

## Synthesis and Reactions of Enamine *N*-Oxides

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A general synthetic route to enamine *N*-oxides ( $\alpha,\beta$ -unsaturated alkylamine *N*-oxides) from the corresponding 2-chloroalkylamines is described. *N,N*-Dimethyl-1-cyclohexenylamine *N*-oxide (**3a**), *N,N*-dimethyl-1-propenylamine *N*-oxide (**3b**), and *N,N*-dimethylvinylamine *N*-oxide (**3c**) were prepared as deliquescent, white crystalline solids. The VPC decomposition and the reactions of **3a** with acylating and other reagents were investigated. The thermal reaction of **3a** ( $>160^\circ\text{C}$ ) gave deoxygenation to the corresponding enamine and  $\beta$  rearrangement to 2-dimethylaminocyclohexanone. The reactions of **3a** with acetic anhydride, benzoyl chloride, and diketene gave products derived from  $\beta$  substitution of an intermediate acyloxyenammmonium salt.

The *N*-oxides of tertiary amines have been studied since the last decade of the 19th century. Current interest in these compounds stems from their use in the detergent and polymer industry and in chemotherapy. Research efforts have also focused on reaction mechanisms and on the biochemical role of amine *N*-oxides. Various aspects of the chemistry of trialkylamine *N*-oxides have been reviewed.<sup>2-5</sup>

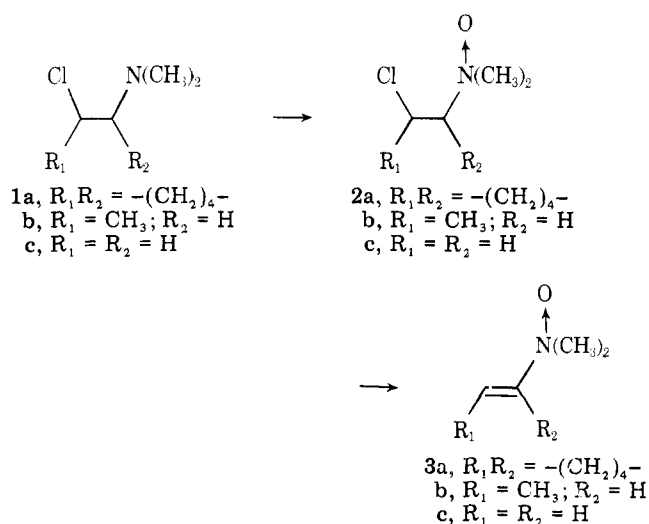
Enamine *N*-oxides ( $\alpha,\beta$ -unsaturated amine *N*-oxides) are a previously unreported class of tertiary amine *N*-oxides. We wish to report a general synthetic route to enamine *N*-oxides and some reactions exhibited by one example of this class of compounds.

### Results and Discussion

**Synthesis of Enamine *N*-Oxides.** Accumulated evidence<sup>6</sup> suggested that direct oxidation of an enamine would not yield the *N*-oxide. Some success had been achieved by pyrolyzing *trans*-2,3-bis(dimethylamino)norborene *N,N*-dioxide to 2-dimethylaminonorborene *N*-oxide;<sup>7</sup> however, investigations in other systems revealed that this was not a general reaction.<sup>8</sup>

The facile synthesis of vinylammmonium salts from the corresponding 2-haloalkylammmonium salts with alcoholic potassium hydroxide<sup>9</sup> suggested that 2-haloamine *N*-oxides might similarly be eliminated. Rate studies on the dimerization of 2-chloro- and 2-bromoalkylamines<sup>10</sup> suggested that it would be more convenient to work with the chlorides. Dimethylamine derivatives were chosen to exclude complications from the Cope elimination reaction.

