Acid, Base, and Uncatalysed Isomerisation of *Z*- to *E*-Amidine. A Mechanistic Study

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The *Z*-amidines (**2Z**) have been prepared by stereospecific reaction of nitrilium ion intermediates and the kinetics of interconversion into the *E*-amidines (**2E**) studied in aqueous solution at 25 °C. The interconversion is strongly catalysed by acid, so that at all pH values < 11, the acid-catalysed pathway (C–N bond rotation in the protonated species) dominates. A pH-independent reaction (uncatalysed nitrogen inversion) is observed over a narrow range at high pH while with one amidine (**5aZ**) carrying the most electron-withdrawing substituent, base catalysis (probably reversible addition of HO^-) is unexpectedly observed. The more reactive amidines [*e.g.* (**5c**)] were formed and their isomerisations studied *in situ*; however, introduction of electron withdrawal in the substituent on the imino nitrogen [such as (**5a**)] or on the amino nitrogen [such as (**2d**)] permitted the isolation of pure *Z*-isomers.

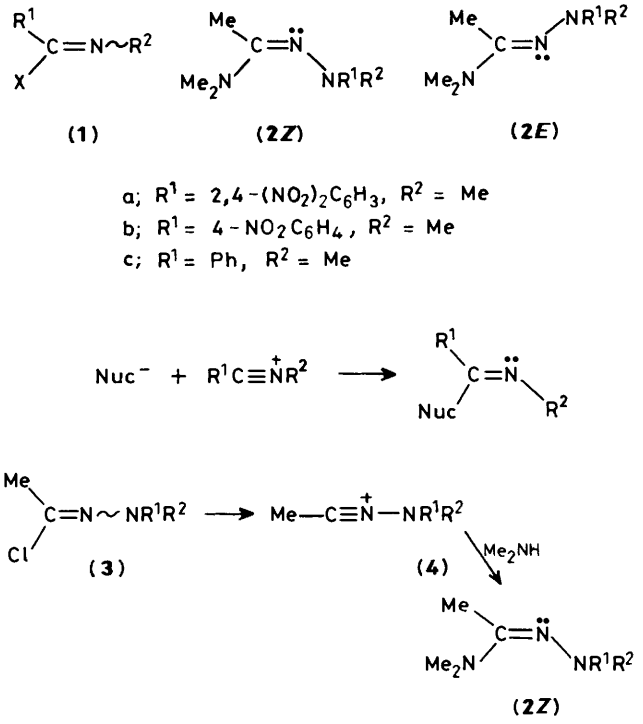
In compounds containing the C=N system there exists the possibility of distinct *E*- and *Z*-isomers. In order that these isomers be separable it is necessary that interconversion between them (*i.e.* isomerisation about the C=N bond) should be relatively slow. The systems which have been studied include those (**1**) where R^1 is alkyl, aryl, or hydrogen, R^2 is alkyl, aryl, alkoxy, or amino, and X is a halide (imidoyl halides), OR^3 (imidates), or NR^1R^2 (amidines).[1,2] The latter class, the amidines, have yet to be studied mechanistically. However, it is expected that these will be highly reactive (as judged from the analogous amidoximes)[2] and show significant catalytic pathways to isomerisation (because of the marked basicity of amidines).

In order to clarify the factors influencing *Z* to *E* isomerisation of amidines the novel acetamidines (**2**) were examined. These structures were chosen since it has been observed previously that the rate of uncatalysed isomerisation can be slowed by the presence of an NR^1R^2 group on the imino nitrogen, particularly if R^1 is itself an electron-withdrawing group such as 2,4-dinitrophenyl.[3]

Results and Discussion

Synthesis of Z-Amidines.—The reaction of a nucleophile and a nitrilium ion is known to occur stereospecifically so that the product is formed with the nucleophilic *trans* to the imino nitrogen lone pair (Scheme 1).[3] Such a reaction, using the nitrilium ion (**4**) formed from the acetimidoyl halide (**3**) was used to prepare the *Z*-amidine (**2Z**) in each case. That these substrates do react *via* initial ionisation to nitrilium ions was confirmed by a preliminary study, which showed (a) the reactivity order for (**3**) of $-NR^1R^2$ is $NMePh > NMeC_6H_4NO_2 > NMeC_6H_3(NO_2)_2$, (b) a large increase in rate on increasing the aqueous content of the solvent, and (c) the observation of a common ion effect. The corresponding bromides (**5**; R = Me and Bu^t) have been investigated in some detail[4] and were also shown to react under all conditions (except with strong nucleophiles in solvents of low ionising power) by the ionisation mechanism.

