Studies of Tertiary Amine Oxides. Part 8.[1,2] Rearrangement of *N*-(2,4-Dinitrophenyl)-piperidines and -morpholine *N*-Oxides in Aprotic Solvents

Abdul-Hussain Khuthier,* Khawla Y. Al-Mallah, and Salim Y. Hanna
Department of Chemistry, College of Science, University of Mosul, Mosul, Iraq

The *N*-oxides of *N*-(2,4-dinitrophenyl)-piperidines and -morpholine undergo thermal rearrangement to the substituted hydroxylamines. The kinetics of the rearrangement were studied in aprotic solvents at four or five temperatures. Steric and polar factors have great influence on the rate of rearrangement. The kinetic results together with cross-over experiments are in full agreement with an intramolecular cyclic mechanism (S_Ni).

Rearrangement of tertiary amine oxides, often known as the Meisenheimer rearrangement,[3] involves the migration of certain groups from N to O forming the corresponding *O*-alkylhydroxylamines [equation (1)]. *N*-Oxidation is a well

$$R^1R^2R^3\overset{+}{N}—\overset{-}{O} \xrightarrow{heat} R^1R^2N—OR^3 \quad (1)$$

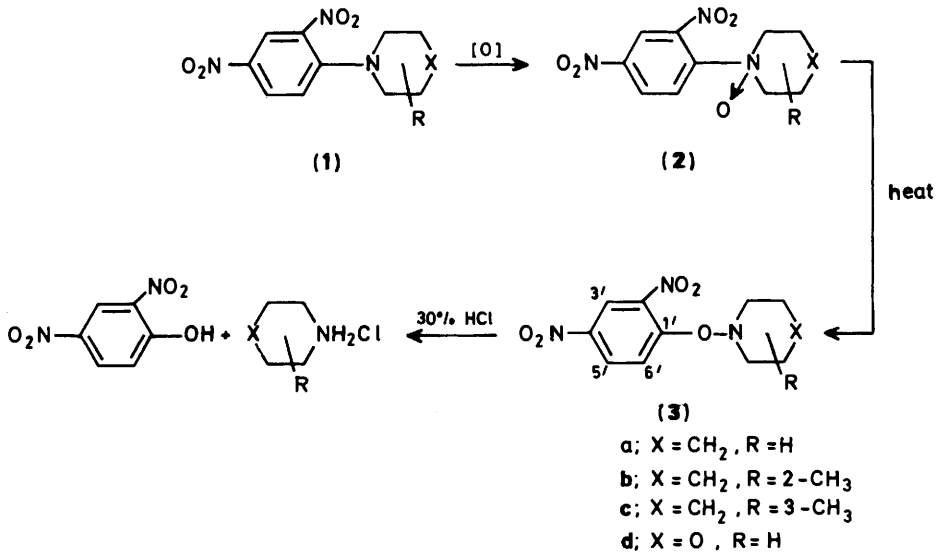
established metabolic process of tertiary amine drugs[4] and the *N*-oxides are often unstable and undergo isomerisation during metabolic studies.[4c] The Meisenheimer rearrangement represents one of the more important reactions of tertiary *N*-oxides that lack a β-hydrogen atom. This rearrangement was limited at its earlier discovery to the migration of allyl or benzyl groups. Later, however, more groups are found to undergo a nitrogen–oxygen shift during thermolysis of some tertiary amine oxides. These groups are neopentyl,[5] tetrahalogenopyridinyl,[6] homoadamantyl,[7] and propargyl.[8] The benzene nucleus, when substituted with electron-withdrawing groups (*e.g.* NO_2), undergoes facile migration from N to O during thermolysis of *N*-arylamine oxides.[9,10] This paper describes the rearrangement of *N*-(2,4-dinitrophenyl)-piperidines and -morpholine *N*-oxides to the corresponding hydroxylamines.

Results and Discussion

Syntheses.—The tertiary amines (**1**) were prepared by reaction of the appropriate secondary amine and 2,4-dinitrofluorobenzene. Oxidation of the tertiary amines with H_2O_2–HCO_2H mixture produced the corresponding *N*-oxides (**2**) in good yields (Table 1). These *N*-oxides were stored as hydrochlorides or picrates and recovered fresh when needed. Analytical and spectral data (n.m.r., i.r., u.v.) confirmed the structure of the tertiary *N*-oxides. A noticeable downfield shift for the aromatic and non-aromatic protons in the ^1H n.m.r. spectra of the *N*-oxides relative to the corresponding protons of the amines is clearly indicated. This is because of the highly polar ⩾N–O group that is introduced into the molecule upon oxidation. Interestingly, the methyl protons in (**2b**) appeared as two doublets (Table 1) in contrast to the same protons in (**2c**) which are indicated by one doublet. This is due to a diastereoisomeric mixture since the rotation about the Ph–N bond in (**2b**) is severely hindered as indicated from Drieding models.

