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STUDIES ON THE MECHANISM OF THE NITRAMINOPYRIDINE REARRANGEMENT

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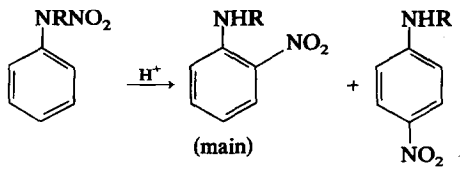
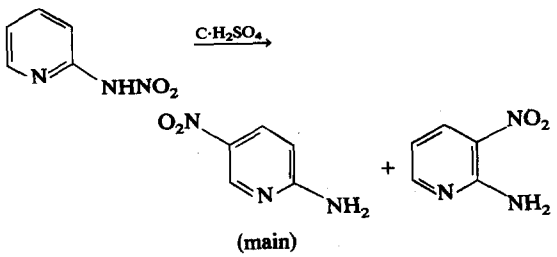
Abstract—The rearrangement of 2-nitraminopyridine and of its 3-,4-,5-,6-methyl,5-bromo, and 3-nitro derivatives in conc sulphuric acid has been investigated. 5-Methyl-2-nitraminopyridine appears to react by a different mechanism from the rest, as a considerable amount of 5-methyl-2-pyridone is also formed. For the others, results at variance with other reports are presented. *trans*-Nitration studies have established that free nitronium ions are produced, second order kinetics are followed, and the rate is equally enhanced by the addition of aminopyridine or potassium nitrate. However, the observation of a 1:1.5 mixture of 3- and 5-nitro products from 4-methyl-2-nitraminopyridine makes a normal S_EAr mechanism unlikely.

The aromatic nitramine rearrangement has been long known and much studied.[1,2] The mechanism is still disputed but it is accepted that the reaction is almost always intramolecular, with breakdown of



the protonated nitramine occurring as the rate determining step, and does not involve formation of nitronium ions.

The same reaction occurs in heterocyclic compounds and is best known in 2-nitraminopyridines. These nitramino compounds are more stable than



their phenyl analogs and rearrangement is generally carried out in concentrated sulphuric acid. Relatively little work has been reported on the mechanism of the reaction in the pyridine series. The preponderance of *para* product suggests an intermolecular pathway. When the rearrangement was carried out in the presence of acetanilide, however, only a small amount of nitroacetanilide was formed,[3] and ^{15}N labelling studies were also interpreted as favouring an intramolecular mechanism.[4]

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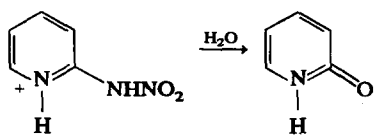
The first kinetic study, only recently reported,[5] found that the rearrangement of 2-nitramino pyridine was first order in nitramine, had a maximum rate in 82% sulphuric acid and was speeded up by electron donating ring substituents (as is the phenyl nitramine rearrangement.)[6]

In this paper, we report on a reinvestigation of some facets of this rearrangement and present results and interpretations at variance with those of recent work. The compounds studied were 2-nitraminopyridine and its 3-,4-,5-,6-methyl, 5-bromo, and 3-nitro derivatives.

RESULTS AND DISCUSSION

Product studies. Our investigations made use of both NMR and UV/VIS spectroscopy and were confined to reactions in "concentrated" sulphuric acid (this was 92.2% by weight). We observed that, in more aqueous acid, the rearrangement is complicated by the simultaneous formation of the corresponding pyridone, probably formed by nucleophilic displacement of the activated nitramino substituent. For example, 2-nitraminopyridine gives 33% 2-



pyridone in 80% sulphuric acid and 80% pyridone in 70% acid. Thus, the previous kinetic study[5] on the effect of acid concentration on the rearrangement is suspect since no account was apparently taken of this competing reaction.