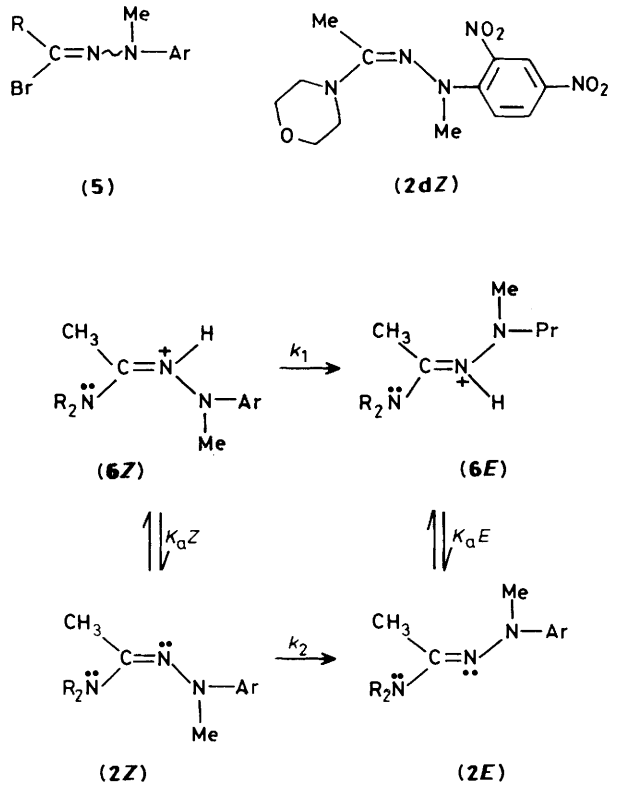
Solvolysis of *N*-(2,4-dinitro-*N'*-methylanilino)ethanimidoyl chloride (**3a**) in a mixture of dimethylamine, water, and acetone gave a single amidine isomer identified as (*Z*)-*N*,*N*-dimethyl-*N'*-(2,4-dinitro-*N''*-methylanilino)ethanimidamide (**2aZ**). It is clear that this is the least stable isomer since, on heating to 70–75 °C, the product liquified before resolidifying and remelting sharply at 122 °C. This behaviour is analogous to that observed for amidoximes where the more hindered *Z*-isomer also formed initially underwent isomerisation to the less crowded *E*-isomer.[2] The amidine (**2aZ**) could be stored indefinitely in the solid state at low temperature (−20 °C) without further reaction.



Scheme 1.

The *N*-*p*-nitrophenylanilinoamidine (**2bZ**) was prepared similarly but was contaminated by a small quantity of the *E*-isomer (**2bE**), reflecting the greater ease of isomerisation in this case (see below). The third amidine (**2c**) could not be isolated in a pure form as a single isomer; it was prepared *in situ* and the subsequent isomerisation then observed.

Isomerisation of Amidines.—The rates of isomerisation of *Z*- to *E*-amidines were measured in aqueous buffer solutions in water at 25 °C. Except in the case of (**2c**), the ionic strength was maintained at 1.0 (by the addition of KCl). Preliminary experiments established the absence of catalysis by buffer



Scheme 2.

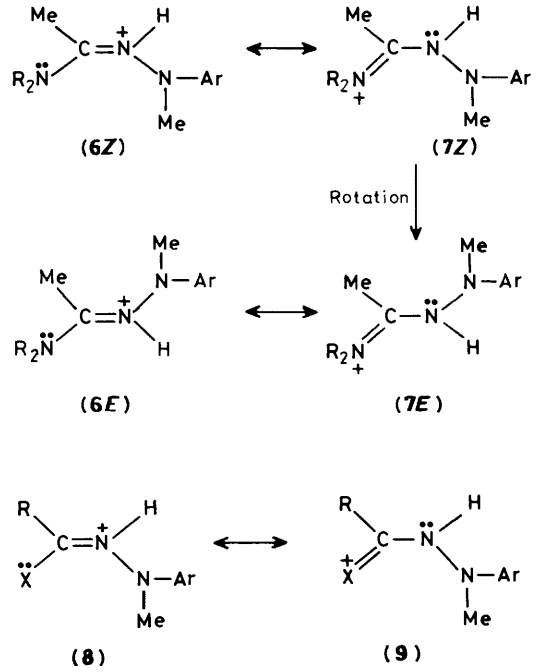
species. Since acid catalysis was observed (see below) *Z*- to *E*-isomerisation was too fast to measure in all cases at pH < 7. The only products isolated (quantitatively) on reaction of the *Z*-isomer under these conditions were the corresponding *E*-isomers. This was shown by actual isolation when carried out on a larger scale (using 1:5 dioxane–water in place of water to improve solubility). The *E*-isomers we also obtained when the *Z*-isomers were allowed to stand in $CDCl_3$ for 2—3 days at ambient temperatures.

