878. *Aromatic Nucleophilic Replacement. Part VII.* *The Reaction of* NN-*Dialkyl-*p-*nitrosoanilines with Aqueous-methanolic Alkali.*

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Cleavage of *NN*-dialkyl-*p*-nitrosoanilines with aqueous-alcoholic alkali has been assumed to be an example of aromatic nucleophilic replacement of the alkylamino-group by hydroxide ion. Evidence is now presented that this is not so and that the mechanism is similar to the basis of the Mannich reaction, the ease of reaction being due to the stability, in solution, of *p*-nitrosophenol as its tautomer, benzoquinone monoxime. The effect of varying the alkyl groups in dialkyl-*p*-nitrosoanilines is briefly discussed.

REACTION of *NN*-dialkyl-*p*-nitrosoanilines with aqueous-alcoholic alkali to produce *p*-nitroso-phenol and a secondary amine is a well-known preparative method. Hydrolysis of dimethyl-*p*-nitrosoaniline in 50% aqueous ethanol was found by Miller and Adams[1] to obey second-order kinetics with an activation energy of 13 kcal. mole^{-1} and log $B = 6$ ($k_2 = B \exp E/\boldsymbol{R}T$). On this basis they concluded that " the mechanism of the reaction may be thought of as a typical aromatic nucleophilic displacement." For 50% aqueous-methanol solutions we have confirmed Miller and Adams's observations but a more detailed investigation reveals serious departures from the behaviour expected for a simple aromatic nucleophilic replacement.

In the reaction between an anion and a neutral molecule, the Hughes–Ingold[2] theory predicts that solvent effects are small and that more ionising solvents retard the reaction. Thus, in the aliphatic series, for the reaction between isopropyl bromide and hydroxide ion[3] the ratio of the bimolecular rate in absolute ethanol to that in 40% aqueous ethanol is 2. In aromatic nucleophilic replacement, *e.g.*, for the reaction 1-chloro-2,4-dinitro-benzene with methoxide ions Briner and Miller[4] give the ratio of the bimolecular rate in methanol–methyl acetate to that in absolute methanol as 3·44 at 0°.

For the reaction of dimethyl-*p*-nitrosoaniline under consideration the effect is in the opposite direction. Increasing the proportion of methanol in aqueous-methanolic solutions leads to a large apparent decrease in rate (see Table 1), and in absolute methanol the reaction does not take place at 30° (for 0·02974M-nitroso-compound and 0·2634N-OMe⁻, the optical density remained constant for 76 hr.†).

TABLE 1. *Reaction of dimethyl-*p-*nitrosoaniline with aqueous-methanolic alkali: variation of second-order rate constant with water content of the solvent at 29·99°.*

H_2O (%)	[Total Alkali]$_0$	$10^6 k_1$	$10^5 k_2 =$ $10^5 k_1/$[Total Alkali]$_0$	$\dfrac{k_2}{k_2[5\% \ H_2O]}$	$10^6 k_1$ *	$10^4 k_2 =$ $10^4 k_1$[OH⁻] *
5	0·3920	2·77	0·707	1	2·77	2·06
10	0·3122	4·32	1·39	1·97	4·32	1·97
50	0·3275	81·7	25·0	35·36	81·7	6·19

* See text, next page.

Product analysis led to the recovery of 92·8% of the starting material after 24 hr. at 30° in absolute methanol, and to isolation of 88·9% of *p*-nitrosophenol when the solvent was 50% aqueous methanol.

Bunnett and Davis[5] showed that methoxide is approximately 33 times more powerful

* Part VI, *J.*, 1956, 4284.

† After ∼120 hr. the optical density of the mixture falls (from 0·338 to 0·302). This is ascribed to reaction, possibly reduction, of the nitroso-group and not to the dimethylamino-part of the molecule.

[1] Miller and Adams, *J. Amer. Chem. Soc.*, 1953, **75**, 4599.

[2] Hughes and Ingold, *J.*, 1935, 252.

[3] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 349.

[4] Briner and Miller, *J.*, 1954, 4682.

