Kinetics and Mechanism of the Fischer–Hepp Rearrangement. Part I.[1] Rearrangement of *N*-Nitroso-*N*-methylaniline in Hydrochloric Acid

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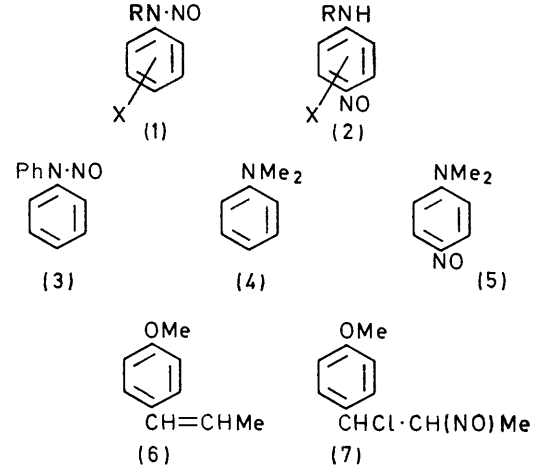
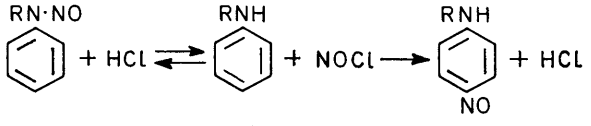
Rate measurements and product analyses have been carried out for the rearrangement of *N*-nitroso-*N*-methylaniline in hydrochloric acid in the acid range 2—8M. The main products were *p*-nitroso-*N*-methylaniline and *N*-methylaniline in amounts which depended on the acidity. The reaction was first-order in the nitrosamine and a linear dependence (slope 1·18) of log (observed rate coefficient) upon $-H_0$ was found up to 6·5M-acid; thereafter the rate became almost independent of the acidity. A solvent isotope effect k_{D_2O} : k_{H_2O} of 2·1 was observed at 3·96M- acid and a ring deuterium isotope effect of 1·7 was found at 5·5 and 7·0M. Rearrangement took place even in the presence of a large excess of urea. These results do not accord with the commonly accepted mechanism involving *C*-nitrosation by nitrosyl chloride but rather suggest that rearrangement occurs intramolecularly by a unimolecular reaction of the protonated nitrosamine. Further it was found that the nitrosamine can transfer the NO group to a suitable acceptor without its becoming kinetically free. This accounts for early observations of cross-nitrosation products.

THE rearrangement of *N*-nitroso secondary aromatic amines (1) to the corresponding *para*-nitroso-isomers (2) has been known for many years following its discovery in 1886 by Fischer and Hepp,[2] and is commonly used as a method of preparation of aromatic *C*-nitroso-compounds. Reaction is usually brought about by hydrogen



chloride in ether or ethanol at room temperature and is quite general[3] for R = alkyl or aryl groups and for a variety of substituents X except when X is *para*. It has been noted that the rearranged product was formed in lower yield in aqueous acid solvents.[4] Better yields of (2) were obtained in hydrochloric acid than in any other strong acid and added sodium nitrite increased the yield of rearranged product.[5] There are many instances in the literature where cross-nitrosation had been observed,[6] *e.g.* *N*-methyl-*N*-nitroso-*p*-toluidine does not undergo rearrangement but will nitrosate added diphenylamine whilst rearrangement of *N*-nitrosodiphenylamine (3) in the presence of the dimethylaniline (4) leads to the formation of some compound (5). Further, the reaction of *N*-nitroso-*N*-methylaniline in hydrogen chloride in the presence of the reactive olefin (6) gave the nitrosyl chloride adduct (7) of the olefin. On the basis of these cross-nitrosations and on the apparent specificity of hydrogen chloride, Houben[5] suggested that the rearrangement was brought about by a reversibly denitrosation of the nitrosamine followed by *C*-nitrosation of the secondary amine thus formed by the nitrosyl chloride also produced, as shown in Scheme 1. This mechanism, although not specifically required by the available experimental evidence, has nevertheless over the years become the accepted mechanism for this rearrangement by reviewers[3] and by writers of textbooks in organic chemistry.[7] The fact that only the product of denitrosation was later found when the reaction was carried out in a large excess of urea at elevated temperatures[8] was naturally taken as supporting evidence.



