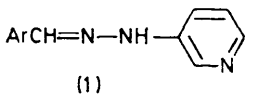
A Change from Rate-determining Bromination to Geometric Isomerisation of Pyridylhydrazones

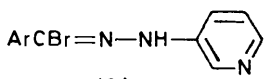
By **Anthony F. Hegarty,* Patrick J. Moroney,** and **Francis L. Scott,** Chemistry Department, University College, Cork, Ireland

The rate-determining step in the bromination of aldehydic 4-pyridylhydrazones has been identified as isomerisation of the predominant *E*-isomer (in which the large groups are *trans*) to the more reactive *Z*-isomer. Substituent and temperature effects favour a transition state with considerable rotational character. The *Z*-isomer was isolated in one case (pyridine-2-carbaldehyde 4-pyridylhydrazone) and shown to brominate rapidly as expected. The change in rate-determining step from bromination to isomerisation in closely related hydrazones is discussed. Representative novel 4-pyridylhydrazonyl bromides, which were formed on bromination, were isolated and characterised.

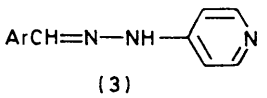
ELECTROPHILIC bromination of the pyridine nucleus occurs exclusively by reaction with the free pyridine although under the reaction conditions used the protonated form may be present in great excess.[1] Only under forcing conditions can any electrophilic substitutions be successful with the protonated species.[2] We have recently found however that substitution on a sidechain attached to a pyridine nucleus may occur through both protonated and unprotonated forms.[3] The 3-pyridylhydrazones (1) are smoothly brominated in



(1)



(2)



(3)

aqueous acetic acid to give hydrazonyl bromides (2); studies at varying acidities (in aqueous solution) showed that the free base (1) was brominated *ca.* 160-fold more rapidly than its conjugate acid (1,H$^+$). The overall kinetic behaviour of these materials (1) was similar to that of other *N*-aryl [*e.g. N*-(*p*-nitrophenyl)] hydrazones in that the rate constants were overall second order, *i.e.* first order both in hydrazone and in bromine.[4] We have now examined the behaviour of the corresponding *N*-(4-pyridyl)-substituted hydrazones (3); the position of attachment of the pyridine nucleus to the hydrazone sidechain has a major effect, not only on the gross ease of electrophilic attack but also on the nature of the step which becomes rate determining for the overall process.

RESULTS AND DISCUSSION

The rate constants obtained for the bromination of a series of arenecarbaldehyde 4-pyridylhydrazones (3) in 70% acetic acid containing 0·1M-potassium bromide are summarised in Table 1. As in the case of the 3-pyridyl derivatives[3] (1) the products obtained were hydrazonyl bromides (see below); in contrast, however, the rates of bromination of (3) are in each case first order in hydrazone alone, *i.e.* they are independent of the concentration of electrophile.

This behaviour was confirmed by using differing initial concentrations of both bromine and of the hydrazone. Normally the hydrazone was in excess (minimally 20 : 1) and bromine concentration *vs.* time plots were then rectilinear. This kinetic behaviour implies that the rate-determining step is independent of the electrophile used; further confirmation of this is provided by the observation that variation of the bromide ion concentration (from 0·025 to 0·1M at constant ionic strength in solution), which has the effect of changing the $Br_2 : Br_3^-$ ratio, does not affect the overall rate of bromine uptake. The two electrophiles Br_2 and Br_3^- (which may in fact be Br^- catalysis of Br_2 reaction[5]) have been shown to be markedly different in reactivity in those cases in which the bromination step is rate determining.

The type of kinetic behaviour shown by the 4-pyridylhydrazones (3) has been observed previously during bromination of other diverse hydrazone and semicarb-

TABLE 1

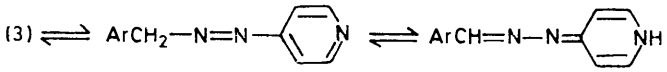
First-order rate constants for *E*–*Z* isomerisation of hydrazones (3; Ar = XC_6H_4) and their *N*-methyl analogues (6; Ar = XC_6H_4) at 25° in 70% acetic acid containing 0·1M-potassium bromide

Substituent X	4-Me	4-Br	4-Cl	3-NO_2	H	4-MeO	4-NO_2	4-Me_2CH	3-Cl	3-Me
					$10^5k_{obs}/s^{-1}$					
Compounds (3)	3·24	2·02	2·34		2·64	3·41	0·81	3·13	1·84	2·72
Compounds (6)	3·53	2·11	2·06	1·36	3·21	4·35	1·23			3·26