The possible modes of isomerisation of the four amidines studied are shown in Scheme 2; in addition there is a base-catalysed path (see below). The derived expression for the observed rate of isomerisation from the Scheme is $k_{obs} = k_2 + k_1 \cdot F$ where k_2 and k_1 are the rates of isomerisation of the amidine and its conjugate acid respectively and F is the fraction of protonated species present at a given acidity $\{F = [H^+]/([H^+] + K_aZ)$; where K_aZ is the acidity constant for the conjugate acid of the *Z*-amidine$\}$. The derived constants obtained using the equation and least-squares fitting are listed in the Table. Since the reaction could not be measured at low pH, the value of k_1 can only be obtained if K_aZ is known. This cannot be measured directly without rapid isomerisation occurring; the values for the *E*-isomers, K_aE, measured spectroscopically, were therefore used to approximate k_1. Since reaction became very slow at high pH, k_2 was not determined for (**2d**).

Considering the acid-catalysed term k_1, it can be seen that k_1 decreases as the electron-withdrawing power of Ar decreases (from 2,4-dinitrophenyl to *p*-nitrophenyl). This is consistent with a mechanism involving rotation about the C=N bond of (**6Z**).[2] The key resonance contribution is (**7Z**) where the bond order of this bond is reduced; the dinitrophenyl group [Ar = 2,4-$(NO_2)_2C_6H_3$] in (**6aZ**) enhances the delocalisation of charge onto the dimethylamino group (**7aZ**).

Table. Observed rate and equilibrium constants for the isomerisation of the *Z*-amidines (**2Z**) to the *E*-amidines (**2E**) in water at 25 °C

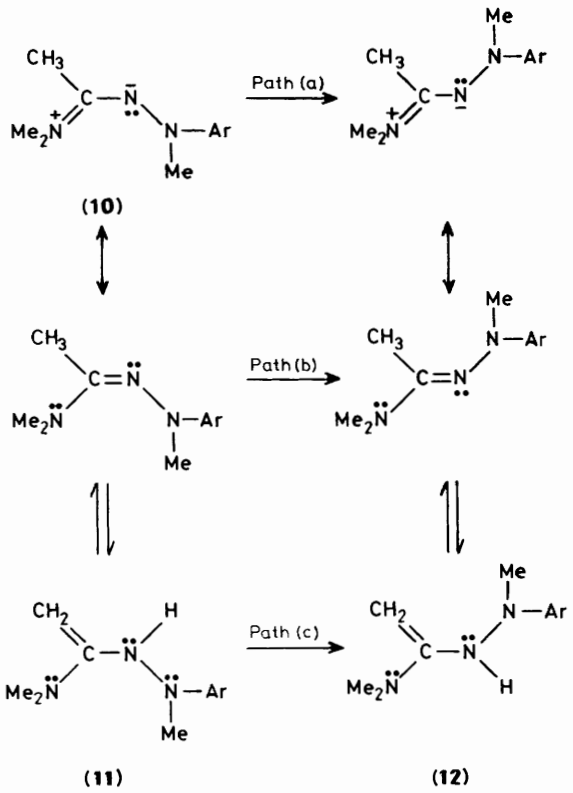
Z-Amidines	k_1/s^{-1}	$10^4k_2/s^{-1}$	pK_aE	10^4k_3/ l mol^{-1} s^{-1}	log k_1/K_aZ
(**2a**)	81.3	1.60	6.1	5.2	8.06
(**2b**)	3.7	7.20	8.0	1.5	8.56
(**2c**)		80			
(**2d**)					6.07



