Mechanism of the Formation of Reactive *N*-Amidinohydrazonyl Bromides and their Conversion to *N*-Amidinobenzohydrazides and 3-Amino-5-aryl-1,2,4-triazoles

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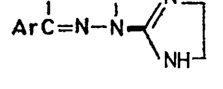
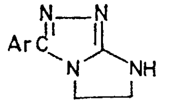
A new group of reactive *N*-amidinohydrazonyl halides is described. These materials may be isolated as stable hydrobromide salts but undergo rapid halide displacement on dissolution in ionizing solvents. Their solvolytic behaviour was investigated in detail in aqueous dioxan; because of the rapidity of the reaction, measurements were possible (at 25°) only in solutions of high acidity and low aqueous content. The initial product formed at all pH values was the corresponding hydrazide (formed by water attack on an intermediate azocarbonium ion) rather than the expected 3-amino-5-aryl-1,2,4-triazoles. The latter is obtained at higher temperatures from the hydrazide in basic solution ($t_{\frac{1}{2}}$ *ca.* 1 h for cyclization at pH 9 at 90°). The mechanism of formation of the *N*-amidinohydrazonyl bromides by direct bromination of the corresponding hydrazones was also investigated and the rate-determining step for this process was shown to be a slow geometric isomerisation (*E–Z*) about the azomethine bond.

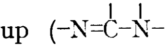
We have recently shown [1] that cyclization of hydrazonyl halides (1) in aqueous dioxan mixtures to the fused imidazotriazoles (2) does not involve rate-determining



(1)



(2)

attack by the neighbouring ring at the azomethine bond. Instead unimolecular C–Cl bond fission occurs over the pH range 3—11, the product (2) being formed by cyclization at the azocarbonium ion centre, after the rate-determining step. Despite the fact that the cyclization involves the formation of a five-membered ring, two factors may have reduced the efficiency of the neighbouring group in (1). First, the involvement of the amidino-group  $(-\mathrm{N}{=}\overset{|}{\mathrm{C}}{-}\overset{|}{\mathrm{N}}{-})$ in a cyclic structure reduces its basicity (and thus presumably its nucleophilicity); the acyclic amidino-group is one of the most powerful nitrogen bases known [2] and may act as a bifunctional reagent (although its role as such is controversial [3]). Secondly the fused system formed (2) is strained by the presence of two C=N double bonds in one ring of the bicyclic material; the presence of the ring in (1) may also force it to adopt a configuration unfavourable for direct nucleophilic displacement of chloride ion. We have thus investigated the behaviour of the open chain analogues (4). Attempts to prepare materials of type (4) by the 1,1,4-trichloro-2,3-diazabuta-1,3-diene route [4] were not successful, as either trisubstitution by the amine occurred or cyclic products were isolated.[5] An alternative route to (4), direct halogenation of the corresponding *N*-amidinohydrazones (3), was therefore investigated. We now report a study of the mechanism of halogenation of these hydrazones and of the solvolytic pattern shown by the hydrazonyl bromides (4).

RESULTS AND DISCUSSION

Bromination of N-*Amidinohydrazones* (3).—The desired *N*-amidinohydrazones (3) were prepared by refluxing *N*-amidinohydrazinium nitrate with the substituted benzaldehydes in the presence of excess of base. The nitrate salt was also prepared in one instance ($3,\mathrm{HNO_3}$; Ar = Ph) by carrying out the condensation in the absence of base.

The bromination of the hydrazones (3) was studied in 7 : 3 acetic acid–water containing 0·10M-potassium bromide. The latter ensured the bromide ion concentration and consequently the $\mathrm{Br_2} : \mathrm{Br_3^-}$ ratio was maintained constant during a kinetic run, thus simplifying the kinetics.[6] The bromide ion also provided a source of bromine, which was introduced to the solution by electrogeneration.

The kinetic behaviour of all the hydrazones (3) studied was similar; in each case the observed rate of uptake of bromine by the hydrazone was independent of the initial concentration of bromine used. The rate was however directly proportional to the hydrazone concentration. This is demonstrated in Table 1, which describes data obtained for the unsubstituted material (3; Ar = Ph). This establishes that the rate law followed is given by

TABLE 1

Observed rate constants for the conversion of (3; Ar = Ph) to (4; Ar = Ph) at 20° in 7 : 3 acetic acid–water containing 0·1M-potassium bromide as a function of initial bromine and hydrazone concentrations

$10^6[\mathrm{Br_2}^*]$/M [a]	10^4[Hydrazone]/M	$10^6k_1/\mathrm{s}^{-1}$
13·5	14·25	5·45
7·9	14·25	5·39
11·1	14·25	5·43
13·5	19·0	5·38
13·5	28·5	5·60
	Mean value	5·45 (±0·06)

[a] $[\mathrm{Br_2}]^* = [\mathrm{Br_2}] + [\mathrm{Br_3^-}]$

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[1] A. F. Hegarty, J. O'Driscoll, J. K. O'Halloran, and F. L. Scott, *J.C.S. Perkin II*, 1972, 1887.

[2] F. M. Menger, *J. Amer. Chem. Soc.*, 1966, **88**, 3081.

[3] H. Anderson, C. Su, and J. W. Watson, *J. Amer. Chem. Soc.*, 1969, **91**, 482; G. Biggi, F. Del Cima, and F. Pietra, *Tetrahedron Letters*, 1971, 2811.

[4] J. K. O'Halloran, D. A. Cronin, J. Cronin, and F. L. Scott, *J.C.S. Perkin I*, 1972, 2214; J. K. O'Halloran, and F. L. Scott *ibid.*, p. 2219.

[5] J. K. O'Halloran and F. L. Scott, *J.C.S. Chem. Comm.*, 1971, 426.

[6] A. F. Hegarty and F. L. Scott, *J. Chem. Soc.* (*B*), 1966, 672.

equation (1). In most cases a large (>20-fold) excess of hydrazone over bromine was used to simplify the

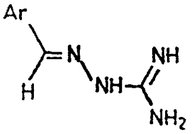
$$-\mathrm{d}[\mathrm{Br}_2]/\mathrm{d}t = k_1[\text{hydrazone}] \qquad (1)$$

kinetics so that the hydrazone concentration remained essentially constant during a kinetic run. The slopes of these linear plots (k_{obs} values) varied as the initial hydrazone concentration was varied. Experiments at several initial hydrazone concentrations were averaged to give the k_1 values quoted in Table 2 for the hydrazones (3).

