Reaction of Propylene Oxide with Certain *N,N*-Dialkylhydroxylamines (1a)

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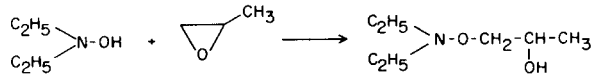
In the course of a study of *N*-alkoxyamines, a sample of 1-diethylaminooxy-2-propanol (**1**) was required. Zinner and co-workers (2) had reported that treatment of *N*-hydroxypiperidine with propylene oxide proceeds *via* *O*-alkylation to yield what was proposed to be 1-piperidinooxy-2-propanol; This product was identified only by an elemental analysis.

Based on these literature reports, it seemed logical to predict that treatment of *N,N*-diethylhydroxylamine with propylene oxide would similarly result in *O*-alkylation to give the desired product (**1**). The sole isolable product of



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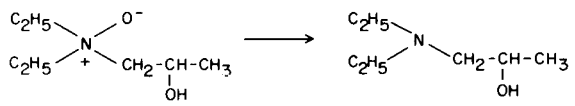
this reaction was one whose aqueous solution was not alkaline to litmus, and whose infrared spectrum showed a band at 950 cm^{-1} (the region characteristic of N-O stretching of tertiary amine oxides), and to which structure **2** was tentatively assigned. This compound was extremely hygroscopic and gave a poor elemental analysis, but a satisfactory analysis was obtained for its hydrochloride salt. This product, on treatment with zinc and acetic acid under conditions which reductively remove the oxygen from amine oxides (3), gave 1-diethylamino-2-propanol (**3**), whose identity was confirmed through its infrared spectrum. This spectrum lacked the N-O band at 950 cm^{-1}.



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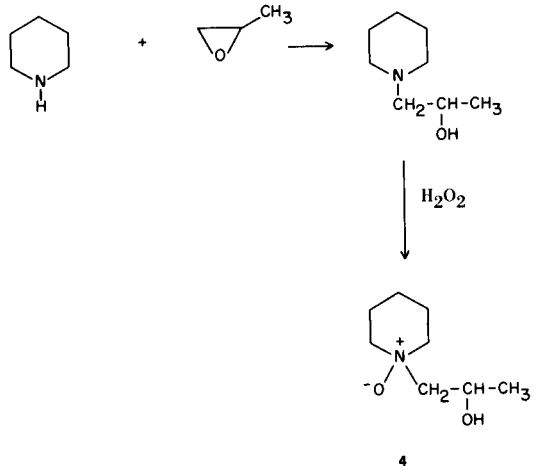
An authentic sample of compound **3** was treated with hydrogen peroxide. The resulting amine oxide product, prepared by an unequivocal method, produced an infrared spectrum identical to the spectrum of the product formed by treatment of *N,N*-diethylhydroxylamine with propylene oxide. Thus, it was proved that the reaction of *N,N*-diethylhydroxylamine with propylene oxide leads, not to *O*-alkylation, but rather to *N*-alkylation. No *O*-alkylated product could be isolated nor detected.

This finding prompted reinvestigation of the literature reports (2) of exclusive *O*-alkylation of *N*-hydroxypiperidine by propylene oxide. When this reaction was performed (either without solvent as in the literature reports, or in methanolic solution), there was isolated a compound whose melting point coincided with the literature (2) for the product. 1-(2-Hydroxypropyl)piperidine *N*-oxide (**4**) was prepared as indicated in Scheme I; It had a melting point identical with that of the product of the Zinner-Ritter reaction (2). In addition, the infrared spectra of the products of the two reaction sequences were superimposable. Thus, contrary to the literature, treatment of *N*-hydroxypiperidine with propylene oxide leads to *N*-alkylation and to the formation of an amine oxide.

SCHEME I



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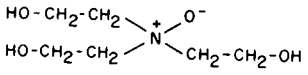
The literature contains few reports of this type of amine oxide formation; Dunstan and Goulding (4) prepared oxides of trimethylamine and of triethylamine by treating hydroxylamine with the appropriate alkyl halide. Jones and Burns (5) found that when hydroxylamine is treated with an excess of ethylene oxide, an amine oxide (**5**) is formed.



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EXPERIMENTAL (6)

1-Diethylamino-2-propanol *N*-Oxide (**2**).

Method A.

A solution of 13.0 g. (0.224 mole) of propylene oxide (Eastman white label) and 10.0 g. (0.112 mole) of *N,N*-diethylhydroxylamine (Aldrich Chemical Co., redistilled, b.p. 130-131°) in 25 ml. of anhydrous methanol was refluxed for 4 hours. The resulting mixture was treated with three successive 75 ml. portions of benzene, each being evaporated under reduced pressure at room temperature. After the third treatment, crystals appeared in the thick, oily product. After standing overnight, the yellow supernatant liquid (which consisted chiefly of unreacted *N,N*-diethylhydroxylamine) was separated from the crystals. Addition of excess ether to the liquid resulted in separation of more crystalline material. The combined crystals were washed with three 75 ml. portions of dry ether, then with Skellysolve B, and finally with dry ether. Yield, 6.2 g. (38%); m.p. 89-90°. IR (chloroform), 950 cm^{-1} (N-O stretching).

