inosine (Ino) and 5'-GMP complexes such as \((\text{NH}_3)_2\text{Pt}(\text{InoH}_2)_2\) and \((\text{NH}_3)_2\text{Pt}(\text{GMPh}_3)_2\); these were attributed to polynuclear complex formation.

Furthermore, there is clear evidence that none of the species formed during the reaction is a Pt complex with two 5'-GMP molecules bound via N7 of the guanine ring to the Pt atom from both 1H and 195Pt NMR data of the cis-[Pt(NH3)2Cl2(5'-GMP)2] complex. The latter exhibits a H8 proton resonance at 3.931 ppm and a 195Pt resonance of -2451.3 ppm which is considerably shifted to high field from the 195Pt resonances of species IG/IIG and IIIG (see Table III). Further, the resonances for the H1' protons in the cis-[Pt(NH3)2(5'-GMP)2] complex are at 2.143 ppm, 0.020 ppm to high field of the corresponding resonance in free 5'-GMP (2.163 ppm), while in species IG, IIG, and IIIG the H1' signals are at ca. 2.28 ppm which is to low field of the corresponding free signal.

From the structures of species IG/IIG given in Figure 9 in which the Pt atom is bound to N7 of the guanine ring, one would expect the 195Pt chemical shift of species IG/IIG to be given approximately by the mean of the 195Pt chemical shifts of cis-[Pt(NH3)2Cl2] and cis-[Pt(NH3)2(5'-GMP)2]; this has a value of -2306.4 ppm which is in excellent agreement with the measured value of -2302.0 ppm.

Comparison of the Kinetics of the Reactions of 5'-AMP and 5'-GMP with Excess cis-[Pt(NH3)2Cl2] in the Presence of KCl. A comparison of the kinetics of the reactions of 5'-AMP and 5'-GMP with excess cis-[Pt(NH3)2Cl2] in the presence of KCl at 80 °C leads to the following observations. Tables I and II show the relationship \(k_{IG} \approx k_{I3A} > k_{I2A} = k_{IA} > k_{3A}\) for the second-order association rate constants, which implies that the dissociation of a Cl atom from cis-[Pt(NH3)2Cl2] is not rate limiting. Considering only the 5'-AMP reaction with cis-[Pt(NH3)2Cl2], we observe that the association rate constant for binding to N7 (\(k_{IA}\)) is larger than that for binding to N1 (\(k_{IA}\)), a finding which correlates inversely with the smaller pK of N7 compared to N1 of the adenine ring.25 However, once a Pt atom is bound to either N1 or N7, the association rate constants (\(k_{IA}\) and \(k_{IA}\)) for binding to the remaining site are equal. This implies an electronic redistribution upon binding of a Pt atom to either N1 or N7, such that the reactivity toward cis-[Pt(NH3)2Cl2] of the remaining available site is less than that of N7 but greater than that of N1 in free 5'-AMP. Considering the schemes for the reaction of 5'-GMP with excess cis-[Pt(NH3)2Cl2], it is clear that species IG and IIG could either be formed simultaneously (as in the case of species IA and IA in the 5'-AMP reaction) or in sequence. Given our proposed structures for species IG and IIG (Figure 9), the latter seems unlikely. Moreover, it is likely that the association rate constants for the formation of the two rotamers, IG and IIG, would be equal and given by \(k_{IG}/2\). Assuming this assumption is correct, we note the relationship \(k_{IA} > k_{IG}/2 > k_{IA}\) for the second-order association rate constants for the binding of the first molecule of cis-[Pt(NH3)2Cl2] to 5'-AMP and 5'-GMP which is inversely correlated with the known relationship \(pK_a(N7)_{5'-AMP} < pK_a(N7)_{5'-GMP} < pK_a(N1)_{5'-AMP}\) for the protonation of ring nitrogen atoms.25

1,2,5-Thiadiazole 1-Oxides. 3. An Experimental and Theoretical Investigation of the Inversion Barrier

Joseph S. Amato, Sandor Karady,* Robert A. Reamer, H. Bernhard Schlegel,* James P. Springer, and Leonard M. Weinstock*