The tertiary *N*-oxides (**2**), when heated in an aprotic solvent, undergo a novel rearrangement in which the dinitrobenzene nucleus migrates from N to O, forming *O*-(2,4-dinitrophenyl)-hydroxylamines (**3**) in quantitative yield (Scheme 1).

Such a rearrangement is reminiscent of the thermal *N*-oxide isomerisation discovered by Meisenheimer in which, however, the migrating group must be allylic or benzylic [*e.g.* equation (1; $R^3 = CH_2Ph$)]. The highly electron-withdrawing nitro groups in (**2**) induce an electron deficiency at the aryl carbon directly attached to the ⩾N–O function, thus providing the driving force for the migration. It should be noted here that the presence of an electron-withdrawing group (such as NO_2) is essential for the migration to occur. Moreover, such a group must be *ortho*

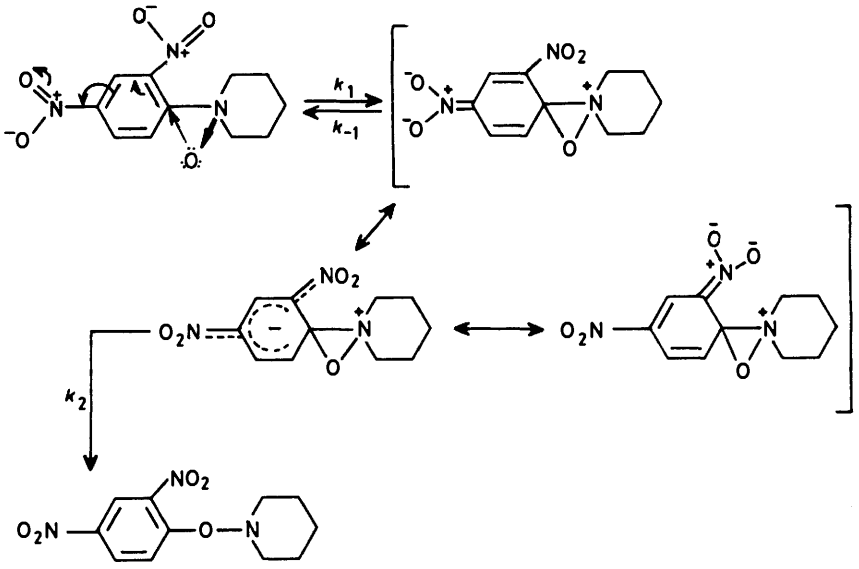


Scheme 1.

Table 1. Properties of the tertiary amine oxides (**2**) and rearrangement products (**3**)[a]

Compound	Yield (%)	M.p. (°C) HCl adduct	$\lambda_{max.}$/nm ($\varepsilon_{max.}$)[b]	Chemical shift δ[d] Aryl	CH_3
(**2a**)	50 + 40R[e]	153—155	250 (8 260)	8.88—7.8 (m, 3 H)	
(**2b**)	60 + 35R	137—140	250 (8 058)	8.93—7.8 (m, 3 H)	1.3, 1.1[c] (d, *J* 7.0)
(**2c**)	55 + 35R	152—156	251 (8 850)	8.9—7.7 (m, 3 H)	1.0 (d, *J* 7.0)
(**2d**)	60 + 30R	122—125	247 (8 789)	8.8—7.8 (m, 3 H)	
(**3a**)	99		250 (7 215)	8.86 (d, 1 H, *J* 3.0)	
			298 (9 485)	8.46 (dd, 1 H, *J* 3.0, 9.0)	
				7.92 (d, 1 H, *J* 9.0)	
(**3b**)	98		248 (8 225)	8.84 (d, 1 H, *J* 3.0)	1.04
			298 (9 920)	8.4 (dd, 1 H, *J* 3.0, 9.0)	(d, *J* 6.5)
				7.94 (d, 1 H, *J* 9.0)	
(**3c**)	98		251 (7 260)	8.86 (d, 1 H, *J* 3.0)	1.02
			296 (10 130)	8.44 (dd, 1 H, *J* 3.0, 9.0)	(d, *J* 6.5)
				7.92 (d, 1 H, *J* 9.0)	
(**3d**)	96		250 (8 395)	8.85 (d, 1 H, *J* 3.0)	
			295 (10 864)	8.45 (dd, 1 H, *J* 3.0, 9.0)	
				7.93 (d, 1 H, *J* 9.0)	

[a] Satisfactory analytical data were obtained for all new compounds. [b] Solvent dioxane. [c] Two doublets; relative intensities 1:3; at 25 °C. [d] *J*/Hz. [e] R = rearrangement product.



