrazide. Thus, the anion (20), although formed in basic solution, is relatively unreactive at 25° with X = OEt. The ethoxide ion was the poorest leaving group of those studied.

(b) *Phenoxy* (X = OPh). Phenyl *N*-phenylbenzohydrazonate (19; R = Ar = Ph; X = OPh) was synthesised by treating the corresponding hydrazonyl chloride (19; R = Ar = Ph; X = Cl) with phenol in benzene in the presence of triethylamine. This novel hydrazonate was treated as described before [(a)], with similar results, *i.e.* the phenyl hydrazonate was relatively insensitive to basic hydrolysis at 25°.

(c) *Azide* (X = N_3). Repeated scans of the u.v. spectrum of a solution of the hydrazonyl azide [19; R = Me_3C, Ar = 2,4-$(NO_2)_2$·C_6H_3, X = N_3] in 70% dioxan at pH 13 (25°) showed a slow conversion into the hydrazide. Although not studied in detail, k_{obs} was *ca.* 10^{-4} l mol^{-1} s^{-1}.

(d) *Nitro* (X = NO_2). The kinetics of conversion of the α-nitro-hydrazone (21) (prepared by direct nitration of benzaldehyde *p*-nitrophenylhydrazone) into the corresponding hydrazide (23) were investigated over a wide pH range (Table 8). At low pH, where the ionisation mechanism would be expected, hydrolysis of the α-nitro-hydrazone was too slow to permit measurement. At higher pH (>*ca.* 8) conversion into the hydrazide was smooth. The observed rate of hydrolysis rose rapidly with pH but gave a pH-independent plateau at higher (>*ca.* 11) pH values (see Figure 7).

TABLE 8

Observed rate constants for the solvolysis of α-nitro-*N*-(*p*-nitrophenyl)benzaldehyde hydrazone in 70% dioxan at 25°

pH	8·1	8·5	9·1	9·5	10·0	10·5
$10^4k_{obs}/s^{-1}$	2·0	4·4	11·2	38·0	66·3	79·2
pH	11·0	11·5	12·0	12·6	13·0	13·5
$10^4k_{obs}/s^{-1}$	111	129	124	125	131	135

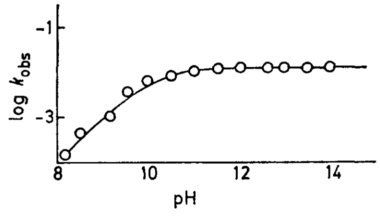


FIGURE 7 Plot of log k_{obs} *vs.* pH for the hydrolysis of the α-nitro-hydrazone (21) in 70% dixoan at 25°. The solid curve has been drawn by use of equation (1) with k_0 = 0, k_1 = 1·35 × 10^{-2} s^{-1}, and K_a = 1·0 × 10^{-10}

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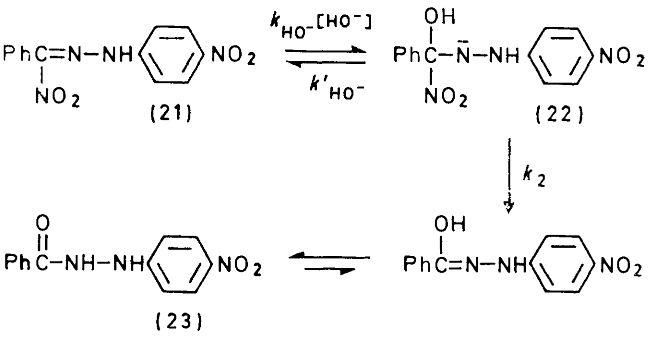
* The value of 4·7 × 10^6 s^{-1} (see Table 5) is a maximal value for k_1; the correct value is at most 10^2—10^3 times less than this since the hydrazonyl bromide would have a pK_a *ca.* 2—3 units lower than the measured value of the hydrazone (see later).