Anal. Calcd. for $C_7H_{17}NO_2$: C, 57.11; H, 11.64; N, 9.51. Found: C, 56.02; H, 12.46; H, 12.46; N, 8.99.

The hydrochloride salt was prepared by passing anhydrous hydrogen chloride through a benzene solution of **2**. The thick yellow oil which separated was washed with dry ether and then was crystallized by addition of a few drops of *n*-butanol. Recrystallization from *n*-butanol-ether gave a white crystalline solid, m.p. 87-89°.

Anal. Calcd. for $C_7H_{18}ClNO_2$: C, 45.77; H, 9.88; N, 7.63. Found: C, 45.51; H, 9.90; N, 7.22.

Method B.

To a chilled solution of 2.5 g. (0.091 mole) of 1-diethylamino-2-propanol (**3**) (Eastman practical grade, redistilled, b.p. 156-158°) in 10 ml. of methanol was added 15 ml. of 30% hydrogen peroxide over 0.5 hour. The reaction mixture was allowed to come to room temperature and to stand for 24 hours. Platinum black (0.25 g.) was added over 1 hour, and the resulting mixture was stirred overnight; it was then filtered and the filtrate was concentrated under reduced pressure at 40° to give a clear, thick oil. This product was treated with four successive portions of dry benzene, each being removed under reduced pressure at room temperature. On standing under reduced pressure, the resulting oil deposited white crystals whose IR spectrum (chloroform) was identical with the spectrum of the product formed by Method A.

Reduction of 1-Diethylamino-2-propanol *N*-Oxide (**2**).

A solution of 4.5 g. (0.0305 mole) of **2** in 15 ml. of glacial acetic acid was added dropwise with stirring to 5.0 g. of powdered zinc in 20 ml. of water immersed in an ice-water slurry. After addition was complete, the mixture was refluxed for 12 hours and the hot solution was filtered. Excess 20% sodium hydroxide solution was added to the cooled filtrate and the resulting mixture was extracted with six 50 ml. portions of ether. The combined ethereal extracts were dried over sodium sulfate, filtered, and the filtrate was concentrated on a steam bath. The residue was distilled at 156-158° (752 mm.) to yield 2.6 g. (76%) of a product whose IR spectrum (chloroform) was identical with that of an authentic sample of 1-diethylamino-2-propanol (**3**).

N-Hydroxypiperidine.

A modification of the method of Auerbach and Wolffenstein (7) was employed. To a mixture of 7.4 g. (0.066 mole) of *N*-ethylpiperidine (Aldrich Chemical Co.) and 20 ml. of 30% hydrogen peroxide was added sufficient ethanol to form a homogeneous system, and the reaction mixture was allowed to stand for 14 days. Platinum black (0.10 g.) was added over 0.5 hour, and the mixture was stirred for 2.5 hours. It was then filtered and the filtrate was concentrated under reduced pressure at 40°. The residue was heated at 90° (17 mm.) until no more liquid distilled. A gray-white solid (*N*-ethylpiperidine *N*-oxide) which remained in the distilling pot was heated in an oil bath at 115-120° until it liquefied. The melt was then allowed to cool and was distilled at 70-90° (17mm.); the distillate was collected in a dry ice-acetone-cooled receiver. Attempts to crystallize this product were not successful.

The hydrochloride salt was recrystallized from *n*-butanol and was washed with dry ether in a dry box, m.p. 143-145°.

Anal. Calcd. for $C_5H_{12}ClNO$: C, 43.63; H, 8.76. Found: C, 44.02; H, 9.07.

1-(2-Hydroxypropyl)piperidine *N*-Oxide (**4**).

Method A. From *N*-Hydroxypiperidine.

A mixture of 0.7 g. (0.007 mole) of *N*-hydroxypiperidine, 1 ml. of methanol, and 0.6 g. (0.012 mole) of propylene oxide was refluxed for 3.5 hours. The solvent was removed under reduced pressure at 40° to leave a hygroscopic solid which was recrystallized from carbon tetrachloride and washed with dry ether, m.p. 177-178° (Lit. (2) m.p. 179-181°). Yield, 0.7 g. (64%); IR (chloroform), 960 cm^{-1} (N-O stretching).

Method B. From 1-(2-hydroxypropyl)piperidine.

A solution of 5.3 g. (0.038 mole) of 1-(2-hydroxypropyl)-piperidine (8) in 15 ml. of water and 15 ml. of 30% hydrogen peroxide was allowed to stand for 14 days. Platinum black (0.25 g.) was added over 0.5 hour and the resulting mixture was stirred for an additional 2.5 hours. After filtration, the filtrate was concentrated under reduced pressure at 40° to a clear, viscous liquid which was treated with four successive 50 ml. portions of benzene which were removed at room temperature under reduced pressure. The resulting liquid was stored under reduced pressure for 4 hours; an off-white solid formed. This was recrystallized from carbon tetrachloride and washed with anhydrous ether to yield a white, hygroscopic solid, m.p. 180-182° (Lit.s(2) m.p. 179-181°). An IR spectrum (chloroform) of this compound was identical with that of the product formed by Method A.

REFERENCES

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(6) All boiling points are uncorrected. Melting points are corrected and were taken on a Thomas-Hoover apparatus. Elemental analyses were by Hufmann Laboratories, Inc., Wheatridge, Colorado. Infrared spectra were recorded on a Beckman IR-5A instrument.

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