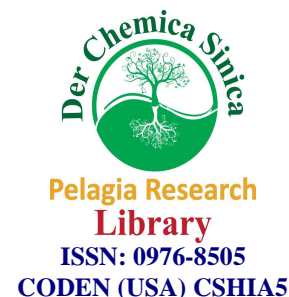




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Synthesis and thermal rearrangement of tertiary amine oxides derived from substituted piperazine

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ABSTRACT

N-Oxides are known to undergo three main thermal degradation reactions, namely deoxygenation, Cope elimination (for N-oxides containing a β -hydrogen) and Meisenheimer rearrangement. In this paper, we report a thermally induced oxygen migration from one N-oxide amine to another tert-amine group present in the same molecule through a six-membered ring transition state. The observed intramolecular oxygen migration resulted in the formation of a new isomeric N-oxide. In addition, we observed novel degradation behavior that happened after the Meisenheimer rearrangement of the newly formed N-oxide: a homolytic cleavage of the N—O bond instead of elimination of an aldehyde or a ketone that usually follows the rearrangement. This communication deals with the synthesis, N, N-dioxidation and thermal rearrangement of N- para substituted phenyl N-methyl piperazine to the corresponding O-aryl hydroxylamine. Spectral data and kinetic measurements have been discussed and tabulated.

Key words: Synthesis, N-oxide, thermal rearrangement, piperazine.

INTRODUCTION

Tertiary amine oxides have received much attention, because of the interesting thermal rearrangement often known as the Meisenheimer [1,2] rearrangement that they undergo to the corresponding O-alkyl amine. For the rearrangement, Only certain groups show a tendency for migration from N to O, such as the migration of a benzene nucleus from N to O in N-aryl piperidine which have been reported recently [3].

This paper describes the synthesis of N, N-dioxide of piperazine moieties and the thermal rearrangement to the corresponding o-aryl hydroxyl amine.

MATERIALS AND METHODS

Instrumentation in NMR spectra were recorded for identification purposes in DMSO-d₆ on varian spectrometer, chemical shifts are expressed in parts per million (ppm) (δ) with the tetramethylsilane (TMS) as the internal standard. Ultraviolet spectra were recorded on a Pye-Unicam SP 1800 spectrophotometer, melting points were determined with a Gallen Kamp apparatuses and are uncorrected.

Solvents

Dioxin was refluxed over sodium wire for 10 hours and then fractionally distilled, tetrahydrofuran was refluxed with lithium aluminum hydride and fractionally distilled, collecting the fraction at 66 °C, dimethylformamide was shaken with solid KOH for three hours and then fractionated collecting the fraction at 152 °C, dimethylsulphoxide was of spectroscopic grade and fractionally distilled.

General procedure for preparation for the tertiary amines (I) [14,15]

A mixture of substituted para fluorobenzene (0.074 moles) and the N-methyl piperazine (0.14 moles) in dimethylsulphoxide (50 ml) was stirred for 36 hours at 80 °C. The tertiary amine was precipitated by the addition of water and recrystallized from the appropriate solvent (Table 1).

General procedure for preparation of tertiary amine oxide (II)

To an ice-cooled solution of the tertiary amine (0.025 moles) in 50 mL of 98 % formic acid was added 17.5 mL of 30 % hydrogen peroxide slowly. The reaction mixture was stirred for 24 hours at room temperature. The formic acid was neutralized with solid anhydrous sodium carbonate with cooling and stirring followed by many extractions with chloroform. The chloroform extracts were dried and evaporated in vacuum and the resulting N-oxide was washed several time with dry ether, removal of the ether under reduced pressure afforded the corresponding N-oxide which recrystallized from the appropriate solvent (see Table 1).

General procedure for the rearrangement of the N-oxide (III)

A suspension of the amine oxide (IIa,II b) (1.5 g) in dry dioxane (60 mL) was heated at reflux with constant stirring for 12 hours. After cooling the solvent was removed and the solid was purified by several washing from ether, crystallization from dioxane afforded pure compound. Table 3 shows the elemental analysis of these compounds.