*N,N*-Dimethyl-2-chlorocyclohexylamine *N*-oxide (**2a**), *N,N*-dimethyl-2-chloropropylamine *N*-oxide (**2b**), and



*N,N*-dimethyl-2-chloroethylamine *N*-oxide (**2c**)<sup>11</sup> were prepared as the stable hydrochloride salts from the corresponding

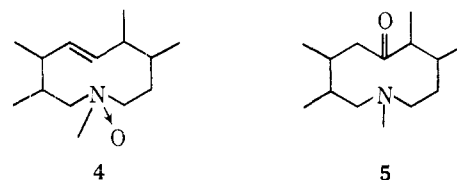
amines **1a-c** in 54–66% yield by oxidation with *m*-chloroperbenzoic acid. Elimination of freshly dried *N*-oxide hydrochlorides was achieved without side reactions by treatment with potassium *tert*-butoxide in *tert*-butyl alcohol to give *N,N*-dimethyl-1-cyclohexenylamine *N*-oxide (**3a**), *N,N*-dimethyl-*trans*-1-propenylamine *N*-oxide (**3b**), and *N,N*-dimethylvinylamine *N*-oxide (**3c**) as solutions in *tert*-butyl alcohol. The solutions were aliquoted under argon and could be reacted directly or lyophilized and sublimed under argon to give crystalline enamine *N*-oxides **3a-c** in 45–60% yield. The *trans* stereochemistry of *N*-oxide **3b** was inferred from a 13-Hz vicinal coupling constant in the NMR spectrum.<sup>12</sup>

Enamine *N*-oxides **3a-c** are extremely deliquescent, white crystalline solids which are stable for months when stored at  $0^\circ\text{C}$  under argon either as crystals or in solution. However, when the crystals are allowed to oil in air, the resultant hydrates decompose within a few hours.

Cyclohexenylamine *N*-oxide **3a**, with the largest alkyl residue, is the only enamine *N*-oxide of the three which is soluble in benzene and carbon tetrachloride. Likewise, **3a** is the most thermally stable *N*-oxide of the three, and it withstands acidification or basification at  $60^\circ\text{C}$ , whereas the acid salts of **3b** and **3c** readily decompose. The attempted formation of the hydrochloride and picrate derivatives of propenylamine *N*-oxide **3b** resulted in the isolation of dimethylamine salts.

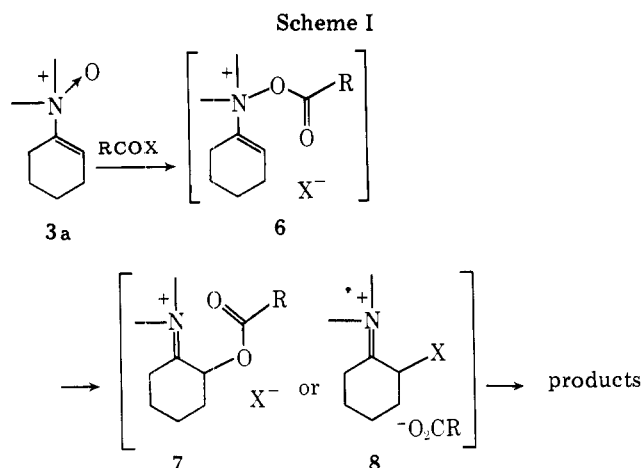
**Reactions of *N,N*-Dimethyl-1-cyclohexenylamine *N*-Oxide (**3a**).** Cyclohexenylamine *N*-oxide **3a** was chosen as a model for study of the reactions of the enamine *N*-oxide system. The reactions were run either on an aliquot of **3a** in *tert*-butyl alcohol or on freshly sublimed **3a**. After aqueous hydrolysis, yields were determined by VPC.

**VPC Decomposition of **3a**.** Injection of a benzene solution of **3a** into the VPC instrument at injection port temperatures from  $170$  to  $260^\circ\text{C}$  gave cyclohexanone (6%), *N,N*-dimethyl-1-cyclohexenylamine (20%), and 2-dimethylaminocyclohexanone (13%) as the major products. The formation of 2-dimethylaminocyclohexanone has precedent in the rearrangement of *N*-oxide **4** to **5** upon heating in an acidic me-

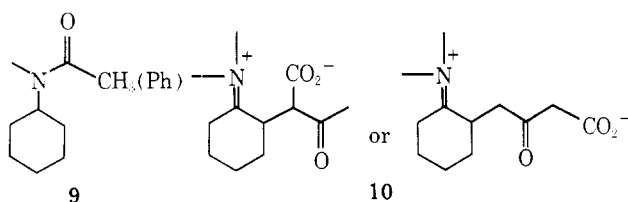


dium<sup>13</sup> and in the formation of *o*- and *p*-dimethylaminophenols from dimethylaniline *N*-oxide upon pyrolysis.<sup>14</sup>