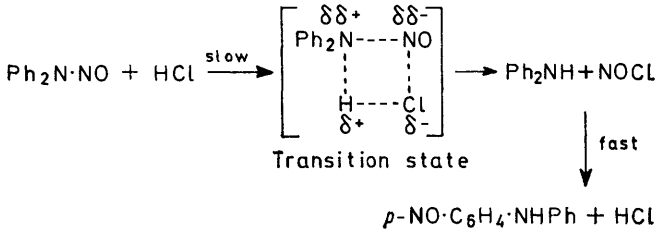
SCHEME 1

However in the absence of rate data showing a dependence on chloride ion the apparent preference for hydrogen chloride may well be due to other factors. In addition there is the very real possibility that the nitrosamine (or its protonated form) can itself act as a nitrosating agent without forming free nitrous acid or a nitrosyl halide. This of course would account perfectly well for the observed cross-nitrosations and for the reaction with urea. The purpose of this work was to establish the mechanism for this rearrangement and to compare this with established mechanisms for other aromatic rearrangements, such as the Orton, benzidine, and nitramine rearrangements.

During the course of our work a publication appeared on the kinetics of the rearrangement of *N*-nitrosodiphenylamine[9] in methanol containing hydrogen chloride.

[1] For a preliminary account of this work see T. D. B. Morgan and D. L. H. Williams, *Chem. Comm.*, 1970, 1671.
[2] O. Fischer and E. Hepp, *Ber.*, 1886, **19**, 2991.
[3] H. J. Shine, 'Aromatic Rearrangements,' Elsevier, Amsterdam, 1967, pp. 231—235, and references cited therein.
[4] O. Fischer and P. Neber, *Ber.*, 1912, **45**, 1093.
[5] J. Houben, *Ber.*, 1913, **46**, 3984.
[6] P. W. Neber and H. Rauscher, *Annalen*, 1942, **550**, 182.
[7] I. L. Finar, 'Organic Chemistry,' Longmans, London, 1967, vol. 1, p. 622, and many other texts.
[8] W. Macmillen and T. H. Reade, *J. Chem. Soc.*, 1929, 585.
[9] B. T. Baliga, *J. Org. Chem.*, 1970, **35**, 2031.

The reaction was first-order in both the nitrosamine and hydrogen chloride and almost independent of added chloride ion. The author proposed the formation of the free amine and nitrosyl chloride in a slow step *via* a four-centre transition state, followed by a fast *C*-nitrosation as shown in Scheme 2. This will be discussed in connection with our results.



SCHEME 2

EXPERIMENTAL

Preparation of Materials.—*N*-Nitroso-*N*-methylaniline was prepared by nitrosation of *N*-methylaniline.[10] It was purified by distillation and by chromatography on alumina in benzene before use.

2,4,6-Trideuterio-*N*-nitroso-*N*-methylaniline was prepared as follows. Hydrogen chloride was passed into a solution of *N*-methylaniline (12 g) in ether until all the salt had been precipitated. This was filtered off, dried, and added to D_2O residues (*ca.* 90% D) to exchange the amino-hydrogen atoms; the water was then pumped off. Deuterium oxide (100 ml; 99·8% D) was added and the whole was left in a thermostat at 80° for a week. The solution was made alkaline with sodium carbonate and then extracted with ether. After removal of the solvent the remaining amine was converted into the *N*-nitroso-compound. N.m.r. and mass spectral analysis showed that the material contained *ca.* 85% trideuterio- and *ca.* 15% dideuterio-*N*-nitroso-*N*-methylaniline. The mass spectrum of the product of rearrangement showed that there was present *ca.* 2 deuterium atoms per molecule.