Table 1 Properties of the Tertiary Amines (I), Tertiary Amine Oxides (II) and rearrangement products (III)

Compound	Yield %	M.p ^o C (Lit value) Recryst. solvent	¹ H NMR (ppm) DMSO-d ₆
I a	50	94 – 95 (83 – 84) ⁽¹⁴⁾ Ethanol	1.95 (s, 3H) COCH ₃ ; 2.3 (s, 3H) N-CH ₃ ; 2.6 (t, 4H) N (CH ₂) ₂ ; 3.35 (t, 4H) N (CH ₂) ₂ ; 6.82 (d, 2H) aromatics, 7.42 (d, 2H) aromatics.
Ib	69	60 Ethanol	2.2 (s, 3H) NCH ₃ ; 2.4 (t, 4H) N (CH ₂) ₂ ; 3.4 (t, 4H) N (CH ₂) ₂ ; 6.8 (d, 2H) aromatics, 7.4 (d, 2H) aromatics; 7.8 (m, 5H) aromatics.
Ic	65	178 – 179 Methanol	2.1 (s, 3H) NCH ₃ ; 2.5 (t, 4H) N(CH ₂) ₂ ; 3.6 (t, 4H) N (CH ₂) ₂ ; 6.9 (d, 2H) aromatics, 7.6 (d, 2H) aromatics; 10.2 (s, 1H)
IIa	55	152 – 153 Chloroform-ether	2.5 (s, 3H) COCH ₃ ; 3.2 (m, 4H) N (CH ₂) ₂ ; 3.0 (s, 3H) NCH ₃ ; 4.5 (m, 4H) N (CH ₂) ₂ ; 8 (s, 4H) aromatics.
IIb	60	123 – 125 Ethanol ether	3.1 (m, 4H) N (CH ₂) ₂ ; 3.3 (s, 3H) NCH ₃ ; 3.8 (m, 4H) N (CH ₂) ₂ ; 7.6 (s, 9H) aromatics.
IIc	62	203 – 204 Methanol ether	-----
IIIa	82	187 – 188 Dioxane	1.85 (s, 3H) COCH ₃ ; 3.4 (s, 3H) NCH ₃ ; 2.6 s, 4H) N(CH ₂) ₂ ; 3.4 (s, 4H) N (CH ₂) ₂ ; 7.2 (d, 2H) aromatics, 8.2 (d, 2H) aromatics.
IIIb	82	193 – 194 Dioxane	2.6 (m, 4H) N (CH ₂) ₂ ; 3.52 (s, 3H) NCH ₃ ; 3.8 (m, 4H) N (CH ₂) ₂ ; 6.85 (d, 2H) aromatics, 7.38 (d, 2H) aromatics; 7.95 (m, 5H) aromatics.

Kinetic Procedure

The kinetics of the rearrangement of compound IIa was studied spectrophotometrically, a Pye- Unicam SP-800 spectrophotometer 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 a freshly prepared N,N-dioxide in the appropriate solvent. Solutions for the kinetic runs were prepared by dilution with a thermostated solvent to obtain $(1-4) \times 10^{-4}$ M.

Measurements of the absorbance at λ max of the rearrangement product pagan immediately, in all the cases the infinite value A_{∞} was determined experimentally for each run by leaving the solution of the N-N-dioxide at the

specified temperature until there was no further change in absorbance. All kinetics runs were carried out in triplicate to 90 % completion at four or five temperatures, rate constants were calculated from the slope of $\ln(A_{\infty} - A_0) / (A_{\infty} - A_t)$ versus time. The error in the K_{obs} is 1-3 % for all solvents. An Arrhenius plot of $\ln K$ vs $1/T$ given the energy of activation and the frequency factor from which the entropy of activation could be calculated by using equations (1) and (2):

$$\ln K - \ln A = E_{act} / RT \dots\dots\dots (1)$$

$$\ln A = \ln (eKT / h \nu) + \Delta s^* / R \dots\dots\dots (2)$$

Table 2 Kinetics of rearrangement of N, N – dioxide IIa in aprotic solvents

Solvent	ϵ	103 K70b sec -1	ΔH^\ddagger Kcal mol-1	ΔS^\ddagger Cal mol-1K-1	Eac Kcal mol-1
Dioxane	2.21	1.136	22.85	- 9.17	23.45
Tetrahydrofuran	7.58	5.50	22.89	- 8.0	23.52
Dimethylformamide	56.71	25.00	24.8	- 6.8	25.40
Dimethylsulphoxide	46.70	33.96	25.65	- 6.5	26.00

a. Last squares plots of the $\ln K$ versus $1/T$ were linear for all experiments
 b. Temperature 70 °C.
 c. Value taken from calibration curve by plotting $\ln K$ versus $1/Y$ for THF