It was possible, by NMR spectroscopy of the product mixtures in acid, to distinguish the rearrangement products and pyridones (chemical shift data are in Table 1). With one exception, all compounds studied underwent reaction in 92% sulphuric acid at room temperature [complete by the time of insertion of the tube in the probe, except

Table 1. Chemical shifts, in c. sulphuric acid, of nitramine rearrangement products

2-Amino pyridine	δ[a]	Mult.	J(Hz)	Proton
3-NO_2	3.10	2d	7.0	H5
	4.12	dd	7.0,1.3	H4
	4.97	dd	7.0,1.3	H6
5-NO_2	3.00	d	9.4	H3
	4.43	dd	9.4,2.0	H4
	4.73	d	2.0	H6
3-Me-5-NO_2	-1.87	s		Me
	4.23	d	1.3	H4
	4.57	d	1.3	H6
4-Me-3-NO_2	-1.43	s		Me
	2.87	d	7.2	H5
	3.77	d	7.2	H6
4-Me-5-NO_2	-1.48	s		Me
	2.80	s		H3
	4.67	s		H6
5-Br-3-NO_2	4.08	d	1.8	H4
	4.93	d	1.8	H6
6-Me-3-NO_2	-1.50	s		Me
	2.83	d	9.6	H5
	4.77	d	9.6	H4
6-Me-5-NO_2	-1.27	s		Me
	2.83	d	9.6	H3
	4.42	d	9.6	H4
5-Me-3-NO_2	-1.83	s		Me
	3.85	d	1.9	H4
	4.78	d	1.9	H6
3,5-$(NO_2)_2$	4.87	bs		H6
	5.35	d	2.0	H4
5-Me	-1.57	s		Me
	3.98	d	8.0	H3
	4.43	s		H6
	4.50	d	8.0	H4
2-pyridone	3.27	m		
	4.00	m		
5-Me-	-1.83	s		Me
2-pyridone	3.07	dd	9.0,2.0	H3
	3.68	bd	7	H6
	4.02	dd	9.0,2.0	H4

[a] In ppm relative to dioxan; positive values are downfield.

for the 5-bromo (few min) and 3-nitro (required warming) compounds] to give a clean conversion to rearrangement products with no significant pyridone formation.

The exception was 5-methyl-2-nitraminopyridine. At the *ca* 0.3 M concentration used in the NMR study, a rapid reaction occurred to give the rearrangement product, 2-amino-5-methyl-3-nitropyridine, and 2-amino-5-methylpyridine in the ratio 1.7:1. The former stayed unchanged while the latter was converted within 10 min to 5-methyl-2-pyridone. At the 10^{-4} M concentration used in the UV monitoring, denitration of the nitramine occurred but there was very little rearrangement product and no conversion of amine to pyridone. It is evident that the pyridone in this reaction arises from the formation of nitrous acid. It was demonstrated that sodium nitrite would react with the amine to produce the pyridone at the 0.3 M scale, but not at 10^{-4} M. It appears that reaction of this nitramine has features in common with the phenylnitramine rearrangement where denitrated nitramine and nitrous acid have been detected.[7] We have shown now that this pyridone formation is the reason that the isolated yield of 2-amino-5-methyl-3-nitropyridine from preparative scale rearrangement[8] (33%) was much lower than the product yields from the other Me isomers (>70%). Because of this behaviour we omitted the 5-Me compound from our kinetic study.

Where more than one rearrangement product was possible, isomer ratios were determined directly and were as follows (5-position: 3-position): 10:1 (2-aminopyridine), 2.8:1 (2-amino-6-methylpyridine), and 1.5:1 (2-amino-4-methylpyridine). These figures are discussed below.

trans-Nitration studies. The nitration of added mesitylene was observed during the rearrangement of 2-nitraminothiazole in concentrated sulphuric acid.[9] However, only a low yield of nitroacetanilides was obtained when 2-nitraminopyridine was rearranged in the presence of acetanilide[3]

and this result supports an intramolecular mechanism.