Acid-catalysed isomerisation has been observed in some cases for other imine systems, imidates,[5] and amidoximes.[2,6] It is absent for the isoimides (**1**; R^1 = Me, Bu^t, and Ph; R^2 = *N*-methyl-2,4-dinitroanilino, *N*-methyl-*p*-nitroanilino, and *N*-methylanilino; X = AcO) and the hydrazonyl ethers (**1**; R^1 = Ph; R^2 = *N*-methyl-2,4-dinitroanilino, *N*-methyl-*p*-nitroanilino, and *N*-methylanilino; X = MeO). Three factors appear to be important: (a) the basicity of the imine system, (b) the ease of delocalisation of charge into the substituent X at carbon, and (c) the rapidity of other isomerisation pathways. When X is oxygen all three factors [see *e.g.* structure (**8**)] would tend to reduce the contribution of the important structure (**9**).

In common with the isoimides, hydrazonoyl ethers, and amidoximes,[3] the amidines (**2**) also undergo isomerisation *via* the pH-independent pathway. However because of the dominance of the acid-catalysed reaction the pH-independent process is observed (if at all) only at high pH. The possible mechanisms of isomerism have been discussed previously in some detail[4] and envisage three limiting pathways: (a) a simple rotation about the C=N bond, (b) imino lone-pair inversion, and (c) tautomerism to an enamine (**11**) and rotation about the C–N bond to (**12**) followed by return to the *E*-amidine (see Scheme 3).

Mechanism (a) is unlikely since it is known[7] to be facilitated by an increase in the contribution of the resonance form (**10**). This contribution would increase as the electron-withdrawing power of the Ar group increases, leading to an increase in the value of k_2 as Ar became more electron withdrawing; in fact the opposite trend is observed. Mechanism (c) has been observed in



Scheme 3.

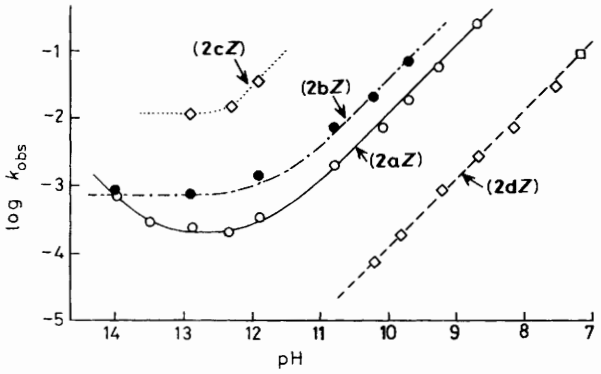
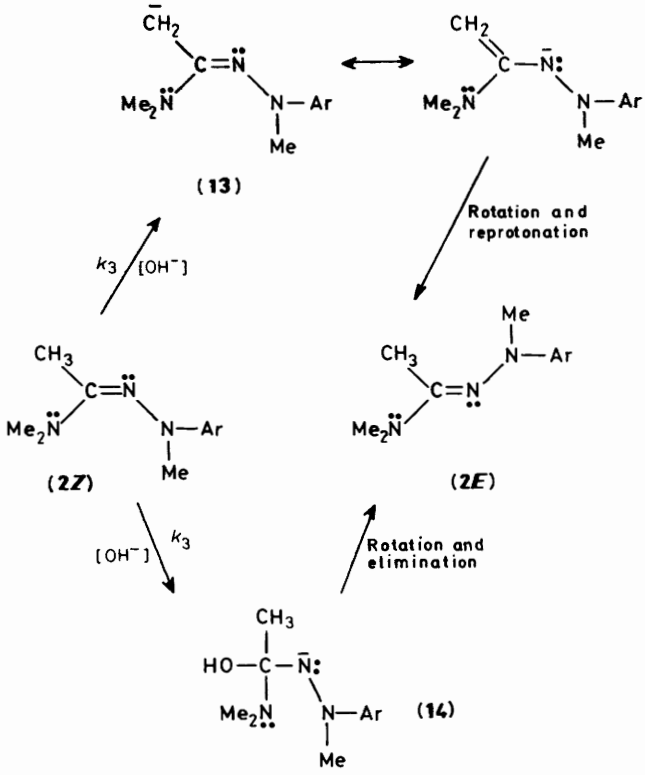


Figure. Plots of the observed rates of *Z*- to *E*-isomerisation of the amidines (**2**) [at 25 °C in H_2O (μ 1.0); $k_{obs.}/s^{-1}$]



Scheme 4.

