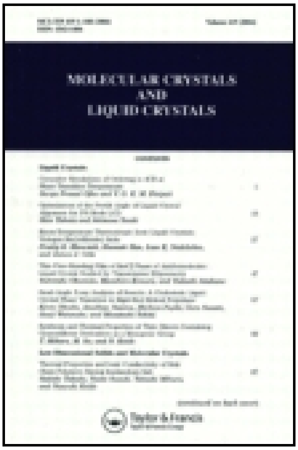

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A Thorough Investigation of the Synthetic Problems of Vic-Bis-Hydroxylamine - the Precursor of Ullman's Nitroxides

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A Thorough Investigation of the Synthetic Problems of *Vic*-Bis-Hydroxylamine – the Precursor of Ullman's Nitroxides

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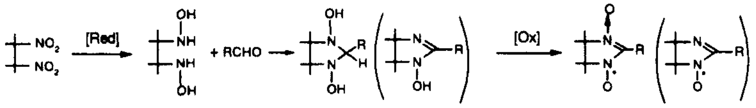
The products formed in the course of the reduction of 2,3-dimethyl-2,3-dinitrobutane to 2,3-dihydroxylamino-2,3-dimethylbutane in a Zn/NH_4Cl/EtOH-H_2O system have been investigated. An improved synthesis of 2,3-dihydroxylamino-2,3-dimethylbutane (and its monosulphate salt) – the key precursor of Ullman's nitroxides – in a Zn/NH_4Cl/THF-H_2O system is proposed.

Keywords: hydroxylamine derivatives; nitroxides

INTRODUCTION

Ullman's nitronyl- and iminonitroxides[1] are attracting much interest from magnetochemists owing to the versatility that they offer for designing molecular magnetic materials[2-4]. One of the key steps in the synthesis of spin-labeled 2-imidazoline derivatives (**4**, **4a**) is the formation of the bis-hydroxylamino precursor, 2,3-dihydroxylamino-2,3-dimethylbutane (**2**), introduced as a free base or its acid salt in subsequent condensation with an appropriate aldehyde (or its synthetic equivalent). Vicinal bis-hydroxylamine

2, in turn, is obtained from 2,3-dimethyl-2,3-dinitrobutane (**1**) by a procedure proposed by Lamchen and Mittag[5], whereby **1** is reduced in a $Zn/NH_4Cl/EtOH\text{-}H_2O$ system, as typically done in the synthesis of hydroxylamines. In the synthesis of **2**, however, this procedure often leads to poorly reproducible or even negative results, calling for a modification of the synthetic procedure[6]. This study is devoted to a detailed investigation of the reaction products forming in the reduction of **1** in $Zn/NH_4Cl/EtOH\text{-}H_2O$ and to the modification of the syntheses of both the free base **2** and its monosulphate salt.



1 **2** **3** **(3a)** **4** **(4a)**

Reduction in a water-ethanol mixture

It is commonly accepted that reduction of **1** to **2** by zinc in a water-ethanol mixture in the presence of NH_4Cl forms "a cake of zinc oxide"[5], which is filtered off and discarded. One can readily admit formation of zinc hydroxide, assuming that the following reactions take place:

$$C_6H_{12}(NO_2)_2 + 4Zn + 8NH_4Cl = C_6H_{12}(NHOH)_2 + 4ZnCl_2 + 8NH_3 + 2H_2O$$
$$\underline{4ZnCl_2 + 8NH_3 + 8H_2O = 4Zn(OH)_2\downarrow + 8NH_4Cl}$$
$$C_6H_{12}(NO_2)_2 + 4Zn + 6H_2O = C_6H_{12}(NHOH)_2 + 4Zn(OH)_2\downarrow$$

