

## Rearrangement. V.<sup>1)</sup> Relative Migratory Aptitude in the Nitrous Acid Deamination of Some Aliphatic Aminoalcohols

By

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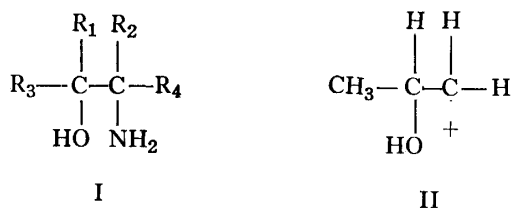
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### Introduction

The nitrous acid deamination of a number of 1,2-aminoalcohols with the general formula I, in which R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> represent either hydrogen atoms or alkyl, aralkyl, or aryl groups, has been investigated by many workers<sup>2)</sup>. In the majority of the cases studied products with rearranged carbon skeletons have resulted, the products being analogous to those of the pinacol rearrangement. If the deamination is carried out under mild acidic conditions, only the groups attached to the same carbon atom as the hydroxyl group actually migrate. The nature of the substituents R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> determines the course of the reaction. The relative migratory aptitude of aryl groups in the deamination of 1,2-aminoalcohols has been investigated extensively by Curtin and his co-workers<sup>3)</sup>. Although only a few examples of the deamination of simple aliphatic 1,2-aminoalcohols have been reported<sup>4-9)</sup>, the relative migratory aptitude of hydride and methyl group has not been studied yet.

In connection with other work<sup>1,10,11,12)</sup>, it was desired to know the migratory aptitude of hydride and methyl group in the rearrangement of simple aliphatic aminoalcohols. Optically inactive 1-amino-2-propanol was chosen as suitable for this study, because on the reaction with nitrous acid it would yield the carbonium ion II, which would subsequently



rearrange through a 1,2-hydride and 1,2-methyl migration as well as it would add bases intramolecularly and also intermolecularly before rearranging.

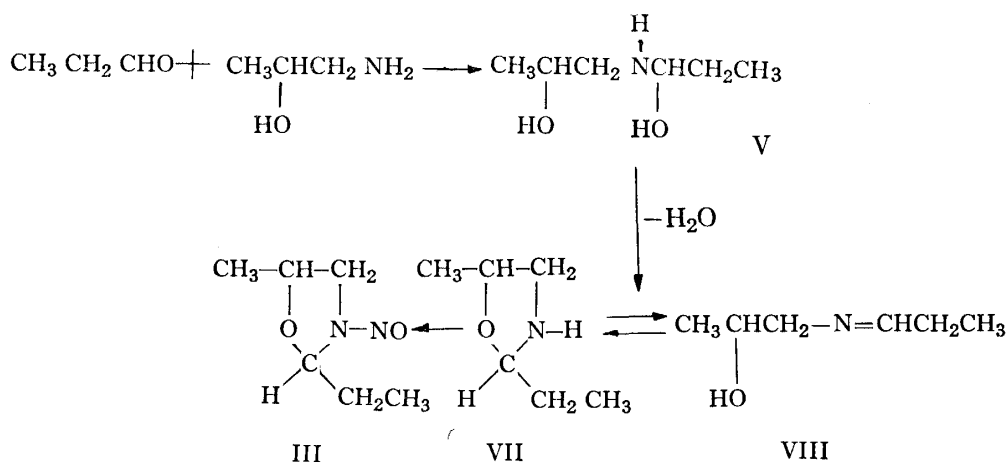
A search of the literature revealed only a few examples of the reaction of 1,3-aminoalcohols with nitrous acid<sup>13-15)</sup>. In view of the limited number of previous studies further investigation seemed desirable. Hence, 3-amino-1-propanol and 3-methoxy-1-propylamine were deaminated to see if the hydroxyl and methoxyl group  $\gamma$  to the amino group would affect the course of the reaction.