Contribution from the Merck Sharp & Dohme Research Laboratories, Division of Merck & Company, Inc., Rahway, New Jersey 07065. Received June 29, 1981

Abstract: The 1,2,5-thiadiazole 1-oxide system was synthesized via cyclocondensation of diethyl oxalimidate or dimethyl thiooxalimidate with thionyl chloride. The alkoxy and alkylthio group in these products are replaced by amines, e.g., pyrrolidine, which produced 3-ethoxy-4-(1-pyrrolidinyl)-1,2,5-thiadiazole 1-oxide from the diethoxy analogue at room temperature. Examination of this product by 13C NMR in the presence of a chiral shift reagent showed two isomers, indicative of a stable pyramidal sulfoxide structure. Reaction of 3,4-dioxy-1,2,5-thiadiazole 1-oxide with optically active amines, e.g., l-ephedrine, produces readily separable diastereomeric mixtures. The diastereoisomers undergo inversion only at elevated temperatures, \(DG^+_{120} = 33 \text{ kcal} \text{ mol}^{-1}\), compared to only ca. 14.8 kcal mol\(^{-1}\) for a thiophene 1-oxide and 36 kcal mol\(^{-1}\) for diaryl sulfoxides. X-ray analysis of 3,4-bis(methylthio)-1,2,5-thiadiazole 1-oxide demonstrates that the ring is essentially nonaromatic and confirms the pyramidal sulfoxide structure. Interaction between the sulfur lone pair and the diene is small, the C3-C4 bond length lying closer to that of cyclopentadiene than of thiophene or thiadiazole. Theoretical calculations indicate that aromaticity effects lower the inversion barrier nearly equally in the thiophene and thiadiazole sulfoxides by stabilizing the planar transition state and destabilizing the nonaromatic pyramidal structure. The reduction of the barrier in the thiadiazole, however, is counteracted by the effect of the electronegative nitrogen atoms, thus raising the inversion barrier back to the range of normal sulfoxides.

1,2,5-Thiadiazole (1) is a planar aromatic ring system with molecular parameters similar to thiophene. The aromaticity of 1 is supported by theoretical calculations, physical measurements, and chemical reactivity.1 The 1,1-dioxides of 1,2,5-thiadiazoles 2, on the other hand, do not appear to exhibit aromatic properties and are much less stable1 thermally and more electrophilic than the nonoxidized form. Little is known, however, about the corresponding monoxides (3). In fact, the literature contains very few detailed accounts of the chemistry of sulfoxides derived from thiaoaromatic systems. Mock2 prepared 2,5-di-tert-octylthiophene 1-oxide (4) and showed spectroscopically that two forms of the pyramidal sulfur can be observed at -10 °C, while at room temperature the sulfoxide undergoes rapid inversion. This low inversion barrier (e.g., ca. 20 kcal mol\(^{-1}\) less than diaryl sulfoxides) was attributed by Mock to be a consequence of either a delo-

With this background we felt that the chemistry of 1,2,5-thiadiazole oxides was a worthwhile field of investigation. Questions to be answered include the aromaticity and relative stability of the pyramidal and planar forms of this system and its chemistry as it relates to the parent system.

In this paper we present (a) the synthesis of some 1,2,5-thiadiazole 1-oxides, (b) the geometry of the system as established by X-ray analysis, (c) preparation of stable diastereomers of optically active sulfoxides, (d) calculation of the inversion barriers from their rate of racemization, and finally (e) the interpretation of the experimental data by ab initio theoretical calculations. Further details regarding the organic chemistry of this system will be reported elsewhere.

Synthesis and Measurement of the Inversion Barrier

Synthesis of the 1,2,5-thiadiazole 1-oxide system is achieved through the reaction of 6a and 6b with thiophenyl chloride producing 6a and 6b. The alkoxy or alkylthio groups of 6a or 6b can be readily replaced with nucleophiles. Thus, the reaction of 6a with pyrrolidine in ethanol at room temperature gave 3-ethoxy-4-(1-pyrrolidinyl)-1,2,5-thiadiazole 1-oxide (7) and 3,4-bis(1-pyrrolidinyl)-1,2,5-thiadiazole 1-oxide (8) with excess pyrrolidine. Primary amines and other nitrogen nucleophiles reacted analogously. This behavior is similar to that of the corresponding thiadiazole dioxides but is in contrast to the nonoxidized thiadiazole analogues which undergo this type of reaction only under forcing conditions.