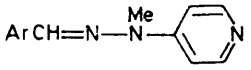
[1] P. J. Bignell, P. E. Jones, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1970, 117.
[2] G. Bianchi, A. G. Burton, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1972, 1950.
[3] A. F. Hegarty, P. J. Moroney, A. Moynihan, and F. L. Scott, *J.C.S. Perkin II*, 1972, 1892.
[4] A. F. Hegarty and F. L. Scott, *J. Chem. Soc.* (*B*), 1966, 672.
[5] J. E. Dubois and X. Q. Huynh, *Tetrahedron Letters*, 1971, 3369; J. A. Pincock and K. Yates, *Canad. J. Chem.*, 1970, **48**, 3332.

azone systems,[6-9] and it is proposed that the same phenomenon, *viz.* a slow prebromination geometric isomerisation in the hydrazone about the azomethine (-CH=N-) bond is responsible in each case. Further evidence (see below) also supports the view that the first-order rate constants listed in Table 1 represent rates of geometric isomerism; the bromination technique therefore constitutes a convenient method for the determination of rates of isomerisation of hydrazones.

As an alternative to slow geometric isomerism the rate-determining prebromination step could have arisen due to the presence of a small amount of a hydrazone tautomer which was very reactive towards bromine. This explanation is untenable for the following reasons. Ene-hydrazine formation is inhibited by the presence of a *C*-aryl group. Tautomerism of (3) to an azoalkane (4)



(4) (5)

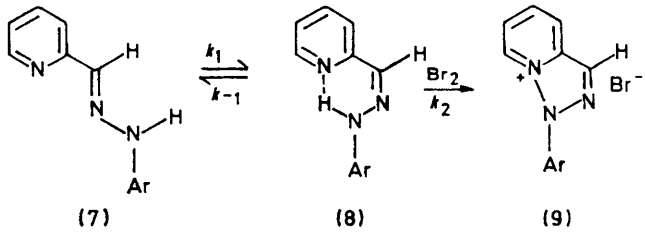


(6)

or 1,4-dihydropyridin-4-ylidenehydrazone (5) isomer is however possible. But the *N*-methyl derivatives of (3) [*viz.* (6)] react in a manner exactly analogous to (3) showing the same kinetic behaviour and substituent effects (see Table 1). In view of the fact that (6) cannot isomerise to (4) or (5) (except by de-*N*-methylation) it is unlikely that either of these is the reactive form of (3).

Aldehyde hydrazones and more particularly arenecarbaldehyde hydrazones have been shown,[10,11] to exist in solution in the *E*- or (*syn*-*) form in which the steric interactions between the substituents on nitrogen and carbon are minimised. Although not directly studied by the n.m.r. technique, it is reasonable to assume that the same is true for the 4-pyridylhydrazones (3). On this basis the rate-determining step would be consistent with a slow isomerisation of the *E*- to *Z*-form which then reacts rapidly with bromine.

This interpretation implies that if the *Z*-isomer of (3) were available for study, then its rate of bromination would involve rate-determining attack by bromine (*i.e.* the observed rate would be overall second order). However the *Z*-isomer may only be isolated when stabilised by special structural features. A possibility is the replacement of the aldehydic aryl ring in (3) by a 2-pyridyl group. This pyridine ring is properly positioned to form a hydrogen bond with the amino-hydrogen atom of the hydrazone only in one of the geometric isomers, the *Z*-isomer (8), which is normally less favoured.



(7) (8) (9)

SCHEME 1

Formation of pyridine-2-carbaldehyde 4-pyridylhydrazone in the normal manner yielded the *E*-isomer (7; Ar = 4-pyridyl) (see below). On irradiation in benzene for 5 h the *Z*-isomer (8; Ar = 4-pyridyl) was formed (in 39% yield) and separated from (7; Ar = 4-pyridyl) chromatographically. The two isomers differ markedly in physical properties which can be ascribed to the presence or absence of the intramolecular hydrogen bond. Thus the *E*-isomer has a higher m.p. (200—202 *vs.* 110—112° for the *Z*-isomer) and is chromatographically less mobile. The *Z*-isomer is readily eluted from an alumina column using benzene and has a larger R_F value than the *E*-isomer (see Experimental section) using a variety of thin-layer chromatographs. In addition the absorption maximum of the *E*-isomer is at shorter wavelength (298 nm) in benzene than in ethanol (306 nm), where intermolecular hydrogen bonding with the solvent is possible; the corresponding absorption maximum of the *Z*-isomer is at a longer wavelength in benzene (313 nm) than in ethanol (306 nm). Similar evidence has been presented for the differentiation of related *E*- and *Z*-isomers (7 and 8; Ar = Ph and 2-pyridyl).[12]

The *E*-isomer (7; Ar = 4-pyridyl) was brominated analogously to the other hydrazones (3) with k_{obs} (= k_1, Scheme 1) = $2{\cdot}4 \times 10^{-5}$ s^{-1} (under the conditions described in Table 1). Thus the 2-pyridyl group acts in this compound as any other substituent, the rate of isomerisation being about the same as the unsubstituted compound (3; Ar = Ph). In contrast, the reaction of the *Z*-isomer is first order in the hydrazone and in bromine, *i.e.* the rate-determining step is bromination in this case k_{obs} (= k_2) = 260 l mol^{-1} s^{-1} under the same conditions.