We initially carried out some *trans*-nitration studies of a different sort by rearranging a nitraminopyridine in the presence of another aminopyridine. It was possible, by suitable choice of substrates, to distinguish between the possible products by NMR spectroscopy. Thus, 5-bromo-2-nitraminopyridine, when rearranged in the presence of a slight molar excess of 2-amino-3-methylpyridine, gave only 2-amino-3-methyl-5-nitropyridine. Similarly, 3-methyl-2-nitraminopyridine was rearranged in the presence of various amounts of 2-amino-6-methylpyridine (4.9, 2.2, 1.0 molar ratio). The final ratio of nitroamino products in each case (4.3, 2.0, 1.0) was close to the reactant ratio, in accord with the similar rates of rearrangement of the two possible nitramines (see kinetic section). The internal product ratio from 2-amino-6-methyl pyridine was the same as from rearrangement of 6-methyl-2-nitraminopyridine (2.8 ± 0.2).

These results could be most simply explained by the formation of free nitronium ions, as required by a completely intermolecular mechanism. As such a conclusion was at variance with the acetanilide *trans*-nitration results mentioned above, we repeated this reaction.

It was qualitatively established that, under the reaction conditions, acetanilide was nitrated much faster than was an aminopyridine. When 3-methyl-2-nitraminopyridine was rearranged in the presence of an equimolar amount of acetanilide, NMR analysis showed a clean reaction with the products being 3-methyl-2-aminopyridine and *p*-nitroacetanilide (which was subsequently isolated).

We can only conclude that the results obtained previously were due to the reaction being apparently conducted on a relatively large scale at room temperature. Such conditions could give rise to vigorous local heating and exothermic decomposition at the point of contact of nitramine and acid.

The *trans*-nitration studies are therefore completely compatible with dissociation of the (protonated) nitramine to provide amine and nitronium ion.

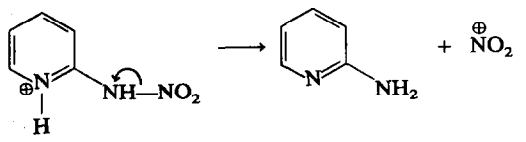
Kinetics. We noted that the rearrangement proceeded much faster at 0.3 M concentration (NMR) than at 10^{-4} M concentration (UV) of nitramine. This observation was inconsistent with the reported first order kinetics[5] and we therefore sought to clarify this aspect by carrying out a detailed kinetic study. Reactions were confined to 92.2% sulphuric acid because of the problems associated with pyridone formation in more aqueous acid solutions.

It was early established that the rate of formation of nitroamino product was dependent on initial nitramine concentration [$t_{1/2}$ = 158 min (0.465×10^{-4} M), 54 min (1.86×10^{-4} M) at 30° for 3-methyl-2-nitraminopyridine] but that a simple integral kinetic order did not apply. However, it was also found (by comparison of experimental and theoretical infinity values) that the yield of rearrangement product was much lower (e.g. *ca* 40% for 5-bromo-2-nitraminopyridine) than was obtained at the higher concentrations of NMR and preparative scale reactions. In these circumstances we then considered only initial rates and obtained the order of reaction for three compounds from the variation in initial rate with added nitramine from the expression[10] $\log (dp/dt)_0 = n \log [\text{nitramine}] + C$. Values of n = 1.85 (6-Me), 2.0 (3-Me), and 2.0 (5-Br) were obtained. Dissociation of the nitramine into nitronium ion and amine fragments prior to the rate determining process would give rise to this apparent second order dependence on nitramine.

This interpretation was further supported by studying the effect of added amine and potassium nitrate. In both cases, the reaction was speeded up, product yields were high, pseudo first order kinetics were now obeyed and, importantly, the derived second order rate constants from the addition of either amine or potassium nitrate were in good agreement. This is shown in detail for two compounds in Table 2 and average rate constants for all compounds obtained in this way are summarised in Table 3. The product isomer ratio from the rearrangement of 6-methyl-2-nitraminopyridine was not altered by the addition of potassium nitrate.