**Reactions of **3a** with Acylating Agents.** The results of the reactions of **3a** with acetic anhydride, benzoyl chloride, and diketene are consistent with the operation of one major reaction pathway (Scheme I). The initially formed acyloxyenammmonium salt **6** yields the  $\beta$ -substitution intermediates **7** and **8**, which are hydrolyzed to the observed products, 2-



substituted cyclohexanones. The detailed mechanisms for the transformations of **6** to **7** and **8** are open to speculation. No CIDNP signals were observed when the reactions were initiated in the probe of an NMR instrument, but this result does not exclude a radical mechanism. Another product, cyclohexanone, is probably the result of deoxygenation followed by hydrolysis. If some type of demethylation reaction to form hydrolyzable methylamine derivatives was occurring, one would expect to find monomethylamides in the product mixtures. However, only dimethylamides were isolated. The expected Polonovski demethylation product **9** was also absent



from the product mixtures. In the reaction with diketene, the expected intermediate **10** must decarboxylate at some stage in the reaction workup.

The reactions of trialkylamine *N*-oxides with trifluoroacetic anhydride have been studied by Potier and co-workers.<sup>15</sup> In a number of examples they found that the intermediate acyloxammonium salts decomposed to give immonium trifluoroacetates as the final products. However, the reaction of **3a** with trifluoroacetic anhydride gave, after hydrolysis, 2-trifluoroacetoxycyclohexanone (32%) and cyclohexanone (18%) as the major products, a result consistent with other reactions of **3a** with acylating reagents (Scheme I). Before aqueous hydrolysis, no vinylimmonium salts corresponding to those of Potier and co-workers could be detected by NMR spectroscopy.

**Other Reactions of 3a.** The reaction of **3a** with *n*-butyllithium gave, after hydrolysis, cyclohexanone (48%) and formaldehyde (present in an undetermined amount in the aqueous phase). The formaldehyde presumably arose from one of the methyl groups of **3a**, a reaction which has analogy to the reactions of *N,N*-dimethylaniline *N*-oxides with *n*-butyllithium and phenyllithium, where monomethylanilines were the major products.<sup>16</sup>

Reaction of **3a** with titanium tetrachloride gave, after hydrolysis, 2-chlorocyclohexanone (47%) and cyclohexanone (19%). This result suggests a mechanism similar to the one proposed for the reaction of **3a** with acylating agents (Scheme I).

The following reagents did not react with **3a**: methyl acrylate, 2-cyclohexenone, *m*-chloroperbenzoic acid, cyclopentadiene, and diazomethane.

## Experimental Section

**General.** Melting points were determined on a Thomas-Hoover "unimelt" capillary melting point apparatus and are corrected. The IR spectra were determined on Perkin-Elmer grating spectrophotometers, Model 237B or 337. NMR spectra were run on Varian spectrometers, Model T-60, A-60, or HA-100, and are reported in ppm downfield from tetramethylsilane as an internal standard. The mass spectra were determined on Hitachi Perkin-Elmer instruments, Model RMU-6D or RMU-6E, and the UV spectra on a Cary Model 14. VPC analyses and/or isolations were performed on F & M Scientific Hewlett-Packard research chromatographs, Model 5750 or 810 (thermal conductivity detectors), using 0.25-in columns packed with 20% silicone rubber UC-W98 on 60–80 mesh Chromosorb W, 10% Carbowax 20 M on 60–80 mesh Chromosorb P, or 15% diethylene glycol adipate (LAC 446) on 60–80 mesh Chromosorb W, or on a Wilkens Instrument and Research, Inc., Aerograph "Hy-F1" Model A-600-B instrument (flame ionization detector), using a 0.125-in column packed with 10% Carbowax 20 M on Chromosorb W. All columns were 4–6 ft in length. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Reactions requiring an inert atmosphere were conducted in an atmosphere of nitrogen or argon, which had been passed through a column of Drierite. When anhydrous conditions were necessary, glassware was dried at 125 °C for 5 h and allowed to cool in a vacuum desiccator. Transfer of all moisture-sensitive compounds was accomplished in a dry atmosphere. Solutions were concentrated on a Büchi rotary evaporator. All solvents were reagent grade or better and were stored over Linde Type 3A or 4A molecular sieves. *tert*-Butyl alcohol was distilled from calcium hydride. Potassium *tert*-butoxide was obtained from MSA Corp. Benzene-*d*<sub>6</sub> was obtained from Aldrich Chemical Co. Gaseous HCl was dried by passage through a column of calcium chloride.