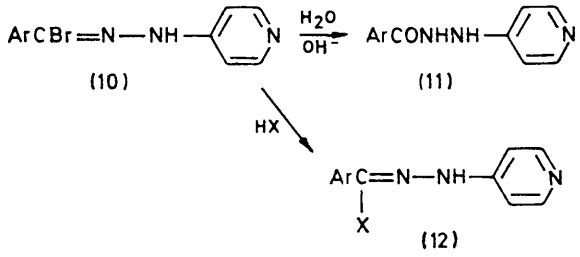
Interestingly, the bromination of the *E*-isomer (7; Ar = 4-pyridyl) was clearly zero order in bromine only when the substrate was added directly in solid form

* The geometric isomer having the group attached to nitrogen and the smaller group attached to carbon *cis* to one another has also been defined [10] as the *syn*-isomer.

[6] A. F. Hegarty and F. L. Scott, *J. Org. Chem.*, 1968, **33**, 753.
[7] F. L. Scott, F. A. Groeger, and A. F. Hegarty, *J. Chem. Soc.* (*B*), 1971, 1141.
[8] J. C. Tobin, A. F. Hegarty, and F. L. Scott, *J. Chem. Soc.* (*B*), 1971, 2198.
[9] F. L. Scott, T. M. Lambe, and R. N. Butler, *J.C.S. Perkin I*, 1972, 1918.
[10] G. J. Karabatsos and R. A. Taller, *J. Amer. Chem. Soc.*, 1963, **85**, 3624.
[11] G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, *J. Amer. Chem. Soc.*, 1964, **86**, 3351; C. I. Stassinopoulu, C. Zioudrou, and G. J. Karabatsos, *Tetrahedron Letters*, 1972, 3671.
[12] C. F. Bell and D. R. Rose, *J. Chem. Soc.* (*A*), 1969, 819.

to the bromine solution in the reaction cell. If the isomer (7; Ar = 4-pyridyl) was made up as a concentrated (10^{-2}M) solution in acetic acid or methanol and then added to the reaction cell complex kinetics result. There is an initial rapid uptake of bromine followed by a slower reaction. If the substrate is allowed to stand for a longer time in acetic acid before being added to the bromine solution then the initial rapid reaction is relatively more important. This is explicable in terms of some isomerisation ($\leqslant 5\%$) of the *E*- to the more reactive *Z*-form occurring in the substrate solution prior to the reaction with bromine.

When bromination of the 4-pyridylhydrazones (3) was attempted on a large scale (relative to that used in the kinetic experiments), the initial product which precipitated (using a 1 : 1 bromine : hydrazone ratio) was a hydrazonyl bromide complexed with one mole of bromine (10,Br_2). On treatment with acetone at reflux this was converted to a hydrazonyl bromide hydro-



bromide (10,HBr) and the acetone was concomitantly brominated. On basification in aqueous dioxan or acetone this yielded a hydrazide (11), a reaction which is typical of hydrazonyl bromides.[3,13] Further chemical evidence for the hydrazonyl bromide structure (10) is the ready conversion of (10,HBr) to amidrazones (12; X = NHPh or morpholino) on treatment with two equiv. of aniline or morpholine.

When a deficiency of bromine was used in the initial reaction with (3) in acetic acid or when one mol. equiv. sodium acetate was added to the reaction then the product which precipitated was the hydrazonyl bromide hydrobromide (10,HBr). Attempts to isolate the free base (10) were unsuccessful, dehydrohalogenation (loss of two mol. equiv. HBr) occurring readily with the formation of, for example, the hydrazides (11). Although the small amount of substrate used in a kinetic experiment precluded a detailed product study under exactly replicate conditions, t.l.c. indicated the presence of the hydrazide (11) on neutralisation of the reaction solutions on completion of a kinetic run.

The products of bromination of hydrazones of type (7) which have a 2-pyridyl group in the aldehydic moiety have been studied by Kuhn and his co-workers.[14,15] When Ar = Ph or substituted phenyl, oxidative ring closure to give triazolium bromides (9) occurred even under mild conditions. In the presence of excess of brominating agent replacement of the methine hydrogen by bromine in the triazolium salt also occurred. It is interesting that the isomers used by Kuhn were originally[14] assigned to the *Z*-configuration (8) on the basis of this facile cyclisation. More recent work,[12,15] however, favours the *E*-configuration for the materials used by Kuhn. This is a significant result since it implies that, in this system at least, *E*—*Z*-isomerisation preceeded bromination. Although the products of bromination were not studied in detail for (7; Ar = 4-pyridyl), this result is entirely consistent with the kinetic behaviour of these materials.