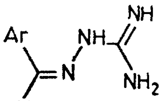
TABLE 2

Observed rate constants for the isomerization of *N*-amidinohydrazones (3; Ar = XC_6H_4) in 7 : 3 acetic acid–water containing 0·1M-potassium bromide

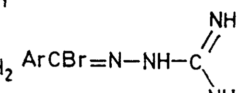
Substituent (X)	*p*-MeO	*p*-Me	*p*-Me_2CH	H	*p*-Cl	*p*-Br
$10^6k_1/s^{-1}$ (25°)	9·55	8·50	8·40	7·51	6·23	6·13
$10^6k_1/s^{-1}$ (20°)	6·87	6·28	6·14	5·45	4·60	4·42
$10^6k_1/s^{-1}$ (15°)	4·42	4·05	3·90	3·50	2·93	2·92



(3a)



(3b)



$$\mathrm{ArCBr{=}N{-}NH{-}C({=}NH)NH_2}$$

(4)

To determine whether the neutral hydrazone (3; Ar = Ph) or the conjugate acid (3,H^+; Ar = Ph) was the species involved in the rate-determining step, the kinetics of bromination of the nitrate salt (3,HNO_3; Ar = Ph) was investigated. At 20° the k_1 value obtained ($5·40 \times 10^{-6}$ s^{-1}) for this material was the same (within experimental error) as the value obtained for the bromination of the free base, also in 70% acetic acid. Furthermore, when the kinetics of bromination of (3; Ar = Ph) were investigated in the presence of one and then twenty equivalents of nitric acid in 70% acetic acid no change was observed in observed kinetic results. The *N*-amidinohydrazones (3) are moderately strong bases [pK_a of (3; Ar = *p*-BrC_6H_4) is 8·72 in water, see Table 3], and the u.v. spectrum of (3; Ar = Ph) in 7 : 3 acetic acid–water is similar to that in acidic solution and does not change on the addition of further strong acid to the aqueous acetic acid. Thus under the conditions used to study the kinetics, the hydrazones are present almost entirely as the conjugate acid (3,H^+) and this is the species undergoing reaction in the slow step.

TABLE 3

pK_a Values measured for various substrates and products at 25° in water and aqueous dioxan

Substrate	Solvent [a]	Wavelength used (nm)	pK_a
(9; Ar = Ph)	A	300	8·36
	B	305	8·46
(3; Ar = *p*-BrC_6H_4)	A	320	8·72
	B	330	8·60
(11; Ar = Ph)	A	330	10·3
		260	4·12
	B	305	12·6
		295	3·8

[a] Solvent A, water (μ = 1·0, KCl); solvent B, 3 : 1 dioxan–water (μ = 0·10, KCl).

Several attempts were made to determine the rate of reaction of the free base (3; Ar = Ph) in a non-acidic medium using methanol containing 0·1M-sodium bromide. The rate of bromine uptake was in all cases too rapid and unmeasurable by the polarographic technique used (which implies a second-order reaction with bromine $>10^5$ l mol^{-1} s^{-1}). Clearly when (3) is unprotonated the halogenation rate is increased enormously.

N-Amidino-*N*′-benzylidene-*N*-methylhydrazine was also investigated. This was brominated in a manner analogous to (3; Ar = Ph), *i.e.* being first order in hydrazone and zero order in bromine. The rate constant determined [k_1 = 1·50 (±0·03) $\times 10^{-6}$ s^{-1} at 20°] showed that introduction of the *N*-methyl group reduced the rate of bromine uptake *ca.* 3·5-fold.

The products obtained on bromination of the hydrazones (3) were the corresponding *N*-amidinohydrazonyl bromides (4). These materials could either be prepared as HBr salts by carrying out the bromination in anhydrous acetic acid or detected chromatographically as intermediates in 7 : 3 acetic acid–water. However since bromine is not involved in the rate-determining step, no information is available about the bromination step in which (4) is formed.

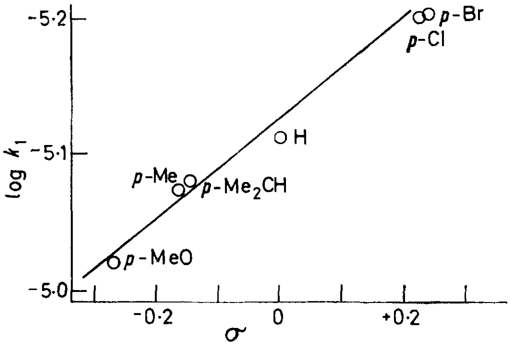


FIGURE 1 Hammett plot for the *E*–*Z* isomerization of the protonated *N*-amidinohydrazones (3; Ar = XC_6H_4) at 25° in 7 : 3 acetic acid–water

The most plausible mechanism consistent with these results involves geometric isomerisation of the protonated hydrazone (3a,H^+) $\longrightarrow$ (3b,H^+) as the rate-determining prebromination step. Substituents in Ar have a small effect on the rate of isomerization of (3). A Hammett plot (Figure 1) of log k_1 *vs.* the σ values of McDaniel and Brown [7] gave a ρ value of $-0·36$ (*r* 0·997) with log $k_0 = -5·125$ at 25°. Similar values were obtained at 15 and 20°. These values are consistent with previously reported data for reactions thought to involve rate-determining isomerization about the C=N

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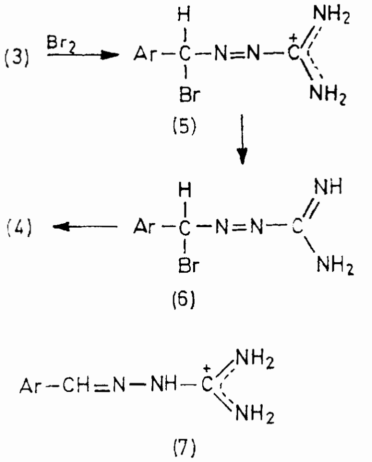
[7] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.

bond in hydrazones, and measured under the same conditions.[8]

The configuration of *N*-amidinohydrazones in solution has not been studied in detail by the n.m.r. method but it is likely that the less crowded *E*-isomer (3a) is thermodynamically more stable than (3b). This has been found for a large variety of *N*-aryl- and *N*-alkyl-hydrazones [9] and semicarbazones [10] which are structurally related to (3).

