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14. ABSTRACT

This project investigated new energetic materials for use with a triazole cured binder system. Research was conducted in five main areas: 1) energetic materials based on the spiro[4.4]nonane system, 2) completion of our work on the 4,4´-(methylenediimino)bis-1,2,5-oxadiazole-3-carboxylic acid and carboxamide, 3) a re-examination of the reaction of glyoxal with 3,4-diamino[1,2,5]oxadiazole, 4) synthesis and chemistry of 3-hydroxymethyl-4-amino[1,2,5]oxadiazole and 5) work on energetic polymers for structural components.

15. SUBJECT TERMS

triazole cure; spiro[4.4]nonane; 4,4´-(methylenediimino)bis-1,2,5-oxadiazole-3-carboxylic acid; 3-hydroxymethyl-4-amino [1,2,5]oxadiazole; poly(4-aminofurazan-3-carboxylic acid)

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The University of Southern Mississippi

Final Technical Report

Project Title: Very High Performance High Nitrogen Energetic Ingredients and Energetic Polymers for Structural Components

Project Period: 10/1/07 – 9/30/11
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Project Objective

Investigate new energetic materials for use with a Triazole Cured Binder System:
Theoretical energetic calculations, synthesis of monomers, mono-propellants and organic oxidizers, and synthesis and characterizations of energetic structural polymers.

Introduction

Research was conducted in five main areas: 1.) energetic materials based on the spiro[4.4]nonane system, 2.) completion of our work on the 4,4′-(Methylenediimino)bis-1,2,5-Oxadiazole-3-carboxylic Acid and Carboxamide, 3.) a re-examination of the reaction of glyoxal with 3,4-diamino[1,2,5]oxadiazole, 4.) Synthesis and chemistry of 3-hydroxymethyl-4-amino[1,2,5]oxadiazole and 5.) work on energetic polymers for structural components.

1.) Energetic materials based on the spiro[4.4]nonane system

The attached papers summarize the work accomplished during the reporting period.

1. Rodney L. Willer, Robson F. Storey and Garrett Campbell, Synthesis of Cyclic N-Nitrourethanes by the Simultaneous Oxidative Desulfurization and Nitration of Cyclic Thiourethanes, Journal of Heterocyclic Chemistry, **00**, 00 (2011).
2. Rodney L. Willer, Christopher G. Campbell, Robson F. Storey, Jeffery Deschamps, Damon Parrish, Calculations on, Synthesis of and Crystal Structures of *d,l* and *l*-3,8-dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione, in preparation

2.) 4,4′-(Methylenediimino)bis-1,2,5-Oxadiazole-3-carboxylic Acid and Carboxamide

The attached paper summarizes the work accomplished during the reporting period.

1. Rodney L. Willer, Robson F. Storey, Jeffery Deschamps and Mark Frisch, Synthesis and Crystal Structure of 4,4′-(Methylenediimino)bis-1,2,5-Oxadiazole-3-carboxylic Acid and Carboxamide, accepted for publication in the Journal of Heterocyclic Chemistry.

3.) A Re-examination of the reaction of Glyoxal and 3,4-Diamino[1,2,5]oxadiazole

The attached paper summarizes most of the the work accomplished during the reporting period.

1. Rodney L. Willer, Robson F. Storey, Christopher G. Campbell, Steven W. Bunte and Damon Parrish, A Reexamination of the Reaction of 3,4-Diamino[1,2,5]oxadiazole with Glyoxal, accepted for publication in the Journal of Heterocyclic Chemistry.

4.) Synthesis and chemistry of 3-hydroxymethyl-4-amino[1,2,5]oxadiazole

The attached paper summarizes on work on the synthesis and chemistry of 3-hydroxymethyl-4-amino[1,2,5]oxadiazole.

1. Synthesis and Crystal Structure of octahydro-5H,12H-4,11-methano-1H,7H-bis[1,2,5]oxadiazole-[3,4-d:3′,4′-j][1,7,3,9]dioxadiazacyclododecine, R. L. Willer, R. F. Storey, W. L. Jarrett and D. Parrish, J. Hetero. Chem, accepted for publication in the Journal of Heterocyclic Chemistry.

5.) Energetic Structural Polymers

All of the work during the project has focused on the poly (4-aminofurazan-3-carboxylic acid). A sample of 4-aminofurazan-3-carboxylic acid (AFCA) was synthesized using the procedure reported by K. G. Meyer.[1] Unfortunately, the ^{13}C NMR chemical shifts of the material we produced and those reported by Meyer did not agree. He had reported chemical shifts of 161.3, 157.1 and 143.3 ppm. The compound we isolated following his procedure gave chemical shifts of 160.7, 156.8 and 140.5 ppm. Most of the other spectral properties were in agreement and this discrepancy was puzzling. It was thought that we may have isolated the dioxime instead of the furazan. However, retreatment of the compound with base under even harsher conditions than described in his paper returned the same compound we had originally isolated. This disagreement continued until we checked the ^{13}C NMR chemical shifts for the compound reported by Shermetev et. al.[2] They reported ^{13}C NMR chemical shifts of 160.5, 156.8 and 140.4 ppm. This gave us confidence that the compound we had isolated was indeed 4-aminofurazan-3-carboxylic acid. It is now apparent that the compound Meyer isolated is the interesting complex formed from a molecule of the acid and a molecule of the potassium salt of the acid. This work has now been published in the attached paper.

1. Rodney L. Willer, Robson F. Storey, Mark Frisch and Jeffery R. Deschamps, Crystal Structures of the "Two" 4-Aminofurazan-3-Carboxylic Acids, Journal of Heterocyclic Chemistry, **00**, 00 (2011).

We next turned our attention to the synthesis of an ester from this material since some of the proposed approaches to the polymer required an ester. There are procedures in the literature for both the methyl[2]and ethyl[3] ester. However, they both use anhydrous HCl as the catalyst and the reactions times are long and yields are modest. We have developed a vastly improved procedure for synthesis of the n-propyl ester that gives essentially quantitative yield and uses concentrated sulfuric acid as the catalyst instead of hydrochloric acid (Figure 1). The n-propyl ester is also lower melting and more soluble in common organic solvents such as THF as compared to the methyl or ethyl ester.

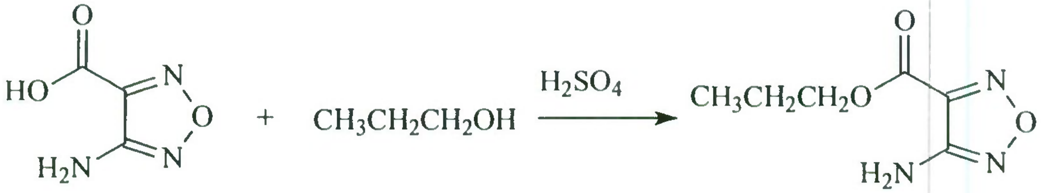

Figure 1. Synthesis of n-propyl 4-aminofurazan-3-carboxylate.

We next turned our attention to the synthesis of the amide. Again, the literature procedure is complicated calling for the use of anhydrous ammonia in an alcohol solvent.[3] We found that simply treating the n-propyl ester with an excess of aqueous ammonia at slightly above room temperature gave an essentially quantitative yield of the amide (Figure 2).

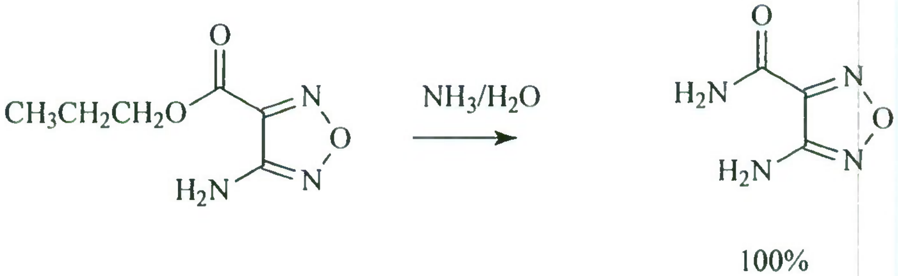

Figure 2. Synthesis of 4-aminofurazan-3-carboxamide.

With these materials in hand, attention turned to the polymerization. A careful perusal of the literature showed that the closest known polymer was poly(anthranilic acid). There is only one report in the literature on the synthesis of this material. In the late 1940's Japanese workers reported that the polymer had been made by the "Leuchs Polymerization" (Figure 3)[4] We were disappointed to find that the "polymer" described in the abstract was actually only a tetramer.

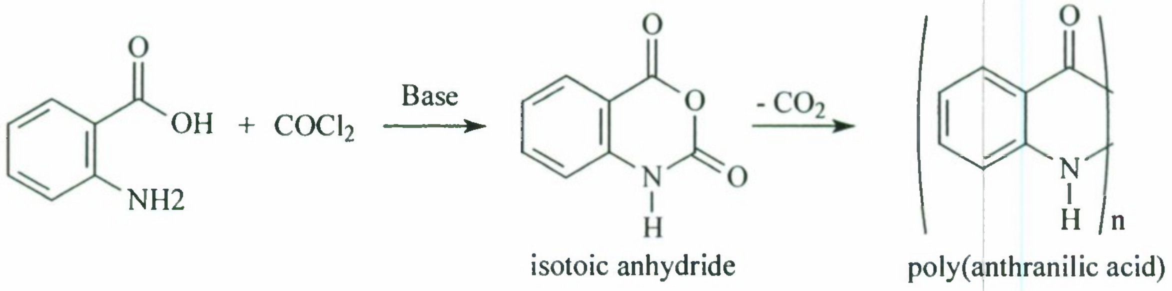

Figure 3. Literature synthesis of poly(anthranilic acid).

We would like to avoid the use of phosgene to make the intermediate. A recent Russian paper claims that anthranilic acid can be reacted with the less hazardous methyl chloroformate to also produce the intermediate, isatoic anhydride.[5] We have tried one experiment and found much to our surprise that we isolated the methyl ester, methyl 4-aminofurazan-3-carboxylate (Figure 4).

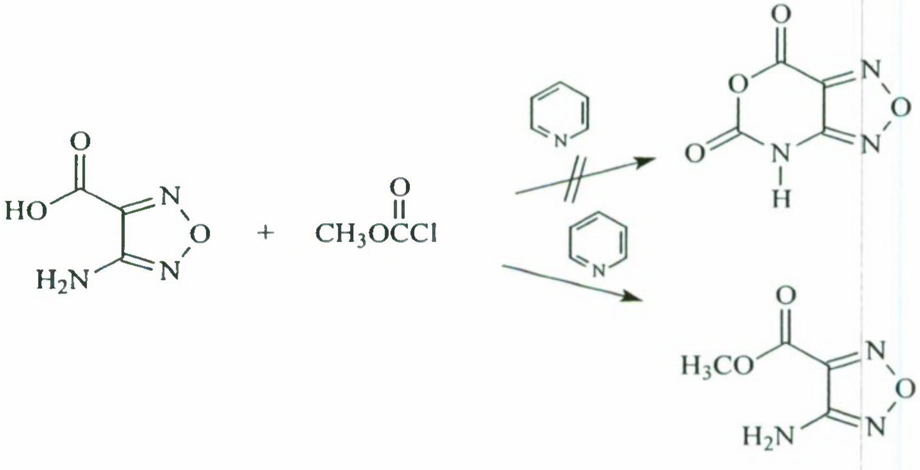

Figure 4. Reaction of methyl chloroformate with AFCA.

Additional methods of forming the polymer were considered. One method considered was the self condensation of the ester under neutral, acidic, or basic conditions. The initial experiment under neutral conditions has been conducted (Figure 5). Heating the neat ester at 110 °C for several hours produced no discernable reaction.

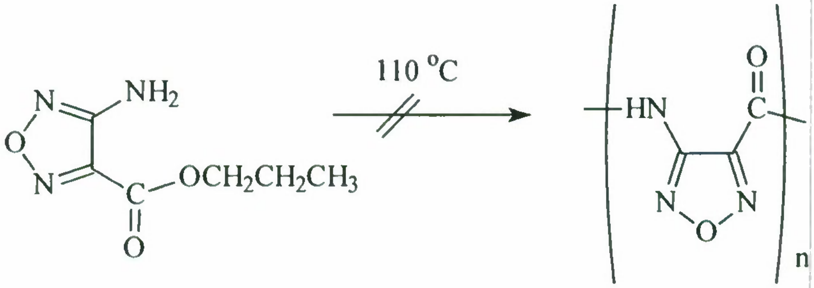

Figure 5. Attempted polymerization of n-propyl 4-aminofurazan-3-carboxylate.

We next turned our attention to basic conditions. Potassium hydride is a strong, non-nucleophilic base that should be able to extract the amine proton from the n-propyl 4-aminofurazan-3-carboxylate. An excellent reference describing the reaction of methyl anthranilate with sodium hydride was located (Figure 6). These investigators found that this reaction produced the interesting dibenzodiazocine in 85% yield.[6]

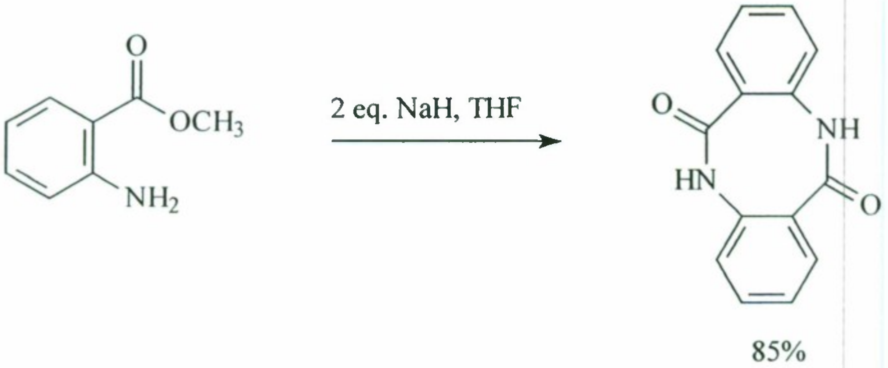

Figure 6. Reaction of methyl anthranilate with sodium hydride.

We chose to examine the reaction of n-propyl 4-aminofurazan-3-carboxylate with the more reactive KH. The first reaction was run using one equivalent of KH. The n-propyl 4-aminofurazan-3-carboxylate was added over a ten minute period to the KH/THF slurry at room temperature. The evolution of hydrogen was slow at first but increased to a noticeable rate accompanied by a slight but noticeable increase in the temperature. After the hydrogen evolution slowed, the temperature was raised to 50 °C for three hours. A very insoluble product was obtained that appeared by C-13 CP/MAS spectrum to be a "dimer" because it contained both furazan resonances and propyl resonances (Figure 7). The reaction was repeated using two equivalents of KH. An even more insoluble product was obtained. Figure 8 and 9 show the C-13 and N-15 CP/MAS spectra of the product. An additional piece of evidence is that the yield is essentially 100% of theory. Recently an additional experiment was conducted where the ester was added very slowly to the slurry of KH/THF at 50 °C. There is some evidence that this procedure produces some of the difurazanodiazocine.