Scheme 2.

and/or *para* to the ⩾N–O function since an NO_2 group *meta* to the *N*-oxide moiety (*e.g.* in *m*-nitrodimethylaniline *N*-oxide[9]) could not induce migration of the benzene nucleus upon pyrolysis of the tertiary *N*-oxide. This essential requirement for the electron-withdrawing group to be *ortho* and/or *para* to the ⩾N–O group is related to the mechanism of the present rearrangement.

The products (**3a—d**) gave analytical values and n.m.r. spectra in full agreement with the proposed structure. In the ^1H n.m.r. spectra the splitting pattern of the aromatic protons is clearly of first-order type and can be determined directly from the spectrum. At the high-field end of the aromatic region there is a doublet (δ 7.9) of unit intensity with *J* 9.0 Hz. This must be assigned to the proton *ortho* to the O–N< function (*i.e.* 6′-H) since it couples with one other proton *ortho* to it (5′-H), it is also *para* to 3′-H (for which *J* can be zero). The two doublets centred at δ 8.4 are assigned to the proton *ortho* to NO_2 (5′-H) with *J* 9 and 3 Hz. The lowest field doublet at δ 8.8 with unit intensity must be due to 3′-H (*J* 3 Hz). In contrast, the aromatic protons of the *N*-oxides appear as a complex band which cannot be analysed by the first-order method, due to the complex splitting between all three protons. Treatment of (**3**) with 30% hydrochloric acid afforded 2,4-dinitrophenol having identical properties with those of a reference sample, providing further support for the structure.

The mechanism of the rearrangement is best described by an intramolecular nucleophilic substitution as shown in Scheme 2, rather than a homolytic process as suggested for Meisenheimer transformations in other systems.[5,7,11,12] Moreover, rearrangement of a mixture of (**2d**) and *N*-(2-nitrophenyl)piperidine *N*-oxide[1] produced a mixture of the corresponding hydroxylamines but with no cross-products. This, together with kinetic results, clearly points to an intramolecular concerted process rather than to a dissociation into radicals.

Table 2. Kinetics[a] of rearrangement of *N*-(2,4-dinitrophenyl)amine oxides in aprotic solvents

Compound	Solvent	$10^4 k_{30}$[b]/s^{-1}	$\Delta H^{\neq}$/kcal mol^{-1}	$\Delta S^{\neq}$/cal mol^{-1} K^{-1}
	Dioxane	38.74	16.34 ± 0.4	−15.5 ± 4
(2a)	THF	73.38	17.29 ± 0.4	−11.09 ± 4
	DMF	83.77	17.7 ± 0.38	−9.6 ± 3.8
	Dioxane	5.42	17.26 ± 0.36	−16.5 ± 4
(2b)	THF	5.82	19.1 ± 0.5	−10.2 ± 4.5
	Dioxane	25.23	12.48 ± 0.5	−29.2 ± 5.6
(2c)	THF	42.50	14.44 ± 0.4	−21.7 ± 3.6
	DMF	61.71	16.13 ± 0.4	−15.4 ± 3
	Dioxane	10.23	19.62 ± 0.3	−7.4 ± 2
	THF	13.78	19.25 ± 0.3	−8.09 ± 3
(2d)	DMF	21.31	19.66 ± 0.4	−5.87 ± 2
	DMSO	23.66	19.50 ± 0.5	−6.0 ± 3

[a] Least-squares plots of ln *k* *versus* $1/T$ were linear for all experiments. [b] Temperature 30 °C.

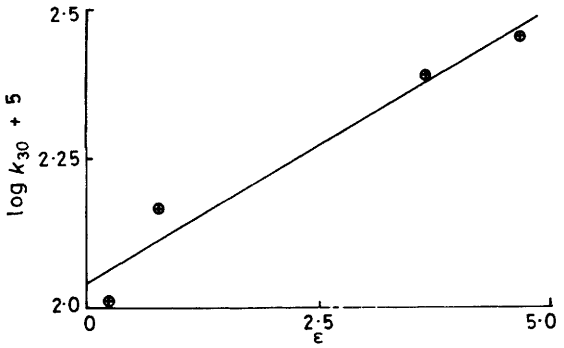
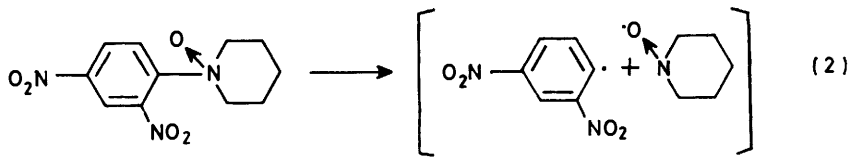