### Results and Discussion

**Reaction of 1-Amino-2-propanol with Nitrous Acid.**—The aminoalcohol was

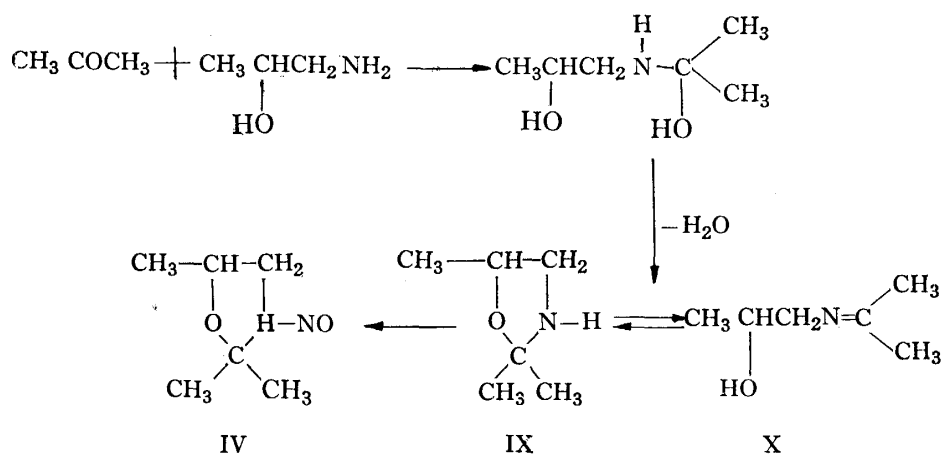
deaminated in the manner described earlier for alicyclic amines<sup>10</sup>). The low-boiling fraction obtained was first analyzed by gas chromatography. Each component was separated in a pure form by preparative-scale gas chromatography and identified by comparing its retention volume with that of an authentic sample. The fraction was shown to be a mixture of propylene oxide (9.2%), propionaldehyde (11.2%), and acetone (30.1%). The NMR analysis confirmed the result obtained by gas chromatography. The resonance line shapes and chemical shifts used for the structural assignment are as follows: propylene oxide (methyl protons, a doublet,  $\tau$  8.68,  $J=6$  c.p.s.; a  $\beta$ -proton *cis* to the methyl group, a quartet,  $\tau$  7.58; a  $\beta$ -proton *trans* to the methyl group, three lines,  $\tau$  7.28; a methine proton, a multiplet,  $\tau$  about 7.02), propionaldehyde (methyl protons, a triplet,  $\tau$  8.92,  $J=7.5$  c.p.s.; methylene protons, a quartet,  $\tau$  7.53,  $J=7.5$  c.p.s.; an aldehydic proton, an incompletely resolved triplet,  $\tau$  0.19), and acetone (methyl protons, a sharp singlet,  $\tau$  7.83).

The high-boiling fraction obtained consisted mainly of a yellow liquid of b.p. 72–73°/3.5 mm., but the expected 1,2-propanediol was obtained in a very small amount (5%). The elemental analysis fitted the formula  $C_6H_{12}N_2O_2$ . It was readily hydrolyzed by dilute mineral acids to give propionaldehyde, acetone, and 1-amino-2-propanol, accompanied by the evolution of a gas. The ratio of the first two compounds was approximately 5:1. The presence of an easily oxidizable group was indicated by a positive Tollens test. It is well known<sup>16</sup>) that the reaction of 1,2-aminoalcohols with carbonyl compounds gives oxazolidines and/or Schiff bases, that the system oxazolidines $\rightleftharpoons$ Schiff bases is in a state of a very mobile equilibrium, and that both oxazolidines and Schiff bases are readily hydrolyzed back by dilute mineral acids to the 1,2-aminoalcohols and carbonyl compounds from which they are synthesized. If the yellow liquid has a Schiff base structure, its infrared spectrum may be expected to show a strong absorption around  $1670\text{ cm}^{-1}$ , due to the aliphatic  $C=N$  group<sup>16</sup>), while an oxazolidine structure should have no corresponding absorption. Its infrared spectrum exhibited no absorption in this region, indicating that it is not a Schiff base. Common functional groups such as  $C=O$ ,  $C=C$ ,  $OH$ , and  $NH$  were absent in the infrared spectrum. The above-mentioned facts suggest that the yellow liquid may be a mixture of 2-ethyl-5-methyl-3-nitrosooxazolidine (III) and 2,2,5-trimethyl-3-nitrosooxazolidine (IV) in the ratio of approximately 5:1 (19.7 and 3.9%, respectively). The tar-like substance obtained in small amounts may be polymerized oxazolidines<sup>16</sup>).