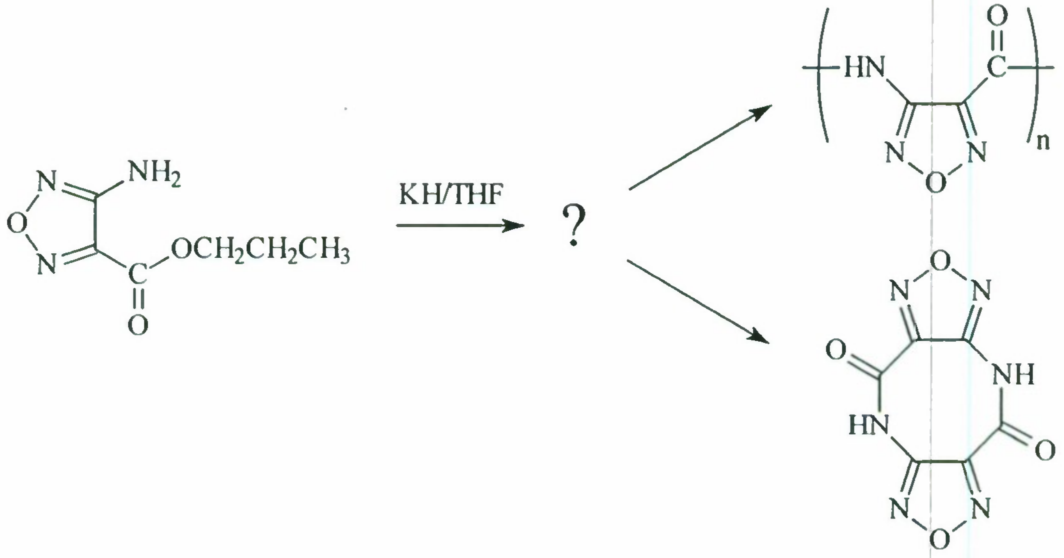

Figure 7. Reaction of n-propyl 4-aminofurazan-3-carboxylate with one equivalent of KH.

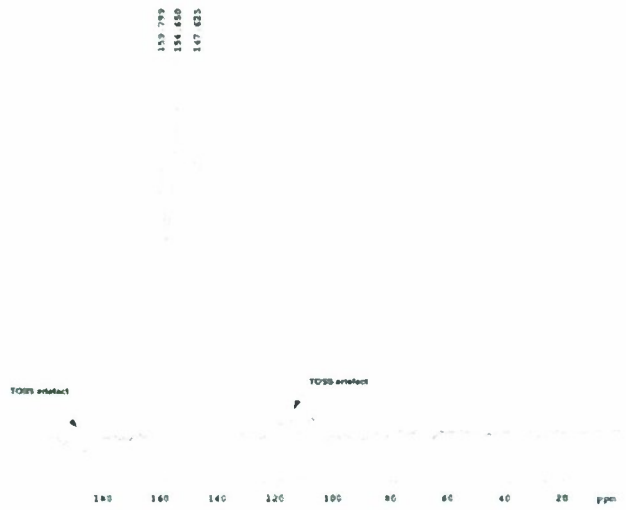

Figure 8. C-13 CPMAS spectrum of poly(4-aminofurazan-3-carboxylic acid).

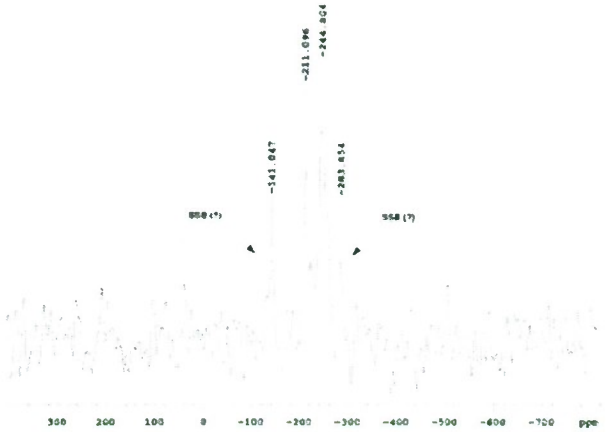

Figure 9. N-15 CPMAS spectrum of poly(4-aminofurazan-3-carboxylic acid).

Last year we have scaled up the synthesis and produced 6 g of polymer. As a structure proof for the polymer, we subjected it to both acidic and basic hydrolysis (Figure 10). In both cases nearly quantitative yields of the parent acid were isolated. Characterization of the polymer has proven to be difficult.

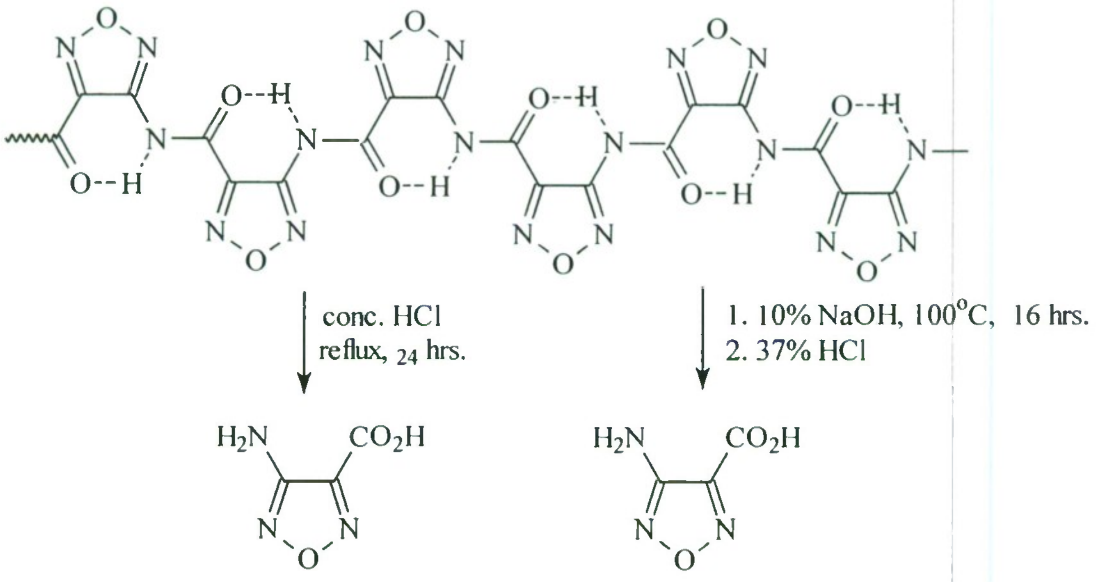

Figure 10. Acid and base catalyzed hydrolysis of Poly(AFCA).

This year we were able to devise a method to partially separate the product into two compounds. The crude product ids dissolved in boiling water (1g/100 ml) give a solution that contains a small amount of un-dissolved material. Filtering the solution through a fiber-glass filter produces a clear solution that when allowed to slowly cool produces “clouds”. This material can be filtered off. This is clearly polymer. The mother liquor can be freeze dried to yield a somewhat crystalline product. Elemental analysis of the two products produced results that differed significantly from the theory for a $(C_3HN_3O_2)_2$ or $(C_3HN_3O_2)_n$ product. The results were similar to what we observed with one of the two 4-amino[1,2,5]oxadiazole-3-carboxylic acids and suggested that we might actually be dealing with potassium salts. Recalculation of the elemental analyses for $(C_3KN_3O_2)_2$ or $(C_3KN_3O_2)_n$ indicated that indeed what we have isolated are the potassium salts. We are currently working on procedures to convert the potassium salts to the proton compounds

This work is currently being drafted into a paper entitled Reaction of n-Propyl 4-amino[1,2,5]oxadiazole-3-carboxylate with KH.

Patents, Publications and Presentations

Patents

1. Rodney L. Willer and Robson F. Storey, Poly(4-aminofurazan-3-carboxylic acid), in preparation

Publications

1. Rodney L. Willer, Calculation of the Density and Detonation Properties of C, H, N, O and F Compounds: Use in the Design and Synthesis of New Energetic Materials, J. Mex. Chem. Soc. **2009**, *53(3)*, 107-118.
2. Rodney L. Willer, William L. Jarrett, Robson F. Storey and Damon Parrish, Synthesis and Crystal Structure of octahydro-5H,12H-4,11-Methano-1H,7H-bis[1,2,5]oxadiazolo[3,4-d:3',4'-j][1,7,3,9]dioxadiazacyclododecine, accepted for publication in the Journal of Heterocyclic Chemistry.
3. Rodney L. Willer, Robson F. Storey, Mark Frisch and Jeffery R. Deschamps, Crystal Structures of the "Two" 4-Aminofurazan-3-Carboxylic Acids, Journal of Heterocyclic Chemistry, **00**, 00 (2011).
4. Rodney L. Willer, Robson F. Storey, Jeffery Deschamps and Mark Frisch, Synthesis and Crystal Structure of 4,4′-(Methylenediimino)bis-1,2,5-Oxadiazole-3-carboxylic Acid and Carboxamide, accepted for publication in the Journal of Heterocyclic Chemistry.
5. Rodney L. Willer, Robson F. Storey and Garrett Campbell, Synthesis of Cyclic N-Nitrourethanes by the Simultaneous Oxidative Desulfurization and Nitration of Cyclic Thiourethanes, Journal of Heterocyclic Chemistry, **00**, 00 (2011).
6. Rodney L. Willer, Robson F. Storey, Jeffery Deschamps, Damon Parrish, Calculations on, Synthesis of and Crystal Structures of *d,l* and *l*-3,8-dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione, in preparation
7. Rodney L. Willer and Robson F. Storey, Synthesis of Pure N,N,N'- tripropargyl- and N, N, N', N'- tetrapropargyl-4,4'-diaminodiphenylsulfone, submitted.
8. Rodney L. Willer, Robson F. Storey, Christopher G. Campbell, Steven W. Bunte and Damon Parrish, A Reexamination of the Reaction of 3,4-Diamino[1,2,5]oxadiazole with Glyoxal, accepted for publication in the Journal of Heterocyclic Chemistry.
9. Rodney L. Willer, William L. Jarrett, and Robson F. Storey, Reaction of n-Propyl 4-amino[1,2,5]oxadiazole-3-carboxylate with KH, in preparation.
10. M. B. Jackson, R. L. Willer, R. F. Storey, J. S. Wiggins, Simulation Method to Predict the Glass Transition Temperature and Density of the Energetic Polymers Poly(glycidyl nitrate) (PGN) and Poly(3-nitratooxetane) (PNO) and Copolymers Therefrom, in preparation.
11. E. Gorman, R. L. Willer, L. K. Kemp and R. F. Storey, Development of a Triazole Cured Resin System for Composites 1. Evaluation of Alkyne Curatives, in preparation.

12. I.E. Gorman, R.L Willer, R.F. Storey, Kinetic and Structural Investigation of a Novel Resin System that Cures by Triazole Ring Formation , J. Polym. Sci., Part A: Polym. Sci., in revision.

Presentations

1. Rodney L. Willer, Christopher G. Campbell and Robson F. Storey, Simultaneous Oxidative Desulfurization and Nitration of Cyclic Thiourethanes: A Facile Synthesis of Cyclic N-Nitrourethanes, 13th NTREM (2010), Pardubice, Czech Republic, April 21st-23rd, 2010.

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Synthesis of Cyclic *N*-Nitrourethanes by the Simultaneous Oxidative Desulfurization and Nitration of Cyclic Thiourethanes

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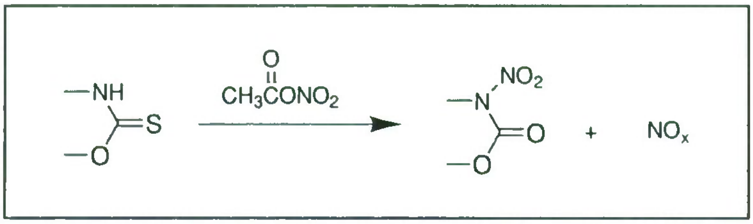
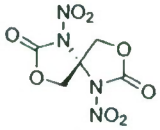


The reaction of five- and six-membered cyclic thiourethanes with acetyl nitrate results in a vigorous reaction that generates copious amounts of red–brown nitrogen oxide fumes and produces the corresponding cyclic *N*-nitrourethanes in high yields (>95%). The overall yield of the cyclic *N*-nitrourethanes starting from an aminoalcohol using the "thiourethane" route is superior to the conventional route going through the cyclic urethane.

J. Heterocyclic Chem., **00**, 00 (2011).

INTRODUCTION

Cyclic *N*-nitrourethanes (*N*-nitrocarbamates) are well known compounds. First reported by Franchimont and Lubin in 1902 [1], they were originally synthesized by the nitration of the corresponding cyclic urethanes with fuming nitric acid. These compounds were extensively studied by White et al. [2] in the mid-1960s, and they introduced the use of acetyl nitrate as the nitrating agent [2]. Modern syntheses of cyclic *N*-nitrourethanes involve reaction of the trimethylsilyl derivatives of the cyclic urethanes with dinitrogen pentoxide in methylene chloride [3]. In the course of our work on energetic compounds, we selected 3,8-dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione, **1**, as a target molecule, because it is calculated to be dense (d = 1.88 g/cc) and energetic [4]. Herein we report a new synthetic approach to **1** and related compounds involving simultaneous oxidative desulfurization and nitration of cyclic thiourethanes using acetyl nitrate.



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RESULTS AND DISCUSSION

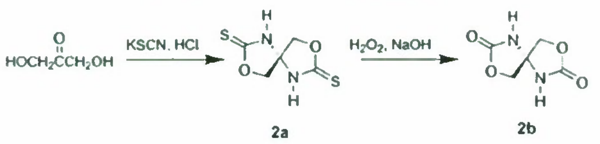
The standard approach to **1** would be nitration of the known 1,6-dioxa-3,8-diazaspiro-[4.4]nonane-2,7-dione [5], **2b**, with acetyl nitrate. Compound **2b** has been synthesized from the analogous spirodithiourethane, **2a**, using basic hydrogen peroxide desulfurization [5] (Scheme 1). The yield for the conversion of **2a** to **2b** is very poor (44%) and the procedure is somewhat lengthy [5].

There is limited literature precedence describing the nitration chemistry of cyclic thiourethanes. Thus, we examined the reaction of **2a** with an acetyl nitrate solution at −10°C as a possible alternative. Surprisingly, a vigorous reaction occurred with the evolution of copious amounts of nitrogen oxides. Upon work-up, the product was identified as the desired spirodinitrourethane, **1**, based on ^{1}H NMR, ^{13}C NMR, FT-IR, and high resolution mass spectroscopy data (Fig. 1). The structure was confirmed by X-ray crystallography [6]. The yield of **1** was greater than 95%.

We examined the scope of this tandem process by studying the reaction of the four monocyclic thiourethanes, **3–6** (Scheme 2), with acetyl nitrate. The cyclic thiourethanes were synthesized using a procedure similar to that reported by Li and Ohtani [7]. Reaction of these four compounds with an acetyl nitrate solution produced high yields (>95%) of the corresponding cyclic *N*-nitrourethanes, **7–10**. Formation of high yields of **10** did require a increase of the reaction temperature to 0°C.

The synthesis of both the monocyclic urethanes and thiourethanes starts from the corresponding aminoalcohols (Scheme 2). Typical yields reported for the synthesis of the five- and six-membered cyclic urethanes from the aminoalcohol and diethyl carbonate range from 40 to 70% [2]. The yields reported by Li and Othani (and

Scheme 1. Synthesis of 2a and 2b.



confirmed by this work) for the corresponding thiourethanes are in the range of 80–95%. It can be easily seen that the "thiourethane" route to the cyclic *N*-nitrourethanes appears to be superior to the "conventional" urethane route.

EXPERIMENTAL

Materials. Reagents and all specialty solvents (anhydrous, NMR) were purchased from Aldrich Chemical Co. and used without further purification. Routine solvents were purchased from Fisher Scientific.

Instrumentation. FT-IR spectra were obtained on a Bruker Equinox 55 spectrometer as KBr pellets or films. High resolution mass spectroscopy (HR MS) analyses were conducted at The University of Iowa HRMSF. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Mercury NMR spectrometer operating at a frequency of 300.13 MHz for proton and 75.5 MHz for carbon. DSCs were obtained on a TA Instruments Model Q200 using hermetically sealed Al pans under a nitrogen purge. They were run from ambient to 300°C at 3°C/min.

1,6-Dioxa-3,8-diazaspiro[4.4]nunane-2,7-dithione, 2a. This compound was made by the procedure of Köll and coworkers [5]. The melting point (mp) was 205–206°C (ref. 5; 206°C).