Mechanism. All the results point to dissociation of the nitramine into amine and nitronium ion and the reaction is therefore intermolecular. It seems likely that, in concentrated acid, dissociation is essentially complete. The UV spectra at the start of kinetic runs agreed with those of the authentic amines and the NMR spectrum of 3-nitro-2-nitraminopyridine (where reaction at room temperature was slow) was identical with that of 2-amino-3-nitropyridine.

The difference between the benzene and pyridine systems requires comment. In protonated phenylnitramine the N—NO_2 bond cleaves toward the NO_2 group. The pyridine system represents a benzene ring containing a strongly electron withdrawing substituent and cleavage in the same direction is



not favoured. It may be that the presence of an electron donating Me group in the 5-position (*para* to the nitramino group) is enough to at least partially switch the mechanism back to benzene like, accounting for the formation of products arising from nitrous acid formation in reaction of this compound.

The simplest explanation for subsequent reaction that accords with the second order kinetics is direct electrophilic nitration on the monoprotonated amine at the most activated 3 and 5 positions. The nitration of 2-dimethylaminopyridine and of its 3-nitro derivative have been suggested to occur by this mechanism in concentrated sulphuric acid.[11] There are similarities between the results for the two reactions. Thus, nitration of 2-dimethylaminopyridine also gives a large preponderance of the 5-nitro product (8:1) and the activation parameters also show the same pattern in the two series (Table 4). It is, however, difficult to reconcile the effect of

Table 2. Rate data for rearrangement of substituted 2-nitraminopyridines at 303 K

Subst.	10^4[nitramine] M	Additive[a] M		$10^4 k_\psi$[b] s^{-1}	$10^2 k_2$ $M^{-1} s^{-1}$
H	1.12	0.0107	A	4.57	4.23
	1.12	0.00535	A	1.99	3.64
	1.12	0.00859	B	3.31	3.80
	1.12	0.0043	B	1.67	3.80
5-Br	3.51	0.00859	B	2.09	2.34
	2.19	0.0043	B	1.04	2.31
	2.63	0.0104	A	2.89	2.71
	2.19	0.0052	A	1.43	2.65

[a] A = Aminopyridine, B = KNO_3 [b] Pseudo first order rate constant

Table 3. Rate data for rearrangement of some substituted 2-nitraminopyridines

Subst.	T(K)	Av. $10^2 k_2 M^{-1} s^{-1}$	Subst.	T(K)	Av. $10^2 k_2 M^{-1} s^{-1}$
H	303	3.87	5-Br	303	2.50
4-Me	303	2.00		319.3	12.8
6-Me	303	13.3		338.5	73.1
3-NO_2	303	0.00861	3-Me	289	4.21
	320	0.0391		303	18.0
	338.5	0.177		310.9	34.6
				319.3	72.7

a 3-nitro substituent on the activation entropy with a common mechanism.

This mechanistic picture is, however, at least for the nitramine reaction, not compatible with the effect of the 4-Me substituent. The 1.5:1 ratio of 5- and 3-nitro products obtained from this compound was quite unexpected when compared with the ratios obtained from the unsubstituted (10:1) and 6-Me (2.8:1) compounds. For a reaction between free nitronium ion and amine entities directly at ring carbon via a σ complex, one would anticipate a greater proportion of 5-nitro product from the 4-Me than from the unsubstituted compound. Consideration of the kinetic results further emphasises this anomaly.

Table 4. Activation parameters

Subst.	$\Delta H^{\neq}_{298}$ (kcal mol^{-1})	$\Delta S^{\neq}_{298}$ (cal K^{-1} mol^{-1})
3-Me[a]	15.9	−9
5-Br[a]	18.9	−3
3-NO_2[a]	16.6	−22
H[b]	13.3	−3.5
3-NO_2[b]	14.1	−22

[a] Nitramine rearrangement in 92% H_2SO_4—this work.
[b] Nitration of 2-dimethylaminopyridine in 97% H_2SO_4—ref. 11.