Product Analyses.—These product analyses were carried out in water or aqueous ethanol at room temperature or, in some cases, at 31°. The acid was neutralised with sodium carbonate and the products were extracted with benzene or chloroform and purified by column chromatography on alumina with benzene as eluant. There were recovered (in amounts depending on the state at which the reaction was stopped and also on the acidity of the reaction medium) *N*-methylaniline and unchanged *N*-nitroso-*N*-methylaniline (which were eluted together but could be separated by aqueous acid extraction from benzene) together with the green rearranged product *p*-nitroso-*N*-methylaniline. Small quantities of a yellow solid product were isolated, particularly when the reaction mixture contained added nitrite. This was recrystallised from light petroleum (b.p. 40—60°) and identified as *p*-nitro-*N*-nitroso-*N*-methylaniline; it had m.p. 102° (lit., 104°) [Found: C, 46·6; H, 4·0; N, 22·7%; *M* (osmometer), 182, 179. Calc. for $C_7H_7N_3O_3$: C, 46·4; H, 3·9; N, 23·2%; *M*, 181].

Deuterium Exchange.—Equivalent amounts (*ca.* 1×10^{-3} mol) of *N*-methylaniline and 2,4,6-trideuteriated *N*-nitroso-*N*-methylaniline were added to a solution of hydrochloric acid (1M; 500 ml) containing urea (*ca.* 15×10^{-3} mol) at room temperature. After 5·0 min the acid was neutralised (Na_2CO_3) and the solution was extracted with benzene. The benzene solution was extracted twice with dilute sulphuric acid after which the benzene was removed and the residual *N*-nitroso-*N*-methylaniline was analysed by i.r. spectroscopy. The acid layer was washed with benzene and then made alkaline (Na_2CO_3); the *N*-methylaniline recovered by benzene extraction was analysed for deuterium by i.r. spectroscopy. The above procedure was repeated using 2·5M- and 4·0M-HCl.

^{15}N *Experiments.*—*N*-Nitroso-*N*-methylaniline was added to a hydrochloric acid solution (and also in 1 : 1 ethanol–water) containing a slight excess of sodium [^{15}N]nitrite (*ca.* 30% ^{15}N enrichment). Aliquots were removed at appropriate time intervals throughout the reaction and unchanged starting material and rearranged product were recovered and separated. The latter was examined for ^{15}N by mass spectrometry, the relative peak heights at 136/137 being measured; difficulties were, however, encountered with the *N*-nitrosamine. It was found to be more convenient to convert it into *p*-nitroso-*N*-methylaniline in a separate experiment (HCl in ethanol) and to examine the rearranged product for ^{15}N.

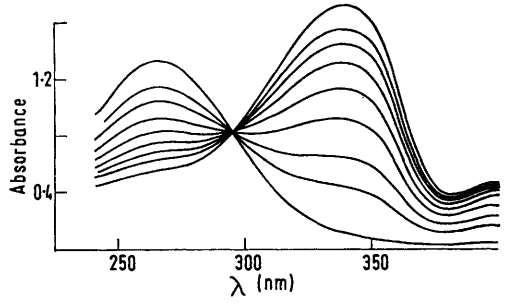


FIGURE 1 Typical run at low acidity *

* For clarity only every third trace is reproduced.

Kinetic Measurements.—The kinetic measurements were carried out in a Unicam SP 800 recording spectrophotometer in cells thermostatted at 31°. The reactant (*N*-nitroso-*N*-methylaniline) concentration was in the range $2—6 \times 10^{-4}$M. At each time point the spectrum was scanned from 450 to 250 nm. Product formation (*p*-nitroso-*N*-methylaniline) was observed by increase in the absorbance at 340 nm (the reactant peak at *ca.* 260 nm decreased with time). Good isosbestic points were obtained in all runs. A typical run is shown in Figure 1. Above *ca.* 6M-acid the maximum absorbance due to the reactant was shifted to lower wavelength, corresponding to significant protonation of the nitrosamine. A small peak from an unidentified product was observed in all runs at 450 nm. Since the product was somewhat unstable in the reaction medium over longer periods it was not possible to use an observed infinity value so that the Guggenheim method for determining the rate coefficient was used from the readings of optical density at 340 nm. The rate coefficient in each case was calculated from the slope of the line. Duplicate runs agreed to with ±2%.