General procedure for 2-thioxo-1,3-*O*,*N*-heterocycles, 3–6 (cyclic thiourethanes). Modified Li and Ohtani procedure [7]. The 2-aminoalcohol (0.1 mol), triethylamine (0.1 mol), and methanol (100 mL) are placed in a two-neck 250-mL flask equipped with a stir bar [7]. The solution is stirred at 0°C, while carbon disulfide (7.62 g, 0.10 mol) is added dropwise. The solution is stirred at room temperature for 30 min. Hydrogen peroxide (30%, 16–20 mL, 0.15–0.2 mol) is then added at such a rate that reflux of the solvent was observed and until the upper solution of the reaction mixture no longer becomes cloudy by addition of extra hydrogen peroxide. The reaction is cooled to room temperature and then filtered. The methanol and water are removed by reduced pressure. The residue is extracted with methylene chloride (2 × 100 mL). The combined methylene chloride extracts are washed with water (2 × 50 mL) and then dried over $MgSO_4$. The organic layer is filtered and then evaporated to dryness under reduced pressure.

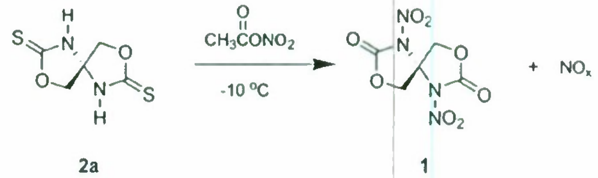


Figure 1. Reaction of 2a with acetyl nitrate.

***1,3-Oxazolidine-2-thione*, *3*.** The compound was recrystallized from benzene to give colorless crystals, mp 97–98°C (ref. 7; 97–99°C).

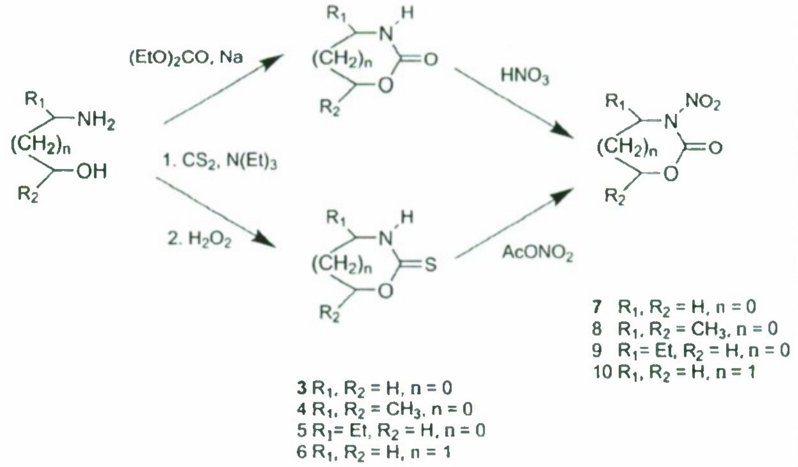
***5-Methyl-1,3-oxazolidine-2-thione*, *4*.** The compound was recrystallized from benzene to give colorless crystals, mp 73–74°C (ref. 7: 74.5–75°C).

***4-Ethyl-1,3-oxazolidine-2-thione*, *5*.** The compound was recrystallized from water to give colorless crystals, mp 74–75°C (ref. 8; 74–75°C).

***Tetrahydro-1,3-oxazine-2-thione*, *6*.** The compound was recrystallized from benzene to give colorless crystals, mp 127–128°C (ref. 7; 128–129°C).

General procedure for the reaction of cyclic thiourethanes with acetyl nitrate. A dry 50-mL round-bottom flask maintained at −10°C (brine/ice bath) and under a nitrogen atmosphere is charged with 4.08 g (4.0 mL) of acetic anhydride. Slow addition of 2.52 g (1.60 mL) of 100% nitric acid forms the acetyl nitrate solution. The temperature is raised to

Scheme 2. Synthesis of cyclic *N*-nitrourethanes via the urethane and thiourethane routes.



10°C for 10 min and then lowered back to −10°C. The cyclic thiourethane (5.0 mmol) is added in two portions, resulting in the immediate generation of a red/brown gas. The reaction is stirred for 1 h and allowed to come to 0°C. The volatiles are removed under high vacuum at room temperature. The crude product is washed with cold distilled water, collected, and dried. The crude products were dissolved in a minimum amount of acetone, filtered, and the acetone allowed to evaporate overnight to give the crystalline product.

In the cases of the liquid compounds (8 and 9), the crude compounds were taken up in 20 mL of ethyl acetate and washed with saturated sodium bicarbonate solution until neutral. The ethyl acetate solution was dried over $MgSO_4$, filtered, and the solvent removed to give the compounds.

3,8-Dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione, 1. Caution: This compound calculates to be a moderate explosive [4] and should be handled with due caution until adequate safety data are available! DSC: Strong exothermic decomposition at 187°C.

^{1}H NMR(acetone-d_6): δ = 4.92(d, J = −11.1 Hz, 1H), 5.29(d, J = −11.1Hz, 1H) ppm. ^{13}C NMR(acetone -d_6): δ = 67.27($C_{4,6}$), 76.37(C_5), 145.16($C_{2,7}$) ppm. FT-IR(KBr) = 3048(w), 2986(w), 2915(w), 1836(vs), 1816(vs), 1598(vs), 1471(m), 1407(m), 1392(m), 1319(s), 1277(s), 1245(s), 1200(s), 1184(s), 1164(s), 1130(s), 1118(s), 1097(s), 1067(s), 1054(s), 976(m), 850(m), 828(m), 786(m), 753(m), 729(s), 707(m), 634(m) cm^{-1}. HR MS (EI); $C_5H_4N_4O_8$ $[M]^+$: calcd. 248.0029; found 248.0034 amu.

3-Nitro-1,3-oxazolidine-2-one, 7. The compound was recrystallized from acetone to give colorless crystals, mp 110–111°C (ref. 1; 111°C).

3-Nitro-5-methyl-1,3-oxazolidine-2-one, 8. This compound is a liquid.

^{1}H NMR(CD_3CN): δ = 1.42(d, J = 7.0 Hz, 3H, —CH_3), 3.95(t, J = 7.0 Hz, 1H, H_4), 4.40(t, J = 7.0 Hz, 1H, H_4), 4.78 (hex, J = 7.0 Hz, 1H, H_5) ppm. ^{13}C NMR(CD_3CN): δ = 19.37(CH_3), 51.82(C_4), 70.43(C_5), 148.30(C_2) ppm. FT-IR(film) = 2990(w), 2940(w), 1809 (vs), 1573(vs), 1479(m), 1456(m), 1392(m), 1357(sh), 1337(sh), 1285(s), 1171(s), 1056(s), 955(m), 880(m), 827(m), 727(sh), 742(m) cm^{-1}. HR MS (EI) ; $C_4H_6N_2O_4$: calcd. 146.0328; found 146.0324 amu.

3-Nitro-4-ethyl-1,3-oxazolidine-2-one, 9. This compound is a liquid.

^{1}H NMR(CD_3CN): δ = 0.95(t, J = 7.5 Hz, 3H, —CH_3), 1.85(p, J = 7.5 Hz, 2H, —CH_2) 4.14(dxd, J = 9.0 Hz, J = 7.5 Hz, 1H, H_5), 4.52(t, J = 9.0 Hz, 1H, H_5), 4.69(m, 1H, H_4) ppm.^{13}C NMR(CD_3CN)): δ = 7.67(CH_3), 24.08(CH_2), 57.96(C_4), 66.07(C_5), 149.01(C_2) ppm. FT-IR(film) = 2976(w), 2884(w), 1817(vs), 1577(s), 1285(s), 1262(sh), 1163(s), 1120(sh), 1057(w), 1015(w), 832(m), 760(w), 738(w), 740(sh) cm^{-1}. HR MS (EI); $C_5H_8N_2O_4$: calcd. 160.0484; found 160.0478 amu.

3-Nitro-tetrahydro-1,3-oxazine-2-one, 10. The compound was recrystallized from methanol to give colorless crystals, mp 75–76°C (ref. 1; 75°C).

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Draft

Synthesis of and Crystal Structures of *d,l* and *l*-3,8-dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione

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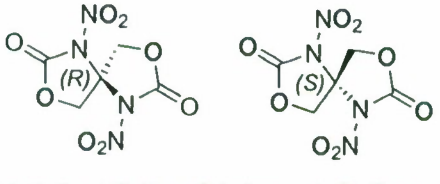
Abstract: Spiro-cyclic compounds are interesting because they frequently have screw type symmetry (C2). The synthesis of the *d,l* -3,8-dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-diones has been previously described. The synthesis of the *l*-compound was accomplished by treatment of the previously described *l*-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dithione with acetyl nitrate as previously described for the racemate. The racemate crystallizes in space group P21/n with density of 1.835 Mg/m^3 (296 K). The *l* compound crystallizes in space group P 21 21 21 with a density was 1.854 Mg/m^3 (296 K). This is the first demonstration of a difference in the density between the racmic and optically active energetic material.



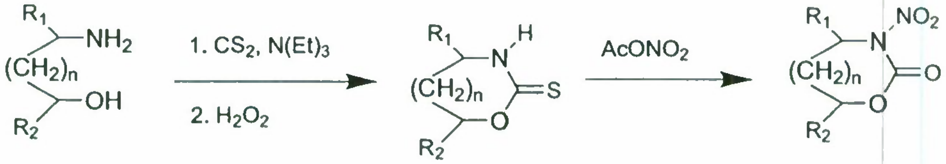
R- and *S*-3,8-dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione

Introduction

The “Holy Grail” in the design of new energetic materials is the accurate prediction of the densities of target compounds. The density is important because detonation properties are proportional to the density squared. [1] The importance of the prediction of density was recognized as early as 1967 when O. Exner published a regression analysis of the densities of known explosives that could predict the densities of unknown molecules. [2] Numerous additional studies of this type have been published [3] including a recent paper by Kotomin and Kozlov where the molecules are broken down into three types (aliphatic, cycloaliphatic, and aromatic) and over 200 different parameters are used.[4] Even this level of parameterization is incapable of differentiating between the density of a racemic mixture and an optically pure compound.

Results and Discussion

We recently developed an interesting synthesis of cyclic N-Nitrourethanes by the tandem nitration-oxidative desulfurization of cyclic thiourethanes using acetyl nitrate(see Scheme 1.).[5]



Scheme 1. Synthesis of Cyclic N-nitrourethanes from Cyclic Thiourethanes.

One of the interesting compounds we were able to make in high yield using this technique was the interesting spirocyclic compound, 3,8-Dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione, **1** (see Figure 1.). The starting compound, 1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dithione, **2**, was synthesized using the procedure of Saul, Kern, Kopf, Pintér and Köll. [6] Both **1** and **2** are interesting compounds because they possess C2 (screw) symmetry and thus exist as a pair of enantiomers. That **1** had this unusual type of symmetry was recognized by Köll et al. [6] and they were able to resolve **2** into optically pure *l*- isomer and slightly impure *d*- compound by forming a complex with Brucine. The Brucine complex with the *l*-**2** is significantly less soluble than the complex with *d*-**2.** The less soluble complex is collected and the *l*-**2** is freed by treating the complex with silica gel. [6] Unfortunately, Köll et al. were unable to get a X-ray crystal structure of *l*-**2** and establish it's absolute configuration (R, S) because the compound decomposed during data collection.[6]

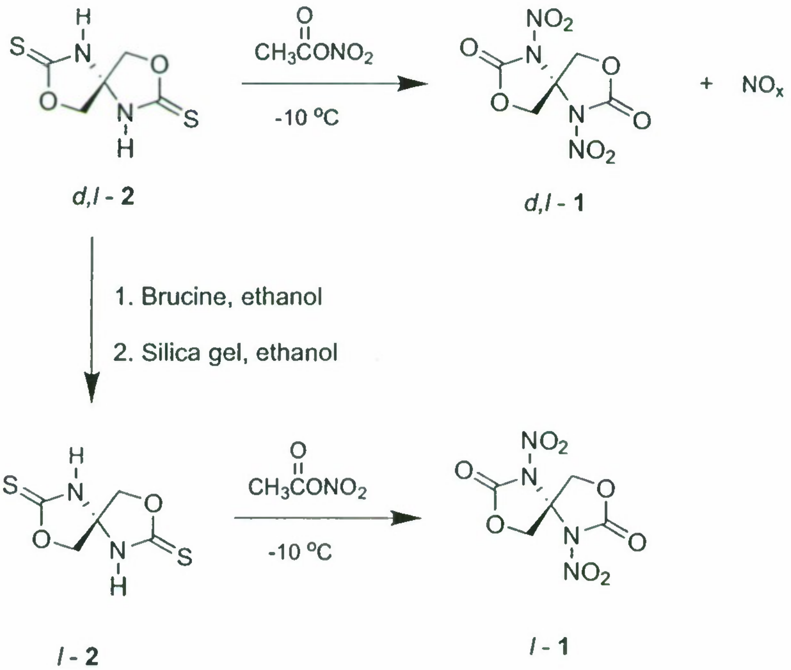


Figure 1. Synthesis of of *d,l*- and *l*-3,8-dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione

Discussion of structures by J. Deschamps and Damon Parrish

Table 2. Crystal Structures for *d.l*- and *l*- 3,8-dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione

Compound	*d,l*- (will15)	*l*- *(will16)*

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Space Group	$P2_1/n$	P 21 21 21
a (Å)	6.8288(19)	6.8491(6)
b (Å)	12.047(3)	19.0036(15)
c (Å)	10.629(3)	19.8039(16)
α	90°	90°
β	91.697(4)°.	90°
γ	90°.	90°
Z	4	16
Volume	874.0(4) Å^3	2577.6(4)
Density (g/cc) @ -173 °C	1.886	1.918
Density (g/cc) @ 20°C	1.835	1.854

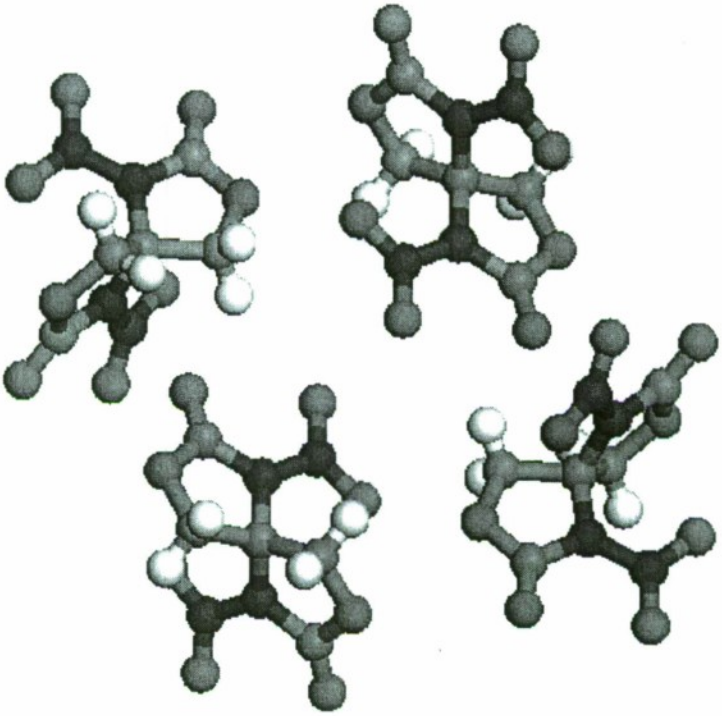

Figure 2. Crystal Structure of d,l-3,8-dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione

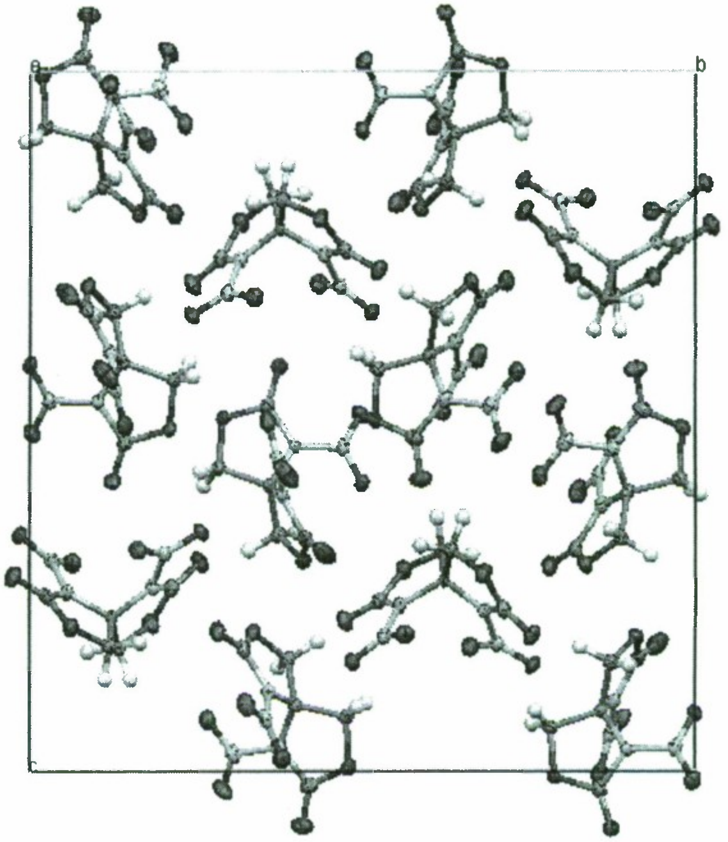

Figure 3. Crystal Structure of *l*-3,8-dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione

Draft

Experimental

Materials. Reagents and all specialty solvents (anhydrous, NMR) were purchased from Aldrich Chemical Co. and used without further purification. Routine solvents were purchased from Fisher Scientific.