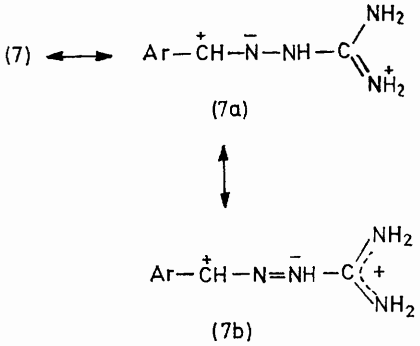
The fact that *E*—*Z* isomerisation of the hydrazone (rather than the halogenation step) is rate-determining is not unexpected in view of previously reported results.[8] It has been shown that those hydrazones with powerfully electron-withdrawing (deactivating) substituents attached to nitrogen (and also those hydrazones which are *NN*-disubstituted) show this behaviour. In these cases the normal mechanism of bromination [5,11,12] [(3) ⟶ (4); Scheme 1] is either blocked or considerably slowed. In the case of *N*-amidinohydrazones (3), the protonated species (7) is the major form present under the conditions used to measure the kinetics. Since (7) already carries a positive charge on the amidino-group, an intermediate of type (5) would be destabilized.

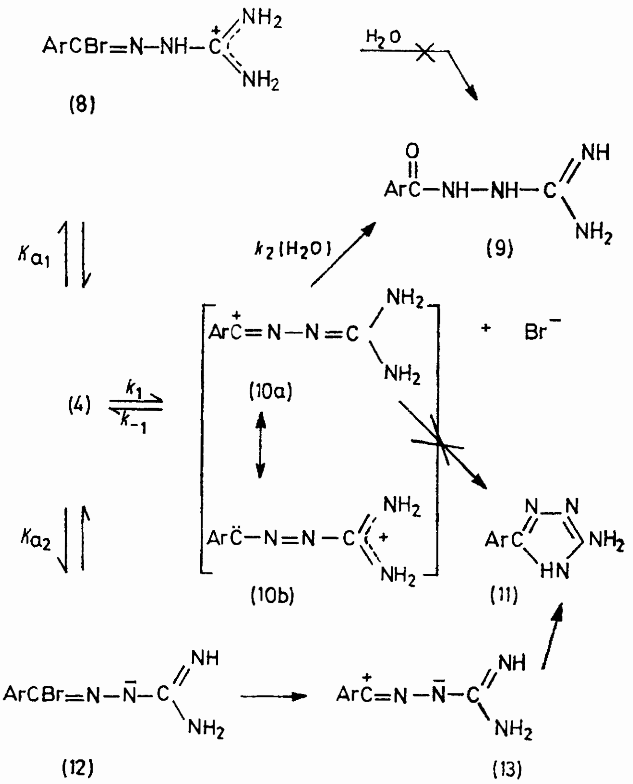


Scheme 1

Polarisation of the azomethine bond in (7) (and consequently isomerization by rotation about this bond) is however facilitated by the adjacent protonated amidino-group [see (7a and b)]. This provides an alternative route for the bromination of the hydrazones, namely, geometric isomerization of the protonated *E*- to protonated *Z*-isomer followed by (rapid) bromination of the less hindered *Z*-isomer, giving the hydrazonyl bromides (4).

Hydrolysis of Hydrazonyl Bromides (4).—As discussed above when *N*-amidinohydrazones (3) were treated with one equivalent of bromine in anhydrous acetic acid, on a large scale, the novel *N*-amidinohydrazonyl bromides were isolated as hydrobromide salts. The salts (4,HBr) were water soluble, but on dissolution underwent rapid conversion to the corresponding hydrazides (9) even at room temperature. The hydrazonyl bromide–hydrazide reaction is characteristic of *N*-arylhydrazonyl bromides,[13] but the facility with which the conversion occurs in this case is unique.





Scheme 2

The isolation of the hydrazide (9), rather than the triazole (11) which would be formed as a result of

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[8] A. F. Hegarty, P. J. Moroney, and F. L. Scott, *J.C.S. Perkin II*, 1973, 1466.

[9] G. J. Karabatsos and C. E. Osborne, *Tetrahedron*, 1968, **24**, 3361; G. J. Karabatsos and R. A. Taller, *ibid.*, p. 3357; G. J. Karabatsos and K. L. Krumel, *ibid.*, 1967, **23**, 1097.

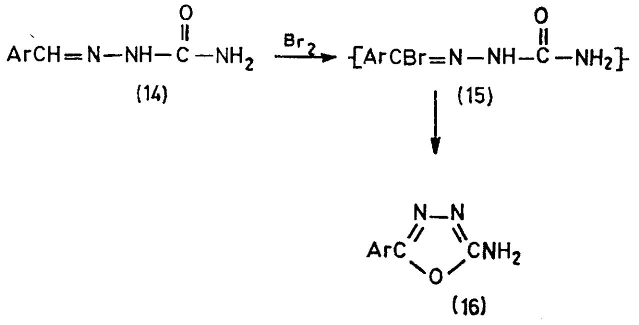
[10] G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, *J. Amer. Chem. Soc.*, 1964, **86**, 3351; G. J. Karabatsos, J. D. Graham, and F. M. Vane, *ibid.*, 1962, **84**, 753; V. I. Stenberg, P. A. Barks, D. Bays, D. D. Hammargren, and D. V. Rao, *J. Org. Chem.*, 1968, **33**, 4402.

[11] J. M. J. Tronchet, B. Bachler, N. Le-Hong, and P. F. Lino, *Helv. Chim. Acta*, 1971, **54**, 921.

[12] M. W. Moon, *J. Org. Chem.*, 1972, **37**, 383, 1686.