The second order rate constants quoted have not been corrected for any diprotonation. If only the monoprotonated amine reacts, then the relative k_2 values are not a true reflection of relative rates. This is probably a reason why, for example, the 5-Br substituent has apparently a very small rate retarding effect compared to the unsubstituted compound; the proportion of monoprotonated species would be higher for the 5-Br compound, thereby offsetting the deactivating effect of the substituent to electrophilic ring attack. The various Me substituents would be expected to have little effect on the extent of second protonation. The limited published data supports this statement.[12]

Table 5. Relative rates for nitration at 3- and 5-positions for substituted 2-aminopyridines

Subst.	H	3-Me	4-Me	6-Me
k^3	1	—	2.3	10
k^5	1	5.1	0.34	2.8

The experimental k_2 values may then be combined with the product isomer figures to deduce relative k_2 values for reaction at the 3- and 5-positions (Table 5).

The substituent effects are small, which is surprising for electrophilic aromatic substitution, but, with the one exception, the relative effects accord with expectation. For the 4-methyl compound, however, the 5-position is *deactivated* to reaction. Such a result seems impossible to reconcile with a standard nitration mechanism.

It is therefore necessary to postulate that the nitronium ion and amine react via a different intermediate, the partitioning of which is affected in an unusual way by ring substituents. The "proton-loss" mechanism of Hartshorn and Ridd,[13] is a possibility in this system, but would not obviously produce the observed substituent effect.

Another intriguing possibility is that, except for the 3-nitro compound, an "intermediate" breaks down to first give a 3-nitro σ-complex which then either loses a proton or rearranges to a 5-nitro complex. The nitramine could well be such an intermediate (Scheme 1) and the kinetics would be satisfied if either formation of the nitramine, or its decomposition to the 3-nitro σ complex, was rate determining (provided in the latter case that, as seems likely, the instantaneous concentration of nitramine is very low). The $3 \rightarrow 5$ rearrangement could conceivably be hindered by a 4-substituent, which would account for the greater proportion of 3-nitro product than expected for the 4-Me compound.

This pathway, which is analogous to one proposed for the phenylnitramine rearrangement, though the migrating group is different, could occur even in the case of the 3-Me compound where the initial reaction would represent favourable *ipso* nitration.[14] It is in this field particularly that the rearrangement of nitro σ-complexes is now well documented. It is interesting that reactions of the 3-Me (giving only 5-nitro product) and 5-Br (giving only 3-nitro product) compounds have similar activation parameters. The 3-nitro compound would be too deactivated for this type of initial reaction at the 3-position and, as the markedly different entropy value suggests, a different mechanism would apply. If this mechanism were correct, then the experimental k_2 values would represent (except for the 3-nitro compound) nitration at the 3-position, and the relative values (see Table 3) seem to be not inconsistent with this possibility.

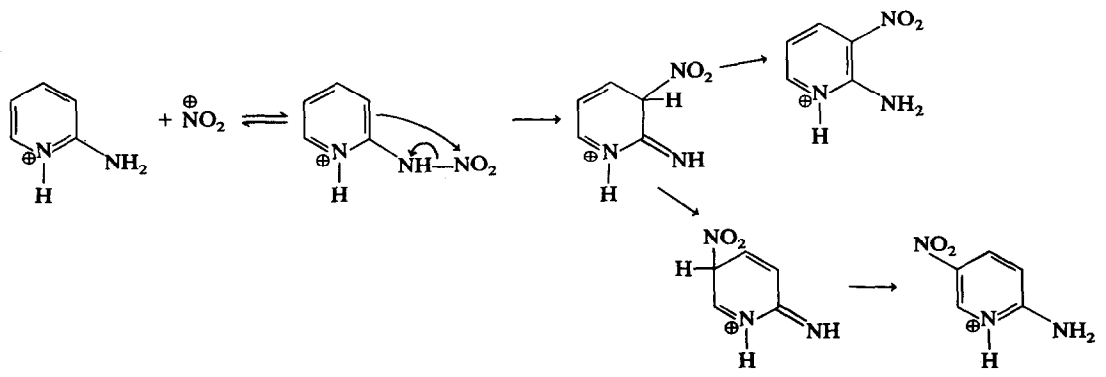
These mechanistic possibilities are conjectural at this stage and more work on the effect of substituents is required. This work has clarified the kinetic nature of the pyridine nitramine rearrangement, and established that dissociation of nitramine to give free nitronium ions occurs. The actual process by which the product nitroamine is formed from the amine and nitronium ion remains an open question.