Two extremes of mechanisms (inversion and rotation) and a continuum between them have been recognised for geometric isomerisations about C=N double bonds.[16,17] Inversion (more generally favoured) involves displacement of the substituent attached to nitrogen through a linear transition state in which the nitrogen adopts linear *sp* hybridisation. The rotation mechanism involves charge separation in the transition state giving partial single C–N bond formation and rotation about the C–N bond.

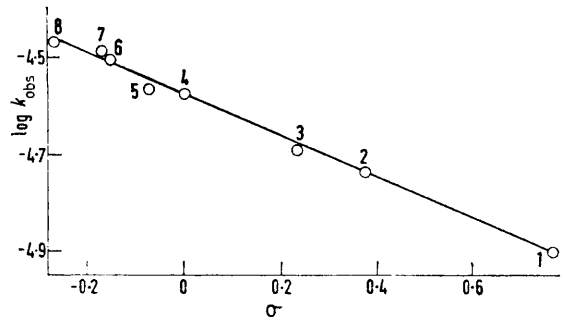
Both mechanisms have attracted support. Because the isomerisation of 4-pyridylhydrazones, which are the subject of this study, was carried out in polar medium (70% acetic acid containing 0·1M-potassium bromide), the rotation mechanism might be favoured. Moreover, the strongly electron-withdrawing nature of the protonated 4-pyridyl group (σ +2·57)[18] would tend to enhance polarisation by stabilising negative charge on nitrogen. The effect of substituents in *C*-aryl ring (Ar) of (3) and of the *N*-methyl analogues (6) tends to support this. The data in Table 1 show that electron-donating substituents promote and electron-withdrawing substituents retard isomerisation. The Hammett ρ value calculated from these data is −0·43 (r = 0·990) for compounds (3) (see Figure). The value for the *N*-methyl analogues (6) is similar (ρ = −0·51). The negative ρ values imply that the substituent is acting in a site (the imine carbon) which generates a partial positive charge in the transition state.

The magnitude of ρ is larger than normally observed for isomerisation *via* the inversion mechanism (*ca.* ρ 0 ±0·1)[17] and indicates substantial polarisation of the C=N bond. Thermodynamic data were obtained for two typical compounds from rate constants at two temperatures (25 and 40°). For (3; Ar = *p*-BrC_6H_4) $\Delta H^{\dagger}$ = 18·7 kcal mol^{-1}, $\Delta S^{\dagger}$ = −17 cal mol^{-1} K^{-1}; for (6; Ar = *p*-ClC_6H_4) $\Delta H^{\dagger}$ = 18·1 kcal mol^{-1}, $\Delta S^{\dagger}$ = −19 cal mol^{-1} K^{-1} The large negative entropy of activation contrasts with values close to zero for isomerisation *via* the inversion mechanism, and is probably indicative of

[13] A. F. Hegarty, M. P. Cashman, and F. L. Scott, *J. Chem. Soc.* (*A*), 1971, 1607.
[14] R. Kuhn and W. Munzing, *Chem. Ber.*, 1952, **85**, 29; 1953, **86**, 858.
[15] D. Schulte-Frohlinde, R. Kuhn, W. Munzing, and W. Otting, *Annalen*, 1959, **622**, 43.
[16] H. Kessler, P. F. Bley, and D. Leibfritz, *Tetrahedron*, 1971, **27**, 1687.
[17] M. Raban and E. Carlson, *J. Amer. Chem. Soc.*, 1971, **93**, 685; H. Kessler, *Angew. Chem. Internat. Edn.*, 1970, **9**, 219.
[18] J. H. Blanch, *J. Chem. Soc.* (*B*), 1966, 937.

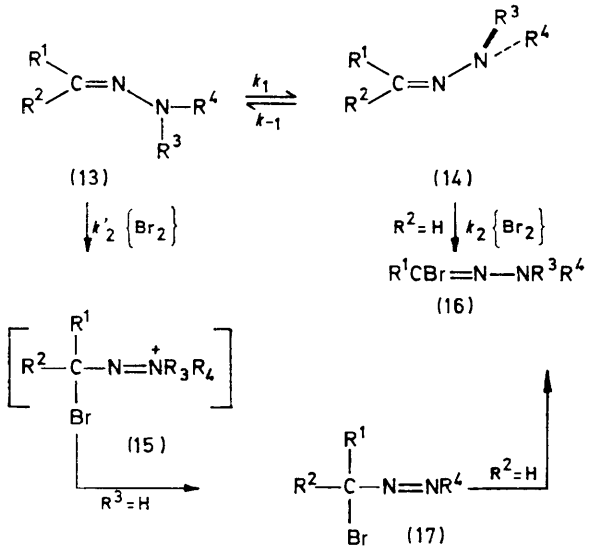
appreciable solvent reorganisation in a charged transition state.