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

amidino-group anchimerism, contrasts with the behaviour of other hydrazonyl bromides which have a nucleophilic group attached to nitrogen.[14,15] In several cases, *e.g.* the conversion of the semicarbazone (14) to the oxadiazole (16),[15] cyclization occurs with such facility that the intermediate hydrazonyl bromides [(15) in this case] have not been isolated. It is probable that the successful isolation of reactive hydrazonyl bromides (4) is due to the presence of the basic amidino-group. Unreactive hydrobromide salts are readily formed which precipitate rapidly from acetic acid solution.



That the structures of the solvolytic products were the hydrazide hydrobromides (9,HBr) rather than the triazole hydrobromides (11,HBr) was consistent with spectral evidence and with the synthesis of authentic samples of both materials by alternative routes. Although the free bases (9) and (11) showed no m.p. depression when mixed together [explicable in terms of cyclization of (9) to (11) on heating], they were obviously two distinct materials since (a) the HBr salts melted at different temperatures and showed depression when mixed and (b) both materials have characteristic u.v. spectra and pK_a values (see Table 3).

Although the conversion of (4,HBr) to (9,HBr) was too rapid to study in 100% water, addition of dioxan slowed the reaction sufficiently to permit study. The hydrolysis of (4,HBr; Ar = *p*-BrC_6H_4) was investigated in 3 : 1 dioxan–water (v/v) over the pH range *ca.* 1·0—2·3. Above pH 2·3 the rate of formation of the hydrazide (9) was too rapid for study even at 25° (see Table 4). When the aqueous content of the solvent was increased to 50%, the rate of hydrolysis also increased (see Table 5) and the reaction was too rapid under these conditions at pH >2·0. In both solvents the rate of hydrolysis increased linearly as the hydrogen ion concentration was decreased (*i.e.* a plot of log k_{obs} *vs.* pH was linear with approximately unit slope).

TABLE 4

Observed rate constants for the hydrolysis of *N*-amidino-*p*-bromobenzohydrazonyl bromide (4; Ar = *p*-BrC_6H_4) at 25° in 3 : 1 dioxan–water (μ = 0·10, $NaClO_4$) [a]

pH	1·08	1·25	1·50	1·92	2·13	2·30
$10^3k_{obs}/s^{-1}$	2·41	4·84	8·06	25·1	35·7	54·6

[a] Slope of plot of log k_{obs} *vs.* pH = +1·08 (*r* 0·996).

TABLE 5

Observed rate constants for the hydrolysis of *N*-amidino-*p*-bromobenzohydrazonyl bromide (4; Ar = BrC_6H_4) at 25° in 1 : 1 dioxan-watcr (μ = 0·10, $NaClO_4$) [a]

pH	1·40	1·60	1·75	1·98
$10^3k_{obs}/s^{-1}$	15·2	21·9	35·2	65·4

[a] Slope of plot of log k_{obs} *vs.* pH = +1·10 (*r* 0·995).

Even though the basicity of the hydrazonyl bromide (4; Ar = *p*-BrC_6H_4) could not be measured directly because of its high reactivity, the pK_a of the conjugate acid of the corresponding hydrazone (3; Ar = *p*-BrC_6H_4) is 8·60 in 3 : 1 dioxan-water (Table 3). It is likely that the electron-withdrawing bromo-group in (4) would reduce this value by about one unit so that its pK_a can be estimated as *ca.* 7·5. Thus under the conditions used to study the kinetics at low pH, the hydrazonyl bromide is present almost entirely as its conjugate acid (8).

The most likely reaction pathway in Scheme 2 which is consistent with the observed kinetic result requires that reaction occur only *via* the free base species (4) in spite of the fact that this is present only in very small quantities at *ca.* pH 1. The free base (4) can undergo unimolecular C–Br bond fission to give a stabilized azocarbonium ion species (10) which then reacts with water to give the hydrazide (9). Direct nucleophilic displacement of Br^- by solvent attack in the protonated species (8) can be ruled out as a reaction pathway since the observed reaction rate in this case would be pH independent (at low pH). Similarly water attack on the free base (4) to give the hydrazide (9) directly is also unlikely since it is difficult to see why water would not react with the protonated species (8) in preference to reaction with (4).

Other criteria also support a mechanism involving conversion of (4) to (9) *via* (10) and the existence of a relatively long-lived intermediate. The reaction rate increases when the solvent is changed from 3 : 1 to 1 : 1 dioxan–water to water (where the rate is too fast to measure), which is evidence for a rate-determining ionization process. Addition of varying amounts of bromide ion (at constant ionic strength and pH) can cause a large decrease in the overall rate of conversion of (4) to (9) (Table 6). This is explicable in terms of preferential reaction of the stabilized carbonium ion

TABLE 6

Observed rate constants for the hydrolysis of *N*-amidino-*p*-bromobenzohydrazonyl bromide (4; Ar = *p*-BrC_6H_4) at 25° and pH 1·6, in 3 : 1 dioxan–water in the presence of varying bromide ion concentration (μ = 0·10, $NaClO_4$ throughout)

$[Br^-]/M$	0·0	0·00125	0·0025	0·005	0·01	0·02
$10^4k_{obs}/s^{-1}$	122	22·7	10·7	4·61	2·69	1·04

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[14] F. L. Scott, D. A. Cronin, and J. K. O'Halloran, *J. Chem. Soc. (C)*, 1971, 2769; F. L. Scott and T. A. F. O'Mahony, *Tetrahedron Letters*, 1970, 1841.

[15] F. L. Scott, T. M. Lambe, and R. N. Butler, *Tetrahedron Letters*, 1971, 2669.

species (10) with bromide ion rather than with water to regenerate the starting hydrazonyl bromide (Scheme 2).[16] From Scheme 2, the observed rate constant (at constant pH) is $k_{obs} = k_2k_1/(k_{-1}[Br^-] + k_2)$. As required by this equation a plot of $1/k_{obs}$ *vs.* $[Br^-]$ is linear (Figure 2). The intercept gave a k_{obs} value which was the same as the observed rate constant determined in the absence of $[Br^-]$; the substrate concentration ($<10^{-4}$M) is apparently sufficiently low for the measurements quoted in Tables 4 and 5 to obviate any back reaction of (10) with bromide ion.

