Oxidation of Nitrosamines. 2. Conversion of *N*-Nitroso-1,2,3,6-tetrahydropyridine, via the Epoxide, to *N*-Nitroso-4-hydroxy-1,2,3,4-tetrahydropyridine

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Oxidation of *N*-nitroso-1,2,3,6-tetrahydropyridine (**2**) with *m*-chloroperbenzoic acid gave the corresponding 3,4-oxide **4**. Under mild basic conditions the epoxide was converted to the allylic alcohol *N*-nitroso-4-hydroxy-1,2,3,4-tetrahydropyridine (**6**) through an E2 elimination. Parallel experiments with *N*-benzoyl-3,4-epoxypiperidine (**11**) gave the expected diol **12**. Treatment of *N*-nitroso-*trans*-3,4-dibromopiperidine (**9**) with silver acetate under basic conditions resulted in the formation of *N*-nitroso-4-acetoxy-1,2,3,4-tetrahydropyridine (**8**), as well as **2**. Compound **8** was also the major product from the oxidation of *N*-nitroso-1,2,3,4-tetrahydropyridine (**3**) with lead tetraacetate.

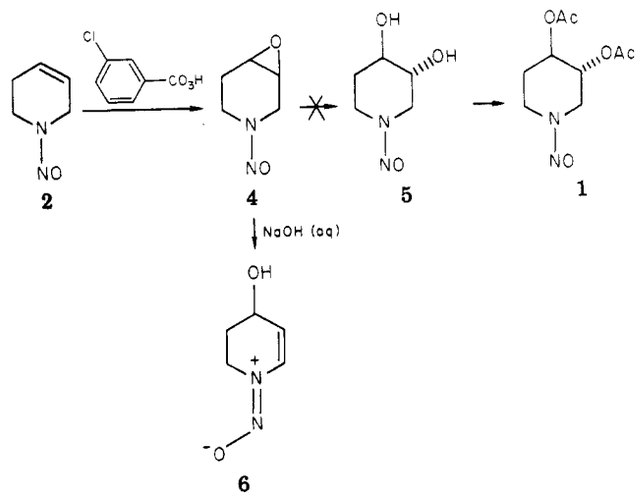
N-Nitrosamines are among the most potent carcinogens known.[1] Keefer and Fodor[2] determined that nitrosamines tend to lose an α-proton to form carbanions in basic solution. That work supported the idea of enzymatic α-proton removal with concomitant hydroxylation as originally proposed by Druckrey et al.[3] Since then, the hypothesis of α-hydroxylation has been widely accepted as a possible first step in nitrosamine carcinogenesis.[4] In compounds such as *N*-nitroso-3,4-epoxypiperidine (**4**) and *N*-nitroso-*trans*-3,4-dibromopiperidine (**9**) the substituents not only help shape the nitrosopiperidine ring but also are reactive functional groups. Our studies indicate that the behavior of these compounds in basic media is governed by the acidity of the protons α to the nitroso function. This should be an important factor in the study of structure–carcinogenicity relationships of nitrosamines.

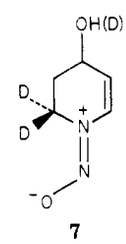
Results and Discussion

We found that nitroso-1,2,3,6-tetrahydropyridine **2** was a product of the decarboxylation of nitrosopipecolic acid.[5] Initially, we expected that subsequent oxidation of **2** with lead tetraacetate would result in the formation of **1**, but when **2** was treated with lead tetraacetate under various conditions, no addition of acetoxy groups across the double bond was observed. However, the various attempts to prepare compound **1** provided us with some interesting information about the chemistry of nitroso-1,2,3,6-tetrahydropyridine **2**, the 3,4-epoxy derivative **4**, and the 3,4-dibromo adduct **9**.

