Electrophilic Intermediate in the Reactions of a 2-(Hydroxylamino)imidazole. A Model for Biological Effects of Reduced Nitroimidazoles

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Observations that important biological effects of 2-nitroimidazoles are associated with reductive metabolism[1] have led to considerable interest in nitromidazole reduction chemistry. Recently we have reported[2] that 2-(hydroxylamino)imidazoles, the products of four-electron reductions, can be prepared in acid but at pH 7 they are unstable. In this paper we identify products of the decomposition and also report kinetic data. A mechanism is then proposed that has novel chemical features and that, moreover, may have biological relevance.

The hydroxylamine **1** of 2-nitro-1-methylimidazole was isolated as its HCl salt after pH 3.5 electrolysis.[2] Product and kinetic experiments were conducted at 25 °C in N_2 bubbled solutions. The hydroxylamine is unstable; at all pHs, products are the cis and trans isomers of **2**. These have been identified from their 360-MHz NMR spectra,[3] and analytically pure samples have been prepared by the reaction of glyoxal and N-methylguanidine hydrochloride.[4,5] First-order rate constants for the reaction (Figure 1) were obtained from the decrease in hydroxylamine absorbance at 230–240 nm. These suggest a mechanism where the neutral hydroxylamine undergoes H^+-catalyzed and noncatalyzed loss of the hydroxyl group, resulting in the cation **5**, a nitrenium ion, which in rapid steps is converted to products. The kinetic equation is rate = $(k_0 + k_H[H^+])[\mathbf{1}]$; this gives $k_{obsd} = (k_0 + k_H[H^+])K_a/([H^+] + K_a)$ assuming rapid equilibration of **1** and $\mathbf{1H^+}$. This equation can be fit to the experimental data using nonlinear least squares to give $k_0 = 0.013\ s^{-1}$, $k_H = 1.2 \times 10^2\ M^{-1}\ s^{-1}$, and $pK_a = 6.9$. The k_0 process is responsible for reaction above pH 4, while the k_H process occurs below pH 4. The pH independency of k_{obsd} in acids arises because of the opposing effects of pH on the rate of decomposition and the relative concentration of the reactive neutral form.

Several supporting pieces of evidence can be provided. (i) The UV spectrum of the hydroxylamine is pH dependent, and by extrapolation to zero time a spectroscopic pK_a of 7.0 has been obtained, in good agreement with the kinetic value. (ii) The 2-(hydroxylamino)-1,3-dimethylimidazolium ion,[6] a model for $\mathbf{1H^+}$

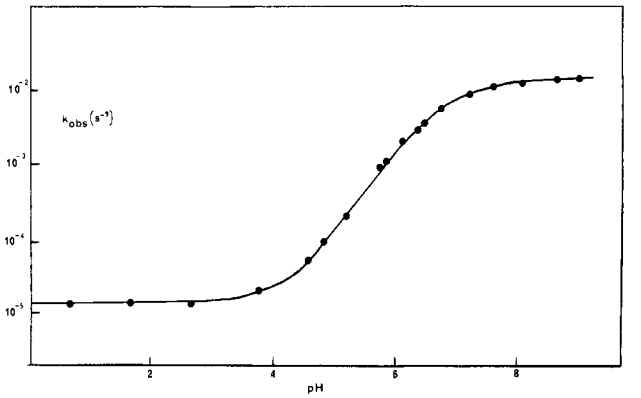
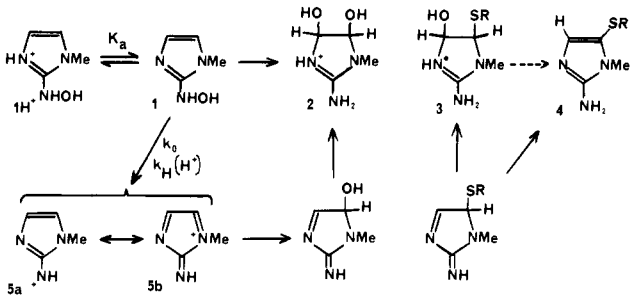


Figure 1. First-order rate constants for the decomposition of **1** (25 °C, under N_2).