cases such as the acetimidoyl halides[8] where the substituent on the imidoyl carbon is electron withdrawing. It is unlikely however that this is the major pathway in the case of the amidine (**2aZ**) since when the isomerisation was carried out in dioxane–D_2O in the presence of 10^{-2}M-HO^-, only 12% mono-deuteriation was noted in the product. Under the conditions, >50% of the reaction flux occurs *via* the pH-independent pathway so that if (c) were the sole operative pathway then 50% (at a minimum) of the production would have been mono-deuteriated at the acetyl position. We therefore conclude that pathway (b) involving inversion of the imino nitrogen lone pair is the most likely for pH-independent isomerisation. The observed substituent effects on k_2 are quite characteristic and consistent with this mechanism. Thus k_2 decreases as the electron-withdrawing power of the Ar group increases. It has been shown that when a group [such as N(Me) in the present instance] is interposed between the imino nitrogen and the aryl group which suppresses direct resonance interaction, the inductive effect dominates;[9] this is also in line with theoretical calculations for isomerisation of related imine systems.[10]

In comparing the values of k_2 for (**2**) with the related isoimides [**1**; R^1 = Me, Bu^t, and Ph; R^2 = –N(Me)-2,4-$(NO_2)_2C_6H_3$; X = AcO] and the hydrazonoyl ethers (**1**; X = MeO) it is clear, when allowance is made for temperature, that the overall rate of inversion varies in the following order as the group X is changed: Me_2N > $O(CH_2CH_2)_2N$ > MeO > AcO.

As seen from the Figure, at pH > 13 there is evidence for an increased reaction rate for the amidine (**2a**) [and possibly for (**2b**)]. Although this rate enhancement was only observed for (**2aZ**) at pH 13.5 and 14.0, it was reproducible and outside the experimental error even at pH 13.5. Such base catalysis of isomerisation of amidines has not been previously observed. The fact that the reaction was indeed isomerisation about the C=N bond and not, for example, base-catalysed hydrolysis of the amidine was shown by the typical u.v. spectrum of the *E*-amidine obtained on completion of reaction. The *E*-amidine was also isolated quantitatively when (**2a**) was treated on a large scale in 1:5 dioxane–water in the presence of 1.0M-NaOH. The dioxane was used to increase the solubility of the substrate and parallel kinetic studies indicated that base catalysis is also observed under these conditions so that > 50% of the reaction flux would occur *via* this pathway in the presence of 1.0M-HO^-. The expected mechanism of isomerisation is rate-determining removal of a proton from the *C*-methyl group to give the anion (**13**) which rapidly undergoes isomerisation and reprotonation (see Scheme 4). However, when the reaction was repeated in the presence of D_2O–DO^-, only 12% of the product amidine molecules contained deuterium, which would appear to rule this out as the major pathway. We therefore favour direct reversible addition of HO^- to the C=N bond [to (**14**)] as the catalytic

mode. It is noted that this mechanism is important only for the amidine (**5a**) which has the most strongly electron-withdrawing substituent.

Conclusions.—The acetamidines (**2a—c**) show a range of isomerisation mechanisms: acid catalysed, base catalysed, and uncatalysed. Acid-catalysed isomerisation of *Z* to *E* forms is so fast that the *Z*-amidines can only be isolated at high pH. Isomerisation *via* the acid-catalysed pathway is faster than that observed for amidoximes mainly due to the lower basicity of the latter. Uncatalysed isomerisation occurs over a limited (high) pH range and probably involves rate-determining nitrogen inversion. The unique base-catalysed pathway observed for (**2a**) may occur only when the imine system carries strongly electron-withdrawing groups on nitrogen and is observed when the other mechanisms are suppressed. Although it occurs only at the margin (highest pH, most electron-withdrawing substituent) in the present instance, it deserves further study.

Experimental

N-(2,4-*Dinitro*-N′-*methylanilino*)*ethanimidoyl Chloride* (**3a**).—A mixture of *N*-(2,4-dinitro-*N*′-methylanilino)ethanamide (5.00 g, 19.7 mmol), phosphorus pentachloride (4.10 g, 19.7 mmol), and dichloromethane (10 ml) was heated at reflux for 10 min to give a dark solution. Concentration *in vacuo* and crystallisation of the residual oil from 1:1 diethyl ether–dichloromethane gave the *chloride* (2.00 g, 7.3 mmol, 37%). A sample was recrystallised from benzene as yellow crystals (Found: C, 39.6; H, 3.1; N, 20.6; Cl, 13.1. $C_9H_9ClN_4O_4$ requires C, 39.6; H, 3.3; N, 20.6; Cl, 13.0%); δ($CDCl_3$) 2.55 (s, MeC=N), 3.44 (s, ArNMe), 7.35 (d, 6′-H, *J* 9 Hz), 8.36 (dd, 5′-H, *J* 9 and 2 Hz), and 8.62 (d, 3′-H, *J* 2 Hz); $\lambda_{max.}$ (dioxane) 357 nm (log ε 4.43).