The true nature of "the cake of zinc oxide," however, has never been determined and this situation hinders the understanding of the process in general. In contrast to the commonly accepted proposition, we have found that $Zn(OH)_2$ never forms in the reduction of **1** to **2** under the conditions of Lamchen and Mittag's synthesis. In fact, the white solid residue that separates as an easily filtered-off precipitate is a mixture of $Zn(NH_3)_2Cl_2$ and the result of its partial hydrolysis - $Zn(OH)Cl$. This mixture is readily identified by the characteristic IR spectrum, which is a superposition of those of $Zn(NH_3)_2Cl_2$ and $Zn(OH)Cl$[7]. The same spectrum was recorded for the solid forming in the treatment of authentic $Zn(NH_3)_2Cl_2$ with a water-ethanol mixture. Formation of the above-mentioned mixture, which is the major component of the residue or even the only component when zinc powder is present in deficiency, was observed in all versions of the reduction of **1** which we investigated. Thus the reaction scheme of the reduction of **1** to **2** may be represented as follows:

$$C_6H_{12}(NO_2)_2 + 4Zn\downarrow + 6NH_4Cl = C_6H_{12}(NHOH)_2 + 2Zn(NH_3)_2Cl_2\downarrow + 2Zn(OH)Cl\downarrow + 2NH_3$$

The composition of the solid phase, however, is not the only feature characterizing the behavior of zinc in the synthesis of **2**. Even more important for understanding the reduction process is the observation that a large amount of zinc (~1-1.5 g under experimental conditions) passes into solution. This is easily detected by trilonometric titration of samples of the reaction mixture filtrate in the course of and after the reduction of **1**. Zn(II) passes into solution as a complex cation $[Zn(C_6H_{12}(NH_2)_2)_2]^{2+}$, where $C_6H_{12}(NH_2)_2$ is 2,3-diamino-2,3-dimethylbutane forming as a result of over-reduction of **2**. This fact agrees with the available literature data on Zn(II) complexes with unsubstituted ethylenediamine[8]. For instance, attempts to prepare Zn(II)-En solutions with a zinc to ethylenediamine ratio of 1:1 or 1:2 gave insoluble $Zn(En)Cl_2$ in all cases; a clear solution could be obtained only when the Zn(II) to En ratio was 1:3 or more[8]. A similar situation takes place in the reduction under study since it is well known that reduction of nitro compounds to hydroxylamines always results in partial over-reduction: 2,3-diamino-2,3-dimethylbutane in this case. When $ZnCl_2$ interacts with 2,3-diamino-2,3-dimethylbutane with a ratio of Zn-L of 1 to 1, $Zn(C_6H_{12}(NH_2)_2)Cl_2$ (see Figure 1), which has poor solubility, separates as a solid. $Zn(C_6H_{12}(NH_2)_2)Cl_2$ dissolves when treated with an excess of 2,3-diamino-2,3-dimethylbutane giving the bis(diamino) species which is well soluble in ethanol and even more in a water-ethanol mixture in which the reduction of **1** to **2** is carried out. It is noteworthy that the complex $[Zn(C_6H_{12}(NH_2)_2)_2]^{2+}$ is fairly stable, since $Zn(OH)_2$, which is actually insoluble in water-ethanol mixtures, completely dissolves when reacting with 2,3-diamino-2,3-dimethylbutane in excess. Therefore, the vic-diamino species transfers zinc into solution.

This is a very important feature, which must be taken into consideration in the synthesis of **2**, especially when condensation with an appropriate aldehyde or its synthetic equivalent is performed using the crude reaction mixture[2]. It is difficult to predict the effect of the presence of large amounts of zinc complex in solution on the condensation process leading to the formation of **3** (or **3a**). This prediction is especially difficult in cases where acetals are used and the condensation is promoted by hydrochloric acid. First, when the acid is added gradually, the system is a buffer for long periods of time due to a neutralization reaction:

$$[Zn(C_6H_{12}(NH_2)_2)_2](OH)_2+4HCl = Zn(C_6H_{12}(NH_2)_2)Cl_2\downarrow+C_6H_{12}(NH_3)_2Cl_2+2H_2O \text{ or}$$
$$[Zn(C_6H_{12}(NH_2)_2)_2]Cl_2 + 2HCl = Zn(C_6H_{12}(NH_2)_2)Cl_2\downarrow + 2C_6H_{12}(NH_3)_2Cl_2$$

and large acid additions may be needed for substantial acidification of the reaction mixture to promote the formation of adduct **3**. Second, an acid addition may lead not only to precipitation of adduct **3** but also to formation of insoluble $Zn(C_6H_{12}(NH_2)_2)Cl_2$ as a solid, which contaminates the target product. Such a species has been isolated and fully characterized by X-ray diffractometry.