Table 3 The elemental analysis of the rearrangement products

Compound	Formula	Elemental analysis / Calc. (Found) %		
		C	H	N
III a	$C_{13}H_{18}N_2O_3$	62.40 (61.92)	7.20 (7.63)	11.20 (11.68)
IIIb	$C_{18}H_{20}N_2O_3$	69.23 (69.66)	6.40 (6.92)	8.90 (8.00)

RESULTS AND DISCUSSION

The tertiary amines (I) were prepared by the reaction of N-methyl piperazine with p-fluoro substituted benzene [4]. Those amines were characterized by physical and spectral methods. The 1H NMR spectra are discussed and shown in table (1). The aromatic protons of the p-substituted phenyl ring give rise to AB quartet, while the heterocyclic protons appeared as a singlet for the N-CH₃ and two triplets for the heterocyclic ring. Oxidation of (I) with a mixture of H₂O₂, HCO₂H produced the corresponding N, N-dioxides (IIa, IIb) in good yields (see experimental). The structures of (IIa, and IIb) was confirmed and established by both physical and spectral data (IR, NMR.). The IR spectra showed bands at 905 – 958 and 980 cm⁻¹ which are attributed to N-O stretching vibrations. The 1H NMR spectra showed a noticeable downfield (δ) values for aromatic and non-aromatic protons, which is mainly due to the high polarity of the N-O group that was introduced upon oxidation. The aromatic protons attached to the piperazine nucleus in compound (II) appeared as a single. It seems that these protons are under the deshielding effect of both the axial N-O and the p-substituted group to approximately equal extent thus making J/ϵ so large that spectrum looked like a single A₂ system. The spectra of the piperazine ring protons appear as multiple due to the effect of the polar N-O bond which indicate that the axial and equatorial protons appears at different chemical shifts with the equatorial protons being at higher field. It is quite reasonable to assume that the oxidation occurred in two steps so that the stereochemistry was determined in the second step (figure 1).

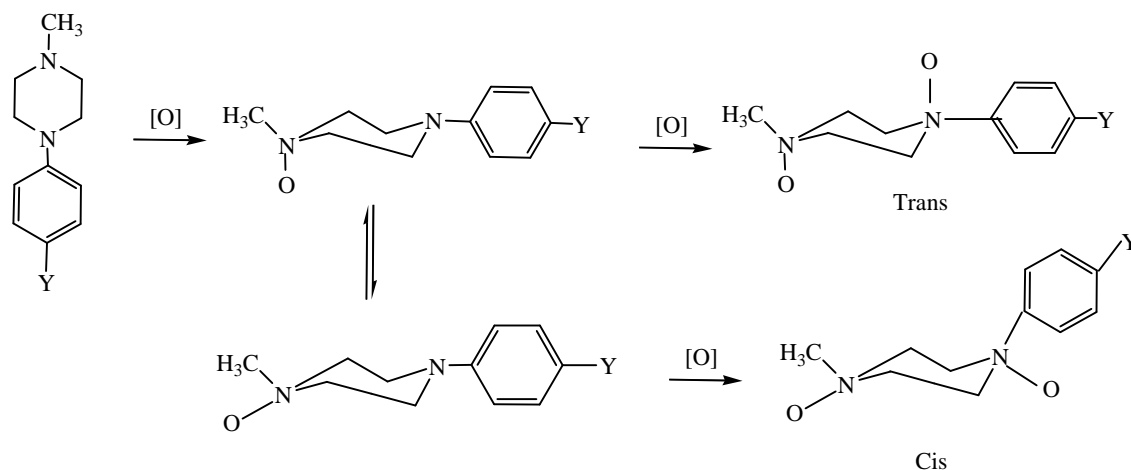


Figure 1

Accordingly the multiplet band for the piperazine protons indicates that the oxidation is stereoselective and that the oxidizing agent approaches the nitrogen atom from the axial position only giving predominantly the trans isomer. The stereo selectivity of this oxidation is presumably due to the steric factors of the bulky aryl group. These results were supported by the early work of Shvo *et al.* [5] on stereo selective formation of 1,4-dimethyl piperazine N,N-dioxide (figure 2) which showed that the N-O bond has taken the axial position and the NMR Spectrum has shown as AB quartet with the equatorial protons appearing at higher field.