When $[Br^-] = 0$, the relationship between the observed rate constant (k_{obs}) and hydrogen ion concentration (a_H) is given by equation (2) assuming that k_1 is the coefficient for the rate-determining step, where K_{a_1} is the acidity constant for (8). At pH values where $a_H \gg K_{a_1}$

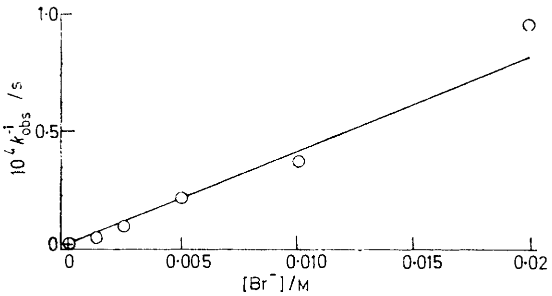

FIGURE 2 Plot of the inverse of the observed rate constant of solvolysis of the hydrazonyl bromide (4; Ar = p-BrC_6H_4) *vs.* $[Br^-]$ at 25° and pH 1·6 in 3 : 1 dioxan-water

$$k_{obs} = k_1K_{a_1}/(K_{a_1} + a_H) \qquad (2)$$

(as in the present instance), equation (2) reduces to $k_{obs} = k_1K_{a_1}/a_H$ (as observed). Assuming a value of *ca.* 3×10^{-8} for K_{a_1} (see above) it can be calculated that k_1, which is a measure of the rate of loss of bromide ion from (4), is *ca.* $6{\cdot}6 \times 10^3$ s^{-1} in 3 : 1 dioxan-water. It is apparent therefore that hydrolysis of the free base species would be very rapid indeed, if it were available for study. The *N*-amidinohydrazonyl bromides are thus by far the most reactive series of hydrazonyl bromides yet investigated.[1,13,17]

The driving force for the ionization of the hydrazonyl bromide (4) is provided by the formation of the stabilized carbonium ion (10). Charge may be delocalized from carbon onto the adjacent nitrogen (' octet stabilization ')[18] and most importantly onto the remote amidino-group (10b). Although in the latter resonance form, carbon carries only six electrons, there is evidence that a surprisingly large fraction of the charge (greater than one-third as judged from substituent effects) is delocalized onto the remote carbon atom.[1,19] The hydrazonyl bromide (1) in which the amidino-group is constrained in the five-membered ring is less reactive, and the corresponding rate of solvolysis (which was also rate-determining azocarbonium ion formation) of the free base species (1; Ar = p-BrC_6H_4) could be measured in 4 : 1 dioxan–water. It can be calculated that the open chain analogue (4; Ar = p-BrC_6H_4) hydrolyses *ca.* 5×10^4-fold more rapidly than (1). This reactivity difference is most likely largely a measure of more efficient stabilization of charge by the amidino-group in (10). This is also reflected in the relative basicities of compounds (4) and (1) [the pK_a of (8) is *ca.* 3—4 units greater than that of $(1, H^+)$].

Hydrazonyl halides in which the amino-hydrogen atom is not disubstituted may also undergo (even at low pH) a facile base catalysed dehydrohalogenation to give a 1,3-dipolar species which can then be trapped internally or by an external dipolarophile.[20] This pathway is also apparently available to (4), which may form (13) *via* rapid bromide ion loss from the anion (12). However, reaction *via* this pathway in the pH region <7 would give a pH rate profile different from that observed (k_{obs} proportional to a_H^{-2} rather than a_H^{-1}) and therefore does not occur at low pH. Cyclization of the 1,3-dipolar ion species (13) (which can also be written as a 1,5-dipolar ion) to (11) should be very efficient. Therefore if 1,3-dipolar ion formation is involved at high pH then the aminotriazole (11) should be formed as product. Because of the rapidity of dehydrohalogenation at high pH no kinetic studies were possible but analysis of the products of reactions at pH 8 and 10 (by t.l.c.) showed that, as at low pH, the hydrazide (9) is the sole product formed. Control experiments showed that 1% of the triazole (11) would have been detected if it were present. At these pH values the major species of substrate present is the free base (4). Thus over the entire pH range the hydrazide (9) is the sole product of solvolysis. The hydrazonyl bromide free base (4) is also implicated as the reactive species at all pH values as the reaction involves rate-determining C–Br bond fission. The azocarbonium ion species (10) could itself also conceivably cyclize to the aminotriazole (11). In fact anchimerism of this type involving azocarbonium ion species is well known and occurs quite efficiently relative to solvent attack. For example, solvolysis of (1) in 4 : 1 dioxan–water at 25° at neutral pH (which involves azocarbonium ion formation) gives [1] exclusively the cyclic material (2). The failure of the azocarbonium ion (10) to cyclize to (11) at any pH is best ascribed to the demonstrated delocalization of charge onto the amidino-group [structure (10b)], lowering its nucleophilicity towards carbon and allowing the external nucleophile (water) to compete successfully.

Thus even though the *N*-amidinohydrazonyl bromides (11) have a more powerfully nucleophilic group than the cyclic analogues (1), the main effect is to provide further stabilization for the developing azocarbonium ion. There is a consequent reduction in the nucleophilicity

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of the neighbouring group leading to a *less* rather than a more efficient cyclization.

Cyclization of Hydrazides (9) *to Triazoles* (11).—Although the hydrazonyl bromides (4) could not be cyclized to the triazoles (11) directly, the hydrazides (9) could be themselves cyclized to triazoles (11) under basic conditions. The best method to effect cyclization was found to be refluxing the hydrazide free base (9) in water for 1—2 h (see Experimental section); the triazoles precipitated in good yield on cooling. An attempt was also made to cyclize the hydrazides in acidic media by refluxing the hydrobromide salts of (9) in water, but either the starting material was recovered unchanged (after 2 h) or some decomposition with the formation of benzoic acid occurred (after 5 h).