***N,N*-Dimethyl-2-chlorocyclohexylamine *N*-Oxide (**2a**) Hydrochloride.** To a stirred, ice bath cooled solution containing 20.0 g (0.12 mol) of *N,N*-dimethyl-2-chlorocyclohexylamine<sup>17</sup> (**1a**) in dry ether was added dropwise a solution containing 25.2 g (0.12 mol) of 85% *m*-chloroperbenzoic acid in dry ether. The reaction was stirred overnight at room temperature, cooled in an ice bath, and treated with 1.1 equiv of dilute HCl. After washing the ether phase with water, the combined aqueous phase was washed with ether, concentrated, dried in vacuo at 65 °C for several days, and recrystallized from acetone to give 14.3 g (54%) of **2a** hydrochloride as white crystals: mp 129–132 °C; IR (Nujol mull) 2800–2300  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  5.13 (m, 1), 4.53 (m, 1), 3.70 (s, 6), and 1.88 (m, 8). Picrate of **2a**: mp 153.5–157.5 °C.

Anal. Calcd for  $\text{C}_{14}\text{H}_{19}\text{ClN}_4\text{O}_8$ : C, 41.33; H, 4.71; Cl, 8.71; N, 13.78. Found: C, 41.32; H, 4.62; Cl, 8.81; N, 13.62.

***N,N*-Dimethyl-2-chloropropylamine *N*-Oxide (**2b**) Hydrochloride.** This was prepared similarly to **2a** to give **2b** hydrochloride in 65% yield as white prisms: mp 112–113.5 °C; IR (Nujol mull) 2800–2300  $\text{cm}^{-1}$ ; NMR ( $\text{D}_2\text{O}$ )  $\delta$  5.1–4.4 (m, 1), 4.12 (d, 2,  $J = 6$  Hz), 3.67 (s, 6), and 1.65 (d, 3,  $J = 6$  Hz). Picrate of **2b**: mp 117.5–120.5 °C.

Anal. Calcd for  $\text{C}_{11}\text{H}_{15}\text{ClN}_4\text{O}_8$ : C, 36.03; H, 4.12; Cl, 9.67; N, 15.28. Found: C, 36.18; H, 4.03; Cl, 9.54; N, 15.38.

***N,N*-Dimethyl-2-chloroethylamine *N*-Oxide (**2c**) Hydrochloride.** This was prepared similarly to **2a**, giving **2c** in 66% yield as off-white needles, mp 128–130 °C (lit.<sup>11</sup> mp 125–127 °C).

***N,N*-Dimethyl-1-cyclohexenylamine *N*-Oxide (**3a**).** The following represents a typical procedure. To a stirred solution containing 2.24 g (20.0 mmol) of potassium *tert*-butoxide in 40 mL of *tert*-butyl alcohol was added dropwise a solution containing 2.14 g (10.0 mmol) of **2a** hydrochloride in 20 mL of *tert*-butyl alcohol. The order of addition did not affect the yield of product. A fine precipitate formed during the addition. The reaction mixture was stirred for several hours and aliquoted into ten equal portions. Lyophilization and sublimation of an aliquot gave, typically, 70–85 mg (50–60%) of **3a** as a deliquescent, white, crystalline solid: mp 94.5–96 °C; decomposition temp, 160 °C; IR ( $\text{CCl}_4$ ) 3012, 2938, 2860, 2839, 1685, 1673, 1456, 1446, 1405, 1379, 1367, 1030, 969, 937, 913, 865  $\text{cm}^{-1}$ ; NMR ( $\text{C}_6\text{D}_6$ )  $\delta$  6.75 (m, 1), 3.08 (s, 6), 2.5–2.2 (m, 2), 2.2–1.9 (m, 2), and 1.8–1.3 (m, 4); mass spectrum (80 eV), *m/e* (relative intensity) 141 (14), 125 (16), 124 (15), 113 (19), 110 (13), 96 (27), 84 (100), 70 (29), 68 (30), 58 (20), 56 (13), 55 (19), 44 (13), 43 (37), 42 (43), 41 (17), and 39 (18); UV max (95% ethanol) end absorption. Picrate of **3a**: mp 122–123.5 °C.