Figure. Variation of rate constants for rearrangement of (**2d**) with dielectric constant of aprotic solvents. Temperature 30 °C

charge of the attacking oxygen of the *N*-oxide moiety. This sort of effect can also be revealed by comparison of the data in Table 2 with others reported previously for *N*-(4-nitrophenyl)- and *N*-(2-nitrophenyl)-piperidine *N*-oxides.[1] For example the ratio of rate coefficients for the rearrangement of (**2a**) and *N*-(4-nitrophenyl)piperidine *N*-oxide in dioxane $k^{\text{piperidine}}_{2,4\text{-dinitro}}/k^{\text{piperidine}}_{p\text{-nitro}}$ is 168. The same ratio for 2-methylpiperidine base; $k^{\text{2-methylpiperidine}}_{2,4\text{-dinitro}}/k^{\text{2-methylpiperidine}}_{p\text{-nitro}}$ is only 1.5 (*i.e.* the rate for the two compounds is almost equal) thus indicating that the *o*-nitro group in *N*-(2,4-dinitrophenyl)-2-methylpiperidine *N*-oxide (**2b**) is almost completely out of the plane of the benzene ring and its effect on the rate of isomerisation is therefore negligibly small. Moreover, the great rate differences for the rearrangement of the present compounds and those of the *o*-nitro congeners[1] [*e.g.* $k^{\text{piperidine}}_{2,4\text{-dinitro}}/k^{\text{piperidine}}_{o\text{-nitro}} = 2.76 \times 10^4$ (dioxane); 7.2×10^4 (THF); 11.02×10^4 (DMF)] clearly indicate the dramatic influence of the *p*-nitro group on the velocity of the rearrangement.

The influence of the solvent on the rate of rearrangement is indicated in Table 2. A mild acceleration in rates is observed as a consequence of increased polarity of the medium. Although a fair correlation (*r* 0.9508) of the observed rate of rearrangement of *N*-oxide (**2d**) with the dielectric constant of the solvent is obtained (Figure), the case is not so clear with other *N*-oxides. Further work is in progress as to the effect of solvent on the present rearrangement.

Table 2 lists the activation parameters for the rearrangement. The energy of activation increases slightly with changes in solvent polarity and is generally small. A compensating entropy effect is indicated in the increase in $\Delta S^{\neq}$ with the same solvent change. The low values of the energy of activation are consistent with the concerted mechanism since the energy lost in breaking the C–N bond in (**2**) is partly compensated by the energy gained in forming the new C–O bond in (**3**). Moreover, the negative values for the entropy of activation found for the present rearrangement are consistent with the involvement of a three-membered transition state, but are inconsistent with a radical cleavage–recombination mechanism as in equation (2). This



(2)

Kinetics

The rate of rearrangement of the *N*-oxides (**2a**—**d**) was measured at four or five temperatures in aprotic solvents by following the appearance of the product as a function of time by u.v. techniques (Table 2). In all cases the reaction yielded the rearrangement product (**3**) in quantitative yield and proved to be first order in substrate. The first-order rate coefficients and the activation parameters are gathered in Table 2 for the reactions at 30 °C.

It is clearly shown in Table 2 that differences in rate of rearrangement exist between the *N*-oxide molecules. The morpholine *N*-oxide (**2d**) rearranged at a slightly slower rate than the piperidine analogue [k(**2a**)/k(**2d**) 4—5 in the solvent indicated]. This could be traced to the presence of the electronegative oxygen in the morpholine ring making the ⩾N–O function less nucleophilic. The lowest rates were found with the 2-methylpiperidine compound (**2b**) [*e.g.* k(**2b**)/k(**2a**) 0.14 in dioxane; 0.08 in THF]. This rate difference is attributed to steric inhibition of conjugation. Because of steric compression the *o*-nitro group is forced out of the plane of the benzene ring thus reducing its important contribution in delocalising the negative

mechanism is expected to be associated with a positive $\Delta S^{\neq}$. Indeed, a positive value for $\Delta S^{\neq}$ (+33 cal mol^{-1} K^{-1}) for the rearrangement of *N*-benzyl-*N*-methylaniline *N*-oxide to *O*-benzyl-*N*-methyl-*N*-phenylhydroxylamine found by Schöllkopf[11] was taken to indicate a radical-pair mechanism.