RESULTS AND DISCUSSION

The reaction was found to be strictly first-order in nitrosamine as shown by the excellent linear first-order

[10] A. I. Vogel, 'Textbook of Practical Organic Chemistry,' Longmans, London, 1954, p. 547.

Guggenheim plots and also by the constancy of the rate coefficient as the initial concentration of nitrosamine was varied by a factor of 2. This eliminates a mechanism whereby the nitroso-group is directly transferred to the *para*-position of another molecule, in which case a second-order dependence on the nitrosamine concentration would be observed.

The variation of the rate coefficient with acidity was examined in the range 2—8M-HCl. The plot of log k_{obs} *vs.* $-H_0$ plot (Figure 2) is a very good straight line as far as 6·5M, thereafter for a short range of acidity, the rate appears to become almost independent of the acidity.

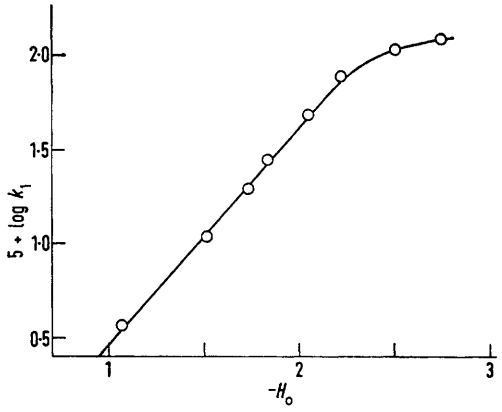
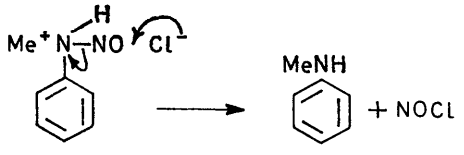


FIGURE 2 Variation of log k_{obs} with $-H_0$

The slope of the line is 1·18 showing a first-order dependence upon H_0. Clearly, if both the proton and chloride ion are separately involved in the detailed mechanism as in Scheme 3 then some sort of second-order dependence on the hydrochloric acid concentration is expected. Our



SCHEME 3

results contrast with those obtained for the Orton rearrangement of *N*-chloroanilides where a clear second-order dependence on the hydrochloric acid concentration has been observed.[11] Baliga also reported [9] a first-order dependence on the hydrogen chloride concentration and a zero-order dependence on added chloride ion concentration for the rearrangement of *N*-nitrosodiphenylamine. Our results suggest that reaction proceeds by a unimolecular decomposition of the protonated nitrosamine. This is supported by the observed solvent isotope effect $k_{D_2O} : k_{H_2O} = 2·1$ at 3·96M acid, *i.e.* on the straight line part of the H_0 plot. The levelling-off of the rate coefficient above 6·5M is consistent with the suggestion that here the nitrosamine becomes fully protonated so that increasing the acid concentration has no further effect on the concentration of this species (and hence on the observed rate-coefficient) as is observed in the acid-catalysed rearrangement of phenylhydroxylamine.[12] This is further supported in our case by the fact that around this acidity the u.v. spectrum of the nitrosamine changes sharply from an absorbance maximum at around 268 nm to one at lower wavelength. This change occurs at a lower overall acid concentration in deuterium oxide and is consistent with the accepted idea that D_3O^+ is a stronger acid than is H_3O^+. The observed solvent isotope effect at 5·45M-acid is 1·6, *i.e.* less than 2·1, as expected since the rate in D_2O will level off at an earlier point in the acid range than will the corresponding H_2O values.