The substituent effects and other data for isomerisation of the 4-pyridylhydrazones are consistent with those



Hammett plot of log k_{obs} (in s^{-1}) *vs.* σ for the isomerisation of 4-pyridylhydrazones (3; Ar = XC_6H_4) at 25° in 7 : 3 acetic acid–water (μ = 0·1, KBr): 1, X = *p*-NO_2; 2, *m*-Cl; 3, *p*-Br; 4, H; 5, *m*-Me; 6, *p*-Pr^i; 7, *p*-Me; 8, *p*-MeO

reported earlier for isomerisation of hydrazones in polar media or in the presence of acidic catalysis (Table 2). For the hydrazone systems (13) which have been studied the ρ value for variation of the substituent when R^1 is a



Scheme 2

substituted phenyl ring varies in the region −0·29 to −0·69; steric effects are also of importance and are the major or dominant feature when the aryl group R^1 contains *ortho*-substituents or when R^1 is a variable alkyl group (with R^2 = H).

There are, however, limitations to the technique of using the bromine trap to measure isomerisation rates in hydrazone systems. The most obvious is that the rate-determining step in the bromination of the hydrazone must be isomerisation (k_1, Scheme 2) and not bromination (k_2 or k_2'). We have found that hydrazones which are closely related structurally may react by different mechanistic pathways. Thus for all *NN*-disubstituted hydrazones (13; R^3 and $R^4 \neq$ H), the rate-determining step is isomerisation, independent of whether the rate-determining step for the *N*-monosubstituted analogue (13; R^3 = H) is bromination or isomerisation.

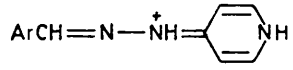
Table 2

Substituent effects on the rates of *E*–*Z* isomerisation of hydrazones (13)[a]

R^1	R^2	R^3	R^4	ρ (Variation of R^1)	Refs.
XC_6H_4	H	H	4-PyridylH$^+$	−0·43	This work
XC_6H_4	H	Me	4-PyridylH$^+$	−0·51	This work
XC_6H_4	H	H	$CONH_2$	−0·65	9
XC_6H_4	H	H	$C(=\overset{+}{N}H_2)NH_2$	−0·36	*c*
XC_6H_4	H	Me	4-$NO_2C_6H_4$	−0·29	7
XC_6H_4	H	H	5-(1-Benzyltetrazolyl)	−0·69	8
Alkyl	H	H	2,4-$(NO_2)_2C_6H_3$	ρ* ∼ 0 δ = +0·49	6
Alkyl	Ph	H	2,4-$(NO_2)_2C_6H_3$ [b]	ρ* = −0·05 δ = +0·49	*d*

[a] Measured in 70% acetic acid at 20 or 25° unless otherwise stated. [b] In chloroform (acid catalysed). [c] T. A. F. Mahony, Ph.D. Thesis, National University of Ireland. [d] J. P. Idoux and J. A. Sikovski, *J.C.S. Perkin II*, 1972, 921.

The second main group of hydrazones which show rate-limiting isomerisation appear to be characterised by a strongly electron-withdrawing R^4 group. The rate-determining step can be shifted from bromination to isomerisation simply by increasing the electron-withdrawing power of R^4. Thus the rate of bromination of 4-nitrophenylhydrazine (7; Ar = 4-$NO_2C_6H_4$) is overall second order (k_{obs} = 24·5 l mol^{-1} s^{-1}), first order in bromine and in hydrazone. However the rate-determining



(18)

step for the *N*-2,4-dinitrophenyl analogue [7; Ar = 2,4-$(NO_2)_2C_6H_3$] was isomerisation (k_{obs} = 1·7 × 10^{-6} s^{-1}; both measured at 25° in 7 : 3 acetic acid–water containing 0·1M-potassium bromide). Other arenecarbaldehyde *p*-nitrophenylhydrazones[7] and alkanal 2,4-dinitrophenylhydrazones[6] also show this changeover in the rate-determining step.