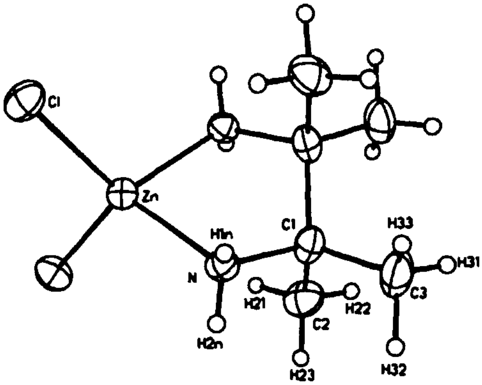


FIGURE 1 Molecular structure of $Zn(C_6H_{12}(NH_2)_2)Cl_2$ (the tetrahedral environment of the Zn atom involves two N and two Cl atoms lying at distances Zn-N 2.038(2) and Zn-Cl 2.2338(7) Å).

Third, with an excess of acid, $Zn(C_6H_{12}(NH_2)_2)Cl_2$ dissolves:

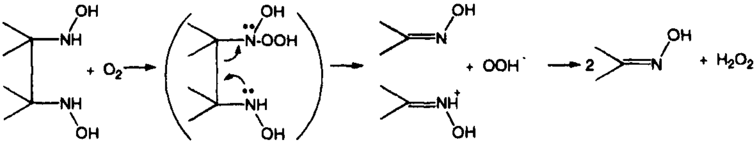
$$Zn(C_6H_{12}(NH_2)_2)Cl_2\downarrow + 2HCl = C_6H_{12}(NH_3)_2^{2+} + ZnCl_4^{2-}$$

forming protonated 2,3-diamino-2,3-dimethylbutane which can interact with the aldehyde to give condensation products, contaminating adduct **3**.

Thus, reduction of **1** by zinc in a $NH_4Cl/EtOH\text{-}H_2O$ system forms **2** as well as 2,3-diamino-2,3-dimethylbutane, which is present in solution as a soluble complex of Zn(II).

Lamchen and Mittag also described the preparation of **2** as the sulphate which precipitates at pH~1-2 on adding an ethanol solution of H_2SO_4 to the reaction mixture. Depending on the pH, different species may be identified. At pH~6-7, one can observe precipitation of $Zn(C_6H_{12}(NH_2)_2)Cl_2$, which dissolves as the pH decreases further. At pH~1-2, the sulphate salt of **2** precipitates, which is always contaminated by $(NH_4)_2SO_4$, whose solubility in water decreases abruptly when ethanol is added. In cases where **2** is over-reduced into the diamino compound and is present in the reaction mixture in insignificant amounts, only $(NH_4)_2SO_4$ separates as a solid after the reaction mixture has been acidified. This accounts for the occasional absence of target product **2** among the final products. It should be noted that use of a water-ethanol mixture always promotes substantial over reduction of bis-hydroxylamine to diamine, and we failed to obtain pure bis-hydroxylamine sulphate from water-ethanol mixtures in yields higher than 20-22 %.

Unfortunately, there are other reasons for obtaining only moderate yields of bis-hydroxylamine. The first one is the consequence of the intrinsic stability of this compound. Indeed, all *vic*-bis(hydroxylamino) derivatives are known to convert to oximes and one identified mechanism involves the action of O_2 and of a synchronous trans-elimination[9].



In the present case, oxidation of **2** by atmospheric oxygen to acetone oxime occurs rather easily to the extent of ~50-60% in THF, CH_3OH, and C_2H_5OH and ~20% in H_2O for 24 h at 25° C (^1H NMR monitoring).