Synthesis (R Willer)

(*d,l*)-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione

(*l*)-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione

(*l*)3,8-dinitro-1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dione

A nitrating mixture is made up by carefully adding 2.52g (1.60 ml) of 100% nitric acid to 4.08 g (4.0 ml) of acetic anhydride in a 50 ml round bottom flask maintained at -10°C. After the addition is complete, the temperature is raised to 10°C for 10 minutes then lower back to-10° C. (-)1,6-dioxa-3,8-diazaspiro[4.4]nonane-2,7-dithione (0.36g, 1.9 mmol) is added in two portions. Red/brown fumes are immediately generated. The reaction is stirred for 2 hrs at 0° C. The volatiles are removed under high vacuum. The crude product is dissolved in a minimum amount of acetone and the acetone is allowed to evaporate overnight. Nice crystals form. They are washed twice with cold methanol and then dried under high vacuum. 220 mg of white product.

Crystal Structures of l-1 and d,l-1 (D. Parrish and J. Deschamps)

Single-crystal x-ray diffraction data on compounds **l-1** and **d,l-1** were collected using MoKα radiation (λ = 0.71073 Å) and a Bruker APEX 2 CCD area detector. Crystals were prepared for data collection coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was placed on a MicroMesh mount (MiTeGen, Ithaca, NY) and transferred immediately to the cold stream on the diffractometer. A full set of diffraction data was collected at 100°K and then the temperature raised to 297°K and a partial data set collected to allow accurate determination of density at room temperature. Corrections were applied for Lorentz, polarization, and absorption effects. The structures were solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite [8]. Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C-H distance set at 0.96 Å. Atomic coordinates for these compounds have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers XXXXXX and YYYYYY). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

Compound d,l-1. The 0.56 x 0.36 x 0.18 mm^3 crystal was monoclininc in space group $P\ 2_1/n$ with unit cell dimensions a = 6.8288(19) Å, b = 12.047(3) Å, c = 10.629(3) Å, and β= 91.697(4)°. Data were 98.4% complete to 25.42° θ (approximately 0.83 Å) with an average redundancy of 13.16. The asymmetric unit contained a single molecule.

Compound l-1. The 0.281 x 0.054 x 0.036 mm^3 crystal was orthorhombic in space group $P\ 2_12_12_1$ with unit cell dimensions a = 6.8491(6) Å, b = 19.0036(15) Å, and c = 19.8939(16) Å. Data were 99.7% complete to 28.46° θ (approximately 0.75 Å) with an average redundancy of 4.00. The asymmetric unit contained a three molecules.

Acknowledgements

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Synthesis and Crystal Structure of 4,4´-(Methylenediimino)bis-1,2,5-Oxadiazole-3-carboxylic Acid and Carboxamide

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Keywords:	1,2,5-oxadiazoles, densities, furazans

Synthesis and Crystal Structure of 4,4´-(Methylenediimino)bis-1,2,5-Oxadiazole-3-carboxylic Acid and Carboxamide

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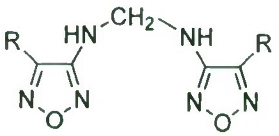
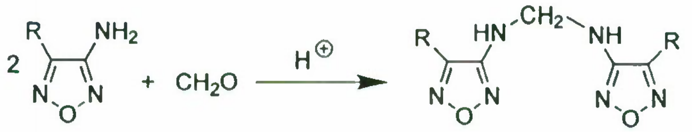
Abstract: 4,4´-(Methylenediimino)bis-1,2,5-oxadiazole-3-carboxylic acid and 4,4´-(methylenediimino)bis-1,2,5-oxadiazole-3-carboxamide have been synthesized by the acid catalyzed condensation of 4-amino-1,2,5-oxadiazole-3-carboxylic acid and 4-amino-1,2,5-oxadiazole-3-carboxamide with formaldehyde. The crystal and molecular structures of the compounds have been determined by X-ray crystallography. 4,4´-(Methylenediimino)bis-1,2,5-oxadiazole-3-carboxylic acid crystallizes in space group *C*2/c, and its measured density is 1.800 g/mL, significantly above the calculated value of 1.68 g/mL. 4,4´-(Methylenediimino)bis-1,2,5-oxadiazole-3-carboxamide crystallizes in space group *P* 2_1/c, and its measured density is 1.623 g/mL, in close agreement with the calculated value of 1.64 g/mL. The structure of the starting amide, 4-amino-1,2,5-oxadiazole-3-carboxamide has also been determined. These data, combined with literature data, suggest that ortho-aminocarboxylic acids have unusually high densities but the reasons for this are unclear.



R = COOH
R = $CONH_2$

Introduction

Several years ago we reported that 3-amino-4-methyl-1,2,5-oxadiazole, **1**, and 3-amino-4-nitro-1,2,5-oxadiazole, **2**, undergo acid catalyzed condensation with formaldehyde to give the 3,3´-(methylenediimino)bis-4-methyl-1,2,5-oxadiazole, **3**, and 3,3´-(methylenediimino)bis-4-nitro-1,2,5-oxadiazole, **4**, in very high yield. [1] Shortly after this report, Tselinskii, Mel´nikova and Vergizov reported that similar chemistry was observed with 3-amino-4-azido-1,2,5-oxadiazole, **5**. [2]



1 R = $-CH_3$
2 R = $-NO_2$
5 R = $-N_3$
7 R = $-CO_2H$
8 R = $-CONH_2$

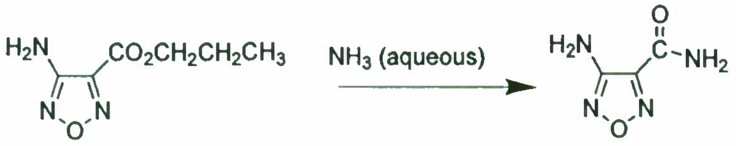
3 R = $-CH_3$
4 R = $-NO_2$
6 R = $-N_3$
9 R = $-CO_2H$
10 R = $-CONH_2$

Scheme 1. Synthesis of Methylenediimino- Compounds from Amino-1,2,5-oxadiazoles

This simple chemistry has very significant consequences. Compounds **2** and **5** are very energetic compounds but are impractical energetic materials because of their high vapor pressure. In contrast, compounds **4** and **6** are usable energetic materials because of their greatly reduced vapor pressure.

Results and Discussion

We have now examined the reaction of the related 4-amino-1,2,5-oxadiazole-3-carboxylic acid, **7**, and 4-amino-1,2,5-oxadiazole-3-carboxamide, **8**, with formaldehyde and have found that the reactions give very high yields of 4,4´-(methylenediimino)bis-1,2,5-oxadiazole-3-carboxylic acid, **9**, and 4,4´-(methylenediimino)bis-1,2,5-oxadiazole-3-carboxamide, **10**. The 4-amino-1,2,5-oxadiazole-3-carboxamide, **8**, was made by treating the known n-propyl 4-amino-1,2,5-oxadiazole-3-carboxylate, **11,** [3] with aqueous ammonia. The yield from this procedure is much higher (98% vs 72%) than the reported procedure of Ichikawa, Kato and Takenishi. [4] This is summarized in Figure1.



11 8

Figure 1. Synthesis of 4-amino-1,2,5-oxadiazole-3-carboxamide, 8.

Table 1. Crystal Data for Compounds 8, 9, and 10

Compound	8	9	10
Empirical formula	$C_3H_4N_4O_2$	$C_7H_6N_6O_6$	$C_7H_8N_8O_4$
Formula weight	128.10	270.18	268.21
Temperature	296(2) K	298(2) K	293(2) K
Wavelength	1.54178 Å	1.54178 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	*P* 21/c	*C* 2/c	*P* 2_1/c
Unit cell dimensions	a = 4.7946(2) Å b = 13.0185(4) Å c = 8.0635(3) Å α= 90° β= 92.058(2)° γ = 90°	a = 18.0547(7) Å b = 4.9647(2) Å c = 14.0765(9) Å α = 90° β = 127.786(2)° γ = 90°	a = 14.338(3) Å b = 17.313(5) Å c = 18.262(4) Å α = 90° β= 104.367(16)° γ = 90°
Volume	502.99(3) Å^3	997.18(8) Å^3	4391(1) Å^3
Z	4	4	16
Density (calc.), g/mL	1.692	1.800	1.623
Absorption coefficient	1.250 mm^{-1}	1.402 mm^{-1}	0.140 mm^{-1}
F(000)	264	552	2208
Crystal size (mm^3)	0.198 x 0.067 x 0.035	0.45 x 0.30 x 0.06	0.283 x 0.117 x 0.061
Theta range for data collection	6.46 to 67.51°	6.20 to 67.33°.	1.46 to 25.59°.
Index ranges	-5<=h<=5 -15<=k<=15 -8<=l<=9	-18<=h<=20 -5<=k<=5 -16<=l<=16	-14<=h<=17, 20<=k<=20 -21<=l<=21
Reflections collected	2586	2487	35280
Independent reflections	840 [R(int) = 0.0338]	834 [R(int) = 0.0361]	7884 [R(int) = 0.0439]
Completeness / θ	91.8 % / 67.51°	93.6 % / 67.33°	98.5 % / 25.00°

Refinement	Full-matrix least-squares on F^2		
Data / restraints / parameters	840 / 0 / 83	834 / 0 / 89	7884 / 12 / 685
Goodness-of-fit on F^2	1.119	1.060	1.028
Final R indices [$I>2\sigma(I)$]	R1 = 0.0466, wR2 = 0.1139	R1 = 0.0508, wR2 = 0.1567	R1 = 0.0507, wR2 = 0.1493
R indices (all data)	R1 = 0.0469, wR2 = 0.1142	R1 = 0.0530, wR2 = 0.1592	R1 = 0.0875, wR2 = 0.1827
Extinction coef.	0.089(7)	0.0022(8)	NA
Largest diff. peak and hole	0.283 and -0.361 e.$\AA^{-3}$	0.473 and -0.527 e.$\AA^{-3}$	0.327 and -0.291 e.$\AA^{-3}$

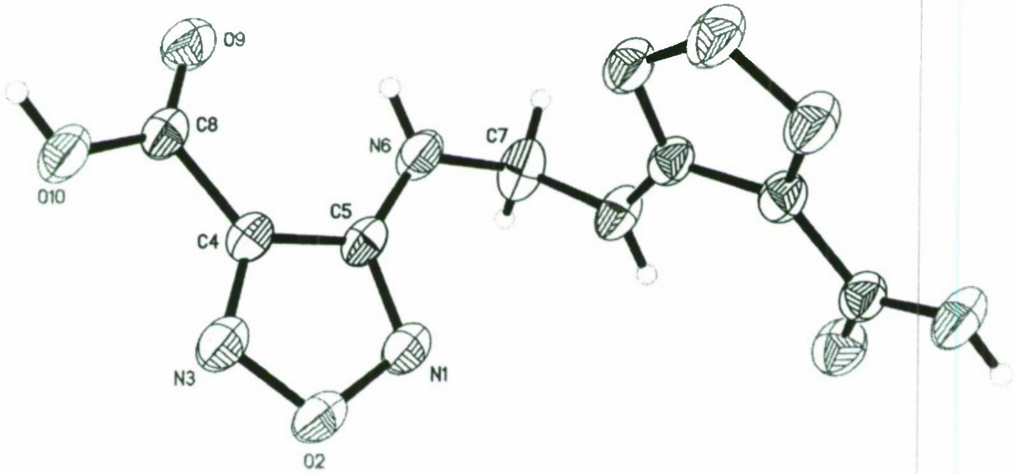


Figure 2. Structure of 4,4´-(methylenediimino)bis-1,2,5-oxadiazole-3-carboxylic acid (**9**) as determined by x-ray diffraction, displacement ellipsoids are at the 50% level. Only the atoms in the asymmetric unit are labeled, all others are symmetry generated equivalents.

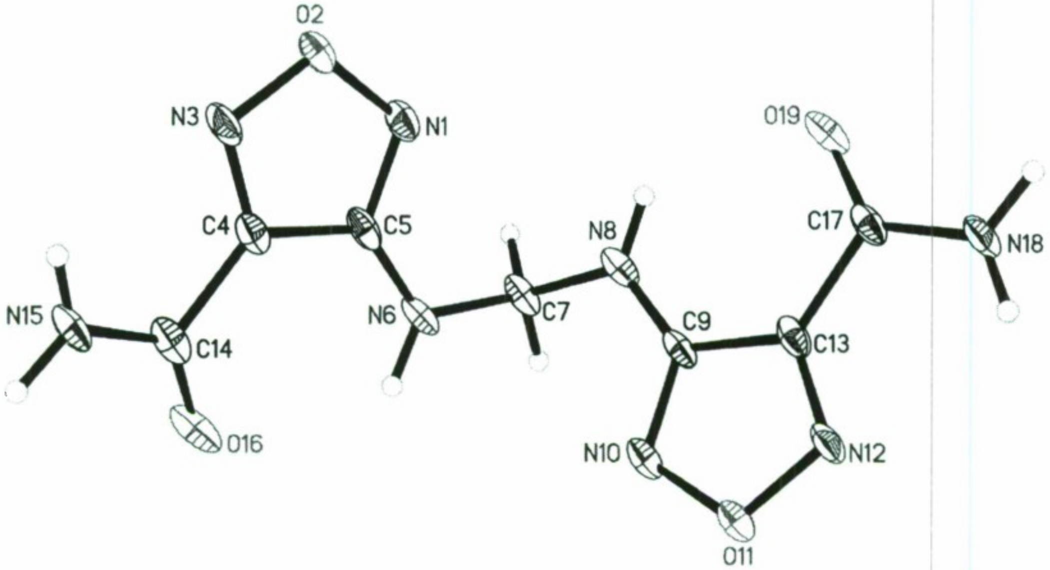


Figure 3. Structure of 4,4´-(methylenediimino)bis-1,2,5-oxadiazole-3-carboxamide (**10**) as determined by x-ray diffraction, displacement ellipsoids are at the 50% level. View shows one of four molecules in the asymmetric unit.