We expected the logical pathway to the preparation of **1** to involve the epoxidation of **2** with *m*-chloroperbenzoic acid to the corresponding epoxy adduct **4**, followed by basic hydrolysis to the trans diol **5** which could then be diacylated to the desired product. The oxidation of **2** proceeded smoothly, and **4** was obtained in good yield. When the epoxide was submitted to basic hydrolysis, the product obtained was *N*-nitroso-4-hydroxy-1,2,3,4-tetrahydropyridine (**6**).

A recent communication by Kupper and Michejda,[6] concerning the formation and equilibration of vinylic and allylic nitrosamines, has shown that β-tosylates of nitrosamines undergo E1cB base-catalyzed elimination. However, β-substituted nitrosamines with poorer leaving groups undergo E2 reactions. Since only one elimination product was observed from the base-catalyzed opening of epoxide **4**, we believed that an E1cB process was taking place. When the reaction was carried out in 20% sodium deuterioxide in D_2O at room temperature, no deuterium exchange was detected. After 1 h at 25 °C, a 26% conversion to the allylic alcohol **6** took place. The extent of reaction could easily be monitored on the NMR spectrometer by the appearance of the olefinic protons, one α to the nitroso group at δ 7.54 (syn) and 7.70 (anti) and the β one at δ 5.48. At 68 °C the elimination took place rapidly to the undeuterated alcohol **6**, and the H–D exchange began to occur at this stage forming the dideuterated derivative **7**. At a reaction time of 15 min the ratio of **6**:**7** was 2:1; at 45 min only compound **7** was present. The ratio calculations were based on the disappearance of the α-methylene signals at δ 3.6–4.1. These results rule out the possibility of an E1cB mechanism and favor a second-order elimination. Due to the acidity of the hydrogens α to the nitroso group,[7] re-





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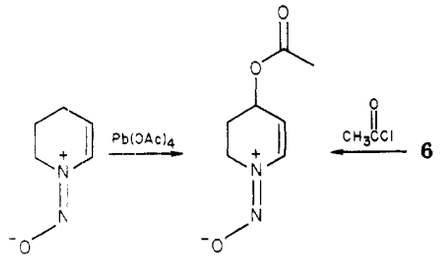
moval of one of these protons is a favored process, forming only one allylic alcohol. Loss of a proton at C-5, β to the nitrosamine function, to form the other possible allylic alcohol does not take place. As described previously,[5] the major product from the lead tetraacetate oxidation of *N*-nitroso-1,2,3,4-tetrahydropyridine (**3**) was the acylated allylic alcohol **8**. For comparison, the allylic alcohol **6** was



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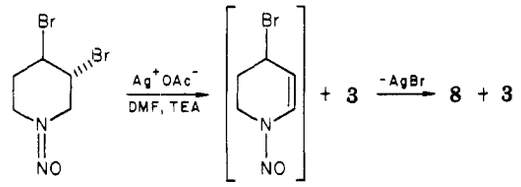
acylated in 88% yield to **8** with acetyl chloride–pyridine in methylene chloride. The physical and spectral properties of this compound were identical with those of the oxidation product of **3**. Reactions at the carbon–carbon double bond of **3** also take place under the experimental conditions used,[5] but the most important reaction here is the allylic oxidation. The activating group in this molecule is the double bond.[8]

The dibromo compound **9** seems to dehydrobrominate in a similar fashion to the epoxide ring opening. This