Another cause of lowering of the yield is directly connected to the use of ethanol as solvent. In a water-ethanol mixture or in pure ethanol, **2** gradually oxidizes ethanol into acetaldehyde, which reacts with another molecule of bis-hydroxylamine to give the corresponding adduct **3**, which is oxidized by atmospheric oxygen to the nitronylnitroxyl radical (**4**, R=CH_3). This side reaction is at the origin of a red color which gradually develops in the solution. The ESR spectrum of that red solution of **2** in ethanol is identical to the spectrum of an authentic sample of **4** (R=CH_3): $a_N = 7.7$ G, $a_{H\text{-}(CH3)} = 3.3$ G. The same identification is also possible on comparing the electronic spectra. For this reason, it is highly desirable to avoid the use of ethanol as solvent in the synthesis of **2**.

Reduction in THF

For reducing **1** into **2**, use of tetrahydrofurane is much more efficient. Unlike the water-ethanol mixture, THF readily dissolves 2,3-dinitrobutane which does not precipitate in contact with aqueous NH_4Cl. (We also noted that a concentrated aqueous solution of NH_4Cl is not readily miscible with THF). In THF the reduction of **1** to **2** proceeds much more smoothly, as indicated by a deep blue coloring of the solution, which is typical for the presence of a persistent nitroso intermediate[10]. Decolorization of the solution, in fact, points to completion of the reduction and is thus a convenient indicator for monitoring the process since its kinetics is considerably affected by the quality and size of zinc powder particles. The only disadvantage (common to all solvents) of using THF is the fact that degradation of **2** by atmospheric oxygen (and other mechanisms) to acetone oxime occurs as easily as in ethanol.

Nevertheless, when performed in THF, the synthesis, which is reproducible, affords bis-hydroxylamine sulphate monohydrate with a 45-50% yield, from which the free base **2** is isolated readily.

Compound **2**, as prepared by the procedure suggested here, is free from acetone oxime and from any inorganic impurities. The presence of impurities is known to catalyze the decomposition of free bis-hydroxylamine[11]. The purest (in our opinion) samples of **2** were described elsewhere[9, 11]. However, when stored in air, these samples decomposed in a few days. The procedure suggested here affords a product which is stable for at least 2 months when stored in normal conditions and for a year when kept in a refrigerator at -20° C. Previously, it was noted that **2** is "very hygroscopic and volatile, and readily distills with ethanol, water and chloroform"[5]. However, a pure sample of **2** is absolutely nonhygroscopic and not volatile and does not distill off when ethanol, methanol, chloroform, or THF solutions are evaporated under reduced pressure. The volatile materials are acetone oxime and 2,3-diamino-2,3-dimethylbutane.

SUMMARY

This study shows that in the key step of the production of Ullman's free radicals, the reduction of **1** to **2**, the solid phase of the reaction is mainly a mixture of $Zn(NH_3)_2Cl_2$ and of the product of its partial hydrolysis. In the course of the synthesis, along with bis-hydroxylamine (and acetone oxime), a product of over reduction 2,3-diamino-2,3-dimethylbutane, accumulates in the solution and effectively transfers Zn(II) ions from this solid phase into solution. After the reduction process is completed, it is not recommended to store **2** in solution for a long period, because it gradually undergoes oxidative decomposition into acetone oxime (rapid precipitation of **2** as the sulphate is a good method for storage). However, the reduction of **1** to **2** proceeds rather slowly even in THF, in which **1** is very soluble and does not separate as a

solid in contact with aqueous NH_4Cl. The reduction, especially its initial step, may not be accelerated by raising the temperature of the reaction mixture, because any, even if local, overheating of the reaction mixture leads to rapid and effective overreduction of **2** to the corresponding diamine. As **1** is slowly reduced into **2**, over reduction to diamine and fragmentation to acetone takes place which result in a lowering of the yield of the bis-hydroxylamino species. The actual better yields (as the monosulphate) were in the range 40-50 %. The following procedure for the synthesis of **2** from the monosulphate, however, affords this compound in pure form and allows its prolonged storage without decomposition.