N-(N′-*Methyl*-4-*nitroanilino*)*ethanimidoyl Chloride* (**3b**).—A mixture of *N*-(*N*′-methyl-4-nitroanilino)ethanamide (3.00 g, 14.3 mmol), phosphorus pentachloride (3.10 g, 14.9 mmol), and dichloromethane (20 ml) was allowed to react until a clear brown solution resulted. Concentration *in vacuo* and crystallisation from diethyl ether yielded the chloride as a yellow solid (0.98 g, 4.3 mmol, 30%), δ($CDCl_3$) 2.55 (s, MeC=N), 3.35 (s, ArNMe), 6.93 (d, 2′-, 6′-H, *J* 9 Hz), and 8.15 (d, 3′-, 5′-H, *J* 9 Hz); $\lambda_{max.}$(dioxane) 360 nm (log ε 3.12).

N-(N′-*Methylanilino*)*ethanimidoyl Chloride* (**3c**).—A mixture of *N*-(*N*′-methylanilino)ethanamide (3.00 g, 19.0 mmol), phosphorus pentachloride (3.90 g, 19.0 mmol), and dichloromethane (10 ml) reacted vigorously. Concentration *in vacuo* and distillation at 78—85 °C (0.2 mmHg) yielded the *product* as a yellow oil (2.10 g, 11.5 mmol, 64%) (Found: C, 59.0; H, 6.2; N, 15.2; Cl, 20.2. $C_9H_{11}ClN_2$ requires C, 59.2; H, 6.1; N, 15.3; Cl, 19.4%); δ($CDCl_3$) 2.46 (s, MeC=N), 3.20 (s, ArNMe), and 6.90—7.40 (m, Ph); $\lambda_{max.}$(dioxane) 285 nm (log ε 3.75).

Hydrolysis of Ethanimidoyl Chlorides. Kinetic Method.—In general *ca.* 5 μl of *ca.* 0.1M solution of the halide in dry dioxane was injected into dioxane–water mixtures in a 3 ml cuvette. The subsequent reaction was monitored by u.v., at a suitable wavelength. Product analysis (formation of the corresponding hydrazides) was by u.v., the initial and final spectra being measured between 200 nm and 500 nm (using methods previously described).

(Z)-N,N-*Dimethyl*-N′-(2,4-*dinitro*-N″-*methylanilino*)*ethanimidamide* (**2a*Z***).—*N*-(2,4-Dinitro-*N*′-methylanilino)ethanimidoyl chloride (200 mg, 0.73 mmol) was added to a mixture of 50% dimethylamine in water (13 ml) and acetone (25 ml) and stirred for 45 min at 0 °C. Some acetone was removed *in vacuo* at 0 °C for 15 min and the solution was then extracted (quickly at room temperature) with diethyl ether. The ether extract was then dried (Na_2SO_4) and concentrated *in vacuo* to yield a crude red solid. Recrystallisation from methanol at −70 to 0 °C gave the *product* (**2a*Z***) as a red solid, m.p. 70—75 °C (followed by resolidification and remelting at 118—121 °C) (Found: C, 46.8; H, 5.3; N, 24.6. $C_{11}H_{15}N_5O_4$ requires C, 47.0; H, 5.4; N, 24.9%); δ($CDCl_3$) 2.02 (s, MeC=N), 3.10 (s, Me_2NC), 3.15 (s, ArNMe), 7.03 (d, 6′-H, *J* 10 Hz), 8.24 (dd, 5′-H, *J* 10 and 2 Hz), and 8.55 (d, 3′-H, *J* 2 Hz), $\lambda_{max.}$(dioxane) 406 nm (log ε 4.23) (420 nm in 1.0M-NaOH–H_2O).