Some preliminary kinetic experiments on the cyclization of the hydrazide are consistent with the free base (9) being the reactive species. Thus the rate of cyclization of (9; Ar = Ph) at 90° in water is independent of pH when the pH of the medium is >9 while at pH <8 the rate of cyclization decreases as the pH is decreased. Since the pK_a of the conjugate acid of (9; Ar = Ph) is 8·36 (Table 3), the rate of cyclization is therefore proportional to the fraction of free base species (9; Ar = Ph) present. The rates of cyclization of the hydrazide free bases (9) do not show a great sensitivity to the nature of the aryl substituent. Thus for the cyclization of the five substituted hydrazides (9; Ar = XC_6H_4) [X = 4-Br ($k_{obs} = 9{\cdot}7 \times 10^{-5}\ s^{-1}$ at 90°); 4-Cl ($9{\cdot}7 \times 10^{-5}\ s^{-1}$); H ($7{\cdot}3 \times 10^{-5}\ s^{-1}$); 4-$Me_2CH$ ($6{\cdot}7 \times 10^{-5}\ s^{-1}$); 4-Me ($6{\cdot}4 \times 10^{-5}\ s^{-1}$)] the Hammett ρ value obtained was +0·44 (*r* 0·991). This small effect is consistent with a mechanism involving rate-determining attack by the neighbouring amidino-function on the hydrazide linkage, since substituents would be expected to have compensating effects on this process. Thus an electron-withdrawing substituent in Ar would aid cyclization by increasing the electrophilicity of the carbonyl group while at the same time would reduce the nucleophilicity of the amidino-function. Since the substituent charge is occurring closer to the carbonyl group, the former effect is greater, accounting for the observed small positive ρ value.

EXPERIMENTAL

M.p.s were measured on an Electrothermal apparatus and are uncorrected. I.r. spectra were measured on a Perkin-Elmer model 137E spectrometer, the samples being prepared as potassium bromide discs. U.v. spectra were measured on a Unicam model 800B spectrometer using 95% ethanol and water as solvents.

Materials.—All inorganic materials were AnalaR grade. The reaction solutions were prepared from water which had been triply distilled from alkaline potassium permanganate; acetic acid, b.p. 117—118°, was distilled from chromium trioxide. The aldehydes used were commercial; liquid aldehydes were distilled before use. Dioxan was AnalaR grade and used without further treatment. Aminoguanidine nitrate was prepared (in quantitative yield) by the method of Thiele[21] and had m.p. 144—145° (from ethanol) (lit.,[21] m.p. 144°).

Hydrazone Substrates.—*N*-Amidino-*N′*-arylidenehydrazines (3) were prepared by refluxing for 30 min equimolar quantities of *N*-amidinohydrazinium nitrate and the substituted benzaldehyde in aqueous ethanol in the presence of an excess of sodium hydroxide. The hydrazones (3; Ar = XC_6H_4) which precipitated on cooling were recrystallized several times from aqueous ethanol had the following m.p.s: X = *p*-MeO, m.p. 191—192° (lit.,[22] m.p. 190°); *p*-Me, 213° (lit.,[23] 206°); *p*-Me_2CH, 151° (Found: C, 64·6; H, 8·0; N, 27·2. $C_{11}H_{16}N_4$ requires C, 64·7; H, 7·8; N, 27·45%); H, 181° (lit.,[21] 178°); *p*-Cl, 208—209° (lit.,[23] 199°); *p*-Br, 214—215° (lit.,[23] 210°). *N*-Amidino-*N′*-benzylidenehydrazinium nitrate was prepared (92% yield) by refluxing *N*-amidinohydrazinium nitrate with benzaldehyde in ethanol and had m.p. 165° (from aqueous ethanol) (lit.,[23] m.p. 168°).

N-*Amidino*-N′-*benzylidene*-N-*methylhydrazinium Nitrate.*—To a solution of *S*-methylisothiouronium sulphate (83·4 g) in warm water (200 ml) was added a solution of barium nitrate (78·4 g) in warm water (700 ml). The precipitated barium sulphate was removed by filtration using Celite and the filtrate concentrated to *ca.* 200 ml by evaporation at reduced pressure. Methylhydrazine (27·6 g) was added over 5 min and the solution refluxed for 1 h. Evaporation of the solvent gave a brown oil which failed to crystallize. The oil was dissolved in ethanol (100 ml) and benzaldehyde (63·6 g) added. The hydrazinium nitrate precipitated (84%), m.p. 212° (decomp.) (from aqueous ethanol) (lit.,[24] 199—200° (decomp.) (Found: C, 45·4; H, 5·4; N, 29·35; O, 20·4. Calc. for $C_9H_{13}N_5O_3$: C, 45·2; H, 5·4; N, 29·3; O, 20·1%).

Bromination of N-*Amidino*-N′-*arylidenehydrazines.*—(a) *In acetic acid. N*-Amidino-*N′*-benzylidenehydrazine (2 g) was dissolved (at 40°) in glacial acetic acid. The solution was cooled to room temperature and bromine (1·4 ml) in glacial acetic acid was added dropwise. The deep red solution was stirred for a further 6 h and cooled to 0°. The light yellow material which precipitated (N-*amidinobenzohydrazonyl bromide hydrobromide*) (2·3 g; m.p. 186—190°) was leached with hot benzene which raised its m.p. to 191—192° (Found: C, 29·95; H, 3·2; Br, 50·1; N, 17·2. $C_8H_{10}Br_2N_4$ requires C, 29·8; H, 3·1; Br, 49·7; N, 17·4%). Ether was added to the acetic acid filtrate and a further quantity of hydrazonyl bromide hydrobromide (1·35 g), m.p. 182—187°, precipitated on standing at 0° for 12 h, giving a total yield of 92%. The other *N*-amidino-substituted benzohydrazonyl bromide hydrobromides (4,HBr; Ar = XC_6H_4) had the following m.p.s and analytical data: X = *p*-MeO, m.p. 201—202° (yield 89%) (Found: C, 30·6; H, 3·5; Br, 45·2; N, 16·05. $C_9H_{12}Br_2N_4O$ requires C, 30·7; H, 3·4; Br, 45·45; N, 15·9%); *p*-Me, 231—232° (84%) (Found: C, 32·1; H, 3·7; Br, 47·9; N, 16·3. $C_9H_{12}Br_2N_4$ requires C, 32·15; H, 3·6; Br, 47·6; N, 16·7%); *p*-Me_2CH, 171—173° (85%) (Found: C, 36·3; H, 4·6; Br, 43·5; N, 15·6. $C_{11}H_{16}Br_2N_4$ requires C, 36·3; H, 4·4; Br, 43·95; N, 15·4%); *p*-Cl, 248—250° (92%) (Found: C, 27·4; H, 2·7; Br, 44·5; N, 16·0. $C_8H_9Br_2ClN_4$ requires: C, 26·9; H, 2·5; Br, 44·9; N, 14·0%); *p*-Br, 249—250° (99%) (Found:

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C, 24·4; H, 2·2; Br, 60·1; N, 14·1. $C_8H_9Br_3N_4$ requires: C, 23·9; H, 2·2; Br, 59·85; N, 14·0%).