All results in this work and in previous studies[1,10] clearly point to a concerted process for the rearrangement of this type of *N*-aryl-tertiary amine *N*-oxide. Thus mechanistic differences can be envisaged depending on molecular environments and reaction conditions.

Experimental

Instrumentation.—N.m.r. spectra were recorded for deuteriochloroform solutions on a Brüker WH90 spectrometer with tetramethylsilane as internal standard. U.v. spectra were recorded on a Pye-Unicam SP-1800 spectrophotometer.

Solvents.—Dioxane was refluxed over sodium wire for 10 h and then fractionally distilled. Tetrahydrofuran was refluxed with lithium aluminium hydride and fractionally distilled

collecting the fraction at 66 °C. Dimethylformamide was shaken with solid KOH for 3 h and then fractionated collecting the fraction at 152 °C. Dimethyl sulphoxide was of spectroscopic grade and fractionally distilled.

Syntheses.—(A) *General procedure for preparation of the tertiary amines.* A mixture of 2,4-dinitrofluorobenzene (0.094 mol) and the appropriate secondary amine (0.282 mol) in dimethyl sulphoxide (50 ml) was stirred for 1 h with cooling. The tertiary amine was precipitated by the addition of water and recrystallised from ethanol.

(B) *General procedure for preparation of tertiary amine oxides.* To an ice-cooled solution of the appropriate amine (0.025 mol) in 98% formic acid (50 ml) was slowly added 30% hydrogen peroxide (17 ml). The mixture was stirred for 36 h at room temperature. After neutralisation with solid sodium carbonate, the mixture was extracted with chloroform (4 × 150 ml). Evaporation of chloroform produced a yellow solid which was washed several times with dry ether. The crude product was further purified by column chromatography with basic aluminium oxide. The *N*-oxide was released by elution with chloroform–methanol (3:1) and recrystallised from ethanol–ether. The ether washings were combined and the resulting semisolid was chromatographed on alumina with 1:1 chloroform–light petroleum as eluant, yielding the hydroxylamines (**3**) (Table 1). The *N*-oxide hydrochlorides were prepared by passing dry HCl gas into a solution of the *N*-oxide in chloroform to the point of turbidity. Refrigeration produced the hydrochlorides (2 HCl) which were recrystallised from ethanol–ether.

(C) *General procedure for the rearrangement of the* N-*Oxides.* A suspension of the amine oxide (1.5 g) in dry dioxane (50 ml) was heated at reflux for 1 h. The solvent was stripped off and the product was chromatographed on neutral alumina with chloroform–light petroleum as eluant, giving the *N*-aryloxyamines (**3**) (Table 1).

Hydrolysis of the N-*Aryloxyamines* (**3**).—A known weight of the aryloxyamines (**3**) was refluxed for 2 h with 3 equiv. 30% HCl. The mixture was extracted with ether. The combined ethereal extracts were dried with K_2CO_3 and the solvent was evaporated. The product was characterised as 2,4-dinitrophenol, m.p. 110—111 °C, by comparison with an authentic sample (mixed m.p., i.r.).

Kinetic Procedures.—The kinetics of the rearrangement of the *N*-oxide (**2**) were studied spectrophotometrically. A Pye–Unicam SP-1800 spectrometer with a thermostat attachment was used. The temperature of the u.v. cuvette was maintained constant within ±0.2 °C. A stock solution was prepared by dissolving freshly prepared amine oxide (**2**) in the appropriate solvent. Standard solutions of (**2**) were prepared by dilution with a thermostatted solvent.

Measurements of the absorbance at $\lambda_{max.}$ of the rearrangement product began immediately. In all the cases the 'infinity' value A_∞ was determined experimentally for each run, by leaving the solution of the amine oxide at the specified temperature until there was no further change in absorbance. All the kinetic runs were carried out in triplicate to 90% completion at four or five temperatures. Rate constants were calculated from the slope of ln $(A_\infty - A_t)$ *versus* time; the error in k_{obs} is ≤1—3% for all solvents and compounds examined. The energies of activation were calculated from the linear regression of ln k *versus* $1/T$ by the least-squares method and the entropies of activation were calculated by the standard formula derived from the absolute theory of reaction rates.

Crossover Procedure.—A mixture of (**2d**) and *N*-(2-nitrophenyl)piperidine *N*-oxide (0.2 g of each) was heated at reflux in dioxane for 10 h. The solvent was stripped off and the resulting residue was analysed by t.l.c. and showed only two spots corresponding to (**3d**) (R_F 0.36; R_F of authentic sample 0.38) and *N*-(2-nitrophenoxy)piperidine, (R_F 0.81; R_F of authentic sample 0.82).

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