Isomerisation of (**2a*Z***) *to* (**2a*E***) *in* $CDCl_3$.—A sample of (**2a*Z***) in $CDCl_3$ was converted into (**2a*E***) (as identified by n.m.r., see below) over 1—3 days. No other product was detected by n.m.r.

(E)-N,N-*Dimethyl*-N′-(2,4-*dinitro*-N″-*methylanilino*)*ethanimidamide* (**2a*E***).—A solution of (**2a*Z***) (100 mg) in dioxane (20 ml) was added to a solution of Na_2CO_3 (0.13 g, 1.23 mmol), $NaHCO_3$ (0.10 g, 1.19 mmol), and KCl (8.59 g, 0.1152 mol) in water (100 ml). The resultant solution showed pH 9.9, and it was stirred for 40 min at 20 °C. After concentration *in vacuo* at 35 °C for 40 min, a red precipitate was collected. A u.v. analysis of the filtrate showed it to contain <3% of any material with $\lambda_{max.}$ 300—500 nm. Recrystallisation of the solid from methanol gave the *product* (**5a*E***) as a red solid, m.p. 122 °C (Found: C, 46.9; H, 5.4; N, 24.7. $C_{11}H_{13}N_3O_4$ requires C, 47.0; H, 5.4; N, 24.9%); δ($CDCl_3$) 2.10 (s, MeC=N), 3.02 (s, Me_2NC), 3.15 (s, ArNMe), 7.04 (d, 6′-H, *J* 10 Hz), 8.17 (dd, 5′-H, *J* 10 and 2 Hz), and 8.53 (d, 3′-H, *J* 2 Hz); $\lambda_{max.}$(dioxane) 401 nm (log ε 4.38) (413 nm in 1.0M-NaOH–H_2O).

N,N-*Dimethyl*-N′-(N″-*methyl*-4-*nitroanilino*)*ethanimidamide* (**2b**).—The halide (**3b**) (100 mg, 0.42 mmol) was added to a mixture of 26% dimethylamine in water (7 ml) and acetone (7 ml) and stirred at 0 °C for 10 min. The solution was then concentrated *in vacuo* at 15 °C for 5 min, extracted with diethyl ether, and dried (K_2CO_3). The extract was then concentrated *in vacuo* at 15 °C to give a red oil. N.m.r. revealed the presence of two isomers of the amidine (**2b**): *Z*-isomer, δ 2.15 (s, MeC=N), 2.94 (s, Me_2N), 3.15 (s, ArNMe), 6.73 (d, 2′-, 6′-H, *J* 10 Hz), and 8.12 (d, 3′-, 5′-H, *J* 10 Hz); *E*-isomer, δ 1.95 (s, MeC=N), 3.12 (s, Me_2N), 3.22 (s, ArNMe), 6.63 (d, 2′-, 6′-H, *J* 10 Hz), and 8.10 (d, 3′-, 5′-H, *J* 10 Hz). Initially the ratio of (**2b*Z***):(**2b*E***) was 2:1 but after 5 min at 25 °C this had changed to 1:1.5 and after 30 min only (**2b*E***) was present.

The E-*isomer* (**2b*E***) was recrystallised from methanol as a red solid (Found: C, 55.5; H, 7.0; N, 23.4. $C_{11}H_{16}N_4O_2$ requires C, 55.9; H, 6.8; N, 23.7%).

N,N-*Morpholino*-N′-(2,4-*dinitro*-N″-*methylanilino*)*ethanimidamide* (**2d**).—The halide (**3a**) (0.5 g, 1.82 mmol) was added to a mixture of morpholine (100 ml), acetone (100 ml), and water (300 ml). After stirring at 10 °C for 30 min (until t.l.c. showed no halide present) ethereal work-up including washing with dilute aqueous NaOH yielded an orange solid (0.11 g, 0.34 mmol, 19%). N.m.r. analysis showed this to be the *Z*-isomer, δ 2.05 (s, MeC=N), 3.20 (s, ArNMe), 3.60—3.70 (m, CH_2N or morpholino), 3.77—3.90 (m, CH_2O or morpholino), and 7.0—8.4 (2,4-dinitrophenyl). After 65 h the *Z*-isomer in $CDCl_3$ had converted in 70% into the *E*-isomer (**2d*E***). An attempt to recrystallise the *Z*-isomer from ethanol yielded only the E-*isomer*, δ($CDCl_3$) 2.12 (s, MeC=N), 3.18 (s, ArNMe), 3.30—3.60 (m, CH_2N of morpholino group), 3.70—3.90 (m, CH_2O of morpholino group), and 6.9—8.6 (2,4-dinitrophenyl) (Found: C, 48.2; H, 5.3;

N, 21.9. $C_{13}H_{17}N_5O_5$ requires C, 48.3; H, 5.3; N, 21.7%); $\lambda_{max.}$ (aqueous carbonate and KCl; pH 9.3) 411 nm.