(b) *In* 7 : 3 *acetic acid–water*. *N*-Amidino-*N′*-*p*-bromobenzylidenehydrazine (0·5 g) was dissolved in 7 : 3 acetic acid–water (40 ml) and stirred at room temperature while bromine (0·106 ml) in 7 : 3 acetic acid–water (7 ml) was added over 30 min. The solution was stirred for a further 2 h, cooled to 0° and ether (1 l) added. The precipitated material (A) (0·49 g), m.p. 210—242°, was shown [t.l.c. on silica gel (Stahl HF 254) with benzene–light petroleum ether (b.p. $<40°$)–methanol (5 : 1 : 4) as mobile phase] to be a mixture of *N*-amidino-*p*-bromobenzohydrazonyl bromide hydrobromide and *N*-amidino-*p*-bromobenzohydrazide hydrobromide. The mixture A (0·30 g) was dissolved in 7 : 3 acetic acid–water (25 ml) and refluxed for 3 h. On evaporation of the solvent under reduced pressure the residue (0·21 g), m.p. 260—275°, was crystallized from ethanol to m.p. 278—280° and proved to be (by mixed m.p., i.r., and u.v. spectra) *N*-amidino-*p*-bromobenzohydrazide hydrobromide (9,HBr; Ar = *p*-BrC_6H_4). In a control experiment the same hydrazide was isolated (81% yield) on solvolysis of an authentic sample of *N*-amidino-*p*-bromobenzohydrazonyl bromide hydrobromide under the same conditions.

Attempted Bromination of N-*Amidino*-N′-*benzylidene*-N-*methylhydrazinium Nitrate*.—Several attempts were made to isolate brominated products from the *N*-methyl analogue PhCH=N–NMeC(=NH)NH_2. Both hot and cold solutions of acetic acid and one or two equiv. of bromine with long reaction times were used. However in each case the major isolable product in yields $>90\%$ (by direct precipitation from the solvent or on addition of ether) was the starting material.

Hydrolysis of N-*Amidinohydrazonyl Bromides*.—*N*-Amidinobenzohydrazonyl bromide hydrobromide (4,HBr; Ar = Ph) (2 g) was dissolved in warm (*ca.* 40°) water (40 ml) and the solution concentrated *in vacuo* at 40—50° to 5 ml. On cooling to 0° *N*-amidinobenzohydrazide hydrobromide precipitated (1·3 g), m.p. 247—250°, which had m.p. 250—251° on recrystallization from ethanol (lit.,[25] m.p. 250—251°). The aqueous filtrate from the reaction solution was evaporated to dryness to give a further quantity (0·24 g) of the hydrazide (total yield 96%). In a control experiment using an authentic sample of the hydrazide hydrobromide it was shown that cyclization to 3-amino-5-phenyl-1,2,4-triazole did not occur to any appreciable extent under these work-up conditions.

N-Amidinobenzohydrazide hydrobromide was also prepared unambiguously as follows. *N*-Amidinobenzohydrazide (prepared by the reaction of benzohydrazide with *S*-methylisothiouronium sulphate [26]) (0·50 g) was dissolved in glacial acetic acid (20 ml) at ambient temperature. To this was added (over 10 min) one equivalent of 48% hydrobromic acid (0·29 ml). The precipitated hydrobromide was collected after 1 h and recrystallized from absolute ethanol. This material was identical (m.p., mixed m.p., and i.r. spectra) with the material formed above on hydrolysis of the hydrazonyl bromide.

The other *N*-amidinohydrazonyl bromide salts (4,HBr) were similarly hydrolysed to the corresponding hydrazide hydrobromides (9,HBr; Ar = XC_6H_4) using the same reaction conditions: X = *p*-MeO, m.p. 251—252° (yield 89%) (Found: C, 37·0; H, 4·65; Br, 27·3; N, 19·3; O, 10·8. $C_9H_{13}BrN_4O_2$ requires C, 37·4; H, 4·5; Br, 27·7; N, 19·4; O, 11·1%); *p*-Me, 270° (100%) (Found: C, 39·25; H, 5·0; Br, 29·8; N, 20·4; O, 5·75. $C_9H_{13}BrN_4O$ requires C, 39·55; H, 4·8; Br, 29·3; N, 20·5; O, 5·2%); *p*-Me_2CH, 264—265° (98%) (Found: C, 43·7; H, 5·8; Br, 26·9; N, 18·8; O, 5·8. $C_{11}H_{17}BrN_4O$ requires C, 43·85; H, 5·6; Br, 26·6; N, 18·6; O, 5·3%); *p*-Cl, 274° (99%) (Found: C, 32·8; H, 3·5; Br, 26·9; N, 19·0; O, 5·8. $C_8H_{10}BrClN_4O$ requires C. 32·7; H, 3·4; Br, 27·3; N, 19·1; O, 5·45%).

The *N*-amidino-substituted benzohydrazide free bases (9) were prepared by dissolving the corresponding hydrobromide salts in water and bringing the pH of the solution to 11 by the addition of 20% sodium carbonate solution. The precipitated hydrazides (9; Ar = XC_6H_4) were recrystallized from ethanol or methanol: X = *p*-Me, m.p. 191° (decomp.) (Found: C, 55·8; H, 6·3; N, 28·8; O, 8·4. $C_9H_{12}N_4O$ requires C, 56·2; H, 6·25; N, 29·2; O, 8·3%); *p*-Me_2CH, 186—187° (decomp.) (Found: C, 59·5; H, 7·3; N, 25·5; O, 7·2. $C_{11}H_{16}N_4O_4$ requires C, 60·0; H, 7·3; N, 25·45; O, 7·3%); H, 184—185° (decomp.) [lit.,[27] m.p. 184° (decomp.)]; *p*-Cl, 196—197° (decomp.) [lit.,[27] m.p. 194—196° (decomp.)]; *p*-Br, 196—197° (decomp.) [lit.,[27] 194—196° (decomp.)].