The formation of the nitrosooxazolidines may be explained as follows: the unreacted 1-amino-2-propanol would react with propionaldehyde and with acetone to yield the addition products V and VI, respectively, which would subsequently give an equilibrium mixture of 2-ethyl-5-methyloxazolidine (VII) and 1-propylideneamino-2-propanol (VIII) and also

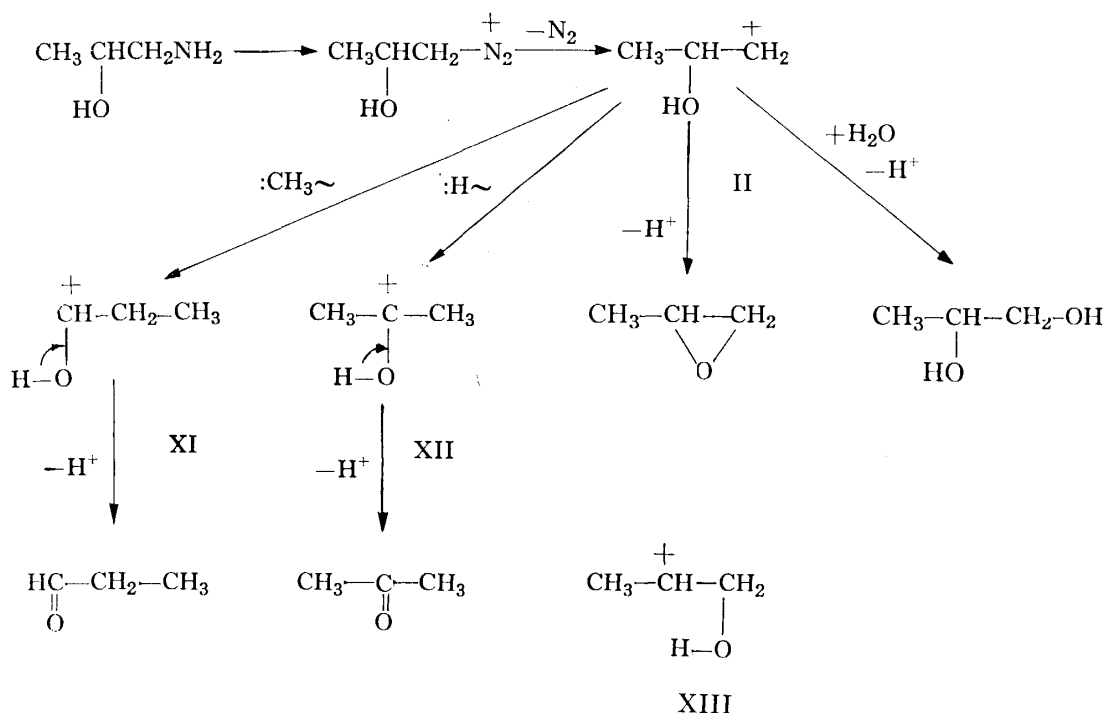
that of 2,2,5-trimethyloxazolidine (IX) and 1-isopropylideneamino-2-propanol (X),



respectively. The nitrosation of the oxazolidines would shift the equilibrium with the formation of the nitrosooxazolidines, and hence remove the Schiff bases from the reaction system. The fact<sup>16)</sup> that ketones are much less reactive than aldehydes toward 1,2-aminoalcohols may explain the lower yield of IV (III:IV=5:1).