Reaction of (**2a*Z***) *in* NaOH–D_2O–*Dioxane.*—A typical experiment was as follows. The amidine (**2a*Z***) (30 mg) was added to a mixture of NaOH (1.44 g, 0.036 mol), D_2O (30 ml), and dioxane (6 ml), and the mixture was stirred at 20 °C for 2 h, at which time u.v. showed only the *E*-amidine (**2a*E***). The mixture was concentrated *in vacuo* and extracted into diethyl ether. After drying (K_2CO_3), concentration *in vacuo* yielded a red oil. The aqueous layer was seen to contain only a trace of material by u.v. analysis and was discarded. A comparison of the mass spectrum of this material with that of an authentic sample of (**2a*E***) showed that the oil, while almost identical to the authentic sample, showed an enhancement of the $M + 1$ peak, indicating that *ca.* 12% deuterium incorporation had occurred. An n.m.r. spectrum of the oil showed it to be (**5a*E***), but no appreciable deuteriation was detectable by this method.

Isomerisation of Amidines. Kinetic Method.—The reactions were followed by monitoring changes in u.v. absorbance of the *E*- and *Z*-amidines. Since the absorbance changes were small (0.1—0.2 absorbance units at the concentrations used) the expanded scale (0.5 or 0.2 unit full scale) of the Cary 219 u.v. spectrophotometer was used. Reactions were run in water at 25 °C (except in two cases noted which were run in 1 : 5 dioxane–water) and buffered using aqueous KOH, and carbonate, phosphate, and borate buffers in appropriate pH ranges. The pH was measured [using a Radiometer pH meter (PHM 25), equipped with a Metrohm 125 combined electrode] before and after a kinetic run and discarded if pH drift was > 0.1 unit. Since buffer catalysis was negligible, all reactions were measured in the presence of 0.02M-buffer and the ionic strength brought up to 1.0 using KCl. Reaction was initiated by injecting 10 μl of a 0.1M solution of the amidine (**2**) in dioxane into 3 ml of the buffered solution in the cell at 25 °C. The isomerisation of the amidine (**2c*Z***) was so rapid that this amidine was difficult to isolate (in the *Z*-form), and so the rates of this isomerisation at pH 11.9 and 12.3 are those obtained by injection of the halide (**3c**) into 0.5 and 2.5% aqueous morpholine respectively. The solvolysis date for compound (**3c**) indicates that reaction of (**3c**) with dimethylamine will be very fast, and so the isomerisation of (**2c*Z***) to (**2c*E***) can be observed subsequently. Rate constants were computed graphically using experimental infinity values and were reproducible to ±3%.

The pK_a values for the conjugate acids of (**2a*E***) and (**2b*E***) were measured by a spectrophotometric titration. Standard amounts (20 μl of 0.1M solution in dioxane) of the amidine were introduced into 3.0 ml of a buffered aqueous solution (acetate, phosphate, and borate buffers) in the pH range 5—9 (0.2 pH unit intervals). The resultant absorbance–pH plots were compared with model titration curves to give the pK_a values.

N,N-*Dimethyl*-N′-(N″-*methylanilino*)*ethanimidamide* (**2c**).—The halide (**3c**) (0.50 g, 2.74 mmol) was added, at 0 °C with stirring to a mixture of 50% dimethyl amine–water (32 ml) and acetone (60 ml). After 1 h, the mixture was concentrated *in vacuo* at 10 °C and then extracted with ether. Drying (K_2CO_3) and concentration *in vacuo* at 0 °C yielded (**2c*E***) as a yellow oil, and δ($CDCl_3$) 2.20 (s, MeC=N), 2.97 (s, ArNMe), 3.00 (s, Me_2N), and 6.6—7.4 (m, Ph). Addition of a catalytic amount of CF_3CO_2H caused no change in the spectrum, nor did standing in $CDCl_3$ for 22 h, clearly showing that this is the more stable *E*-isomer (**2c*E***).

Acknowledgements

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