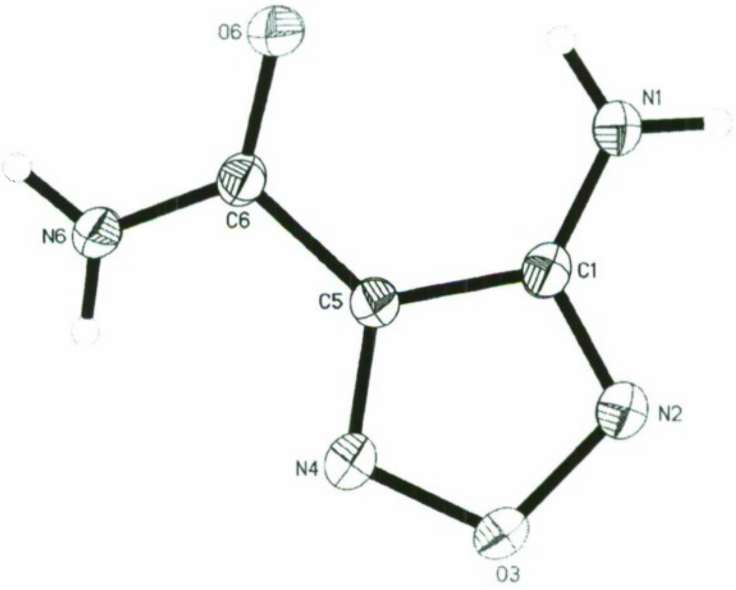


Figure 4. Structure of 4-amino-1,2,5-oxadiazole-3-carboxamide (**8**) as determined by x-ray diffraction, displacement ellipsoids are at the 50% level.

The X-ray crystal structures of **9** and **10** were determined, and these are shown in Figures 2 and 3. We had earlier determined the X-ray crystal structure of 4-amino-1,2,5-oxadiazole-3-carboxylic acid, **7**. [5] For completeness, the X-ray crystal structure of the 4-amino-1,2,5-oxadiazole-3-carboxamide, **8,** was also determined, and this is shown in Figure 4. The X-ray crystal data for the three compounds (**8**, **9**, **10**) are summarized in Table 1.

Density is an important physical property of energetic materials because performance is proportional to density squared. [6] Table 2 compares the densities and melting points of the starting amino-1,2,5-oxadiazoles with the produced methylene-bis compounds.

Table 2. Density and Melting Points of Aminofurazans and Methylene-bis Compounds

Compound	Density, g/mL	MP, ºC	Compound	Density, g/mL	MP, ºC
1	1.37 [8]	74 [6]	**3**	1.398 [1]	198 [1]
2	1.86 [9]	122 [7]	**4**	1.768 [1]	141 [1]
5	1.660 [10]	87 [8]	**6**		112 [2]
7	1.859 [5]	220(dec)	**9**	1.800	190 (dec)
8	1.692	175	**10**	1.623	248

It is instructive to first look at the remarkable difference in density between the starting 4-amino-1,2,5-oxadiazole-3-carboxylic acid, **7** and 4-amino-1,2,5-oxadiazole-3-carboxamide, **8** (i.e. the difference in density is 9.9%). In fact, **7** is essentially as dense as 3-amino-4-nitrofurazan, **2**, which is considered to be an exceptionally dense compound. Two other molecules that are generally considered to be exceptionally dense are TATB and Fox-7. All three molecules contain the "*ortho*-aminonitro" moiety (see Figure 5.). For comparison, we examined the densities of anthranilic acid, **12** [12], and anthranilamide, **13** [13]. There is a complication with **12** because it exists in three polymorphs but the difference in density between **12** and **13** ranges from 5.0-7.9%. This is still quite large considering the minor change in structure. It would appear that like the "*ortho*-aminonitro" moiety, the "*ortho*-aminocarboxylic acid" moiety also leads to exceptionally dense molecules. One might be tempted to coin the phrase "densaphore" to describe a combination of functional groups that leads to exceptionally high densities.

In general there are two trends in the data in Table 2. The first is that the methylene-bis compounds are slightly less dense than the parent compounds (except for the methyl compounds) which can be attributed to the dilution by the low density methylene group. Unfortunately the density of **6** has never been reported. The same large difference in density between the carboxylic acid and carboxamide is seen in the methylene-bis compounds **9** and **10**. In this case, the difference in densities of the two compounds is 10.9%. We have carefully reviewed the hydrogen bonding in the study compounds to see if this was responsible for the higher densities of the acids as compared to the amides. Although the acids (i.e. **7** and **9**) are denser than the amides (**8** and **10**), the greatest number of hydrogen bonds per molecule are actually found in compounds **8** and **10**, the less dense amides. Hydrogen bonding may be a 'very powerful player' but it is not responsible for the density difference observed in the study compounds. We also considered other close contacts and their relationship to the density of the study compounds. One might assume that larger numbers of close contacts would be an expected result of higher density. Yet, for anthranilic acid/anthranilamide and the dimers (i.e. compounds **3**, **4**, **9**, and **10**) the inverse would appear to be true. Thus, the increased number of close contact could be viewed as a destabilizing force leading to lower densities. Even this is too simplistic as no trend was seen in the monomers (compounds **1**, **2**, **7**, and **8**). These studies are summarized in the supplemental material.

The second trend is that the melting points of the methylene-bis compounds are higher than the starting aminofurazans, as long as true melting is observed. In the case of **7** and **9** true melting is not observed and this trend is not followed.

Our laboratory is not equipped to conduct standard safety testing (impact, esd and friction) for energetic materials. However, all four compounds are insensitive to a "hammer test", indicating they are very insensitive to impact much like TATB.

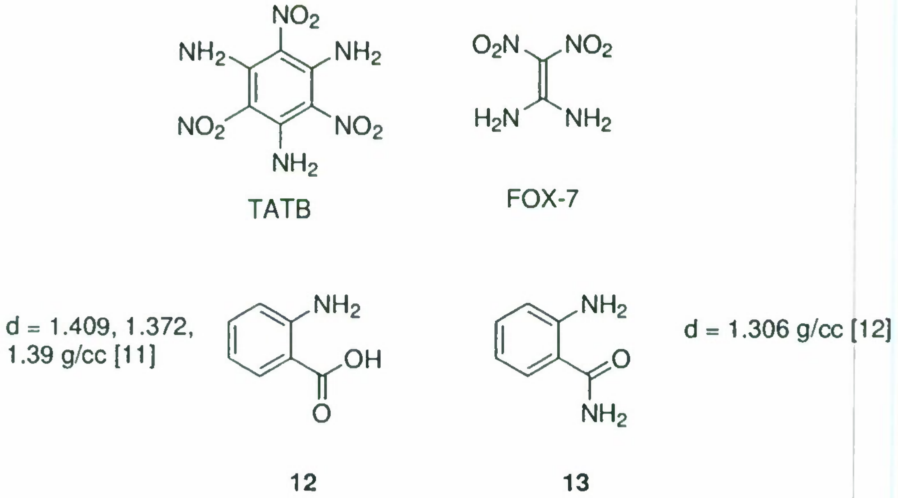


Figure 5. High density molecules

In conclusion, it appears that aromatic *ortho*-aminocarboxylic acids have unexpectedly high densities that rival those of aromatic *ortho*-aminonitro- compounds but the reasons for this are unclear at this point.

Experimental

Materials. Reagents and all specialty solvents (anhydrous, NMR) were purchased from Aldrich Chemical Co. and used without further purification. Routine solvents were purchased from Fisher Scientific.

FTIR spectra were obtained on a Bruker Equinox 55 spectrometer as KBr pellets. The spectral width was from 400 to 4000 cm^{-1} with a spectral resolution of 4 cm^{-1}.

Routine ^{1}H and ^{13}C NMR spectra were obtained using a Varian Mercury^{plus} NMR spectrometer operating at a frequency of 300.13 MHz for proton and 75.5 MHz for carbon. All shifts were referenced either automatically by the software (VNMR 6.1C) or manually using the resonance frequency of the deuterated solvent.

DSC was performed with a TA Instruments Model Q200 using hermetically sealed Al pans under a nitrogen purge. Analyses were run from ambient to 300 °C at 3 °C /min.

4-amino-1,2,5-oxadiazole-3-carboxylic acid, 7. This compound was prepared by the procedure of Willer et al. [5] The decomposition point by DSC was 220 °C (lit. 220 °C [5]).

***n-Propyl 4-amino-1,2,5-oxadiazole-3-carboxylate,* 11.** This compound was prepared by the procedure of Willer et al. [3] The melting point was 90-91 °C (lit. 90-91 °C [3]).

4-Aminofurazan-3-carboxamide, 8. *n-Propyl 4-amino-1,2,5-oxadiazole-3-carboxylate*, **11**, (3.42 g, 0.02 mole) and 40 mL of 28% aqueous ammonia are placed in a 100 mL round bottom flask equipped with a magnetic stirring bar. The mixture is stirred for 30 min at room temperature, then for 4 h at 40 °C. The reaction is transferred to a 125 mL Erlenmeyer flask, and the mixture is then heated until everything goes into solution and the volume is reduced to about 20 mL. This solution is allowed to cool, and the product crystallizes as small platelets and is collected. The yield is 2.50 g (0.019 mole, 98 %). The melting point is 172-175 °C (lit 174-177 °C [4]).

4,4´-(methylenediimino)bis-1,2,5-oxadiazole-3-carboxylic acid, 9. 4-Amino-1,2,5-oxadiazole -3-carboxylic acid (1.28 g, 0.01 mole) is dissolved in a minimum amount of water at 90 ℃ in a 100 mL round bottom flask equipped with a magnetic stirring bar. Aqueous formaldehyde (0.81 g, 0.01 mole) is added. Six drops of 37% HCl are then added. The mixture is heated for one hour at reflux and then cooled, and the product collected. The yield is 1.30g (0.0048 mole, 96%). The compound melts with decomposition at 198-200 ℃. It can be recrystallized from DMSO/water. ^{1}H-NMR (DMSO-d_6): δ= 10.27 (bs, 1H, $COO\underline{H}$), 6.83(t, 1H, J= 6 Hz, $N\underline{H}CH_2N\underline{H}$), 4.76(t, 1H, J=6 Hz, $NHC\underline{H_2}NH$) ppm.^{13}C-NMR(DMSO-d_6): δ= 160.49(COOH), 156.08($C_{4,4'}$), 140.33($C_{3,3'}$), 53.94($NH\underline{C}H_2NH$) ppm. FT-IR(KBr) = 3385(s0, 2887(s,vb), 1707(s), 1604(s), 1554(s), 1468(m), 1447(m), 1382(m), 1249(m), 1174(s), 1018(m), 792(m), 759(s), 706(m) cm^{-1}. HRMS (NCI) ; $C_7H_5N_6O_6$ [M-H]$^-$: calcd. 269.0271; found 269.0279.

Methylene 4,4´-(methylenediimino)bis-1,2,5-oxadiazole-3-carboxamide), 10. 4-Amino-1,2,5-oxadiazole-3-carboxamide (128 mg, 1.0 mmol) is added to 1 mL of water in a 25 mL round bottom flask equipped with a magnetic stirring bar. Aqueous formaldehyde (81 mg, 1 mmole) is added, and the sample is heated. One drop of 37% HCl is added when the amide has dissolved. The mixture is heated for 15 min more and then cooled, and the product collected. The yield is 125 mg (0.47 mmole, 93.2%). The compound melts at 258-260 ℃. ^{1}H-NMR (DMSO-d_6): δ= 8.53 (s, 1H, $CON\underline{H_2}$), 8.16 (s, 1H, $CON\underline{H_2}$), 7.01(t, 1H, J= 6 Hz, $N\underline{H}CH_2N\underline{H}$), 4.78(t, 1H, J=6 Hz, $NHC\underline{H_2}NH$) ppm.^{13}C-NMR(DMSO-d_6): δ= 160.01(CONH2), 155.97($C_{4,4'}$), 140.54($C_{3,3'}$), 53.85($NH\underline{C}H_2NH$) ppm. FT-IR(KBr) = 3437(s), 3272(s), 3197(s), 1701(vs), 1623(m), 1592(m), 1547(s), 1457(w), 1380(m), 1332(w), 1192(m), 1117(m), 1060(w), 1001(m), 925(w),875(w), 793(w), 734(w),675(m) cm^{-1}. HRMS (NCI) ; $C_7H_7N_8O_4$ [M-H]$^-$: calcd. 267.0590; found 267.0598.

Single crystal X-ray diffraction analysis of 8, 9 and 10.

Single crystal x-ray diffraction data on compounds **8** and **9** were collected using CuKα radiation ($\lambda = 1.54178$ Å) and a Bruker Platinum-135 CCD area detector while x-ray diffraction data on compound **10** was collected using MoKα radiation ($\lambda = 0.71073$ Å) and a Bruker APEX 2 CCD area detector. Crystals were prepared for data collection by coating with high viscosity microscope oil. The oil-coated crystal was mounted on a micro-mesh mount (Mitergen, Inc.) and transferred to the diffractometer. The structures were solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite. [14] Corrections were applied for Lorentz, polarization, and absorption effects. Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were included using a riding model [coordinate shifts of parent atom applied to H atoms]. Complete information on data collection and refinement is available in Table 1.

For compound **8** a 0.198 x 0.067 x 0.035 mm^3 crystal was prepared for data collection and a data set collected at 296 K. The crystal was monoclinic in space group $P\,2_1/c$, with unit cell dimensions a = 18.0547(7), b = 4.9647(2), c = 14.0765(9) Å, and $\beta = 92.058(2)°$. Data was 91.8% complete to 67.51° θ (approximately 0.83 Å), with an average redundancy of 2.79. The final anisotropic full matrix least-squares refinement on F^2 with 83 variables converged at R1 = 4.69%, for the observed data and wR2 = 11.42% for all data.

For compound **9** a 0.45 x 0.30 x 0.06 mm^3 crystal was prepared for data collection and a data set collected at 298 K. The crystal was orthorhombic in space group $C\,2/c$, with unit cell dimensions a = 18.0547(7), b = 4.9647(2), c = 14.0765(9) Å, and $\beta = 127.786(2)°$. Data was 93.6% complete to 67.33° θ (approximately 0.84 Å), with an average redundancy of 2.66. The final anisotropic full matrix least-squares refinement on F^2 with 89 variables converged at R1 = 5.08%, for the observed data and wR2 = 15.92% for all data.

For compound **10** a 0.283 x 0.117 x 0.061 mm^3 crystal was prepared for data collection and a data set collected at 293 K. The crystal was orthorhombic in space group $P\,2_1/c$, with unit cell dimensions a = 14.338(3), b = 17.313(5), c = 18.262(4) Å, and β = 104.367(16)°. Data was 98.5% complete to 25.59° θ (approximately 0.82 Å), with an average redundancy of 4.02. The final anisotropic full matrix least-squares refinement on F^2 with 685 variables converged at R1 = 5.07%, for the observed data and wR2 = 18.27% for all data.