[5] Bunnett and Davis, *J. Amer. Chem. Soc.*, 1954, **76**, 3011.

than hydroxide as a nucleophile in aromatic nucleophilic substitution, and have used this, together with Hine and Hine's observation [6] that methanol is a stronger acid than water, to explain the preponderance of ether, formed in the reactions of activated aryl halides with aqueous-alcoholic sodium and potassium hydroxide. On this basis the main product of reaction of dimethyl-*p*-nitrosoaniline with alkali in 50% aqueous methanol should be *p*-nitrosoanisole: in fact, we isolated 88·9% of *p*-nitrosophenol and no anisole.

If, for the system $RO^- + H_2O \rightleftharpoons ROH + OH^-$, it is assumed that the only nucleophile that can react to completion with dimethyl-*p*-nitrosoaniline is the hydroxide ion, then isolation of *p*-nitrosophenol from aqueous-methanolic solutions and the absence of reaction in absolute methanol are provided with a ready explanation; moreover, the anomalous solvent effect becomes intelligible.

Hine and Hine,[6] for the reaction $HA + Pr^iO^- \rightleftharpoons A^- + Pr^iOH$, gives the following values for k_e (defined as $k_e = [A]/[HA][Pr^iO^-]$): for HA = H_2O, $K_e = 1·20$; for HA = MeOH, $k_e = 4·0$. Thus, $k_e(H_2O)/k_e(MeOH) = [MeOH][OH^-]/[H_2O][OMe^-] = 0·3$. If we assume that $[OH^-] \ll [H_2O]$, the hydroxide-ion concentration in various methanol–water mixtures can be calculated (see the last two columns of Table 1). Hence within the limits of the calculation, the second-order rate constant for reaction with hydroxide ion increases approximately threefold in going from 5% to 50% aqueous methanol.

The greater part of the increase in rate in Table 1 is attributed on this basis to the fact that the hydroxide ion is the only effective reagent. The residual increase corresponds to that observed [7] in the reaction between *o*-dinitrobenzene and methoxide ion when a change from absolute methanol to 50% aqueous methanol increases the rate by a factor of 1·5. That the rate of reaction does increase with increasing dielectric constant of the solvent is shown, as illustrated below, by comparing the rate in 60% aqueous dioxan with that in 50% methanol corrected for hydroxide-ion concentration.

Solvent	ε	$10^4 k$	Relative rate
60% dioxan	26 [a]	3·07	1
50% methanol	57 [b]	6·19	2

[a] Hartmann, *Z. phys. Chem.*, 1942, *A*, **191**, 197.   Calc. from results of Jones and Davies, *Phil. Mag.*, 1939, **28**, 207.

There is also a considerable difference between the values of the log *B* factors found in these reactions (7·0 for the dimethyl compound in both aqueous methanol and dioxan, and 8·6 for the diethyl compound) and that of ~11 for the reactions of anions with activated aromatic halides.[8] Recently, Arrhenius parameters have been given [9] for the reaction between 1-benzylpyridinium bromide and ethoxide ion in ethanol ($E = 12·8$ kcal. mole^{-1} and log $B = 6·2$). This reaction probably involves attack by an anion on the α-carbon of the pyridine ring (cf. Bergstrom [10]), and the probability factor is of the same order as for the reaction under discussion. This is consistent with the view that the reaction under discussion is essentially attack on the carbon of a $\diagdown C{:}N^+\diagup$ bond.

Evidence from ultraviolet and infrared spectroscopy, dipole moments, polarography, and kinetics [11] shows that the dimethyl-*p*-nitrosoaniline molecule has a large contribution from the structure $Me_2N^+{:}C_6H_4{:}N{\cdot}O^-$, and in acid solution the ultraviolet spectrum shows that the nitroso-group does not exist as such, *i.e.*, the proton is attached to the oxygen atom [12] and the stable form of *p*-nitrosophenol is its tautomer, *p*-benzoquinone monoxime. Jaffe [13] calculated that the quinonoid form is 4—6 kcal. mole^{-1} more stable than the