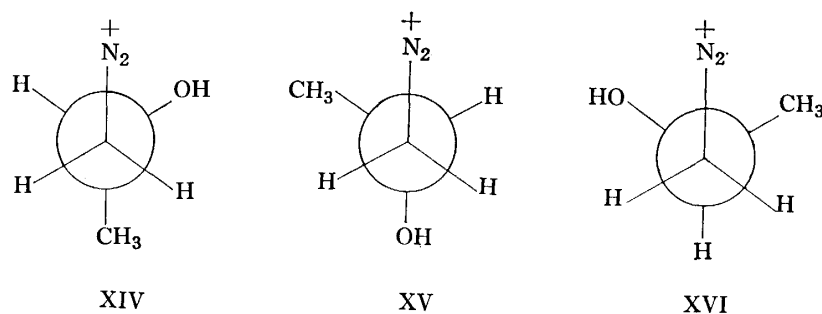
Recent extensive investigations<sup>2c)</sup> have established that the reaction of amines with nitrous acid gives, first, a nitrosamine, then a diazohydroxide, and finally a diazonium ion. Such a diazonium ion is highly unstable in an aliphatic system and decomposes rapidly to give a carbonium ion, followed by substitution, elimination and rearrangement, namely, an S<sub>N</sub>1-E1 mechanism. In recent years, Streitwieser<sup>17)</sup>, proposed an S<sub>N</sub>2-E2 mechanism with an extreme degree of neighbouring group participation. However, since such very pronounced an extreme degree of neighbouring group participation. However, since such very pronounced participation by neighbouring groups is most unusual, the final decision on the acceptability of the mechanism cannot yet be made<sup>2c,2d)</sup>. In the present paper a possible mechanism of the deamination of aminoalcohols will be discussed in terms of an open carbonium ion.

Propionaldehyde would be formed from the carbonium ion II through (A) the 1,2-methyl migration from the C-2 to C-1 (II→XI), (B) the 1,2-hydroxyl migration from the C-2 to C-1, followed by the 1,2-hydride migration from the C-1 to C-2 (II→XIII→XI), (C) the acid-catalyzed isomerization of propylene oxide, or (D) the acid-catalyzed dehydration at the C-2 of 1,2-propanediol, followed by the 1,2-hydride migration from the C-1 to C-2 (XIII→XI). The route B would involve propylene oxide or its protonated form as an intermediate. Hence, the route B may essentially be the same to the route C. Although many examples of the isomerization of propylene oxide to propionaldehyde have been reported, the routes B and C seem unlikely here, because the control experiments revealed that the isomerization did not occur under the deamination conditions employed. The route D was also eliminated by the control experiments. Hence, the route A seems most likely. Acetone may be formed from the carbonium ion II through the 1,2-hydride migration from the C-2 to C-1 (II→XII). Propylene oxide may be formed through the intramolecular substitution of the carbonium ion II by the hydroxyl group, while 1,2-propanediol through the intermolecular substitution by water. The formation of 1,2-propanediol through the acid-catalyzed hydration of propylene oxide also was eliminated here. To summarize, 31% of the products obtained can be attributed to a methyl migration, 47% to a hydride migration, 14% to an intramolecular substitution, and 8% to an intermolecular substitution.



The ratio of a hydride to methyl migration was about 1.5:1, and that of an intramolecular to intermolecular substitution was 1.8:1.

It is recognized<sup>2c,2d,18)</sup> that the alkyldiazonium ion decomposes in the conformation from which it is formed, before the rotation about a C-C bond can occur (an activation energy of the rotation about a C-C bond is 3-4 kcal/mole and probably greater than that of the decomposition of the alkyldiazonium ion), that the resulting "hot" carbonium ion also is followed by the subsequent reaction before the rotation about a C-C bond becomes significant, and that the mobility of substituents is, therefore, largely controlled by the conformations of the diazonium ion and the substituent *trans* to the diazo group in the most stable conformation is most mobile. The diazonium ion formed from 1-amino-2-propanol exists in staggered conformations, the order of population of which may be XIV > XV > XVI.



The methyl group is then in the favored position for rearrangement. The observed hydride/methyl migration ratio (1.5:1) was, however, not in accord with the relative populations of the conformations of the diazonium ion. Apparently other factors may also be responsible for the proportion of the products obtained, that is, the relative stabilities of the carbonium ions formed through rearrangement. The hydride migration leading to the formation of the relatively more stable carbonium ion XII is more favored than the methyl migration which