Recently Russian workers have claimed [13] that the rearrangement of *N*-nitrosoaromatic amines in sulphuric acid is, in part, intramolecular. The evidence for this suggestion is that rearrangement takes place even in the presence of a large (up to 10^4 fold) excess of urea or sulphamic acid both of which are known to react very rapidly with nitrous acid or species derived from nitrous acid. Previously Macmillen and Reade [8] had failed to observe any *C*-nitroso-compound from the reaction of *m*-nitro-*N*-nitroso-*N*-methylaniline in sulphuric acid containing a large excess of urea. Neither of these sets of authors consider the possibility that the nitrosamine itself (or more probably its protonated form) can react as a nitrosating agent, *e.g.* with urea or any other amine. We propose to show, in this paper in the case of *N*-methylaniline and in a future publication [14] in the case of urea, that these reactions do, in fact, take place.

We have confirmed that rearrangement takes place in the presence of a large excess of urea in hydrochloric acid although the yield of the *C*-nitroso-product decreases as the concentration of urea is increased as shown in Table 1. It is clear that under these conditions no *C*-nitroso-product could arise from a free nitrite species as this would have been quantitatively removed very rapidly by reaction with urea. These results together with the kinetics argue for an intramolecular mechanism as has been demonstrated for the benzidine rearrangement of hydrazobenzenes,[15] the nitramine rearrangement

TABLE 1

Variation of the yield of *C*-nitroso-product * with urea concentration at 5·90M-HCl

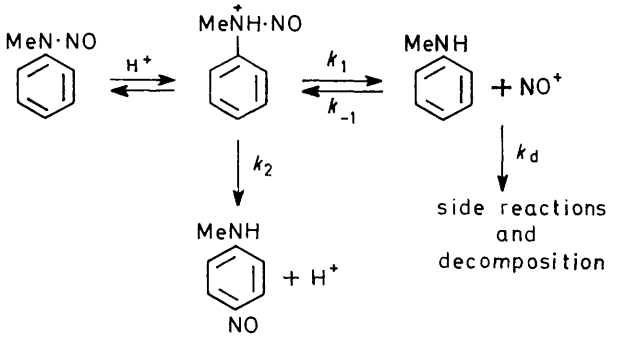
[Urea] (M)	Yield (%) of *C*-nitroso-product
0	28
3×10^{-3}	19
1×10^{-2}	11
3×10^{-2}	6

* [*N*-Nitroso-*N*-methylaniline] is 3×10^{-4}M in each case.

[11] J. J. Blanksma, *Rec. Trav. chim.*, 1902, **21**, 366; 1903, **22**, 290; see also ref. 3, pp. 221—228.
[12] H. E. Heller, E. D. Hughes, and C. K. Ingold, *Nature*, 1951, **168**, 909.
[13] T. I. Aslapovskaya, E. Y. Belyaev, V. P. Kumarev, and B. A. Porai-Koshits, *Reakts. sposobnost. org. Soedinenii*, 1968, **5**, 456.
[14] T. D. B. Morgan and D. L. H. Williams, to be published.
[15] D. V. Banthorpe, *Topics in Carbocyclic Chemistry*, 1969, **1**, 1.

of *N*-nitroamines,[16] and the rearrangement of alkyl substituted benzenes.[17]

In aqueous solution the rearrangement is by no means quantitative even in the absence of urea, and is accompanied by often considerable amounts of the product of denitrosation, *viz* the secondary amine. Our results show that the yield of rearranged product decreases with increasing acidity from 56% at 2·84M to 7% at 9M-HCl. There is a corresponding increase in the amount of *N*-methylaniline formed. We suggest that both the product of rearrangement and that of denitrosation arise from the protonated nitrosamine in parallel reactions as shown in Scheme 4, and that the variation in yield is dependent on