Since $k_0 \approx 0$, equation (1) simplifies to equation (3),

$$k_{obs} = k_1K_a/(K_a + a_H) \qquad (3)$$

which is plotted in Figure 7 with $k_1 = 1{\cdot}35 \times 10^{-2}$ s^{-1} and $K_a = 1{\cdot}0 \times 10^{-10}$.

Although equation (3) closely fits the observed kinetic data, the term K_a could be due to phenomena other than the more obvious ionisation of the α-nitrohydrazone. An alternative and kinetically equivalent mechanism is shown in Scheme 4. The rate expression



Scheme 4

derived from this is given in equation (4), which is of the same type as equation (3). Scheme 4 involves

$$k_{obs} = \frac{k_2(K_wk_{HO^-}/k'_{HO^-})}{(K_wk_{HO^-}/k'_{HO^-}) + a_H} \qquad (4)$$

attack by hydroxide ion on the neutral hydrazone (21) give the anion (22). At low pH, formation of the intermediate could be rate-determining; at higher [HO$^-$] the second step could become controlling.

Fortunately, with the hydrazone (21), it was possible to distinguish between the mechanism of Scheme 4 and the 1,3-dipolar ion formation of Scheme 2. In basic solution, above pH 10, the u.v. spectrum of (21) showed an extra band at 510 nm, characteristic of anion formation. Spectrophotometric titration of (21) in this pH region (see Figure 8) gave a pK_a value of 10·0 for ionisation of the hydrazone. Thus the apparent constant K_a obtained from the kinetic data (see Figure 7) is identical with the acidity constant of the hydrazone. This observation adds strong support to the 1,3-dipolar ion mechanism involving a reactive α-nitrohydrazone anion. Moreover, as shown before, direct hydroxide ion attack on the related hydrazonyl bromides (8) is rendered unlikely by the observed relative lack of reactivity of the *N*-methylhydrazonyl bromide (5; R = Me) in basic solution.

An approximate value of 14·2 was estimated for the pK_a of benzaldehyde *p*-nitrophenylhydrazone (18; R = Et, Ar = *p*-$NO_2{\cdot}C_6H_4$) (Figure 6). On this basis, the electron-withdrawing α-nitro-group of the hydrazone (21) reduced the pK_a by *ca.* 4·2 units. The less powerfully electron-withdrawing bromo-group would therefore be expected to reduce the pK_a of the hydrazonyl bromide (relative to the hydrazone) by *ca.* 2—3 units (a value used before).

Some of the results obtained for different leaving groups are summarised in Table 9. Whereas the hydrazonyl bromide anion is highly reactive, replacement of bromide by a less powerful leaving group can reduce the reactivity of the anion to the point where the anion is essentially stable in aqueous solution at 25°.

Table 9

Summary of rate constants for loss of X$^-$ from

$RCX{=}N{-}\bar{N}Ar$

Leaving group X	pK_a [a]	Ref.[b]	k_1/s^{-1}
Br	−9·00	9	10^3—10^6
NO_2	3·29	10	$1{\cdot}35 \times 10^{-2}$
N_3	4·72	11	*ca.* 10^{-4}
OPh	9·95	12	v. slow
OEt	16	13	v. slow

[a] pK_a Of conjugate acid of leaving group; most of these are thermodynamic values at 25°; no attempt has been made to correct the values reported under different conditions. [b] Lit. reference to pK_a of HX.