[6] Hine and Hine, *J. Amer. Chem. Soc.*, 1952, **74**, 5266.
[7] Lobry de Bruyn and Steger, *Rec. Trav. chim.*, 1899, **18**, 41.
[8] Bevan and Hirst, *J.*, 1956, 254.
[9] Bevan, *J.*, 1960, 347.
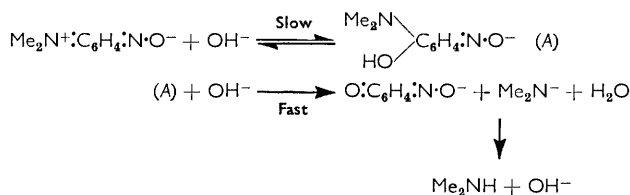[10] Bergstrom, *Chem. Rev.*, 1944, **35**, 77.
[11] Gowenlock and Luttke, *Quart. Rev.*, 1958, **12**, 321.
[12] Schors, Kraaijeveld, and Havinga, *Rec. Trav. chim.*, 1955, **74**, 1243.
[13] Jaffe, *J. Amer. Chem. Soc.*, 1955, **77**, 4448.

benzenoid structure. Hadzi showed by infrared spectroscopy [14] that in the solid state *p*-nitrosophenol is completely in the quinonoid form; Schors *et al.* showed by ultraviolet spectroscopy [12] that the benzenoid form is present only to about 20% in methanolic and to a small extent in aqueous solution.

On the above basis we propose that the mechanism of hydrolysis under discussion is:

$$Me_2N^+ : C_6H_4 : N \cdot O^- + OH^- \underset{\text{Slow}}{\overset{}{\rightleftharpoons}} \underset{HO}{\overset{Me_2N}{\diagdown}} C_6H_4 : N \cdot O^- \quad (A)$$

$$(A) + OH^- \xrightarrow{\text{Fast}} O : C_6H_4 : N \cdot O^- + Me_2N^- + H_2O$$

$$\downarrow$$

$$Me_2NH + OH^-$$

Although the second stage is written as a bimolecular reaction it could take place by a unimolecular mechanism: the kinetics of the reaction do not distinguish between the two.

The system, as formulated, is a pseudobasic one, similar to that given by Ingold [15] as the basis of the Mannich reaction, $Me_2N^+ : C \diagdown + OH^- \rightleftharpoons Me_2N \cdot \overset{|}{C} \cdot OH \longrightarrow Me_2NH + \diagdown CO$, the driving force being the extreme stability of *p*-benzoquinone monoxime.

This, we believe, is the reason for the specificity of hydroxide ions rather than of alkoxide ions. Further, if decomposition of the intermediate is a bimolecular process, depending on the abstraction of a proton by a second molecule of base, then reaction by alkoxide cannot take place.

Although in the proposed reaction scheme the first stage is represented as slow, there is little direct evidence for this. In several runs the zero readings gave concentrations agreeing within experimental error with the weight taken; hence either the first step is slow or, if a rapid equilibrium is established, it must lie very much to the left.

Progressive replacement of methyl by ethyl in the dialkylamino-group decreases the rate, owing to an increase in activation energy (see Table 2). This is thought to be a steric

TABLE 2. *Effect of change of the alkyl groups in p-NRR'·C₆H₄·NO. Reactions in 50% aqueous methanol at 30·34°.*

RR'	$10^4 k_2$	$k_2/k_2(Me_2)$	E (kcal. mole^{-1})	$\log B$
Me₂	2·50	1	15·2	7·36
EtMe	1·23	0·49		
Et₂	0·507	0·20	18·0	8·66

effect though the change in entropy is in the opposite direction to that in nucleophilic substitution at a saturated carbon atom.[16] This can be explained as follows. In the ground state of the molecule the presence of a double bond severely limits the number of stable conformations, a restriction that is not present in the intermediate; moreover, owing to the presence of α-methyl groups this effect should be greater in the diethyl than in the dimethyl compound. Thus, an increase in activation energy from the dimethyl to the diethyl compound would be expected owing to steric strain, but the latter should show a larger entropy of activation.