The sulfoxide moiety because of its pyramidal structure can give rise to asymmetry. Carbon-13 NMR was used to differentiate the optical isomers of 7 employing a chiral shift reagent, tris(heptafluoropropyl)hydroxymethylene-d-camphorato]europium(III). The pyrrolidine and ethyl carbons showed non-equivalence in the presence of the shift reagent, indicating that 7 can exist in two isomeric forms and that the interconversion is not rapid at room temperature. Table I presents these data for 7 and gives the results with a control shift reagent, tris[6,7,8,8-heptafluoro-2,2-dimethyl-3,5-octanediolato]europium(III).

Table I. 13C Chemical Shift Data for 7a,b

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<th>Compd</th>
<th>Solvent</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
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<td>14.1</td>
<td>51.1</td>
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<tr>
<td>7b</td>
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<td>14.1</td>
<td>51.1</td>
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<tr>
<td>7d</td>
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<td>48.6</td>
<td>26.5</td>
<td>24.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Concentration of [7] = 0.5 M in CDCl3, chemical shifts in parts per million from internal Me3Si (δ = 0.0). b Pyrrolidinyl carbons non-equivalent due to restricted rotation. c Chiral shift reagent, tris[(heptafluoropropyl)hydroxymethylene-d-camphorato]europium(III).

table shifts in parts per million from internal Me3Si (δ = 0.0).

Table II. 13C Chemical Shift Data for the Diastereomers of 9 and 10a

<table>
<thead>
<tr>
<th>Compd</th>
<th>Solvent</th>
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<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8</th>
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<tbody>
<tr>
<td>9</td>
<td>CDCl3</td>
<td>69.1</td>
<td>14.1</td>
<td>51.1</td>
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<td>26.5</td>
<td>24.0</td>
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<tr>
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<td>151.7</td>
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<td>92.8</td>
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</tbody>
</table>

*a Chemical shifts in parts per million from internal Me3Si (δ = 0.0).

With this background we felt that the chemistry of 1,2,5-thiadiazole oxides was a worthwhile field of investigation. Questions to be answered include the aromaticity and relative stability of the pyramidal and planar forms of this system and its chemistry as it relates to the parent system.

In this paper we present (a) the synthesis of some 1,2,5-thiadiazole 1-oxides, (b) the geometry of the system as established by X-ray analysis, (c) preparation of stable diastereomers of optically active sulfoxides, (d) calculation of the inversion barriers from their rate of racemization, and finally (e) the interpretation of the experimental data by ab initio theoretical calculations. Further details regarding the organic chemistry of this system will be reported elsewhere.

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crystallization produced the pure diastereomers which were characterized by $^{13}C$ NMR (Table II). These diastereomers were stable at room temperature but epimerized rapidly in the presence of trace amounts of acid. The rate of epimerization of 9 in CD$_3$CN at 120 °C, monitored by $^1$H NMR of the C$_5$ hydrogen ($\delta$ 5.7 and 3.3) is 0.40 s$^{-1}$. This rate constant was derived from the decay of the epimeric signal and was used to calculate the inversion barrier of thiadiazole oxide (pyramidal and planar) shown in Figure 2. The theoretical geometries agree well with the experimental structures, where the latter are available. On a more subtle level the thiadiazole ring of 11 is planar to within 0.01 Å while the sulfur atom in 6b is a small but significant 0.16 Å below the plane of the other four atoms. The oxygen atom in 6b is 0.99 Å above this plane while the S-O bond forms an angle of 61° with the plane defined by N-S-N. The decrease in the N-S-N angle from 99.2° in 6b to 96.4° in 11 is also consistent with a slight puckering in the ring of 6b.