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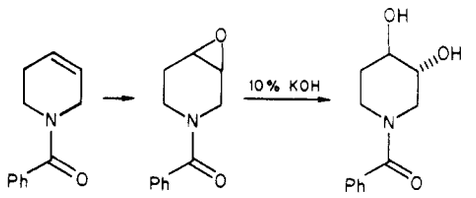
compound was prepared from *N*-nitroso-1,2,3,6-tetrahydropyridine (**2**) as described by Lijinsky et al.[9] The dibromide **9** was dissolved in a 1:1 solution of *N*,*N*-dimethylformamide and triethylamine and stirred at 25 °C for 60 h with excess silver acetate. Gas chromatographic analysis of the reaction mixture indicated that 59% of it was the tetrahydropyridine **2** and that 41% was *N*-nitroso-4-acetoxy-1,2,3,4-tetrahydropyridine (**8**). The latter resulted from the elimination of HBr and the displacement of the remaining bromide with an acetoxy group. The method described by Moreland[10] for the displacement of a bromide with an acetoxy group was not successful in the case of **9**. However, when silver acetate was added to the solution of **9** in acetic acid, acetone, and triethylamine, and refluxed for 48 h, 47% of **8** was formed, together with 16% of **2** and 8% of *N*-nitroso-1,2,3,4-tetrahydropyridine (**3**). The rest of the mixture was the starting material. The tetrahydropyridine **3** was formed by the epimerization of **2**.[6] The dibromide **9** in methylene chloride was inert to silver acetate without a base catalyst. To further demonstrate that the apparently abnormal epoxide opening to the allylic alcohol **6** was actually due to the activation of the α position by the nitroso group, we studied *N*-benzoyl-1,2,3,6-tetrahydropyridine (**10**). This compound was oxidized to the 3,4-epoxy derivative **11** with *m*-chloroperbenzoic acid. The epoxide **11** was refluxed for



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3 h in 10% aqueous potassium hydroxide to give the trans diol **12**, constituting a normal base-catalyzed epoxide opening. The conditions for the opening were sufficiently mild to prevent the loss of the benzoyl group.

The allylic alcohol formation has been observed with simple alkene oxides. Sheng[11] converted cyclooctene oxide to the allylic alcohol by the use of lithium phosphate or potassium *tert*-butoxide. Kissel and Rickborn[12] cleaved cyclohexene oxide with several lithium alkylamides to a series of alcohols; one of them was the allylic alcohol. A general procedure for the conversion of epoxides to allylic alcohols via hydroxy selenides was developed by Sharpless and Lauer.[13] Our work demonstrates a mild but direct formation of an allylic alcohol in the presence of an activating group (N–NO) β to the epoxide ring.[14]

Experimental Section

Ultraviolet spectra were run as aqueous solutions on a Beckman Acta MVI spectrophotometer. Melting points were determined on an Electrothermal capillary melting point apparatus and were not corrected. Proton magnetic resonance spectra were measured on a Varian XL-100 using $CDCl_3$ (0.5% Me_4Si) as the solvent. The IR spectra were obtained on a Perkin-Elmer 467 spectrophotometer. Mass spectra were taken on a Finnigan 3300 mass spectrometer equipped with a Finnigan 6000 MS data system. Gas chromatographic analyses were carried out on a Shimadzu Model 4BM chromatograph equipped with a Hewlett-Packard 18652A A/D converter coupled to the recorder of a flame-ionization detector. An 8 ft, 8% HI-EFF-1BP coated on Gas Chrom Q column was used (Applied Science Laboratories, Inc., State College, PA). Elemental analyses were done by Galbraith Laboratories, Inc., Knoxville, TN.

***N*-Nitroso-3,4-epoxypiperidine (4).** A partial solution of 17.5 g (0.101 mol) of *m*-chloroperbenzoic acid in 125 mL of chloroform was cooled to 5 °C. A 0.5 M solution of 8.39 g (0.075 mol) of *N*-nitroso-1,2,3,6-tetrahydropyridine (**2**)[5] in chloroform was added dropwise. The mixture was stirred for 24 h at toom temperature, washed with 10% sodium hydroxide solution, and dried over sodium sulfate. The solution was filtered through a pad of magnesium sulfate, and the solvent was removed under vacuum. The crude product was fractionally distilled to give 6 g (63%) of the epoxide **4**: bp 85 °C (0.25 mmHg); IR (film) 3010, 2920, 1510, 1424, 1355, 1338, 1320, 1160 cm^{-1}; NMR ($CDCl_3$) δ 2.0–2.4 (m, 2 H), 3.37 (t, 1 H), 4.57 (t, 1 H), 4.65 (br, 1 H), 3.48 (br, 1 H), 3.8–4.8 (m, 2 H). Anal. Calcd for $C_5H_8N_2O_2$: C, 46.86; H, 6.29; N, 21.86. Found: C, 46.69; H, 6.09; N, 21.91.