Table 3

pK_a Values for hydrazones (3; Ar = XC_6H_4) and their *N*-methyl analogues (6; Ar = XC_6H_4) at 25° (μ = 0·1, KBr) in 1 : 4 methanol–water

Substituent X	H	4-Cl	4-Br	4-Me	4-MeO	3-Me	3-NO_2
pK_a (3)	8·36	8·30	8·28	8·42	8·44		
pK_a (6)	7·60	7·56	7·51	7·75		7·70	7·36

The behaviour of hydrazones with a basic *N*-substituent can also be rationalised in these terms. The

4-pyridylhydrazones (3) are more basic (see Table 3) than the 3-pyridylhydrazones [3] (1) by *ca.* 3 pK_a units. Thus in acidic solution at a given pH the fraction of free hydrazone (3) is 10^3-fold less than in the case of the 3-pyridyl isomer (1). The greater basicity of (3) is most likely a result of the stabilisation of the protonated form by resonance structures such as (18), which are not possible for (1,H^+). Since the substituent attached to nitrogen is most important in determining the rate of the bromination step ($\rho = -2{\cdot}2$),[7] the protonated 4-pyridyl group will particularly strongly deactivate the hydrazone system towards bromination. This also applies to the protonated *N*-amidino- and *N*-tetrazolyl-hydrazones (see Table 2); in each of these cases isomerisation becomes rate determining. The basicity of the 4-pyridyl group can be reduced by conversion to the corresponding *N*-oxide. We have found that the rate of bromination of 4-(4-methylbenzylidenehydrazino)pyridine *N*-oxide (13; $R^1 = p$-MeC_6H_4; $R^2 = R^3 = H$, $R^4 = 4$-$C_5H_4N{\rightarrow}O$) is overall second order ($k_{obs} = 1{\cdot}15 \times 10^2$ l mol^{-1} s^{-1}), as in the case of the 3-pyridylhydrazone (1).

These results can be rationalised in terms of the unified reaction (Scheme 2). *N*-Substituted hydrazones undoubtedly exist largely in the less crowded *E*-form (13), particularly so when R^1 is an aryl group since the equilibrium concentration of the *Z*-form cannot then be detected spectrophotometrically.[10,11] When $R^3 = H$ and R^4 is not strongly electron withdrawing, the bromination step k_2' {or possibly k_2 if the equilibrium between (13) and (14) is rapidly established, *i.e.* $k_{-1} \gg k_2[Br_2]$} is rate determining. The detailed mechanism of bromination involves formation of the stabilised ammonium species (15) followed by loss of an amino-proton to give the azoalkane intermediate (17). Tautomerism of (17) gives the observed product in all cases, the hydrazonyl bromide (16).

When $R^3 = Me$ this pathway is blocked and an intermediate of type (15) must lose a CH proton ($R^2 = H$) to give (16) directly. The possibility arises that this causes an appreciable slowing down in the rate of the bromination step, with C–H bond cleavage becoming rate determining. Strongly electron-withdrawing substituents R^4 also act to slow down the normal bromination route (k_2'). Under these conditions, if $k_2 \gg k_2'$, then k_1, the rate of isomerisation will become rate determining for the overall process. Since electron-withdrawing substituents attached to nitrogen (R^4) enhance the rate of isomerisation [17] it is likely that k_1 is very slow for those hydrazones which show bromination as the rate-determining step, that is, bromination of the *E*-isomer (15) alone occurs. The greater reactivity of the *Z*-isomer (14) relative to (13) towards bromine possibly arises from two factors: (a) (14) has a *cis*-configuration in which the bulky groups R^1 and $-NR^3R^4$ are on the same side of the azomethine bond and (b) the electron-withdrawing substituent R^4 in (14) may not, because of steric interactions between R^4 and R^1, have as powerful a deactivating effect on the hydrazone as it does in the *E*-isomer (13).

[19] F. G. Mann, A. F. Prior, and T. J. Wilcox, *J. Chem. Soc.*, 1959, 3080.

EXPERIMENTAL

Materials.—Aqueous acetic acid (7 : 3 v/v) (containing 0·1M-potassium bromide) which was used for the kinetic experiments was prepared at 25°. AnalaR acetic acid was twice distilled from chromium trioxide and had b.p. 117—118°; deionised water was twice distilled from alkaline potassium permanganate. Potassium bromide, potassium nitrate, and all other inorganic materials were AnalaR grade and were dried at 120° for 3 h before use.