Scheme I



which cannot give a structure analogous to the neutral **1**, is stable at pH 7. (iii) 5-Carbomethoxy-2-(hydroxylamino)-1-methylimidazole[6] is also stable at pH 7. This has a strong electron-withdrawing group at C-5 which destabilizes the cation. (iv) An electronic effect is also observed at N-1. The 2-hydroxylamine with $1\text{-}CH_2CONHCH_2CH_2OH$[6] has $k_0 = 0.0015\ s^{-1}$, 8 times smaller than the value for 1-Me. (v) Decomposition of **1** in the presence of cysteamine results in additional products. Two of these have NMR spectral characteristics[8] similar to those of the two isomers of **2** and we propose that these are structural analogues with one or possibly two RS groups in place of OH. Structure **3** shown in Scheme I is one possibility. A third product is also present with a singlet proton resonance in the aromatic region.[8] A product of this type has previously been characterized from glutathione and the 2-nitroimidazole misonidazole.[9] By analogy we draw structure **4** in the present system. While the structural assignments of **3** and **4** are tentative what is important is that the rate constants are independent of the extent of their formation; that is, there is no dependence on thiol concentration. Thus a mechanism is required where the thiol enters after the rate-limiting step.

Our proposed mechanism is directly analogous to the Bamberger rearrangement of benzenoid hydroxylamines,[10] with two important differences. First the benzenoid reaction produces aromatic products,[11] whereas saturation of C4–C5 is the usual result with the imidazole. This undoubtedly reflects the resonance energy differences in the two systems. Second, nitrenium ion formation with the benzenoids requires acid catalysis (or activation of the

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(3) *Trans*-**2**-Cl (75%): δ 5.18 (1 H, d, J = 0.7 Hz), 5.07 (1 H, d, J = 0.7 Hz), 3.03 (3 H, s). *cis*-**2**-Cl (25%): δ 5.38 (1 H, d, J = 5.5 Hz), 5.24 (1 H, d, J = 5.5 Hz), 2.95 (3 H, s). Stereochemical assignments have been made using the Karplus relationship.

(4) *N*-methylguanidine hydrochloride and a 10% excess of glyoxal were left at pH 8 for 5 days, the water was removed and methanol added, and the pure **2**-Cl (as a cis/trans mixture) precipitated in 85% yield by addition of ether.

(5) The product is a 4,5-dihydro-4,5-dihydroxyimidazolium salt. For similar preparations involving 1,2-dicarbonyl compounds and amidines or guanidines, see: Conforth, J. W.; Huang, H. T. *J. Chem. Soc.* **1948**, 731–735. Shapiro, R.; Hachmann, J. *Biochemistry* **1966**, *5*, 2799–2807. Imbach, J. L.; Jacquier, R.; Lacombe, J. M.; Maury, G. *Bull. Soc. Chim. Fr.* **1971**, 1052–1062. Nishimura, T.; Nakano, K.; Shibamoto, S.; Kitajima, K. *J. Heterocycl. Chem.* **1975**, *12*, 471–476. Nishimura, T.; Kitajima, K. *J. Org. Chem.* **1976**, *41*, 1590–1595; **1979**, *44*, 818–824.

(6) Prepared as described for the methyl derivative.

(7) These products are unstable and thus far we have been unable to isolate them in pure form.

(8) A: δ 5.37 (1 H, d, J = 1.6 Hz), 4.95 (1 H, d, J = 1.6 Hz), 3.06 (3 H, s). B: δ 5.56 (1 H, d, J = 6.5 Hz), 5.31 (1 H, d, J = 6.5 Hz), 2.96 (3 H, s). C: δ 7.27 (1 H, s), 3.53 (3 H, s). A complex set of signals at δ 3.4–3.0 associated with the CH_2CH_2 group is also present.

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(11) For an exception to this, see: Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 2448–2449.

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hydroxyl by conversion to a good leaving group[12]). With the imidazole an efficient noncatalyzed reaction occurs. This difference is explained by relative nitrenium ion stability.[13] With the heterocyclic system, a resonance contributer **5b** can be written with all atoms satisfying the octet rule.

In conclusion we note that nitrenium ions are now generally accepted as important intermediates of the metabolism of aromatic amines,[14] responsible for covalent binding to various biological nucleophiles. These same nucleophiles also interact with reduced nitroimidazoles.[1] The results of this study suggest that a mechanism involving an electrophilic intermediate is entirely plausible with this system also.

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Registry No. 1·HCl, 94944-71-5; *cis*-**2**-Cl, 94944-72-6; *trans*-**2**-Cl, 94944-73-7; *N*-methylguanidine hydrochloride, 21770-81-0; glyoxal, 107-22-2.