***N*-Nitroso-4-hydroxy-1,2,3,4-tetrahydropyridine (6).** A solution of 480 mg (3.75 mmol) of the epoxide **4** in 4 mL of 10% aqueous sodium hydroxide was heated to 78 °C in an oil bath for 15 min. The solution was allowed to cool to 25 °C, and the product was then extracted with methylene chloride. The solution was dried over sodium sulfate and filtered, and the solvent was removed under vacuum. The residual oil was vacuum distilled to give 426 mg (89%) of *N*-nitroso-4-hydroxy-1,2,3,4-tetrahydropyridine (**6**): bp 69–70 °C (0.1 mmHg); IR (film) 3380, 3090, 1650, 1440, 1300 cm^{-1}; NMR ($CDCl_3$) δ 1.86–2.2 (m, 3 H), 3.6 (m, 1.2 H, syn), 4.1 (m, 0.8 H, anti), 5.48 (m, 1 H), 7.54 (d, 0.3 H, syn)

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7.70 (d, 0.7 H, anti); UV λ_{max} 280 (ϵ 10565), 206 (7140). Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.86. Found: C, 46.64; H, 6.38; N, 21.73.

***N*-Nitroso-4-acetoxy-1,2,3,4-tetrahydropyridine (8).** A 0.5 M solution of 167 mg (1.3 mmol) of enamine **6** in methylene chloride was cooled to 5 °C. To this was added 0.158 mL (2 mmol) of dry pyridine followed by the slow addition of acetyl chloride. The resulting mixture was stirred at 5 °C under nitrogen for 30 min. The pyridinium chloride was removed by filtration. The solution was washed with 10% hydrochloric acid, followed by 5% aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and evaporated under reduced pressure to give a yellow residue. Vacuum distillation of the crude product gave 194 mg (88%) of **8**: bp 48–49 °C (0.2 mmHg); IR (film) 3080, 2920, 1733, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.9–2.18 (2 m, 2 H), 2.06 (s, 3 H), 3.42 (m, 1 H), 4.18 (d of t, 1 H), 5.40 (m, 2 H, CH and O–CH), 7.6 (d, 0.17 H, syn), 7.8 (d, 0.73 H, anti); MS, *m/z* (rel intensity) 170 (M^+, 0.07), 155 (0.8), 127 (0.07), 111 (0.07), 81 (30), 80 (28), 59 (11.25), 43 (100). Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.18; H, 5.97; N, 16.42.

Sodium Deuterioxide-Induced Ring Opening of Epoxide 4. A solution of 139 mg (1.08 mmol) of **4** in 2 mL of 20% sodium deuterioxide in deuterium oxide was heated to 68 °C for 15 min. GLC analysis of the reaction mixture indicated that most of the epoxide **4** had opened to the allylic alcohol. The nuclear magnetic resonance spectrum of the product at this stage indicated that 33.5% of the allylic alcohol was the dideuterated form **7**. When the reaction mixture was heated to 68 °C for 45 min, only compound **7** was present. The reaction was worked up by extraction of the product into methylene chloride. The organic layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent gave 104 mg of **7** which was pure enough for NMR analysis: NMR ($CDCl_3$) δ 1.78–2.2 (m, 3 H), 4.46 (m, 1 H), 5.48 (m, 1 H), 7.56 (d, 0.26 H), 7.72 (d, 0.74 H).