Cyclization of N-*Amidinobenzohydrazides to* 3-*Amino*-5-*aryl*-1,2,4-*triazoles*.—The following describe a typical experiment. *N*-Amidino-*p*-chlorobenzohydrazide (9; Ar = *p*-ClC_6H_4) (0·32 g) was refluxed in water (40 ml) for 5 h. On cooling the triazole (11; Ar = *p*-ClC_6H_4) precipitated out (0·26 g), m.p. 227—229°; recrystallization from water improved the m.p. to 228—229° (lit.,[27] m.p. 227—229°) (yield 90%). Concentration of the filtrate *in vacuo* yielded a further 6% of the triazole.

The other 3-amino-5-(substituted phenyl)-1,2,4-triazoles (11; Ar = XC_6H_4) were similarly prepared: X = *p*-Me, m.p. 207° (yield 98%) (Found: C, 61·8; H, 5·7; N, 32·5. $C_9H_{10}N_4$ requires C, 62·1; H, 5·75; N, 32·2%); *p*-Me_2CH, 192° (99%) (Found: C, 64·9; H, 7·1; N, 27·8. $C_{11}H_{14}N_4$ requires: C, 65·35; H, 6·9; N, 27·7%); H, 191° (94%) (lit.,[28] m.p. 186—187°); *p*-Br, 233—234° (94%) (lit.,[27] 227°).

Cyclization in Base.—*N*-Amidinobenzohydrazide (0·25 g) was refluxed in water (12 ml) containing two equiv. of sodium carbonate (0·30 g) for 30 min. From the cooled solution precipitated 3-amino-5-phenyl-1,2,4-triazole, m.p. 191—192° in 89% yield.

Attempted Cyclization in Acid.—(a) *N*-Amidinobenzohydrazide hydrobromide (4,HBr; Ar = Ph) (0·25 g) in water (12 ml) was refluxed for 2 h. Removal of the solvent *in vacuo* left a solid, m.p. 248—250°, which was shown to be the uncontaminated starting material (recovery *ca.* 100%) using t.l.c., i.r. spectra, and mixed m.p.s.

(b) *N*-Amidinobenzohydrazide (0·25 g) was refluxed in water (13 ml) containing two equiv. of 48% hydrobromic acid (0·32 ml) for 20 min. The solution was then evaporated (at 40—50°) to give a residue (0·34 g, 94%), m.p. 239—245°. This was shown to be the hydrobromide of the starting material by mixed m.p. (249—251°) with an authentic sample.

(c) The hydrazide (9; Ar = Ph) (0·50 g) was refluxed in water (25 ml) containing two equiv. of 48% hydrobromic

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acid (0·64 ml) for 5 h. On cooling the white solid which precipitated (0·16 g, 48%) was shown to be benzoic acid, m.p. 120—122°. The aqueous filtrate was evaporated to dryness *in vacuo* and the residue (0·49 g), m.p. 170—211°, was dissolved in water and basified by the addition of 1N-sodium hydroxide (6 ml). The precipitated solid was identified as starting material (0·20 g, 41%), m.p. 183—184° (decomp.).

Kinetic Measurements.—Bromination. The kinetics of bromination of substituted *N*-amidinohydrazones were measured by an electrometric method which has previously been described in detail.[6,29] The method used low concentrations of bromine (*ca.* 10^{-4}—10^{-6}M) which were detected by measurement of the diffusion current at a spinning platinum electrode. Since the reactions were zero order in bromine, the initial concentrations of bromine had to be accurately known. Bromine was therefore introduced to the solution electrochemically by controlled electrolysis of the potassium bromide solution using the Metrohm model E211 coulometer to produce a constant current.[29] The hydrazone substrate (usually made up in acetic acid in 0·03M solution) was added to the bromine solution and bromine concentration *vs.* time curves recorded. Since the hydrazone was in large (>20-fold) excess, the reactions were pseudo-zero order in hydrazone also. Thus bromine concentration *vs.* time plots were rectilinear. The slopes of these [Br_2] *vs.* time plots, expressed in mol l^{-1}, were shown to be independent of the initial [Br_2] but proportional to [hydrazone]. The kinetic experiments were carried out at 15, 20, and 25°. Each of the values reported in Table 2 are averaged from a minimum of four experiments, and are accurate to ±2%. The solvent used for the kinetic experiments was 7 : 3 (v/v) acetic acid–water containing 0·1M-potassium bromide, allowance being made for the substrate which was added in acetic acid solution.

In one case (bromination of *N*-amidino-*N'*-benzylidene-*N*-methylhydrazinium nitrate) the rate of bromine uptake was too slow to permit convenient measurement by the electrometric technique. The reaction was therefore followed by placing the reaction solution (substrate and bromine in 7 : 3 acetic acid–water containing 0·1M-KBr) in a series of sealed ampoules at 20°. The contents of the ampoules were analysed at appropriate time intervals by addition of excess of potassium iodide followed by titration of the iodine released using standard sodium thiosulphate with electrometric detection of the end-point.[30]

Solvolysis studies. The course of the solvolysis reactions were determined (in aqueous or water–dioxan solution) using the spectrophotometric technique. In those cases where the reactions were run in the absence of buffers, pH was maintained by a Radiometer pH-stat assembly mounted in the cell compartment of a Cary 14 u.v. spectrophotometer.[20] Otherwise 1 cm pathlength cells were used on a Unicam SP 800B spectrometer. The pH values quoted were measured with a Metrohm EA 125U pH electrode with a Radiometer PHM 26 pH meter. For measurements in dioxan–water solution the electrode was initially standardized in aqueous buffers and then steeped in the mixed solvent for at least 30 min; the indicated ' pH ' values thus obtained are quoted throughout.

[3/746 *Received, 9th April,* 1973]

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