**Theoretical Studies**

Ab initio molecular orbital calculations have been very successful in predicting equilibrium geometries and computing inversion barriers. It seemed, therefore, that they could help in understanding the inversion barrier of thiadiazole 1-oxide in comparison with thiopeine 1-oxide and dimethyl sulfoxide. The calculations discussed below draw heavily from two related theoretical investigations in progress. Since three d orbitals are necessary for the correct description of sulfoxides,$^{10,11}$ d orbitals have been included for all calculations reported here.

The theoretically optimized geometries for thiadiazole and thiadiazole oxide (pyramidal and planar) are shown in Figure 3. The analogous calculated structures in the thiophene series are shown in Figure 2. The theoretical geometries agree well with the experimental structures, where the latter are available. On average, bond lengths differ by ±0.02 Å and angles by ±2.5°. Although the theoretical geometry optimizations of the sulfoxides were constrained to keep the heterocyclic ring planar, the residual forces on the ring atoms indicate a puckering in the same direction as observed in the X-ray structure and in earlier calculations.$^{12}$ The observed and calculated changes in geometry on S-oxidation are in even better agreement than the geometries themselves.

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Total Energy = -582.57112 a.u.

Figure 2. Comparison of the optimized geometry and total energy for thiophene and thiophene oxide in the planar and pyramidal structures.

Barrier to Inversion = 19.6 kcal mol\(^{-1}\)

Figure 3. Comparison of the optimized geometry and total energy for thiadiazole and thiadiazole oxide in the planar and pyramidal structures.

Barrier to Inversion = 31.9 kcal mol\(^{-1}\)

Figure 4. Comparison of the optimized geometry and total energy for thiadiazole and thiadiazole oxide in the planar and pyramidal structures.

Barrier to Inversion = 31.9 kcal mol\(^{-1}\)

substituents (also see Figure 4). Both CH\(_3\) and NH\(_2\) stabilize the SO bond relative to hydrogen, affecting the pyramidal structure more than the planar and thereby increasing the barrier

compared to H\(_2\)SO (43.5 kcal mol\(^{-1}\) (calcd)). The more electronegative substituent raises the barrier by preferentially stabilizing the pyramidal structure.

Aromaticity and conjugative effects are more difficult to measure directly. As argued above for the X-ray structure, changes in the C\(_3\)-C\(_4\) bond length of the calculated geometries can provide a clue to the relative aromaticity of the planar and pyramidal geometries of thiophene and thiadiazole oxides. Both pyramidal sulfoxides show a significant shortening of R(C\(_3\)-C\(_4\)), indicating destabilization due to a loss of aromaticity. In contrast, the planar forms show a decrease in R(C\(_3\)-C\(_4\)), signaling greater aromatic stabilization of the transition structure. Both changes reduce the barrier; the effect on thiadiazole 1-oxide is similar to, or possibly slightly larger than, the effect on thiophene 1-oxide. The strain introduced by closing the five-membered ring is estimated to contribute less than 2 kcal to the inversion barrier.

The nature of the inversion barrier in thiadiazole and thiophene 1-oxides can also be examined with an isodesmic reaction. Comparison with (CH\(_3\))\(_2\)SO and (NH\(_2\))\(_2\)SO instead of H\(_2\)SO to a large extent separates the “aromaticity” influence from the electronegativity trends (Figure 4). These values confirm the qualitative arguments based on bond length. The pyramidal thiadiazole and thiophene 1-oxides are destabilized compared to the acyclic sulfoxide, while the planar structures are slightly stabilized. The changes in the two heterocyclic sulfoxides are almost the same, indicating that an argument based solely on “lack of aromaticity” cannot explain the high inversion barrier in thiadiazole 1-oxide relative to thiophene 1-oxide.

methylene chloride and 580 mL of pyridine (7.2 mol) was added dropwise and 780 mL (9.63 mol) of pyridine was added dropwise with cooling. 195 evaporator. NMR spectra were recorded on Perkin-Elmer... was stirred for 2 h at room temperature. After extractive workup, the product was precipitated with ether, removed by filtration, washed with ether, and dried to yield 401 g (86%) of 6b: mp 109–112 °C; MS, m/z 194 (M*); IR (cm⁻¹, CHCl₃) 1625 (C=–N), 1115 (SO); ¹H NMR (CDCl₃, 60 MHz) δ 2.7 (s), 67.9. Anal. Calcd for C₄H₇N₂O₅S: C, 37.4; H, 3.12; N, 14.42; S, 49.69.