***N*-Benzoyl-1,2,3,6-tetrahydropyridine (10).** A solution of 4 g (0.048 mol) of 1,2,3,6-tetrahydropyridine in 5% aqueous sodium hydroxide solution was cooled to 5 °C. To this was added 5.8 mL (0.05 mol) of benzoyl chloride, and the mixture was then stirred at 25 °C for 30 min. The product was extracted with methylene chloride and washed with 10% hydrochloric acid and then with 5% sodium bicarbonate. The solution was dried over potassium carbonate and the solvent removed under vacuum, leaving a clear oil which crystallized on standing. Recrystallization of the crude product from aqueous ethanol gave 3.9 g (97%) of **10**: mp 60.5–61.5 °C (lit.[15] mp 60–62 °C); IR (KBr) 3020, 1640, 1600 cm^{-1}.

***N*-Benzoyl-3,4-epoxypiperidine (11).** A partial solution of 2.9 g (0.017 mol) of *m*-chloroperbenzoic acid in 17 mL of chloroform was cooled to 5 °C. A 0.5 M solution of 2.1 g (0.011 mol) of *N*-benzoyl-1,2,3,6-tetrahydropyridine (**10**) in chloroform was added dropwise and the resulting solution stirred at room temperature overnight. The mixture was washed with 10% aqueous sodium hydroxide, and the organic layer was separated and dried over sodium sulfate. Evaporation of the solvent under vacuum gave 2.6 g of a clear gum:[16] NMR ($CDCl_3$) δ 2.6 (m, 2 H), 3.34 (br, 4 H), 3.80 (br, 1 H), 3.93 (br, 1 H), 7.44 (s, 5 H); IR (film) 3055, 2990, 1780, 1763, 1630, 1600, 1548, 1430 cm^{-1}.

***N*-Benzoyl-*trans*-3,4-dihydroxypiperidine (12).** A mixture of 384 mg (1.89 mmol) of *N*-benzoyl-3,4-epoxypiperidine (**11**) in 10 mL of 10% potassium hydroxide was heated to boiling, and the resulting solution was refluxed for 2 h. The solution was evaporated to near dryness under vacuum and the residue extracted with chloroform. This solution was dried over magnesium sulfate and evaporated to give a clear glass. The crude product was crystallized from ethyl acetate, giving 123 mg (29%) of the trans diol **12**: mp 143–145 °C (lit.[16] mp 148–150 °C); IR (KBr) 3400, 3050, 1620, 1575 cm^{-1}.

***N*-Nitroso-*trans*-3,4-dibromopiperidine (9).** This compound was prepared in 67% yield by the bromination of **2** as described by Lijinsky:[9] mp 85–87 °C (lit.[9] mp 86–87.5 °C).

Reaction of *N*-Nitroso-*trans*-3,4-dibromopiperidine (9) with Silver Acetate. A. To a solution of 10 mg (0.035 mmol) of **9** in 0.25 mL of *N,N*-dimethylformamide and 0.25 mL of triethylamine was added 17 mg (0.1 mmol) of silver acetate. The resulting mixture was stirred at 25 °C for 60 h. The mixture was then diluted with methylene chloride, washed with 10% hydrochloric acid, and dried over potassium carbonate. The solution was analyzed by gas–liquid chromatography and was found to contain 59% *N*-nitroso-1,2,3,6-tetrahydropyridine (**2**) and 41% *N*-nitroso-4-acetoxy-1,2,3,4-tetrahydropyridine (**8**). The structures were confirmed by GLC/MS analysis.

B. To a solution of 152 mg (0.56 mmol) of **9** in 5 mL of glacial acetic acid, 2.5 mL of triethylamine, and 15 mL of acetone was added 340 mg (2 mmol) of silver acetate. The resulting mixture was refluxed for 48 h. The mixture was filtered, and the filtrate was washed with 10% hydrochloric acid, followed by 5% sodium bicarbonate. The solution was dried over magnesium sulfate and analyzed by gas–liquid chromatography and GLC/MS. Four compounds were identified: *N*-nitroso-1,2,3,4-tetrahydropyridine (**3**, 8%), *N*-nitroso-1,2,3,6-tetrahydropyridine (**2**, 16%), *N*-nitroso-4-acetoxy-1,2,3,4-tetrahydropyridine (**8**, 47%), and starting material **9** (29%).

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