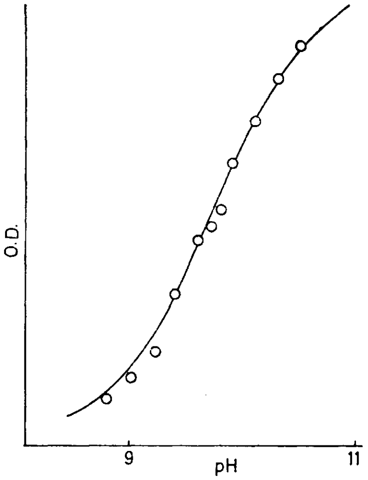


Figure 8 Optical density at 510 nm *vs.* pH plot for the α-nitrohydrazone (21) in 70% dioxan at 25°. The curve has been drawn with pK_a = 10·0

This is readily explicable in terms of the pK_a values of the conjugate acids of the leaving groups. The difference of pK_a between HBr and HNO_2 is *ca.* 12 units; the corresponding rate decrease in changing the leaving group from Br$^-$ to NO_2^- is *ca.* 10^5—10^8-fold, *i.e.* the variation in reactivity (on a log scale) is about half that found for pK_a variation.

EXPERIMENTAL

Materials.—All inorganic chemicals used were AnalaR grade. Potassium nitrate, sodium azide, sodium acetate,

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[10] I. M. Kolthoff, 'Treatise on Analytical Chemistry,' Interscience Encyclopedia Inc., New York, 1959.

[11] J. Bjerrum, G. Schwarzenbach, L. G. Sillèn, G. Berecki-Biedermann, L. Maltensen, S. E. Rasmussen, and F. J. C. Rossotti, 'Stability Constants,' *Chem. Soc. Special Publ.*, No. 7, 1958.

[12] M. M. Flickling, A. Fischer, B. R. Maun, J. Packer, and J. Vaughan, *J. Amer. Chem. Soc.*, 1959, **81**, 4226.

[13] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1960, **82**, 795.

and potassium bromide were dried at 120° for 3 h before use. The solvent used for the kinetic experiments was 70% dioxan (dioxan–water, 7 : 3 v/v). The dioxan was B.D.H. AnalaR grade. The water was passed through a mixed cation–anion exchange resin and then distilled twice from alkaline permanganate. The ionic strength, μ, was maintained constant at 0·10 by the addition of potassium nitrate.

Substrates.—The synthesis of the *N*-(2,4-dinitrophenyl)-alkanohydrazonyl bromides will be described later,[14] the *N*-(2-bromo-4-substituted phenyl)benzohydrazonyl bromides have been previously reported.[4]

Ethyl N-*(2,4-Dinitrophenyl)-2,2-dimethylpropionohydrazonate* [19; R = Me_3C, Ar = 2,4-$(NO)_2 \cdot C_6H_3$, X = OEt].—*N*-(2,4-dinitrophenyl)-2,2-dimethylpropionohydrazonyl bromide[15] (1·0 g) was heated under reflux for 90 min in 95% ethanol (300 ml) buffered with anhydrous sodium acetate (340 mg). The *ethyl hydrazonate* precipitated from the cooled solution as a bright yellow solid (200 mg), m.p. 135°. The filtrate was extracted with ether and the dried ($MgSO_4$) ethereal washings were evaporated to give more ethyl hydrazonate (500 mg) (Found: C, 48·7; H, 5·6; N, 17·4. $C_{13}H_{18}N_4O_5$ requires C, 48·7; H, 5·6; N, 17·5%).

N-*(2,4-Dinitrophenyl)-2,2-dimethylpropionohydrazonyl Azide* [19; R = Me_3C, Ar = 2,4-$(NO_2)_2 \cdot C_6H_3$, X = N_3].—*N*-(2,4-dinitrophenyl)-2,2-dimethylpropionohydrazonyl bromide (100 mg) was dissolved in dioxan–water (4 : 1 v/v; 20 ml). To this was added sodium azide (37·8 mg) dissolved in 2 ml of the same solvent. The solution immediately became orange and the hydrazonyl azide precipitated out (80 mg, 90%), m.p. 140°. Addition of water (20 ml) to the filtrate precipitated a further 5 mg of the crude azide, m.p. 141° (lit.,[15] 141) (from acetone–water).