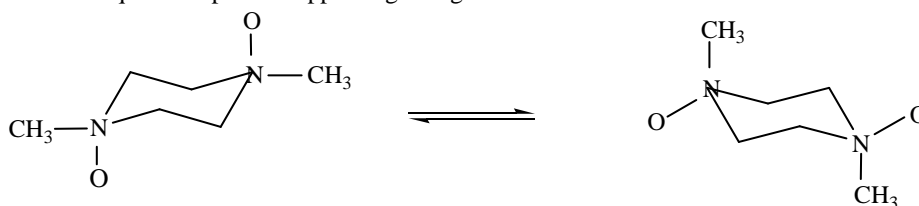
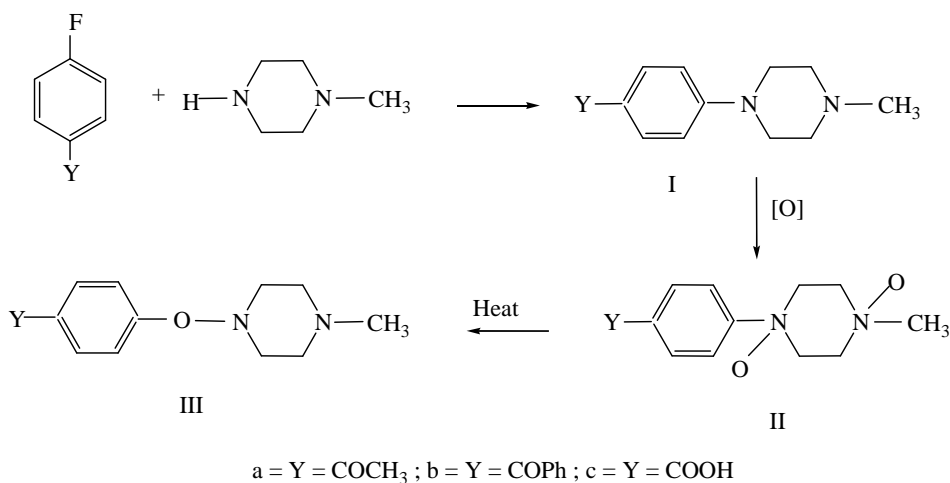


Figure 2

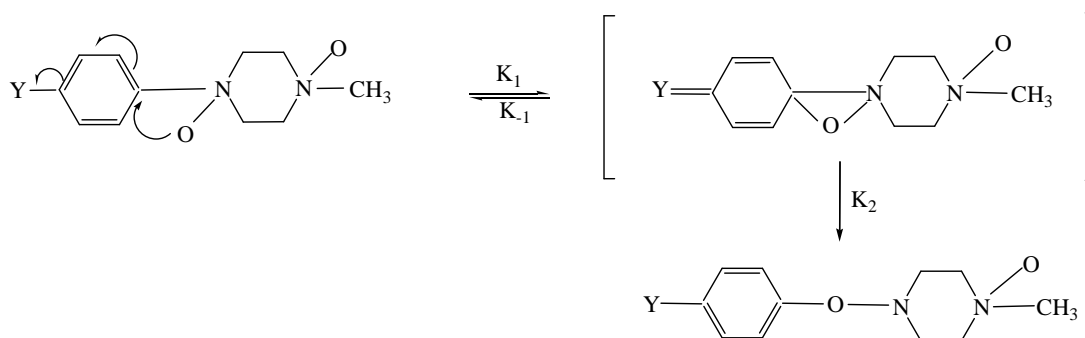


Scheme 1

It is worth mentioning at this point that oxidation of (p-carboxyl phenyl) N-methyl piperazine (Ic) gives anomalous results. The oxidation product isolated as white powder in good yield and it was insoluble in most organic solvents.

Its physical and analytical data are inconsistent with corresponding N, N-dioxide (IIc). Thus it is therefore, suspected that IIc is infarct a zwitterions (as ion formation has been reported earlier) [6]. Such compound is stable to heat and does not undergo rearrangement on pyrolysis [7]. The compounds (IIa, IIb), when heated in an aprotic solvent, undergo a novel rearrangement in which the substituted phenyl ring migrates from N to O forming the O-phenyl hydroxyl amines III in quantitative yield (Scheme 1).