(12) See: Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498-1499.
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Total Synthesis of Streptazolin: An Application of the Aza Analogue of the Ferrier Rearrangement

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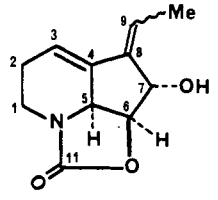
Streptazolin (**1**) is a lipophilic neutral compound first isolated by Drautz and Zähner in 1981 from cultures of *Streptomyces viridochromogenes*.[1] Due to the ease with which streptazolin



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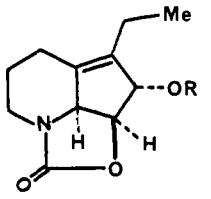

2, R = H

3, R = Ac

polymerizes in concentrated form, its purification and characterization were made additionally difficult. Its dihydro derivative **2** does, on the other hand, represent a stable compound. An X-ray structural analysis[2] as well as extensive NMR studies were carried out on the acetate derivative **3** of this dihydro material. 3,9-Dihydrostreptazolin has been found to exhibit marginal antibacterial and antifungal activity.[1]

A total synthesis effort directed toward streptazolin is made particularly intriguing because of the necessity of generating this molecule in a manner that is suited to its interception and detection in dilute form. Starting from the allyl-substituted tetrahydropyridine **4**, prepared by a Ferrier-like reaction between allyltrimethylsilane and *N*-carboethoxy-4-hydroxy-1,2,3,4-tetrahydropyridine as described previously,[3] the terminal double bond was hydrated,[4] the intermediate alcohol oxidized to aldehyde,[5] and the oxime derivative **5** generated (Scheme I).

An INOC reaction of this oxime was then induced with sodium hypochlorite to provide the isoxazoline **6**.[6] The N-O bond was cleaved by Raney nickel/acetic acid hydrogenolysis with maintenance of the cis ring fusion stereochemistry (J = 8.5 Hz)[7] and the resulting β-hydroxy ketone transformed to α-bromo ketal **7** by exposure to bromine in ethylene glycol. The hydroxyl group was protected as its MOM ether,[8] and dehydrobromination was brought about by DBU/Me_2SO treatment. Since attempts to epoxidize the double bond of the ketone derived from **8** failed, the carbonyl group of **9** was reduced to alcohol, and epoxidation with 3,5-dinitroperoxybenzoic acid[9] was carried out. That the epoxidation reaction had occurred from the concave face of the cis-fused ring system (hydroxyl directed)[10] was made apparent from the subsequent transformations.

The alcohol was now reoxidized to ketone, and elimination of the MOM-protected β-alcohol was triggered by 1 N NaOH treatment. A standard Wittig reaction on the resulting enone **11** employing ethylidenetriphenylphosphorane (from the phosphonium bromide and *n*-BuLi) in ether (sealed tube, 65 °C) afforded a 2:1 mixture of the E olefin **12a** and the Z olefin **12b**. By using the phosphorane prepared from the corresponding iodide and conducting the reaction at room temperature, the E/Z ratio varied from 2/1 to 7/6.[11] Since the structures of these Wittig products could not be firmly established through chemical shift comparisons, NOE difference experiments were carried out.[12] The data acquired provided good support for the assignment of E stereochemistry to **12a** and Z stereochemistry to **12b**. On treating this E/Z mixture with sodium methoxide, ring opening of the epoxide at its allylically activated site occurred with concomitant intramolecular attack by the newly freed alkoxide anion on the neighboring urethane carbonyl group. The moderately stable *O*-methyl ether derivative **13** of streptazolin was so formed (2:1 E/Z mixture). To ensure the structure of this material, especially as regards the stereochemical relationships among carbon centers 5, 6, and 7, the synthetic material was hydrogenated over palladium on carbon to the tetrahydro derivative **14**. Authentic dihydrostreptazolin acetate, kindly provided by Professor Drautz, was converted to dihydrostreptazolin by methanolic ammonia treatment and this intermediate was O-methylated and hydrogenated to furnish **14**. The 300-MHz ^1H NMR spectrum of this "naturally derived" substance matched *precisely* that obtained for the synthetic material (Scheme II).

To prepare streptazolin itself, opening of the epoxide with an easily deprotectable hydroxyl derivative was required. Surprisingly, sodium acetate in acetic acid led in 71% yield to the hydroxy acetates **15** as an E/Z mixture. These poorly stable intermediates were separated by HPLC and then admixed individually with

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(12) The NOE data are available as supplementary material.

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