Experimental section

N,N'-Dihydroxy-2,3-diamino-2,3-dimethylbutane monosulphate monohydrate. 20 g of 2,3-dimethyl-2,3-dinitrobutane (0.11 mole) were dissolved in 300 ml of THF. To this solution was added NH_4Cl (25 g, 0.45 mole) and 30 ml of water. The mixture was cooled in a ice bath and 40 g of zinc were added in portions during 1 hour whereupon the mixture was stirred for 12-14 h at 10-20 ° C. The solution gradually acquired blue coloring, which disappeared completely at the end of the reaction. The mixture was filtered and the precipitate washed with three 100 ml portions of THF. The pale yellow filtrate was evaporated under vacuum until THF ceased to distill off. To the residue were added 200 ml of ethanol, and the resulting solution was filtered to remove unchanged 2,3-dinitrobutane. A 10% ethanol solution of sulfuric acid was added dropwise to the filtrate with cooling to 0°C until pH 3 was reached (to thymol blue). The precipitate was filtered off, washed with ethanol, and dried in air. Yield 14-16 g (45-50%, mp. 172-174 °C) Anal Calcd for $C_6H_{12}(NHOH)_2$ H_2SO_4 H_2O: N, 10.6; H, 7.6; N, 27.3. Found: N, 10.6; H, 7.3; N, 27.4. The particle sizes of the Zn powder used are listed in the table ("Malvern 3600 E", water).

Size, µm	Percentage
54.9-33.7	0.3
33.7-23.7	3.1
23.7-17.7	8.4
17.7-13.6	16.4
13.6-10.5	10.0
10.5-8.2	22.7
8.2-6.4	22.6
6.4-5.0	4.5
5.0-3.9	11.1
3.9-3.0	0.9

N,N'-Dihydroxy-2,3-diamino-2,3-dimethylbutane. 10.00 g of $C_6H_{12}(NHOH)_2$ H_2SO_4 H_2O were suspended in 150 ml of methanol. Solid NaOH (3.02 g; excess alkali should be avoided!) was added to this mixture in small portions with vigorous stirring and cooling (0^0 C) for 1 h; then the mixture was stirred until NaOH dissolved completely. The precipitate was separated on a centrifuge and discarded. The solution was evaporated on a rotary evaporator until dry. The residue was dissolved in dry tetrahydrofurane, the solution was filtered to remove Na_2SO_4, and the filtrate was again evaporated in vacuum. The resulting white crystalline powder was washed with 10 ml of hexane, and dried in air. Yield 50-60%, mp. 160-161 °C. Anal. Calcd for $C_6H_{12}(NHOH)_2$: C, 48.6; H, 10.9; N, 18.9. Found: C, 48.5; H, 10.5; N, 18.8.

$Zn(C_6H_{12}(NH_2)_2)Cl_2$. A mixture of $ZnCl_2$ (0.22 g) and $C_6H_{12}(NH_2)_2\,2HCl$ (0.31 g) was dissolved in 15 ml of water. The solution was filtered, and 3.27 ml of 1 M aqueous NaOH were added. Colorless crystals formed immediately which were filtered off, washed with water and dried in air. Yield 75%. Anal. Calcd for $Zn(C_6H_{12}(NH_2)_2)Cl_2$: Zn, 25.9; C, 28.5, H, 6.4; N, 11.1; Cl 28.1. Found: Zn, 26.1; C, 28.0; H, 6.4; N, 11.2; Cl, 27.8.

$Zn(NH_3)_2Cl_2$. A sample of pure $Zn(NH_3)_2Cl_2$ was specially synthesized for IR spectrum verification[4] by the reaction of Zn with a solution of NH_4Cl in methanol for 3 days. Anal. Calcd for $Zn(NH_3)_2Cl_2$: Zn, 38.4. Found: Zn, 38.3.

Acknowledgments

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