Such a rearrangement is reminiscent of the thermal N-oxide isomerization discovered by Meisenheimer [1]. The electron withdrawing groups in (II) 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 groups such as (CH₃CO, PhCO), is essential for the migration to occur more over, such a group must be ortho or para to the N-O function since meta substitution to the N-oxide moiety could not induce migration of benzene nucleus upon pyrolysis of the tertiary N-oxide. This essential requirement for the electron withdrawing group to be para to the N-O group [7] is related to the mechanism of the present rearrangement. The product (IIIa, IIIb) gave analytical values and NMR spectra in full agreement with the proposed structure. In the ¹H NMR spectra the splitting pattern of the aromatic protons is clearly of the first order type and can be determined directly from the spectrum (see Table 1). The mechanism of the rearrangement is best described by an intermolecular nucleophilic substitution as shown in scheme 2, rather than a hemolytic process as suggested for Meisenheimer transformation in other systems [8-11].



Scheme 2

Kinetics

The rate of rearrangement of compound(IIa) was recorded by U.V spectroscopy in aprotic solvents, the rates were clearly first order and the rate constants were found to be sensitive to solvent.

Activation Parameters

The energy of activation for the rearrangement of (IIa) is little affected by the solvent and is generally small. The low ΔH value is consistent with concerted mechanism in which the energy lost in breaking the carbon-nitrogen bond in (IIa) is compensated for in part by the energy gained in forming the C-O bond in (IIIa). The entropy of activation is negative in all cases, indicating a considerable decrease in randomness in the activated complex, this is in accord with the notion that a three membered transition state is involved (Scheme 2).

The influence of the solvent on the rate of rearrangement is indicated in table (2), a mild acceleration in rates is observed as consequence of increased polarity of the medium. A fair correlation ($r = 0.9487$) of the observed rate of rearrangement of N, N-dioxide (IIa) with the dielectric constant of the solvent has been noticed (Figure 3). Table (2) lists the activation parameters for the rearrangement, the energy of activation increases slightly with changes in solvent polarity and is generally small.

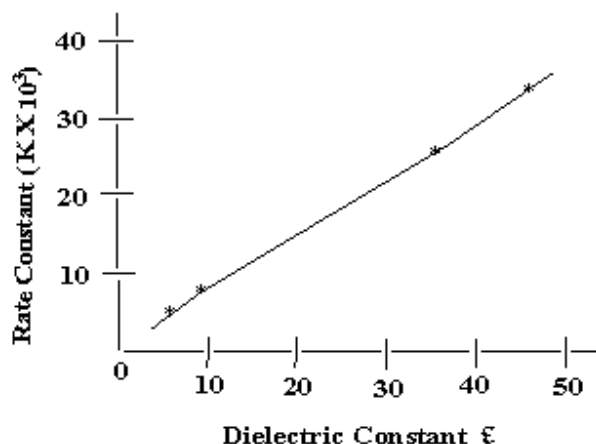


Fig. 3: Plot of the rate constant V_s the dielectric constant (ϵ) for N,N-dioxide in aprotic solvents

A compensating entropy effect is indicated in the increase in ΔS^\ddagger 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 (IIa) is partly compensated by the energy gained in forming the new C-O bond in (IIIa).

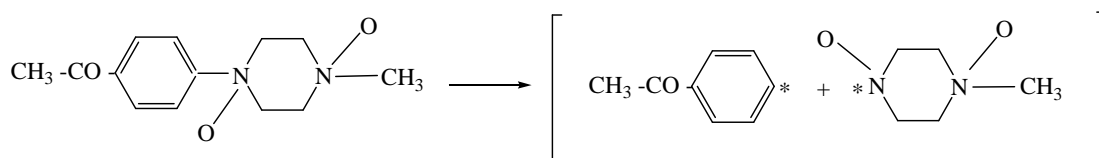


Figure 4

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 (figure 4). This mechanism is expected to be associated with a positive ΔS^\ddagger [12-13]. Thus, the negative ΔS^\ddagger by itself includes the intermediacy of free radicals (figure 2) and is more in support of a concerted process.

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