EXPERIMENTAL

Commercial dimethyl-, diethyl-, and ethylmethyl-aniline were refluxed with acetic acid and acetic anhydride and then distilled. The nitroso-compounds were obtained by reaction with nitrous acid. M. p.s were as follows: dimethyl- (from light petroleum), m. p. 86—87°, diethyl- (from acetone), m. p. 85—86°, and ethylmethyl-*p*-nitrosoaniline (from di-isopropyl ether), m. p. 68—69°.

p-Nitrosophenol, prepared by nitrosating phenol and sublimed, had m. p. 139° (decomp.).

[14] Hadzi, *J.*, 1956, 2725.
[15] Ref. 3, p. 581.
[16] Ref. 3, p. 408.

Magnesium (10 g.) and iodine (0·5 g.) were dissolved in " AnalaR " methanol (2 l.), which was then refluxed for $\frac{1}{2}$ hr. and distilled.

Solvents were made up by volume. *E.g.*, 10% aqueous methanol was obtained by mixing 10 c.c. of distilled water with 90 c.c. of methanol.

Kinetic Runs.—Optical density measurements were taken on a Unicam S.P. 500 spectrophotometer. Thermostat temperatures were constant within 0·02°. Dimethyl-*p*-nitrosoaniline has an absorption maximum [1] at 675 mμ, and optical density measurements were done at this wavelength, although $\lambda_{max.}$ for diethyl-*p*-nitrosoaniline is at 655 mμ (ε 62·5) and for ethylmethyl-*p*-nitrosoaniline at 647 (ε 66·3). At 675 mμ all the dialkyl-*p*-nitrosoanilines and *p*-nitrosophenol obeyed Beer's law in all solvents over the range of concentrations used.

Method. (*a*) Under conditions giving first-order kinetics. A weighed amount of the dialkyl-*p*-nitrosoaniline was dissolved in, and made up to 150 c.c. with, methoxide solution at thermostat temperature and placed in the thermostat for 5 min. before the zero reading was taken. Samples (5 c.c.) were pipetted into " AnalaR " methanol periodically, the volumes made up to 50 c.c., and the optical densities determined immediately.

(*b*) Under conditions giving second-order kinetics. Solutions of dimethyl-*p*-nitrosoaniline in the neutral solvent, and alkali in the same solvent, were allowed to come to thermostat temperature. Aliquot portions of the two solutions were then mixed so as to give the required concentrations. The reaction was stopped and readings were taken as described in (*a*).

Calculations. From an analysis of the Beer's law graphs, confirmed for known mixtures of dialkyl-*p*-nitrosoanilines with *p*-nitrosophenol, it was found that the concentration of dialkyl-*p*-nitrosoaniline remaining at any time in a run can be obtained for the formula: [Nitroso-compound] $= (\text{O.D.} - 2\cdot938x)/(k_1 - 14\cdot69)$, where O.D. is the optical density reading, x the initial concentration (moles l.$^{-1}$) calculated from the weight of dialkyl-*p*-nitrosoaniline used, and k_1 is for dimethyl- 58, for diethyl- 58·47, and for ethylmethyl-*p*-nitrosoaniline 59·83.

When the ratio of the concentrations of dialkylaniline to alkali was 1 : 10, the first-order formula $k_1 = (2\cdot303/t)$ log $a/(a - x)$ was used, and the second-order constant obtained by dividing k_1 by the original concentration of alkali. Where the concentration ratio was 1 : 2, the second-order formula was used:

$$k_2 = \frac{2\cdot303}{t(a - b)} \log \frac{b}{a} \cdot \frac{(a - x)}{(b - x)}$$

Results. See Tables.

Determination of k_2 (l. sec.$^{-1}$ mole^{-1}) *for reaction of dimethyl-*p-*nitrosoaniline with* OH^- *in 60% aqueous dioxan at* 30·34°. *Initial* [Nitroso] $= 0\cdot02988$N; [OH^-] $= 0\cdot06258$N.

T (min.) ...	0	180	300	360	480	570	707	789	955
O.D.	0·342	0·300	0·275	0·263	0·244	0·236	0·212	0·207	0·189
[Nitroso] ...	0·02932	0·02447	0·02159	0·02020	0·01801	0·01709	0·01432	0·01374	0·01166
[OH^-] ...	0·06202	0·05717	0·05429	0·05290	0·05071	0·04979	0·04702	0·04644	0·04436
10^4k_2	—	2·82	2·94	3·03	3·04	2·87	3·17	3·02	3·13

Mean $k_2 = 3\cdot00 \times 10^{-4}$ (duplicate $3\cdot13 \times 10^{-4}$).