Atomic coordinates for **8**, **9** and **10** have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers: 800450, 800451, and 800452). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

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A Reexamination of the Reaction of 3,4-Diamino[1,2,5]oxadiazole with Glyoxal

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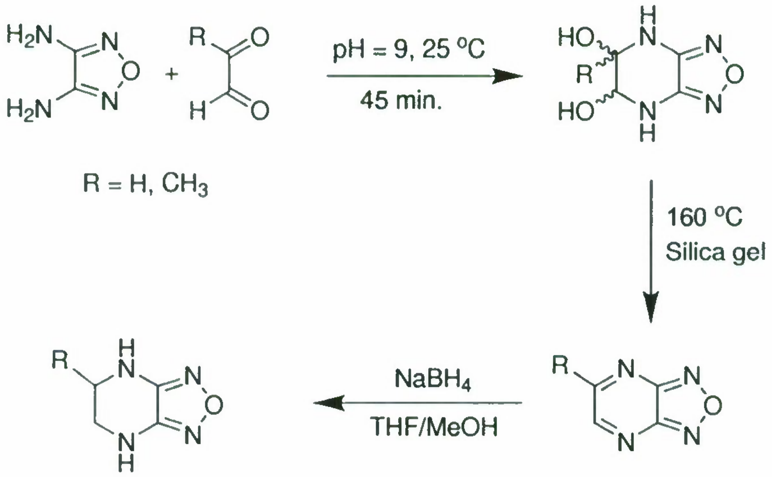
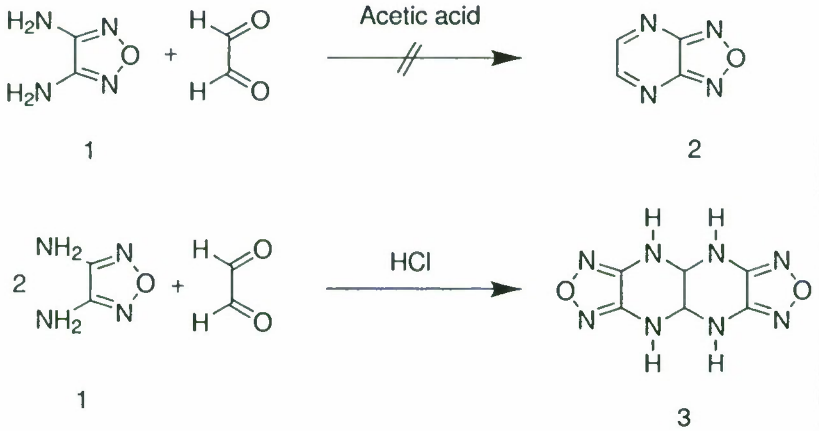
Reaction coordinate mapping was used to study the reaction of 3,4-diamino-[1,2,5]oxadiazole (3,4-diaminofurazan) and 3,4-diamino[1,2,5]thiadiazole with glyoxal. The thiadiazole was known to give a good yield of [1,2,5]thiadiazolo[3,4-b]pyrazine, while the oxadiazole had not yielded, until now, [1,2,5]oxadiazolo[3,4-b]pyrazine (or furazano[2,3-b]pyrazine). The calculations suggested that the diols, 5,6-dihydroxy-4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine and 5,6-dihydroxy-4,5,6,7-tetrahydro[1,2,5]thiadiazolo[3,4-b]pyrazine should be stable intermediates, and once formed, should provide a pathway to the target compounds via two dehydration steps, under forcing conditions. With this information in mind, the reaction of 3,4-diamino-[1,2,5]oxadiazole with glyoxal and pyruvic aldehyde were re-examined. The reaction of 3,4-diamino-[1,2,5]oxadiazole with glyoxal and pyruvic aldehyde produced, under slightly basic conditions, a near quantitative yield of the expected initial products, 5,6-dihydroxy-4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine and the 5-methyl analog, respectively. The diols were easily isolated by lyophilizing the aqueous reaction mixture. The diols were pyrolized on silica gel at 160 °C to give the desired [1,2,5]oxadiazolo[3,4-b]pyrazine and the 5-methyl analog. Both compounds were easily reduced to the corresponding 4,5,6,7-tetrahydro- derivative using

sodium borohydride in THF/methanol. The [1,2,5]oxadiazolo[3,4-b]pyrazine also displayed other interesting chemistry.



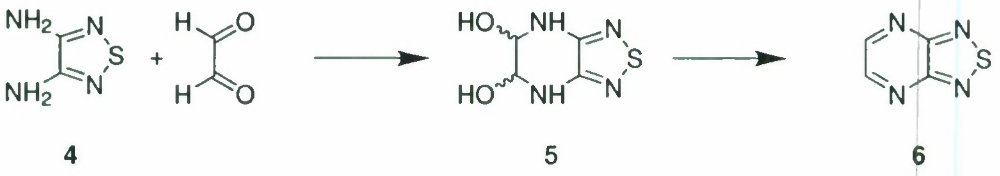
Introduction

The reaction of 3,4-diamino[1,2,5]oxadiazole (3,4-diaminofurazan), **1**, with glyoxal has been examined several times in the past. In 1978, Sato and Adachi investigated the reaction of **1** and aqueous glyoxal at a 1:1 stoichiometry utilizing acetic acid as the catalyst with the hopes of synthesizing [1,2,5]oxadiazolo[3,4-b]pyrazine (or furazano[3,4-b]pyrazine), **2**. [1] They reported that the reaction produced no product. In 1985, Willer and Moore re-examined the reaction of **1** with glyoxal using hydrochloric acid as the catalyst and found that when using a 2:1 stoichiometry of **1** to glyoxal they could isolate an almost quantitative yield of the tetracyclo-compound **3**. [2]



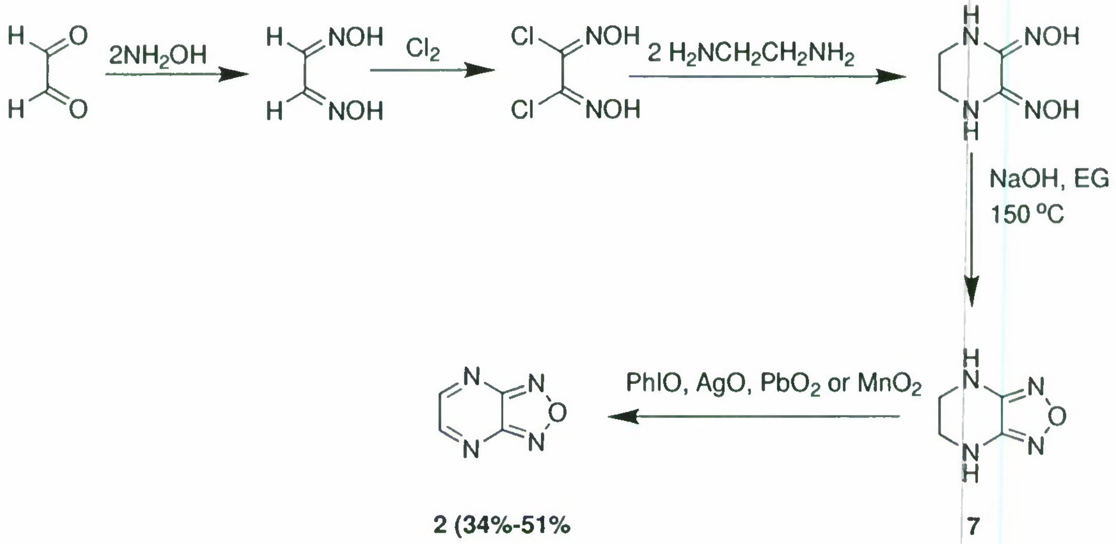
Scheme 1. Reported reactions of 3,4-diamino[1,2,5]oxadiazole with glyoxal.[1,2]

These results stand in stark contrast to the results of the reaction of the related 3,4-diamino[1,2,5]thiadiazole, **4**, with glyoxal. In 1976, Komin and Carmack reported on the reaction of **4** with glyoxal and biacetyl. [3] They found that **4** initially reacted with aqueous glyoxal at 100 °C to produce a chloroform insoluble precipitate that appeared to be the diol adduct, **5** (see Scheme 2). Continued heating dissolved some of the precipitate. Extraction of the reaction mixture with chloroform gave the desired [1,2,5]thiadiazolo[3,4-b]pyrazine, **6**. Reheating the aqueous layer and re-extracting with chloroform gave a total yield of **6** of 81.5%.



Scheme 2. Reaction of 3,4-diamino[1,2,5]thiadiazole with glyoxal. [3]

An important question arises from an examination of this literature. Is the failure to form [1,2,5]oxadiazolo[3,4-b]pyrazine from the reaction of **1** with glyoxal simply a result of not using the proper reaction conditions or is it the result of the 1,2,5]oxadiazolo[3,4-b]pyrazine being unstable relative to the diol intermediate? It should be noted that in a review in 2003, Sheremetev and Yudin mentioned that the synthesis of **2** had been accomplished by the dehydrogenation of 4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine, **7**, but no experimental details or properties of the compound were reported. [4] **7** had been synthesized by the 4-step procedure of Willer and Moore. [2] This overall very low yield, 5-step synthesis of **2** is summarized in Scheme 3. These results are important in that they show that **2** is a stable molecule but they shed no light on why **2** could not be directly synthesized from **1** and glyoxal.



Scheme 3. Literature synthesis of 2. [2,4]

Results and Discussion

To understand why attempts to make **2** directly from **1** and glyoxal have been unsuccessful, Reaction Coordinate Mapping was used to examine the reaction of both **1** and **4** with glyoxal. [5,6,7] The results are shown in Figures 1 and 2.

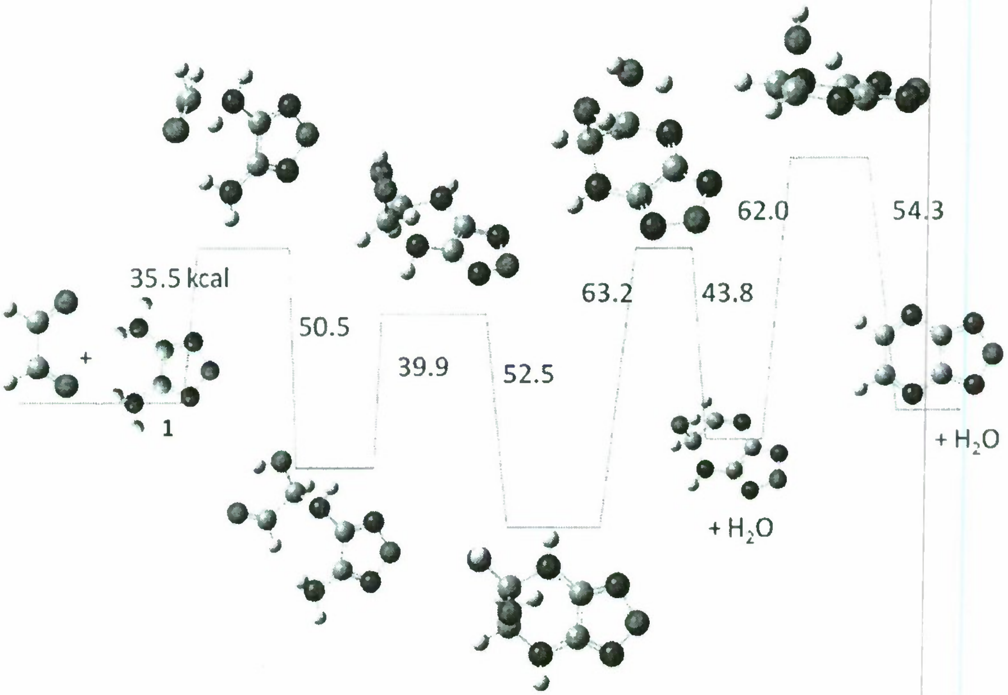


Figure 1. Reaction Coordination Mapping of the Reaction of 1 with Glyoxal

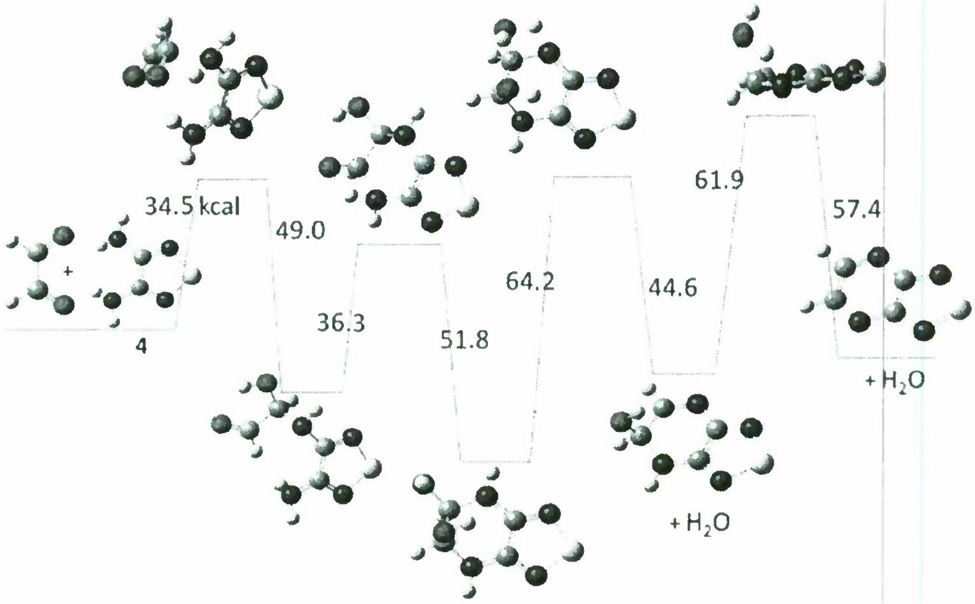


Figure 2. Reaction Coordination Mapping of the Reaction of 4 with Glyoxal

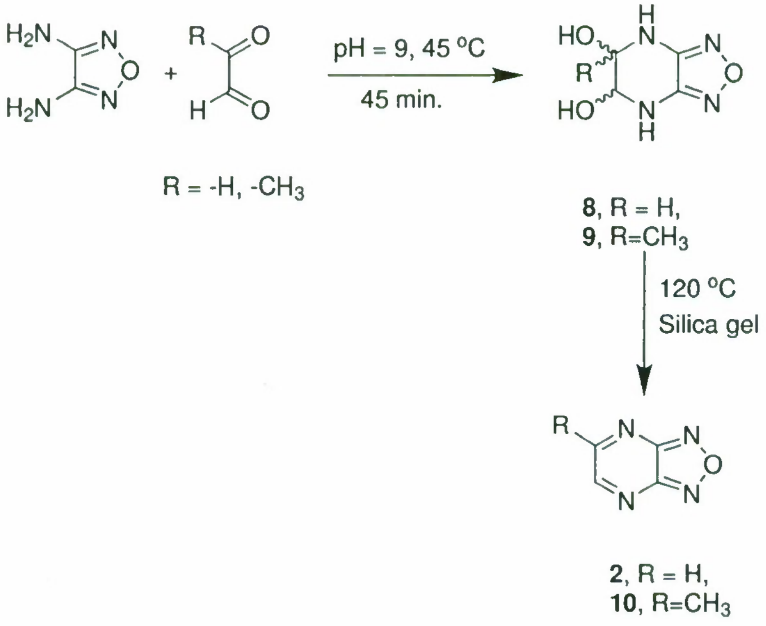
First, both reactions appear to be exothermic, with the thiadiazole reaction being the more exothermic of the two. Second, both reactions occur via a similar mechanism, namely, a carbonyl carbon on glyoxal is attacked by an amine group on **1** or **4** followed by a similar attack on the other glyoxal carbon by the remaining amine nitrogen on **1** or **4**, resulting in a diol intermediate, **5** or **8.** The reaction then proceeds to product via two dehydration steps. Third, the energetics of the two reactions are qualitatively similar. Fourth, the diol intermediates (**5** and **8**) appear to be significantly more stable than the reactants, increasing the chances that they could be isolated.

Given that the calculations on both reactions result in the same qualitative picture, coupled with the fact that Komin and Carmack produced [1,2,5]thiadiazolo[3,4-b]pyrazine, **6**, via the reaction of **4** with glyoxal, we believe that the failure of the analogous reaction of **1** with glyoxal to give

[1,2,5]oxadiazolo[3,4-b]pyrazine, **2**, is most plausibly ascribed to the use of improper reaction conditions rather than instability of **2** relative to the diol intermediate. This conclusion is further supported by the fact that Sato and Adachi, rather than observing the diol intermediate, were unable to isolate any product, whatsoever.

The prediction that the diol was a stable compound prompted a search for better conditions for its synthesis and isolation. A paper by Vail, Moran and Barker stressed the importance of keeping the reaction slightly basic and the reaction temperature low in the reaction of amides with glyoxal to give N,N'-dihydroxylethylenebisamides. [8] The reaction of **1** with glyoxal at 45 ºC under these conditions produced a clear solution that, when examined by ^{13}C NMR, clearly contained a single product. To isolate this product under very mild conditions, the solution was frozen and the water removed by lyophilization. The resulting white powder was identified as the expected 5,6-dihydroxy-4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine, **8**, based on spectroscopic data; although we have yet been unable to establish its stereochemistry. It was later found that if the reaction temperature was lowered to 20 ºC the product would actually crystallize from the reaction mixture.