SCHEME 4

the rate of decomposition (and side reactions) of NO^+ or species derived from it which will be a function of the acidity. The observed rate coefficient k_{obs} is, of course, a composite quantity involving k_1, k_{-1}, k_2, and k_d so that it is perhaps somewhat fortuitous that we observed a 'good' first-order dependent upon H_0. Nevertheless it argues for reactions *via* the protonated nitrosamine when taken in conjunction with the observed solvent isotope effects. A more detailed analysis of the separate rate coefficients will appear in Part II of this series.[14]

Often it has been possible to demonstrate the intramolecularity of a reaction using labelling techniques. We have carried out the rearrangement in the presence of added sodium [^{15}N]nitrite. Our first experiments [18] indicated that there was very little pick-up of ^{15}N in the *C*-nitroso-product both from hydrochloric acid and sulphuric acid solution, but further work has shown that complete ^{15}N exchange between the added nitrite and the nitroso-nitrogen in the nitrosamine takes place at a very early stage during the reaction. This was shown by removing samples at various times and recovering both the 'unchanged' nitrosamine and the *C*-nitroso-product (B in Table 2). Both were analysed for ^{15}N by mass spectrometry. It was more convenient to convert the nitrosamine into the *C*-nitroso-isomer (A in Table 2) in a separate experiment before ^{15}N analysis because of the difficulty in getting a reasonable parent-ion peak on the mass spectrum of the nitrosamine. One set of results are shown in Table 2 for the reaction in water. Duplicate results were similar as were those obtained from 1 : 1 ethanol–water solvent. We are unable to explain our first results, but it is probable that the nitrite was quickly decomposed by some impurity. The results show that

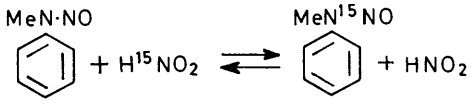
TABLE 2

Ratios 137 : 136 as % from the mass spectra of *p*-nitroso-*N*-methylaniline *

% Conversion	(A) from recovered reactant	(B) from product
6	20·9	20·7
20	21·1	21·1
45		21·3
75		21·1

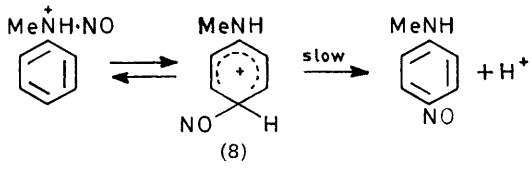
* 21% Corresponds to complete equilibration.

this labelling technique cannot be used as a criterion for distinguishing intra- from inter-molecularity in this case because of the exchange reaction shown (Scheme 5) which takes place at a rate far greater than that of the rearrangement.



SCHEME 5

It is not easy to see how the NO group can be transferred from the amino-nitrogen to the *para*-position in the ring without becoming detached from the aromatic system. Various mechanisms have been suggested at different times to account for the intramolecularity of other aromatic rearrangements, involving polar transition states, π complexes, or caged radical-ion pairs. With the evidence available at present we cannot present a detailed mechanism for the rearrangement step in terms of these or any other concepts. Further work, including the effect of substituents is in progress. There is, however, a primary isotope effect $k_H : k_D$ of 1·7 on the observed rate coefficient when the rates of *N*-nitroso-*N*-methylaniline and its 2,4,6-trideuteriated analogue are compared. This value was obtained at both 5·5M- and 7·0M-HCl and shows that proton loss from the *para*-position is rate-determining. It is conceivable that migration of the NO group and proton-loss take place synchronously but it seems to us more likely that the σ-complex (8) is formed relatively rapidly and then undergoes a slow proton-loss (Scheme 6). Primary



(8)

SCHEME 6

isotope effects, although not common in general in electrophilic aromatic substitution are well established

[16] D. V. Banthorpe, E. D. Hughes, and D. L. H. Williams, *J. Chem. Soc.*, 1964, 5349.

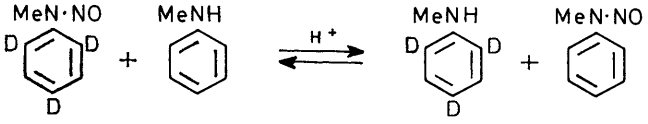
[17] Ref. 3, pp. 2—32.