C-2, a quintet,  $\tau$  8.30; methylene protons on the C-1, a triplet,  $\tau$  6.40; a hydroxyl proton, a singlet,  $\tau$  6.62), 1-methoxy-2-propanol (a methoxy group, a singlet,  $\tau$  6.72; methylene protons on the C-3, three lines,  $\tau$  6.81; a methine proton, weak ten lines,  $\tau$  about 6.27; methyl protons, a doublet,  $\tau$  8.87,  $J=6.8$  c.p.s.; a hydroxyl proton, a singlet,  $\tau$  6.68), and methyl allyl ether (a methoxy group, a singlet,  $\tau$  6.72; methylene protons on the C-1, two triplets,  $\tau$  4.13; a proton on the C-2, ten lines,  $\tau$  about 6.0; a proton on the C-3, *cis* to the proton on the C-2, multiplet,  $\tau$  5.13; a proton on the C-3, *trans* to the proton on the C-2, multiplet,  $\tau$  5.25). The deamination of 3-amino-1-propanol and 3-methoxy-1-propylamine may proceed through the schemes shown below:

The deamination of 1-propylamine<sup>20)</sup> yields only about 7% 1-propanol, but 32 to 40% 2-propanol and 28% propylene. Comparison between the product proportions obtained from 1-propylamine and 3-amino-1-propanol indicates that the presence of the hydroxyl group  $\gamma$  to the amino group did affect the course of the reaction. The proportion of propionaldehyde (including the propionaldehyde structural unit in XVIII) among the products obtained was about 50%. The predominant formation of propionaldehyde may be explained as follows: the relatively unstable primary carbonium ion XIX would mainly rearrange to the relatively stable secondary carbonium ion XX, and then to the resonance-stabilized carbonium ion XXI, which would then give propionaldehyde by the loss of a proton. This explanation may be supported by the fact<sup>9)</sup> that the carbonium ion XXII yields predominantly *n*-butyraldehyde. The carbonium ion XXI would be also formed directly from the unstable carbonium ion XIX through the 1,3-hydride migration from the C-3 to C-1 (XIX $\rightarrow$ XXIII $\rightarrow$ XXI). This may also be supported by the fact<sup>21)</sup> that the 1,3-hydride migration does occur in the deamination of 1-propylamine-1,1,2,2- $d_4$ .

With 3-methoxy-1-propylamine, the unrearranged products predominated. No explanation is, however, apparent to account for the predominant formation of 3-methoxy-1-propanol.

### Experimental

All boiling points are uncorrected.

**Reaction of 1-Amino-2-propanol with Nitrous Acid.**—In a 1-1. four-necked flask fitted with a mechanical stirrer, dropping funnel, thermometer, and reflux condenser there were placed 34.2 ml. (0.5 mole) of 85% orthophosphoric acid and 360 ml. of water. The flask was surrounded by ice-water, to which 45 g. (0.6 mole) of 1-amino-2-propanol was added with stirring. A solution of 50.4 g. (0.73 mole) of sodium nitrite in 100 ml. of water was added to the cold mixture with stirring. The top of the reflux condenser was connected to two traps connected in series, the first was cooled in an ice-water bath, and the second in a Dry Ice methanol bath. The dropping funnel was then substituted with a gas inlet capillary tube, the end of which was dipped in the reaction mixture. Then a slow stream of nitrogen gas was introduced. The mixture was kept at room temperature with stirring for 30 min., then heated to 80°, and kept at this temperature for 1 hr. The products collected in the traps weighed 13.8 g. and submitted to gas chromatographic analysis. When the reaction solution was cooled, it was neutralized with dilute sodium hydroxide, and then extracted with six 100-ml. portions of ether, and the aqueous layer was saved.

The ether extract was dried over anhydrous magnesium sulfate, and the ether was distilled through a 40-cm. Vigreux column. The gas chromatographic analysis of the distilled ether showed the presence of approximately equal amounts of propionaldehyde, propylene oxide, and acetone. The yield of these compounds was estimated to be 3.75 g. The residue was distilled to give a mixture of 2-ethyl-5-methyl-3-nitrosooxazolidine and 2,2,5-trimethyl-3-nitrosooxazolidine (yield 10 g.), b.p. 72–73°/3.5 mm., leaving about 2.5 g. of a tarry substance.

In several runs the yield of the nitrosooxazolidines ranging from 8 to 11 g. was obtained.