*α-Nitro-*N-*(*p*-nitrophenyl)benzaldehyde Hydrazone* (21).—Benzylidene *p*-nitrophenylhydrazone (1·0 g) was suspended in ether (50 ml) at room temperature and the mixture was vigorously stirred while concentrated sulphuric acid–nitric acid (1 : 1; 4 ml) was added dropwise during 10 min. All the solid material dissolved and the acid layer was coloured deep red. After a further 15 min, the acid was neutralised with saturated aqueous sodium carbonate. Evaporation of the dried ($MgSO_4$) ethereal solution gave the *hydrazone*, m.p. 141—142° (Found: C, 54·8; H, 3·4; N, 19·4; O, 22·15. $C_{13}H_{10}N_4O_4$ requires C, 54·6; H, 3·5; N, 19·6; O, 22·4%).

Phenyl N-*Phenylbenzohydrazonate* (19; R = Ar = Ph, X = OPh).—*N*-Phenylbenzohydrazonyl chloride (prepared by the method of Huisgen *et al.*[16]) (1·0 g) was dissolved in dry benzene (10 ml), and phenol (2·05 g) in dry benzene (5 ml) was added. Triethylamine (2·5 ml) was added to the solution, which was kept at room temperature for 30 min. The triethylamine hydrochloride which separated was filtered off and the solution was concentrated to 3 ml. The *solid* which crystallised (1·06 g, 85%) had m.p. 152—153° and on recrystallisation from methanol this was raised to 155° (Found: C, 79·4; H, 5·8; N, 9·8. $C_{19}H_{16}N_2O_2$ requires C, 79·2; H, 5·6; N, 9·7%). The i.r. spectrum of the product showed it was not the isomeric *N'N'*-diphenylbenzohydrazide (absence of C=O absorption) which has m.p. 191—193°.[17] On heating to 200° rearrangement to the hydrazide occurred.[18]

Kinetic Measurements.—All kinetic experiments and pK_a determinations were carried out in 70% dioxan at 25°, with μ = 0·10M (KNO_3). The rates of hydrolysis of hydrazonyl bromides were followed by recording the decrease in optical density at a convenient wavelength. Since the rates vary with base concentration a technique was used in which pH was maintained constant by the addition of alkali controlled by a Radiometer pH-stat. A 25 ml thermostatted cell (*ca.* 3 cm path length) was placed in the sample chamber of a Unicam SP 1800 u.v. spectrometer which was linked to a Unicam AR 25 Linear Recorder. The contents of the cell were stirred magnetically, the drive motor being located in the sample chamber. Into the cell, but above the light beam, dipped a Metrohm EA 125U pH electrode (which both recorded the pH of the solution and controlled the addition of base) and a capillary Teflon tube (through which base was added). The Radiometer pH-stat assembly consisted of a type PHM 26 pH meter, a Titrator II type TTT II b, Titrograph type SBR 2C, and an Autoburette type ABUIC.

Solutions of hydrazonyl bromides were usually 5 × 10^{-3}M in AnalaR dioxan at 25°. Typically the wavelengths used to follow the kinetics were: 375 nm for *N*-(2,4-dinitrophenyl)alkanohydrazonyl bromides; 348 nm for *N*-(2-bromo-4-substituted phenyl)benzohydrazonyl bromides. The solvolysis of α-nitro-*N*-(*p*-nitrophenyl)benzaldehyde hydrazone (21) over pH 8—9·5 was studied at 440 nm, at higher pHs the isosbestic point (428 nm) was used.

In a typical kinetic experiment, solvent (20 ml) was pipetted into the cell and stirred, and the temperature was allowed to reach equilibrium (15 min). The pH was then adjusted to, and maintained at, the desired value with the pH-stat assembly. The substrate (0·2 ml) in dioxan was added and the recorder plotted a hydrazonyl bromide *vs.* time curve. On completion of a run, the product was investigated spectrophotometrically in the same cell.