Substrates.—Arenecarbaldehyde 4-pyridylhydrazones. The hydrazones were prepared by the addition of an equimolar amount of the appropriate substituted benzaldehyde, in the presence of excess (1·5 equiv.) of sodium acetate, to 4-hydrazinopyridine hydrochloride (prepared from 4-chloropyridine hydrochloride [19]). The hydrazones, which were obtained in >80% yield, were recrystallised several times from benzene to constant m.p.: substituent = H, m.p. 200—201° (lit.,[19] 200°); *p*-Me, 206—207° (Found: C, 74·05; H, 6·6; N, 19·8. $C_{13}H_{13}N_3$ requires C, 73·9; H, 6·2; N, 19·9%); *p*-Cl, 219—220° (Found: C, 62·5; H, 4·4; N, 18·0. $C_{12}H_{10}ClN_3$ requires C, 62·2; H, 4·35; N, 18·1%); *p*-Br, 239—240° (Found: C, 52·4; H, 3·8; Br, 28·7; N, 15·1. $C_{12}H_{10}BrN_3$ requires C, 52·2; H, 3·65; Br, 28·9; N, 15·2%); *p*-MeO, 187—188° (Found: C, 69·1; H, 5·95; N, 18·5. $C_{13}H_{13}N_3O$ requires C, 68·7; H, 5·8; N, 18·5%); *p*-NO_2, 276—277° (from ethanol–methanol) (Found: C, 59·6; H, 4·05; N, 22·95. $C_{12}H_{10}N_4O_2$ requires C, 59·5; H, 4·1; N, 23·1%); *p*-Pr^i, 188—189° (Found: C, 75·4; H, 7·4; N, 18·0. $C_{15}H_{17}N_3$ requires C, 75·3; H, 7·2; N, 17·6%); *o*-Me, 148—149° (Found: C, 73·5; H, 6·2; N, 19·9. $C_{13}H_{13}N_3$ requires C, 73·9; H, 6·2; N, 19·9%); *o*-Cl, 229—230° (from ethanol) (Found: C, 61·9; H, 4·4; N, 18·1. $C_{12}H_{10}ClN_3$ requires C, 62·2; H, 4·35; N, 18·1%).

Arenecarbaldehyde methyl-(4-pyridyl)hydrazones. The *N*-methyl hydrazones were prepared using the method described above; *N*-methyl-*N*-(4-pyridyl)hydrazine hydrochloride, which was prepared by refluxing together 4-chloropyridine (1 equiv.) and methylhydrazine (1·1 equiv.) in n-propanol for 2·5 h, had m.p. 205—206°. The *meta*- and *para*-substituted benzaldehyde hydrazones were recrystallised from benzene (twice) and n-hexane and had the following m.p.s: substituent, H, m.p. 124—125° (Found: C, 73·55; H, 6·25; N, 19·7. $C_{13}H_{13}N_3$ requires C, 73·9; H, 6·2; N, 19·9%); *p*-Me, 185° (Found: C, 74·25; H, 6·8; N, 18·5. $C_{14}H_{15}N_3$ requires C, 74·6; H, 6·7; N, 18·65%); *p*-Br, 146—147° (Found: C, 54·2; H, 4·2; Br, 27·4; N, 14·1. $C_{13}H_{12}BrN_3$ requires C, 53·8; H, 4·2; Br, 27·5; N, 14·5%); *p*-Cl, 147—148° (Found: C, 63·8; H, 5·0; Cl, 14·3; N, 16·8. $C_{13}H_{12}ClN_3$ requires C, 63·5; H, 4·9; Cl, 14·4; N, 17·1%); *p*-MeO, 167—168° (Found: C, 69·45; H, 6·5; N, 17·2. $C_{14}H_{15}N_3O$ requires C, 69·7; H, 6·3; N, 17·4%); *m*-NO_2, 195° (Found: C, 60·8; H, 4·7; N, 21·6. $C_{13}H_{12}N_4O_2$ requires C, 60·9; H, 4·7; N, 21·9%); *m*-Me, 105—106° (Found: C, 74·5; H, 6·8; N, 18·6. $C_{14}H_{15}N_3$ requires C, 74·6; H, 6·7; N, 18·65%); *m*-Cl, 91° (Found: C, 63·3; H, 5·0; Cl, 14·5; N, 17·2. $C_{13}H_{12}ClN_3$ requires C, 63·5; H, 4·9; Cl, 14·4; N, 17·1%); *p*-NO_2, 181—182° (Found: C, 60·9; H, 4·85; N, 21·55. $C_{13}H_{12}N_4O_2$ requires C, 60·9; H, 4·7; N, 21·85%).

4-(4-Methylbenzylidenehydrazino)pyridine N-oxide. 4-Hydrazinopyridine 1-oxide (which was obtained *via* 4-

chloropyridine 1-oxide,[20] starting from 4-nitropyridine 1-oxide [21]) was heated at 50° in absolute methanol with an equimolar quantity of *p*-tolualdehyde for 10 min. On cooling the *hydrazone* precipitated (70%; recrystallised from absolute ethanol), m.p. 236—237° (Found: C, 68·6; H, 5·5; N, 18·6. $C_{13}H_{13}N_3O$ requires C, 68·7; H, 5·8; N, 18·5%).