*Anal.* Calcd. for  $C_6H_{12}N_2O_2$ : C, 49.98; H, 8.34; N, 19.43. Found: C, 49.71; H, 8.25; N, 19.35.

The deamination aqueous layer was concentrated to about 200 ml., saturated with sodium chloride, and extracted with five 100-ml. portions of ether. After drying over anhydrous magnesium sulfate the ether was removed from the ether extract to yield 2.3 g. of 1,2-propanediol. (identified by gas chromatography).

To the aqueous residue, from which 1,2-propanediol was extracted, there was added approximately 30 g. of potassium hydroxide pellets. The mixture was extracted with four 100-ml. portions of ether and the ether extract was dried. The ether was distilled off, leaving 6 g. of 1-amino-2-propanol (identified by gas chromatography).

The nitrosooxazolidines were treated with 10% hydrochloric acid at room temperature for 30 min. The reaction mixture was saturated with sodium chloride and extracted with ether. The aqueous layer residue was made strongly basic by potassium hydroxide pellets and extracted with ether. The above two ether extracts were analyzed by gas chromatography without distillation.

**Reaction of 3-Amino-1-propanol and 3-Methoxy-1-propylamine with Nitrous Acid.**—The deamination was carried out in the manner described for 1-amino-2-propanol. 3-Amino-1-propanol gave 2-ethyl-3-nitrosotetrahydro-1,3-oxazine in 36.7% yield, b.p. 70–70.5°/3 mm.

*Anal.* Calcd. for  $C_6H_{12}N_2O_2$ : C, 49.98; H, 8.34; N, 19.43. Found: C, 49.73; H, 8.35; N, 19.59.

The other products obtained are given in the text. The acid cleavage of the tetrahydro-1,3-oxazine was carried out in the manner described for nitrosooxazolidines.

**Product Analysis.**—Gas chromatographic analysis was carried out using 500×0.35 cm. (A, B, and C) and 300×0.35 cm. (D) columns packed with 80–100 mesh Celite which was coated with the appropriate stationary phase. The stationary phases employed were: (A) 30% by weight of diethyl phthalate, (B and D) 30% by weight of polyethylene glycol 1500, and (C) 30% by weight of high vacuum silicone grease. The Celite used for a column C was pretreated with an 5% sodium hydroxide solution before coating. Columns A and B were used to analyze low-boiling products at 55° and 30°, respectively. Alcohols, aminoalcohols, nitrosooxazolidines, and tetrahydro-1,3-oxazine were analyzed using columns C and D between the temperatures of 100–150°. The helium outlet flow rates were 60 cc./min. The relative thermal conductivity cell response per mole of the authentic samples of the compounds under discussion was determined. The mole ratio of the compounds in the product was determined from the above relative response and from the apparent peak areas, which was obtained by half-width and peak-height measurements.

NMR analysis was run at 25° in carbon tetrachloride (5–10%) on a Varian Associates Model V-4311 high resolution spectrometer operating at 60 Mc., using tetramethylsilane ( $\tau$  10.00) as an internal standard.

The infrared spectra were obtained with a rocksalt prism on a double-beam spectrophotometer.

### Summary

1. The deamination of optically inactive 1-amino-2-propanol yielded propionaldehyde, propylene oxide, acetone, 1,2-propanediol, 1,3-propanediol, 2-ethyl-5-methyl-3-nitrosooxazolidine, and 2,2,5-trimethyl-3-nitrosooxazolidine. The rearranged products predomi-



nated. The hydride/methyl migration ratio was 1.5:1, and the intramolecular/intermolecular substitution ratio was 1.8:1. The possible mechanism is discussed.

2. The deamination of 3-amino-1-propanol gave propylene oxide, propionaldehyde, 1,2-propanediol, 1,3-propanediol, and 2-ethyl-3-nitrosotetrahydro-1,3-oxazine, the rearranged products predominating. The predominant formation of propionaldehyde is discussed.

3. The deamination of 3-methoxy-1-propylamine yielded 3-methoxy-1-propanol, 1-methoxy-2-propanol, propionaldehyde, and methyl allyl ether, the unrearranged products predominating.

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