Anal. Calcd for  $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_8$ : C, 45.41; H, 4.90; N, 15.13. Found: C, 45.29; H, 4.81; N, 15.04.

***N,N*-Dimethyl-1-propenylamine *N*-Oxide (**3b**).** This was prepared similarly to **3a** to give **3b** in 45% yield as a deliquescent, white, crystalline solid: mp 122–123.5 °C; decomposition temp, 122 °C; IR

(CHCl<sub>3</sub>) 1665, 1462, 1440, 1385, 1380, 950, 934, and 900 cm<sup>-1</sup>; NMR (C<sub>6</sub>D<sub>6</sub>) δ 6.87 (d of q, 1, *J* = 13, 7 Hz), 5.92 (d of broad peaks, 1, *J* = 13 Hz), 2.87 (s, 6), and 1.45 (d of d, 3, *J* = 7, 2 Hz).

***N,N*-Dimethylvinylamine *N*-Oxide (3c).** This was prepared similarly to 3a to give 3c in 52% yield as deliquescent, white, feathery crystals: mp 96–100 °C; decomposition temp, 145 °C; IR (CHCl<sub>3</sub>) 1650, 1465, 1450, 952, 910, and 895 cm<sup>-1</sup>; NMR (C<sub>6</sub>D<sub>6</sub>) δ 6.3–6.1 (m, 2), 4.9–4.7 (m, 1), and 2.85 (s, 6).

**Reactions of *N,N*-Dimethyl-1-cyclohexenylamine *N*-Oxide (3a).** **General.** Except where noted, the reactions of 3a were run under an atmosphere of nitrogen or argon either on an aliquot of 3a in *tert*-butyl alcohol or on a sublimed sample of 3a dissolved in benzene-*d*<sub>6</sub> in an NMR tube. Reactions were monitored by NMR spectroscopy and worked up by addition of water and extraction with CHCl<sub>3</sub>. The CHCl<sub>3</sub> extract was washed with saturated NaCl and dried (MgSO<sub>4</sub> or CaSO<sub>4</sub>). The products were isolated by VPC and identified by comparison of VPC retention times and spectra with those of authentic samples. The authentic samples were obtained commercially, as gifts,<sup>18</sup> or by synthesis using known routes. Yields are based on comparison of the VPC peak area of a known amount of hydrocarbon standard, which had been added to the reaction mixture before workup, with the product peak areas, which had been corrected by determination of the response factor of the authentic sample vs. the hydrocarbon standard.

**VPC Decomposition of 3a.** Injection of part of a solution containing 38.9 mg (0.28 mmol) of 3a and 11.2 mg (0.061 mmol) of *n*-tridecane (as standard) in 0.25 mL of benzene-*d*<sub>6</sub> onto a column packed with silicone rubber UC-W98 with an injection port temperature of 270 °C and a thermal conductivity detector temperature of 230 °C gave cyclohexanone (6%), *N,N*-dimethyl-1-cyclohexenylamine (11; 20%), and 2-dimethylaminocyclohexanone (13%) as the major products. Coinjection of water with the sample resulted in an enhanced yield of cyclohexanone and the disappearance of 11. Similar results were obtained at an injection port temperature of 170 °C.

**Reaction of 3a with Acetic Anhydride.** A 71.4-mg (0.51 mmol) sample of 3a was treated with 57 mg (0.56 mmol) of acetic anhydride to give, after aqueous workup, cyclohexanone (4%), *N,N*-dimethylacetamide (20%), and 2-acetoxycyclohexanone (78%). Similar results were obtained when the reaction was run in *tert*-butyl alcohol or CHCl<sub>3</sub>.