3-Ethoxy-4-(1-pyrrolidinyl)-1,2,5-thiadiazole 1-Oxide (7). To a solution of 6a (1.85 g, 10 mmol) in 10 mL of ethanol was added 0.72 g (10 mmol) of pyridinium, and the mixture was stirred for 30 min at room temperature, concentrated to one-fourth volume and diluted with ether. The crystals were filtered and washed with ether. IR (cm⁻¹, CHCl₃) 3450 (OH), 1625 (C=–N), 1115 (SO); 'H NMR (CDCl₃, 60 MHz) δ 60.9 (45 mmol) in 50 mL of methanol was added edrophine (8.3 g, 50 mmol) and 1 mL of disopropylethylamine. The solution was stirred for 3 h at room temperature and concentrated in vacuo to yield 8 g of a clear oil. Crystalization from acetone/tetrahydrofuran produced 2.0 g of a single diastereomer of 9: mp 166–168 °C; [α]D = 61.2° (c = 0.59; MS, m/z 245 (M*); IR (cm⁻¹, CHCl₃) 3450 (OH), 1100 (SO); ¹H NMR (CDCl₃, 60 MHz) δ 7.7 (s, 5 H), 5.8 (d, J = 3 Hz, 1 H), 3.8 (m, 1 H), 3.13 (s, 3 H), 1.4 (d, J = 6 Hz, 3 H). Anal. Calcd for C₇H₉NO₃S: C, 45.74; H, 4.98; N, 15.96; S, 12.18.

3-Bis(1-pyrrolidinyl)-1,2,5-thiadiazole 1-Oxide (8). The same reaction as above, carried out with 2 molar equiv of pyrrolidine produced 8: mp 191–194 °C; MS, m/z 240 (M*), 170 (M*–C₄H₇N), 144 (M*–C₆H₃N₄), 96 (C₄H₇N₄, 70 (C₆H₃N₄); ¹H NMR (CHCl₃, 60 MHz) δ 3.65 (m, 8 H), 2.0 (m, 8 H).

Synthesis of 9. Into a stirred solution of 6a (9.5 g, 50 mmol) in 50 mL of methanol was added 1-pyrrolidinyl (8.3 g, 50 mmol) and 1 mL of disopropylethylamine. The solution was stirred for 3 h and concentrated in vacuo to an oil. After the usual workup the product was crystallized from ethyl acetate to yield 1.3 g of a single diastereomer of 10: mp 166–168 °C; [α]D = 61.7° (c = 0.59; MS, m/z 245 (M*); IR (cm⁻¹, CHCl₃) 3450 (OH), 1100 (SO); ¹H NMR (CDCl₃, 60 MHz) δ 6.5 (m, 2 H), 4.6 (m, 2 H), 3.7 (m, 2 H). The remaining filtrate was concentrated to yield an oil which crystallized on standing. The crystals were filtered and washed with ethyl acetate to yield 1.0 g of the other diastereomer of 10: mp 115–120 °C; [α]D = 18.7° (c = 0.59; MS, m/z 245 (M*); IR (cm⁻¹, CHCl₃) 3450 (OH), 1100 (SO); ¹H NMR (CDCl₃, 60 MHz) δ 5.15 (m, 1 H), 4.6 (m, 2 H), 3.7 (m, 2 H). The crystals were formed thick yellow needles from methylene chloride/ethanol solutions. The crystal structure was solved by using a multiscan tiltogram-orienting formula approach and refined by using full-matrix least squares. The calculated density was 1.58 g/cm³ for Z = 4. All unique reflections with 2θ ≤ 114° were measured with an automatic four-circle diffractometer using Cu Kα radiation (λ = 1.5418 Å).