The observed optical density *vs.* time curves corresponded to pseudo-first-order kinetics, and stable and reproducible infinity values were obtained. The rate constants were determined graphically either (*a*) using the experimental infinity value or (*b*) by the method of Guggenheim, the change in optical density being measured to *ca.* three half-lives.

In several cases rates were also followed without using the spectrometer by recording the volume of base added *vs.* time. A larger concentration of substrate was used (typically 20 mg in 20 ml) for this method, so that a reasonable amount of HBr was produced on solvolysis and this resulted in solubility difficulties in some cases.

pK_a *Determinations.*—The acid dissociation constants of the hydrazones and the α-nitro-hydrazone were determined at 25° in 70% dioxan (μ = 0·10, KNO_3), by use of the cell already described. A known quantity of hydrazone was added to the cell and the pH was adjusted to *ca.* 8. Aliquot portions of 4·0N-potassium hydroxide were added and the change in optical density at a convenient wavelength was recorded at each 0·5 pH interval (0·1 pH interval near the pK_a). The total volume of base added did not exceed

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[14] A. F. Hegarty, M. P. Cashman, and F. L. Scott, in preparation.

[15] A. F. Hegarty and F. L. Scott, *J. Org. Chem.*, 1968, **33**, 753.

[16] R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, 1962, **17**, 3.

[17] R. Huisgen, J. Sauer, and M. Seidel, *Chem. Ber.*, 1958, **94**, 2503.

[18] A. F. Hegarty, J. A. Kearney, M. P. Cashman, and F. L. Scott, *Chem. Comm.*, 1971, 689.

0·2 ml (1% of total volume), so dilution corrections were not necessary. Theoretical titration curves were plotted from equation (5). The plot of optical density (O.D.) *vs.* pH was compared with the theoretical titration curves to give the pK_a.

$$\text{O.D.}_{\text{obs}} = \text{O.D.}_{\text{max.}} K_a/(a_H + K_a) \qquad (5)$$

The measurement of the acid dissociation constant of the hydrazone (21) was complicated by the fact that at the pH values around the pK_a the rate of hydrolysis is appreciable (*ca.* 6×10^{-3} s^{-1}). The pH-stat assembly was not able to maintain the pH constant within rigorous limits so a buffer was used to maintain pH. A half-neutralised solution was found to have an apparent pH of *ca.* 10 in 70% dioxan; solutions at pH 9—11 were then made up using piperidine–sulphuric acid as buffer, the ionic strength being maintained at 0·10M. Extrapolation of the O.D.–time plot to zero time then gave the O.D. value for the unhydrolysed substrate at that pH. The O.D. *vs.* pH curves obtained by this method were reproducible and fitted precisely theoretical curves.

Product Analysis.—Over all the pH range studied the products of hydrolysis of the hydrazonyl bromides were the corresponding hydrazides, which were prepared by the following general method.

Solvolysis of N-(2,4-*Dinitrophenyl*)*propionohydrazonyl Bromide.*—*N*-(2,4-Dinitrophenyl)propionohydrazonyl bromide (300 mg, 10 mmol) was dissolved in dioxan–water (1 : 1 v/v; 50 ml) and heated under reflux for 90 min. On cooling and adding water (40 ml) N-(2,4-*dinitrophenyl*)-*propionohydrazide* (207 mg, 90%) precipitated, m.p 184° (Found: C, 42·4; H, 4·2; N, 22·3. $C_9H_{10}N_4O_5$ requires C, 42·5; H, 4·1; N, 22·1%). Extraction of the filtrate with ether yielded a further quantity (5 mg, 2%) of the crude hydrazide, m.p. 176—180°. The spectrum of this hydrazide was identical with the spectrum of the product formed on hydrolysis of the hydrazonyl bromide (after a kinetic experiment).

The other hydrazides used were available from previous work.[4,15] In each case the corresponding hydrazide was shown to be formed from the hydrazonyl bromide on hydrolysis under the conditions used to study the kinetics.

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