EXPERIMENTAL

Materials. The aminopyridines were commercial samples and were checked for identity and purity by NMR and m.p. 2-Amino-6-methylpyridine was dried by azeotropic distillation with benzene. The nitramines were all known compounds and were prepared by adding fuming HNO_3 to an ice-cold soln of the amine in conc H_2SO_4. They were recrystallised from aqueous EtOH. The sample of 6-methyl-2-nitraminopyridine had m.p. 165–166° (dec), different from that previously reported[15] (94°). (Found: C, 46.8; H, 4.7; N, 27.6. Calc. for $C_6H_7N_3O_2$: C, 47.1; H, 4.6; N, 27.5). Authentic samples of nitroaminopyridines were obtained from rearrangement of the appropriate nitramine. Where applicable, the 3-nitro product was separated from the 5-nitro isomer by steam distillation. 2-Pyridone was a commercial sample while the 5-Me derivative was obtained by treating the amine with $NaNO_2$ in HSO_4.

The H_2SO_4 was analytical grade and was found to be 92.2% by weight. It was noted that absolute reaction rates varied significantly between various batches of acid of approximately the same composition. All kinetic results reported here were obtained using a single batch of acid.

Product studies. In general, solid nitramine was cautiously added to cold acid and the soln was then allowed to reach room temp. Products from single rearrangements were analysed directly from NMR spectra of the acid solns, recorded on Varian T60 and Perkin-Elmer R32 spectrometers. Dioxan was used as an internal reference (Table 1).



Scheme 1

trans-Nitration products from 3-methyl-2-nitraminopyridine + acetanilide were likewise analysed. The spectrum contained only peaks for 2-amino-3-methylpyridine [δ (dioxan), −1.51 (CH_3), 3.90 (t, H5), 4.42 (d, H4, 6) ppm] and *p*-nitroacetanilide [δ (dioxan), −1.46 (CH_3), 3.55 (d, J = 9 Hz), 4.20 (d, J = 9 Hz) ppm]. When the mixture was poured onto ice, the *p*-nitroacetanilide, m.p. 212° (EtOH) (lit.[16] m.p. 216°) was obtained. *trans*-Nitration reactions involving 3-methyl-2-nitraminopyridine + 2-amino-6-methylpyridine and 5-bromo-2-nitraminopyridine + 2-amino-3-methylpyridine were performed on a 1g scale. The reactions were carried out at room temp, the solution was poured onto ice, neutralised with ammonia, and the resulting yellow precipitate of nitroamines was filtered, dried, and analysed by NMR (in acid—Table 1). It was shown that at least 96% of a nitroamine was obtained by this isolation method, while the amines remained in solution.

An impurity peak partially overlapped the H6 signal of 2-amino-4-methyl-3-nitropyridine in the NMR spectrum of the acid solution from rearrangement of 4-methyl-2-nitraminopyridine. In this case, the free nitroamines were obtained by treatment with ammonia followed by extraction with chloroform. The dried extract was evaporated and the spectrum of the residue was obtained in $CDCl_3$/DMSO soln.

Kinetics. Reactions were monitored using a Varian-Techtron 635 spectrophotometer with thermostatted 1 cm cells. A stock solution of the nitramine in methanol was prepared and a suitable volume of this soln was pipetted into a reaction flask and the MeOH evaporated. Reaction was initiated by adding an appropriate amount of acid or aminopyridine/acid or potassium nitrate/acid. The formation of nitroaminopyridine was followed at the following wavelengths (nm): H, 310; 5-Br, 381; 3-Me, 308; 4-Me, 302; 6-Me, 313; 3-NO_2, 300.

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