(E)-*Pyridine-2-carbaldehyde 4-pyridylhydrazone.* Pyridine-2-carbaldehyde was added to an equimolar amount of 4-hydrazinopyridine in acetic acid containing 2 equiv. of sodium acetate. The solution was heated for 10 min at 50° and, on cooling, the E-*isomer* was precipitated (83%) by the addition of ammonia and recrystallised from alcohol–benzene, m.p. 200—202° (Found: C, 66·8; H, 5·2; N, 28·1. $C_{11}H_{10}N_4$ requires C, 66·6; H, 5·1; N, 28·3%). The *Z*-isomer was formed as follows. The *E*-isomer (1·02 g) in benzene (300 ml) was irradiated (medium pressure Hanovia lamp used without a filter) under nitrogen for 5 h. The solution was then reduced *in vacuo* to *ca.* 75 ml and chromatographed on alumina (activity III) using benzene as eluant. The pale yellow *Z-isomer* (39%) was isolated from the early fractions and recrystallised from benzene, m.p. 110—112° (Found: C, 66·7; H, 5·1; N, 28·15%). The course of the separation was monitored using t.l.c. on alumina; the *Z*-isomer had R_F 0·42, the *E*-isomer R_F 0·11 using 93 : 7 chloroform–methanol.

Bromination of Benzaldehyde 4-Pyridylhydrazone.—The hydrazone (2·0 g) was dissolved in glacial acetic acid (18 ml) and vigorously stirred while bromine (0·5 ml; 1 equiv.) in glacial acetic acid (3 ml) was added dropwise over 15 min. An orange solid (A) began to precipitate from solution when *ca.* half the bromine was added; this was collected on completion of addition and washed with acetic acid, m.p. 239—241°. Treatment of (A) with acidified potassium iodide indicated the presence of one mol. equiv. of oxidising bromine, characteristic of the *N*-bromopyridinium bromide character; [22] analysis indicated the presence of three atoms of bromine (Found: C, 32·7; H, 2·5; Br, 54·7; N, 9·5. $C_{12}H_{10}Br_3N_3$ requires C, 33·0; H, 2·5; Br, 55·0; N, 9·6%). When the solid (A) was refluxed for 15 min in acetone it was converted to a solid (B); the acetone was concomitantly brominated. The solid (B), m.p. 257—259°, did not liberate iodine and analysed for *N-4-pyridylbenzohydrazonyl bromide hydrobromide* (Found: C, 39·9; H, 3·1; Br, 44·5; N, 11·8. $C_{12}H_{11}Br_2N_3$ requires C, 40·4; H, 3·1; Br, 44·8; N, 11·8%). The hydrazonyl bromide (B) was dissolved in boiling water, allowed to cool, and basified (sodium carbonate). *N-4-Pyridylbenzohydrazide* precipitated as a pale yellow solid, m.p. 230—231° (from ethanol–benzene × 3) (Found: C, 67·7; H, 5·3; N, 20·1. $C_{12}H_{11}N_3O$ requires C, 67·6; H, 5·2; N, 19·7%). This had the characteristic [23] benzohydrazide carbonyl absorption at 1665 cm^{-1}. The hydrazonyl bromide hydrobromide (B) (0·1 g) was stirred into a paste with morpholine (2 ml) and heated at 60° for 10 min. On cooling the *morpholide* was precipitated on addition of ice–water; on recrystallisation from 1 : 1 benzene–cyclohexane (×2) it had m.p. 132—135° (Found: C, 68·35; H, 5·8; N, 19·8. $C_{16}H_{18}N_4O$ requires C, 68·1; H, 6·4; N, 19·85%). A similar reaction of the hydrazonyl bromide hydrobromide with aniline gave (on neutralisation of an initially formed hydrobromide with sodium carbonate) the *amidrazone* (12; Ar = Ph, X = NHPh), m.p. 176—178° (Found: C, 75·5; H, 5·85; N, 19·8. $C_{18}H_{16}N_4$ requires C, 75·0; H, 5·6; N, 19·4%).

Kinetic Measurements.—The rate of bromination was measured by an electrometric technique which has already been described in detail.[3,4,7] The rate constants quoted in Table 1 are average values for several replicate runs using variable initial concentrations of both bromine and the hydrazone and are accurate to ±4%. In most cases the hydrazone was added in a concentrated form (usually *ca.* 10^{-2}M in methanol or acetic acid) to the reaction solution containing bromine in the cell. However, (7; Ar = 4-pyridyl) was added directly as a solid; it dissolved readily in the 70% acetic acid so a homogeneous solution was obtained in 1—2 s. The pK_a measurements on the hydrazones could not be done in aqueous solution because of low solubility in basic solution. The pK_a values were therefore measured using a spectrophotometric technique [24] in 1 : 4 methanol–water in the presence of 0·1M-potassium bromide.

[3/605 *Received, 22nd March,* 1973]

[20] A. R. Katritzky, *J. Chem. Soc.*, 1956, 2404.
[21] E. Ochiai, *J. Org. Chem.*, 1953, **18**, 549.
[22] M. S. Gibson, *Tetrahedron*, 1963, **19**, 1587.
[23] J. B. Aylward and F. L. Scott, *J. Chem. Soc.* (*B*), 1969, 1080.
[24] A. F. Hegarty, M. P. Cashman, and F. L. Scott, *J.C.S. Perkin II*, 1972, 44.