Determination of k_1 (sec.$^{-1}$) *for the reaction of ethylmethyl-*p-*nitrosoaniline with* OH^- *in 50% aqueous methanol at* 30·34°. *Initially* [Nitroso] $= 0\cdot03030$N; [OH^-] $= 0\cdot3077$N.

T (min.) ...	0	80	100	150	180	210	330	350	400
O.D.	3·336	0·294	0·284	0·264	0·250	0·245	0·205	0·201	0·187
[Nitroso] ...	0·02736	0·02271	0·02160	0·01938	0·01783	0·01728	0·01285	0·01241	0·01085
10^5k_1	—	3·88	3·94	3·83	3·96	3·65	3·82	3·77	3·85

Mean $k_1 = 3\cdot84 \times 10^{-5}$; $k_2 = 1\cdot25 \times 10^{-4}$ (l. sec.$^{-1}$ mole^{-1}) (duplicate $k_2 = 1\cdot22 \times 10^{-4}$).

*Reaction of dimethyl-*p-*nitrosoaniline.*

(*a*) *In 50% aqueous methanol at* 30·36°. (k_2 corr. for solvent expansion.) *

[OMe]$_0$	[Nitroso]	[NaClO$_4$]	10^4k_2
0·06350	0·03	0	2·94
0·06350	0·03	0·2995	2·16
0·3275	0·03	0	2·50

* This table illustrates salt effect and the lack of catalysis by excess of OH^-.

(b) *Activation energy in 50% aqueous methanol.*

Temp.	10^4k_2
39·92°	5·68
30·36	2·50
20·06	1·09

Average E = 15·2 (kcal. mole^{-1})
Average log B = 7·3601

(c) *In 60% aqueous dioxan.* $[OH^-]_0$ = 0·06258N; $[Nitroso]_0$ = 0·03N. k_2 calc. by second-order formula.

Temp.	10^4k_2
20·06°	1·41
30·34	3·07
40·23	7·04

Average E = 14·6 (kcal. mole^{-1})
Average log B = 7·0246

Activation energy for diethyl-p-nitrosoaniline in 50% aqueous methanol.

Temp.	20·13°	30·34°	40·23°
10^4k_2	0·153	0·507	1·19

Average E = 18·0 (kcal. mole^{-1})
Average log B = 8·66

Isolation of Products.—(*a*) Dimethyl-*p*-nitrosoaniline (0·7474 g.; m. p. 84—85°) was left in 0·2043N-methoxide (100 c.c.) at 30·34° for 24·75 hr. The mixture was acidified with methanolic hydrogen chloride, and the methanol removed by bubling warm oxygen-free nitrogen under reduced pressure. The residue was extracted with ether and dilute aqueous ammonia; the ethereal solution was washed three times with water and dried (Na$_2$SO$_4$). Evaporation under reduced pressure gave a residue, m. p. 83° (mixed with original material, 84—85°) (Found: C, 64·2; H, 7·2; N, 18·3. Calc. for C$_8$H$_{10}$N$_2$O: C, 64·0; H, 6·7; N, 18·7%).

The recovery of dimethyl-*p*-nitrosoaniline (0·6935 g.) corresponds to 92·8%.

(*b*) Dimethyl-*p*-nitrosoaniline (0·5130 g.) in 50% aqueous methanol (100 c.c.) 0·2896N in alkali was left at 20·99° for 24·5 hr. The solution was poured into ice-cold water (400 c.c.) containing 2N-sulphuric acid (15 c.c.); 2N-sulphuric acid was added to acidity to Congo Red. The mixture was extracted with ether, and the extract washed three times with water and dried (Na$_2$SO$_4$). Evaporation gave a residue (0·3682 g.), m. p. 128° (decomp.) [mixed with *p*-nitrosophenol 129—130° (decomp.)].

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