Theoretical Calculations

Ab initio computations were carried out with the GAUSSIAN 78 series of programs. Theoretical studies on a variety of normal...
and hypervalent sulfur compounds indicate that the STO-3G* basis adequately models geometry and trends in barrier heights. However, an extensive series of calculations with the STO-3G* basis parallel to those reported demonstrated that it is not flexible enough to handle the subtle balance between aromaticity and electronegativity encountered in thiadiazole I-oxide. Accordingly, the 4-31G* split valence basis set was used augmented by a set of six Cartesian d functions on sulfur (denoted by 4-31G+d). The GAUSSIAN exponent, \( \alpha = 0.54 \), was optimized for pyramidal H$_2$SO. This basis set overestimates the SO bond length by ca. 0.02 Å but predicts the inversion barrier approximately as well as the 4-31G* basis which contains d orbitals on first and second row atoms. Because of strongly coupled internal coordinates, cyclic structures pose a special problem for geometry optimization. To overcome these difficulties, equilibrium geometries were determined with a conjugate gradient method using analytically calculated energy derivatives. All structures were fully optimized, with the exception that the heterocyclic rings were constrained to be planar, by using the 4-31G+d basis set.

Acknowledgment. We are grateful to Drs. Arthur A. Patchett and G. B. Smith for useful discussions and Mr. Jack Smith for the mass spectra. Special thanks are due to Dr. Raymond Firestone for many helpful suggestions.

Registry No. 4, 31681-45-5; 5a, 13534-15-1; 5b, 79844-63-6; 6a, 79844-64-7; 6b, 79844-65-8; 7, 80028-45-1; 8, 79844-66-9; 9, 80028-46-2; 10 isomer 1, 80028-47-3; 10 isomer 2, 80028-48-4; 11, 4057-61-8; pyridoline, 123-75-1; l-ephedrine, 321-98-2; (S)-2,3-dihydroxy-1-(tert-butyldimino)propane, 30315-46-9; H$_2$SO, 25540-60-7; (CH$_3$)$_2$SO, 67-68-5; (NH$_2$)$_2$SO, 36986-61-5.

Supplementary Material Available: The final fractional coordinates and temperature parameters for 6b from the X-ray experiments (1 page). Ordering information is given on any current masthead page.

A New Thermal Rearrangement in the 4-Isoxazoline System. Some Chemical and Stereochemical Properties of a Benzodiazepine Oxide–Ethyl Propiolate Adduct

Jeremiah P. Freeman,\textsuperscript{1,7} David J. Duchamp,\textsuperscript{1} Constance G. Chidester,\textsuperscript{1} George Slomp,\textsuperscript{1} Jacob Szmuszkovicz,\textsuperscript{1,7} and M. Raban\textsuperscript{1}

Contribution from the Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001, and Department of Chemistry, Wayne State University, Detroit, Michigan 48202. Received July 22, 1981

Abstract: Reaction of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide, 3, with ethyl propiolate afforded the expected 4-isoxazoline 4 and a rearrangement product 5. Product 5 and a further rearrangement product, 6, could be obtained from 4 upon treatment with boiling ethanol which also yielded a dihydroquinoxaline 7. The structures of isomers 4, 5, and 6 were determined by X-ray diffraction analyses. The conformational and configurational properties of these compounds were further studied by NMR. The rearrangement of 4 to 5 represents a new reaction path for 4-isoxazolines.

4-Isoxazolines, 1, whose isolable members are relatively rare,

\[ \text{Product} \]

are markable heterocycles because of the number of interesting rearrangements which arise from them. Baldwin\textsuperscript{1} has shown that in the simplest case they interconvert with ketoaziridines and 2-oxazolines. Often these primary reactions are masked by secondary reactions and one rearrangement product, 6, was observed with the pyrrolone N-oxide.\textsuperscript{2} Extensive rearrangement also was observed with the 4-isoxazolines derived from fervenulin 4-oxides.\textsuperscript{3} In most of these cases and others the 4-isoxazolines were not isolable and were proposed as transient, first-formed intermediates.

\textsuperscript{1} Visiting Professor, Summer 1981. Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556.

\textsuperscript{2} The Upjohn Company.

\textsuperscript{3} Wayne State University.

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