Thermal analysis (DSC) and high resolution mass spectrometry (HRMS) of **8** were extremely enlightening. The DSC thermogram is shown in Figure 3. The two endotherms at 113 °C and 151 °C were very suggestive of a stepwise dehydration process leading to the desired [1,2,5]oxadiazolo[3,4-b]pyrazine, **2,** which is consistent with the theoretical prediction. In the mass spectrum of **8**, the molecular ion (158.0431) was relatively weak. A peak of almost equal intensity was observed at 140.0334 daltons (M-H_2O), and a very strong peak was observed at 122.0265 daltons (M-2 H_2O).



Scheme 4. Synthesis of [1,2,5]oxadiazolo[3,4-b]pyrazine, **2**, and its 5-methyl analog.

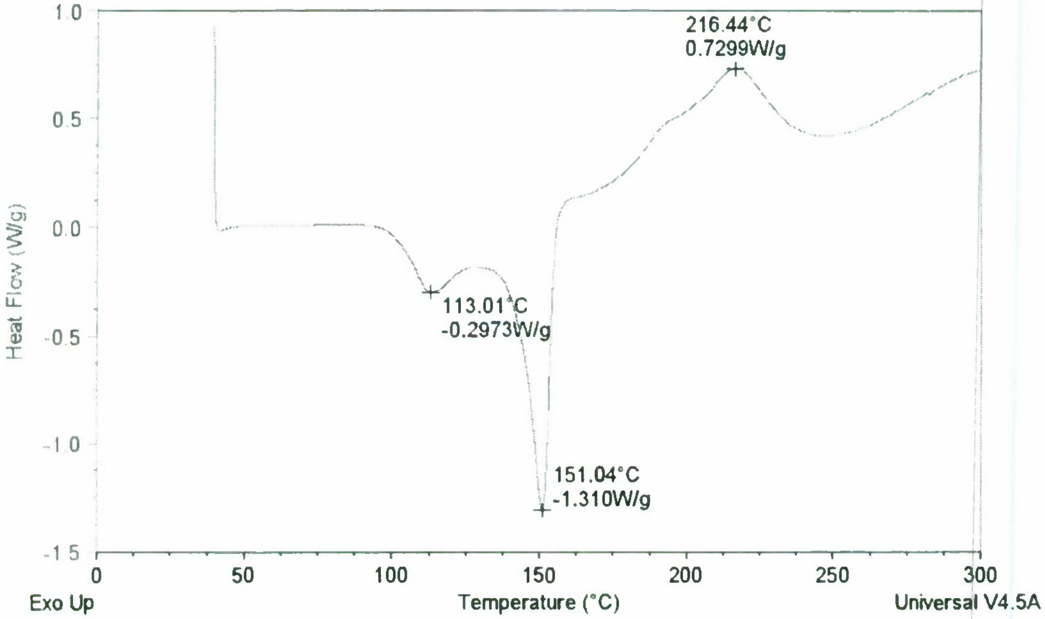
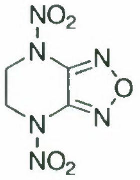


Figure 3. DSC thermogram of 5,6-dihydroxy-4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine, **8**.

Both of these facts were very suggestive that pyrolysis of **8** might be a viable route to the desired [1,2,5]oxadiazolo[3,4-b]pyrazine, **2**. Komin and Carmack had used pyrolysis of 1,2,3,4-tetrahydro-2,3-dihydroxypyrazano[2,3-b]quinoxaline to give pyrazano[2,3-b]quinoxaline. [3] Pyrolysis of **8** at 130 °C and 2 torr for two hours produced a small amount of a light–yellow, crystalline material on the cold finger and a substantial amount of a brown residue. The light–yellow, crystalline material was easily identified as the desired [1,2,5]oxadiazolo[3,4-b]pyrazine, **2**, based on spectroscopic data. The brown residue was very impure **8** based on standard spectroscopic data. Repeating the pyrolysis at 160 °C and 0.5 torr produced similar results. It was theorized that the low yield of 2 might be due to the molecules of **8** reacting with each other in the "melt" phase. A significant improvement to the yield was obtained when the diol was deposited on silica gel in a 1:10 ratio and this material was pyrolyzed at 160 ºC. The product was isolated in approximately 30% yield by extracting the material off the silica gel with hot anhydrous chloroform. The product could be purified by sublimation or column chromatography ($CHCl_3$, silica gel, R_f=0.7).

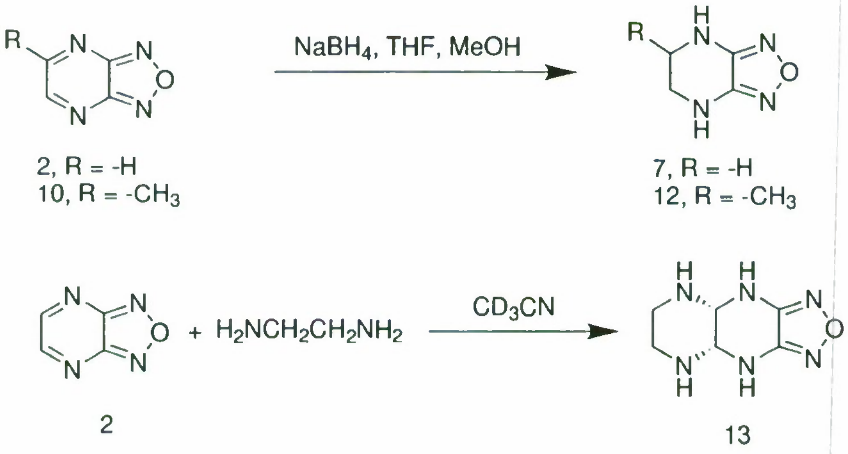
Similar results were obtained when pyruvic aldehyde was substituted for glyoxal. The diol, **9**, was much less stable and could not be characterized except by NMR and IR. Pyrolysis of the material on silica gel gave only a 10% yield of 5-methyl-[1,2,5]oxadiazolo[3,4-b]pyrazine, **10**, which is stable and was completely characterized (see Experimental section).
The principal reason for the great interest in the synthesis of **2** is that it might offer a shorter synthetic route to 4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine, **7**. Sato and Adachi had shown that more highly substituted [1,2,5]oxadiazolo[3,4-b]pyrazines could be reduced to the tetrahydro- analogs using sodium borohydride or lithium aluminum hydride. [1] Compound **7** is of interest because it is the precursor to 4,7-dinitro-4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine, **11,** a well known energetic material. [2] It has also shown interesting electronic properties. [9-11] The original four-step synthesis of **7** is shown in Scheme 3. [2] We have

indeed established that both **2** and **10** can be reduced to **7** and **12** in very high yields using sodium borohydride in methanol/THF(see Scheme 5).



11

Reaction Coordinate Mapping calculations showed that tetraamino ethane compounds, obtained by addition of amines to **2**, are significantly more stable than **2** itself. This suggested that **2** would readily react with amines. As an example, the reaction of **2** with ethylene diamine was studied. A vigorous reaction occurred, yielding **13** as the sole product. The stereochemistry of the ring juncture appears to be *cis*- based on the ^{1}H NMR data. This assignment was made on the following basis: the ethylene group protons appear as two multiplets typical of a conformationally mobile AA'BB' system, [12] and the ^{13}C satellites for the bridgehead protons show that there is a small coupling of 4.2 Hz between them which is consistent with the *cis*-stereochemistry.



Scheme 5. Chemistry of [1,2,5]oxadiazolo[3,4-b]pyrazine and its 5-methyl analog.

2 also reacts vigorously with other primary amines and, at slightly elevated temperatures, primary alcohols. These reactions can produce very interesting [1,2,5-]oxadiazole containing polymers if di- or trifunctional amines and alcohols are used. These results will be reported separately.

The X-Ray crystal structure of **2** was determined and is shown in Figure 4; crystallographic data are listed in Table 1. The experimental density (1.536 g/cc) is very close to that calculated by the "Energy" program (1.55 g/cc). [13] The ^{1}H NMR chemical shifts in both **2** and the sulfur analog, **6**, are very close (8.97 versus 9.06 [3]), and are shifted approximately 0.5 ppm downfield from the ^{1}H NMR chemical shifts in pyrazine. The ^{13}C NMR chemical shifts for **2** are 152.03 and 153.04 ppm. They are easily assigned because of the lack of an NOE enhancement for the oxadiazole carbons (152.03). The pyrazine type carbons are shifted downfield from pyrazine (145.7 ppm) by over 7 ppm. Unfortunately, the ^{13}C NMR chemical shifts for **6** were not reported.

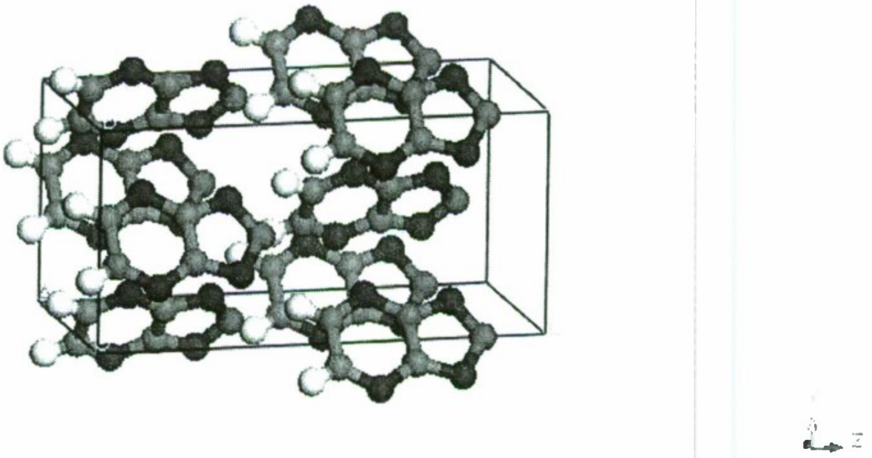


Figure 4. X-ray structure of [1,2,5]oxadiazolo[3,4-b]pyrazine, **2**.

Table 1. Crystal data and structure refinement for 1,2,5]oxadiazolo[3,4-b]pyrazine, **2.**

Empirical formula	$C_4H_2N_4O$	
Formula weight	122.10	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Aba2	
Unit cell dimensions	a = 6.395(8) Å	α= 90°.
	b = 6.179(8) Å	β= 90°.
	c = 12.669(16) Å	γ = 90°.
Volume	500.6(11) $Å^3$	
Z	4	
Density (-173℃)	1.620 Mg/m^3	
Density (20℃)	1.536 Mg/m^3	
Absorption coefficient	0.126 mm^{-1}	
F(000)	248	
Crystal size	0.18 x 0.15 x 0.14 mm^3	
Theta range for data collection	4.86 to 26.52°.	
Index ranges	-8<=h<=7, -7<=k<=7, -15<=l<=13	
Reflections collected	1606	
Independent reflections	469 [R_{int} = 0.0413]	
Completeness to theta = 26.52°	97.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9825 and 0.9776	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	469 / 1 / 42	

Goodness-of-fit on F^2	1.158
Final R indices [I>2sigma(I)]	$R_1 = 0.0570$, $wR_2 = 0.1707$
R indices (all data)	$R_1 = 0.0597$, $wR_2 = 0.1751$
Largest diff. peak and hole	0.493 and -0.788 e.$Å^{-3}$

In conclusion, a direct synthesis of [1,2,5]oxadiazolo[3,4-b]pyrazine, **2**, from 3,4-diamino[1,2,5]-oxadiazole has been developed. The compound exhibits interesting and useful chemistry and studies to improve the yield and explore its chemistry continue.

Experimental

Reaction Coordinate Mapping

All calculations describing the potential energy surface (PES) were performed using the Gaussian 09x quantum chemistry suite.[14] Critical points on the PES were determined using the BHandHLYP functional and the 6-311++G(2df,2p) basis set. The gradients for all geometry optimizations were converged to the default settings. Each critical point on the PES was characterized through normal-mode analysis. All transition states reported here had one imaginary frequency, and all minima had no imaginary frequencies. The transition states were subjected to IRC calculations (using the default step size) to facilitate connection with minima along the reaction path. Each IRC terminated upon reaching a minimum as defined by the default criteria provided in G09. For those points that did not terminate in this fashion, the last converged point on the reaction path was used as the initial structure for a full geometry optimization. For each instance in which such an optimization was attempted, a local minimum was found. It is assumed that this is the minimum to which the IRC would have converged if convergence problems had not been encountered.

3,4-Diamino[1,2,5]oxadiazole (3,4-diaminofurazan), 1. This compound was made by the procedure of Visalok and Ostrovskoya. [15] The melting point was 179-180 °C (lit [15] 180 °C).

5,6-Dihydroxy-4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine, 8. Finely ground (≈105-177µ) 3,4-Diamino[1,2,5]oxadiazole (2.0g, 20 mmol), 40% aqueous glyoxal (3.0g, 21 mmol) and sodium bicarbonate (25 mg) are placed in a 20 mL scintillation vial equipped with a magnetic stirring bar. The mixture is stirred at 20°C for one hour. The clear solution is frozen in liquid nitrogen and the water removed by lyophilization. The white product is slurried with acetonitrile and collected. The yield is 3.05 g (19.2 mmol, 96%). The compound does not melt, but it exhibits two decomposition endotherms at 113 °C and 151 °C. ^{1}H-NMR(DMSO-d_6): δ= 4.65 (s, 1H), 5.92(bs, 1H), 7.79(s, 1H) ppm. ^{13}C-NMR(DMSO-d_6): δ= 75.45, 146.52 ppm.

FT-IR(KBr) = 3143 (vs), 1720(sh), 1709(vs), 1599(m), 1532(m), 1385(vs), 1061(s), 945(m), 828(w), 770(w), 765(w), 715(w), 601(m) cm^{-1}. HRMS (EI); $C_4H_6N_4O_3$; [M]+: calcd. 158.0440; found 158.0431amu.

[1,2,5]Oxadiazolo[3,4-b]pyrazine, 2 **(method 1)** 5,6-Dihydroxy-4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine (0.79 g, 5 mmol) is placed in a sublimation apparatus, which is then heated at 160 °C for 2 h at 0.5 mm. A yellow crystalline material deposits on the cold finger. The apparatus is cooled and dried and kept under vacuum. It is transferred to a dry box and opened. The light yellow crystals are collected and stored under nitrogen. The yield is 0.06 g (0.1 mmol, 10%). DSC shows that the compound melts at 89 °C and undergoes a very exothermic decomposition starting at 240 °C with a maximum at 266 °C.

[1,2,5]Oxadiazole [3,4-b]pyrazine, 2 **(method 2).** 5,6-Dihydroxy-4,5,6,7-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine (0.79 g, 5 mmol) is dissolved in 10 mL of acetone, and the resulting solution is added to a slurry of 8 g of silica gel and 30-40 mL of acetone in a 100 mL round bottom flask. This mixture is stirred for 1 h; then most of the acetone is removed at reduced pressure. A tall condenser is attached, and the mixture is stirred at room temperature under high vacuum until frothing ceases. The mixture is slowly heated to 160 ºC under high vacuum and held for 2 h. Yellow crystals deposit near the top of the flask. The flask is allowed to cool, and the crystals apparently are reabsorbed onto the silica gel. The silica gel is extracted with two 70 mL portions of chloroform. The chloroform extracts are combined and stripped at reduced pressure. The yield of slightly impure product was 0.20 g (1.6 mmol, 33%). ^{1}H-NMR(CDCl$_3$): δ= 8.97 (s) ppm. ^{13}C-NMR(CDCl$_3$): δ= 152.03, 153.04ppm. FT-IR(KBr) = 1984(w), 1957(w), 1716(w), 1558(m), 1524(m), 1447(m), 1390(w), 1358(m), 1344(sh), 1270(w), 1237(m), 1024(m), 980(m), 946(m), 882(m), 868(m), 750(m), 638(w), 603(m) cm^{-1}.