[18] G. Steel and D. L. H. Williams, *Chem. Comm.*, 1969, 975.

in the nitrosation of phenols;[19] more recently it has been shown[20] that such effects occur with a variety of substrates.

The tentative mechanism proposed by Baliga[9] outlined in the introduction to this paper is not consistent with many of our results. It is difficult to envisage how the H_0 correlation, the levelling-off of the rate coefficient at high acidity and the solvent isotope effects can be accommodated by the four-centred transition-state mechanism proposed. More serious perhaps is the fact that we observe a primary deuterium ring-isotope effect which is contrary to the proposed mechanism since the whole *C*-substitution process follows the rate-determining step. Further, we and other workers[13] have shown that rearrangement takes place in the presence of a large excess of either urea or sulphamic acid ruling out a mechanism involving a free nitrite species.

Trapping of a migrating group by reaction with a suitable added substrate has often been used as the sole evidence for the intermolecularity of a rearrangement. This does not cater for the possibility that the reactant or an intermediate derived from the reactant can transfer the migrating group directly to the substrate in a bimolecular (S_N2-like) reaction. Examples of this are known in the rearrangement of alkylaromatics[21] where the direct transfer of an alkyl group from a σ-complex to another molecule has been demonstrated, and in the rearrangement of diazoaromatics where the ArN_2^+ group from a protonated triazene becomes substituted in phenols and amines without forming the free ArN_2^+ ion.[22] We have examined the possibility that the transfer of the NO group to an added amine can occur during rearrangement using deuterium labelling. Equivalent amounts of 2,4,6-trideuteriated-*N*-nitroso-*N*-methylaniline and unlabelled *N*-methylaniline and a 15-fold excess of urea were allowed to react for 5·0 min at room temperature in 1M-, 2·5M-, and 4M-hydrochloric acid solutions. The reaction was then stopped and the nitrosamine and amine were recovered and separated by acid extraction. Each was examined for deuterium by i.r. spectroscopy by analysis of the bands characteristic of the [^{1}H]- and [^{2}H]-compounds of each, *e.g.* the unassigned band at *ca.* 1600 cm^{-1} in the unlabelled nitrosamine is shifted to 1580 cm^{-1} on 2,4,6-deuterium substitution. Deuterium exchange was observed in each component to an extent of *ca.* 10% at 1M-, 50% at 2·5M-, and 70% at 4M-acid. Complete equilibration was achieved when the reaction mixture was left for sufficiently long periods (when significant amounts of rearrangement had taken place). This shows that the cross-nitrosation (Scheme 7) shown, is taking place without the formation of free NO^+ or other species derived from NO^+. Since this exchange is clearly acid catalysed it is likely that the protonated form of the nitrosamine is acting as a primary nitrosating agent. Obviously this form of *N*-nitrosation (followed by intramolecular rearrangement) satisfactorily accounts for the cross-nitrosations that have been observed with added amines and also in the case of nitrosation of a reactive olefin.



SCHEME 7

These results emphasise the dangers implicit in proposing reaction mechanisms from product-analysis evidence alone and, in particular, draw attention to that fallacy that the ability to trap out the migrating group necessarily requires an intermolecular mechanism for the rearrangement process.

[1/820 *Received, May* 21*st*, 1971]

[19] K. M. Ibne-Rasa, *J. Amer. Chem. Soc.*, 1962, **84**, 4962.
[20] B. C. Challis, R. J. Higgins, and A. J. Lawson, *Chem. Comm.*, 1970, 1223.
[21] D. A. McCauley and A. P. Lien, *J. Amer. Chem. Soc.*, 1953, **75**, 2411; H. Jungk, R. Smoot, and H. C. Brown, *J. Amer. Chem. Soc.*, 1956, **78**, 2176, 2182, 2185.
[22] E. D. Hughes and C. K. Ingold, *Quart. Rev.*, 1952, **6**, 34.