**Reaction of 3a with Benzoyl Chloride.** A 73.7-mg (0.522 mmol) sample of 3a was treated with 80.6 mg (0.57 mmol) of benzoyl chloride to give, after aqueous workup, cyclohexanone (2%), 2-chlorocyclohexanone (25%), benzoic acid (46%), *N,N*-dimethylbenzamide (32%), and 2-benzoxycyclohexanone (20%).

**Reaction of 3a with Diketene.** A 50.7-mg (0.36 mmol) sample of 3a was treated with 30.3 mg (0.36 mmol) of diketene (freshly distilled) to give, after aqueous workup with dilute HCl, cyclohexanone (15%), *N,N*-dimethylacetamide (15%), and 2-acetonylcyclohexanone (14%) as the major products.

**Reaction of 3a with Trifluoroacetic Anhydride.** To a 46.0-mg (0.33 mmol) sample of 3a in 1 mL of CD<sub>2</sub>Cl<sub>2</sub> at -78 °C was added 68.5 mg (0.33 mmol) of trifluoroacetic anhydride. A yellow color formed immediately and gradually turned dark orange. After aqueous workup, the major products identified were 2-trifluoroacetoxycyclohexanone (32%) and cyclohexanone (18%).

**Reaction of 3a with *n*-Butyllithium.** A 55.8-mg (0.40 mmol) sample of 3a was treated with 0.25 mL (0.40 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. After shaking the reaction mixture for 10 min, 0.5 mL of D<sub>2</sub>O was added. NMR analysis of the aqueous phase indicated the presence of some unreacted 3a. Aqueous workup gave cyclohexanone (48%). The presence of formaldehyde in the aqueous phase was inferred from a VPC retention time comparison with a formalin solution on a column packed with Carbowax 20M (flame ionization detector).

**Reaction of 3a with Titanium Tetrachloride.** To a 34.4-mg (0.24 mmol) sample of 3a was added 26.8 mg (0.24 mmol) of titanium tetrachloride at 0 °C. The solution turned brown immediately. After aqueous workup, the major products were 2-chlorocyclohexanone (47%) and cyclohexanone (19%).

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**Registry No.**—1a, 4580-81-8; 1b, 108-14-5; 1c, 107-99-3; 2a HCl, 66172-49-4; 2a picrate, 66172-51-8; 2b HCl, 66172-52-9; 2b picrate, 66172-54-1; 2c HCl, 66172-55-2; 3a, 66172-56-3; 3a picrate, 66172-57-4; 3b, 66172-58-5; 3c, 66172-59-6; cyclohexanone, 108-94-1; *N,N*-dimethylacetamide, 127-19-5; 2-acetoxycyclohexanone, 17472-04-7; 2-chlorocyclohexanone, 822-87-7; benzoic acid, 65-85-0; *N,N*-dimethylbenzamide, 611-74-5; 2-benzoxycyclohexanone, 7472-23-3; *N,N*-dimethylacetamide, 2044-64-6; 2-acetonylcyclohexanone, 6126-53-0; 2-trifluoroacetoxycyclohexanone, 66197-69-1.

## References and Notes

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## Synthesis of *N,N,N',N'*-Tetrasubstituted 1,1-Diaminoethylenes and Their Thermal Rearrangement

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Various *N,N,N',N'*-tetrasubstituted 1,1-diaminoethylenes (5) have been prepared by the reaction of *N,N*-disubstituted (trimethylsilylethynyl)amines (silylaminines 1, 2, and 3) with secondary amines. At 200 °C in amine solvent, 5 afforded a mixture of [1,3] alkyl rearrangement products (7) and dealkylation products (8 and/or 9).

*N,N,N',N'*-Tetrasubstituted 1,1-diaminoethylenes are the simplest enamines having two tertiary amino groups on the same carbon and may be useful intermediates for organic

synthesis. Several 1,1-bis(disubstituted amino)ethylenes have been prepared by the reaction of a secondary amine with a ketene acetal<sup>1</sup> or triethyl orthoacetate,<sup>2</sup> dimethylacetamide