5-Methyl[1,2,5]oxadiazolo[3,4-b]pyrazine, 10. Finely ground (≈105-177μ μ) 3,4-Diamino[1,2,5]oxadiazole (1.0 g, 10 mmol), 40% pyruvic aldehyde (1.85 g, 10.5 mmol) and sodium bicarbonate (100 mg) are placed in a 20 mL scintillation vial equipped with a magnetic stirring bar. The mixture is stirred at 25°C for one hour. The 3,4-Diamino[1,2,5]oxadiazole slowly dissolves. The crude product is diluted with 10 mL of dry acetonitrile, and the resulting solution is slowly added to a mixture of 50 mL of acetone and 12 g of silica gel. The solvents are then evaporated under reduced pressure. A reflux condenser is attached to reduce the loss of the silica gel when a vacuum is applied, and the mixture is placed under high vacuum at room temperature to remove the remaining acetone and any water. The apparatus is placed in a 50 °C oil bath, and the contents are stirred. After 20 min the temperature is raised first to 120 °C and then to 160 °C. The mixture darkens considerably, and the 5-methyl[1,2,5]oxadiazolo[3,4-b]pyrazine starts to collect at the top of the flask and in the condenser. After one hour, the apparatus is removed from the oil bath and allowed to cool. The product that had sublimed is readsorbed onto the silica gel. Methylene chloride (300 mL) is poured down the condenser, and the mixture is stirred for 30 min. The silica gel is removed by filtration and extracted with two 50 mL portions of methylene chloride. The methylene chloride extracts are combined and stripped to give the crude product that is slightly red in color. The yield of slightly impure product is 0.14 g (0.1 mmol, 10%). The melting point is 57-58 °C. ^{1}H-NMR(CDCl$_3$): δ= 2.88 (s, 3H), 7.79(s, 1H) ppm. ^{13}C-NMR(CDCl$_3$): δ= 23.06, 149.97, 150.71, 154.51, 162.88 ppm. FT-IR(KBr) = 3143 (vs), 1720(sh), 1709(vs), 1599(m), 1532(m), 1385(vs), 1061(s), 945(m), 828(w), 770(w), 765(w), 715(w), 601(m) cm^{-1}. HRMS (EI); $C_4H_6N_4O_3$; [M]+: calcd. 136.0385; found 136.0382 amu.

1,4,5,6-Tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine, 7. [1,2,5]Oxadiazolo[3,4-b]pyrazine (122 mg, 1.0 mmol) is placed in a 50 mL round bottom flask equipped with a magnetic stirring bar. Anhydrous THF (10 mL) is added. Sodium borohydride (80 mg, 2.1 mmol) is added as a solid. A dark solution is obtained. The mixture is stirred for 1 h without apparent reaction. Approximately 1 mL of methanol is added, and the reaction becomes quite vigorous. It is stirred for an additional one hour. Two mL of water is added, and the solution is stirred for one hour. The solution is stripped to give a solid. The crude product is taken up in 3 mL of acetonitrile, and the solution is syringe filtered to give a clear solution. The solution is evaporated under a stream of nitrogen to give 116 mg (0.92 mmol, 92%) of 1,4,5,6-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine, **7**, as colorless crystals. The melting point is 153-155 ºC (lit [2] 153-155 ºC).

5-Methyl-1,4,5,6-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine, 12. 5-Methyl[1,2,5]oxadiazolo-[3,4-b]pyrazine (68 mg, 0.5 mmol) is placed in a 25 mL round bottom flask equipped with a magnetic stirring bar. Anhydrous THF (5 mL) is added. Sodium borohydride (38 mg, 1.0 mmol) is added as a solid. A dark solution is obtained. The mixture is stirred for 1 h without apparent reaction. Approximately 0.5 mL of methanol is added, and the reaction becomes quite vigorous. It is stirred for an additional one hour. Two mL of water is added, and the solution is stirred for one hour. The solution is stripped to give a solid. The crude product is taken up in 3 mL of acetonitrile, and the solution is syringe filtered to give a clear solution. The solution is evaporated under a stream of nitrogen to give 65 mg (0.46 mmol, 92%) of 5-methyl-1,4,5,6-tetrahydro[1,2,5]oxadiazolo[3,4-b]pyrazine as colorless crystals, melting point 97-99 ºC. ^{1}H-NMR(CD$_3$CN): δ= 1.90 (d, J=6.3Hz, 3H), 2.98(d x d, J=11.7 and 8.1Hz, 1H), 3.33(d x m, J=11.7Hz, 1H), 3.56(m, 1H), 5.45(bs, 2H) ppm. ^{13}C-NMR(CD$_3$CN): δ= 18.38, 46.76, 47.07, 148.41, 148.93 ppm. FT-IR(KBr) = 3274(vs), 2972(m), 2930(m), 2871(m), 1646(sh), 1598(vs), 1343(m), 1284(w), 1170(m), 1071(m), 996(m), 813(m) cm^{-1}. HRMS (EI); $C_4H_6N_4O_3$; [M]+: calcd. 140.0698; found 140.0698 amu.

1,4,4a,5,6,7,8,8a-Octahydro[1,2,5]Oxadiazolo[3,4-b]pyrazino[2,3-e]pyrazine, 13. [1,2,5]Oxadiazolo[3,4-b]pyrazine (61 mg, 0.5 mmol) is dissolved in 0.5 mL of CD$_3$CN in a small test tube equipped with a small magnetic stirring bar. The solution is stirred, and ethylene diamine (30 mg, 0.05 mmol) is added via a microliter syringe. The solution gets very warm, and a white precipitate forms almost immediately. The CD$_3$CN is evaporated under a stream of nitrogen to give the product. The yield of **13** is 91 mg (0.5mmol, 100%). ^{1}H-NMR(DMSO-d$_6$): δ= 2.53(m,1H), 2.82(m,1H), 2.93 (bs, 1H), 4.12(s, 1H), 7.01(bs, 1H) ppm. ^{13}C-NMR(DMSO-d$_6$): δ= 41.85, 63.18, 148.07 ppm. FT-IR(KBr) = 3377(vs), 3316 (vs), 3001(m), 2982(m), 2934(m), 2886(m), 1640(sh), 1598(vs), 720(sh), 1463(m), 1428(m), 1404(m), 1331(s), 1290(m), 1222(m), 1214(m), 1140(m), 1029(s), 988(m), 945(m), 824(m), 767(m), 740(sh)cm^{-1}. HRMS (EI); $C_6H_{10}N_6O$; [M]+: calcd. 182.0916; found 182.0910 amu.

Single-crystal X-ray Diffraction Analysis of [1,2,5]oxadiazolo[3,4-b]pyrazine, 2

$C_4H_2N_4O$, FW = 122.10, Orthorhombic, Aba2, a = 6.395(8) Å, b= 6.179(8) Å, c = 12.669(16) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, V = 500.6(11) Å^3, Z = 4, $d_{\mathrm{calc}} = 1.620$ Mg/m^3, $\mu = 0.126$ mm^{-1}, $F(000) = 248$, $R_1 = 0.0570$ for 451 observed (I > 2δI) reflections and 0.0597 for all 1606 reflections, Goodness-of-fit = 1.158, 42 parameters.

A yellow crystal of dimensions 0.18 x 0.15 x 0.14 mm^2 was mounted on a MiteGen MicroMesh using a small amount of Cargille Immersion Oil. Data were collected on a Bruker three-circle platform diffractometer equipped with a SMART APEX II CCD detector. The crystals were irradiated using graphite monochromated MoK$_\alpha$ radiation (λ = 0.71073). An Oxford Cobra low temperature device was used to keep the crystals at a constant 100(2)°K during data collection.

Data collection was performed and the unit cell was initially refined using *APEX2* [v2010.3-0].[16] Data reduction was performed using *SAINT* [v7.60A] [17] and *XPREP* [v2008/2]. [18] Corrections were applied for Lorentz, polarization, and absorption effects using *SADABS* [v2008/1]. [19] The structure was solved and refined with the aid of the programs in the *SHELXTL-plus* [v2008/4] system of programs. [20] The full-matrix least-squares refinement on F^2 included atomic coordinates and anisotropic thermal parameters for all non-H atoms. The H atoms were included using a riding model. The molecule lies on a special position, with only half the molecule being crystallographically unique.

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DoD Supercomputing Resource Center of the Department of Defense High Performance Computing Modernization Program.

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Synthesis and Crystal Structure of Octahydro-5H,12H-4,11-methano-1H,7H-bis[1,2,5]oxadiazolo[3,4-d:3′,4′-j][1,7,3,9]dioxadiazacyclododecine

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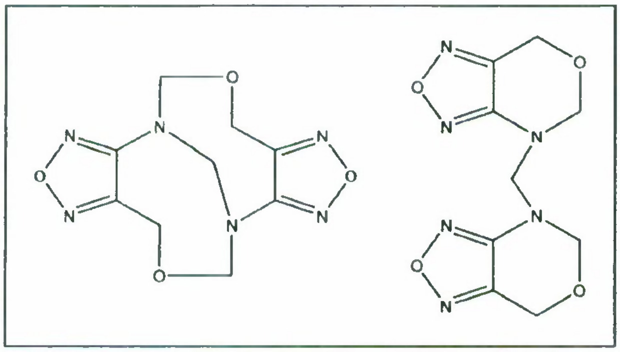

The unusual 12-membered ring compound, octahydro-5H,12H-4,11-methano-1H,7H-bis[1,2,5]oxadiazolo[3,4-d:3′,4′-j][1,7,3,9] dioxadiazacyclododecine is obtained from the acid catalyzed reaction of 3-amino-4-hydroxymethylfurazan with formaldehyde instead of the expected methylene-bridged compound, 4,4′-Methylenebis[4,5-dihydro-7H-[1,2,5]oxadiazolo[3,4-d][1,3]oxazine]. The compound crystallizes in Tetragonal, $P4_32_12$, $a = 6.4141(4)$ Å, $b = 6.4141(4)$ Å. $c = 26.525(3)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 1091.27(16)$ Å^3, $Z = 4$. $d$calc = 1.614 Mg/m^3.

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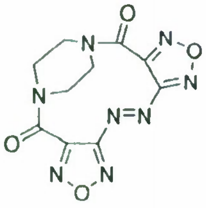
INTRODUCTION

Compounds with furazan rings fused to saturated heterocyclic rings have been of interest for a number of years as energetic materials [1], pharmaceuticals [2], and electronic materials [3]. For example, Sheremetev *et al.* recently synthesized the unusual 12-membered macrocyclic lactam, **1**, by oxidizing the corresponding linear diamine to the azo compound [4]. We are currently interested in synthesizing furazans fused to saturated 1,3-heterocycles such as 4,4′-methylenebis [4,5-dihydro-7H-[1,2,5]oxadiazolo[3,4-d][1,3]oxazine], **2**, or 4,5,6,7-tetrahydro-[1,2,5-oxadiazolo[3,4-d] pyrimidine, **3**. These compounds are related to the 4,5,6,7-tetrahydro-1,2,5-oxadiazolo[3,4-b] pyrazine, **4**, synthesized a number of years ago [1]. Compound **4** is the precursor to the well known energetic material, DNFP, **5** [1], and has interesting electronic properties [3]. These materials would allow us to study the effect of moving the amine group into a different location in the ring or the effect of substituting an ether linkage for the amine on the chemical and electronic properties of these compounds and the nitramines derived from them.



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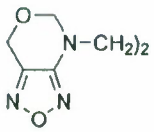

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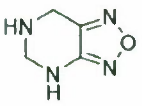

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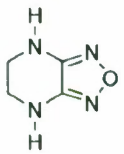

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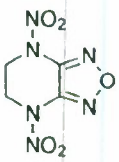

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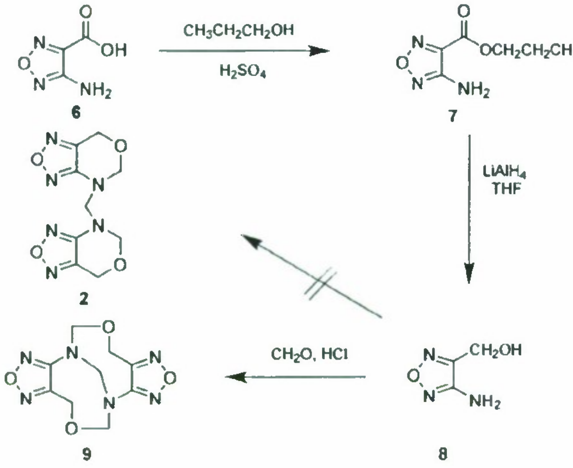
Scheme 1. Synthesis of octahydro-5H,12H-4,11-methano-1H,7H-bis[1,2,5]oxadiazolo[3,4-d:3′,4′-*j*][1,7,3,9] dioxadiazacyclododecine, **9**.



RESULTS AND DISCUSSION

We initially targeted compound **2** via the synthetic S1 route shown in Scheme 1. The known 4-aminofurazan-3-carboxylic acid, **6** [5], was converted to its propyl ester, **7**, in essentially quantitative yield using excess *n*-propanol in the presence of concentrated sulfuric acid. Alternatively, either the methyl or ethyl ester could have been utilized [4,6], however, both methods use anhydrous HCl and the alcohol. In addition, they require long reaction times and produce only modest yields. The propyl ester has several advantages; it has a lower melting point (90°C vs. 154–155°C [4] and 100–103°C [6] for the methyl and ethyl esters, respectively) and it is more soluble in solvents such as THF. The propyl ester was reduced in high yield to the alcohol, **8**, using $LiAlH_4$ in THF. It should be noted that, to our knowledge, this is the first example of the successful reduction using $LiAlH_4$ of an ester group directly attached to a furazan ring; although Sato and Adachi have shown previously that certain furazanopyrazines can be reduced to furazanopiperazines with $LiAlH_4$ [7]. The reaction of the amino alcohol with formaldehyde was performed with a small excess over the required 1:1.5 molar ratio. Initial ^1H and ^{13}C-NMR analyses appeared to support the synthesis **2**. A HRMS confirmed an elemental formula of $C_9H_{10}N_6O_4$. However, a more careful examination suggested a different product had been formed. The FTIR spectrum had approximately 26 absorptions between 400 and 1500 cm^{-1} as compared to only 12 for the starting alcohol, suggesting a very rigid structure. The carbon spectrum consisted of five peaks; two in the aromatic region (153.53 ppm and 145.11 ppm) and three in the aliphatic region (82.17 ppm, 66.71 ppm, and 60.56 ppm) in close agreement with predicted chemical shifts [8]. However, the proton spectrum did not support **2**. The two ring methylene groups both appeared as AB quartets with large chemical shift differences (see Fig. 1), consistent with a rigid structure. Since the structure F1 of the compound was isomeric with **2** based on the HRMS, the only possible alternate structure was the unusual methylene bridged 12-membered ring compound, octahydro-5H,12H-4,11-methano-1H,7H-bis [1,2,5]oxadiazolo [3,4-d:3′,4′-j][1,7,3,9] dioxadiazacyclododecine, **9**. All of the spectral data is consistent with this compound.

The product's structure was confirmed via single crystal X-ray structure diffraction on a crystal grown from DMSO. The crystal structure is shown in Figure 2. The F2 X-ray data are summarized in Table 1. T1

The preference for forming the twelve-membered ring is intriguing. It is well known that aminofurazans readily undergo acid-catalyzed condensations with formaldehyde to yield methylene-bis compounds [9,10]. Thus, the methylene-bis (4-amino-3-hydroxymethylfurazan), **10**, should form first (see Scheme 2). Crystal structures S2 of the analogous methyl and nitro- compounds show that they adopt conformations where the two furazan rings are pointed in opposite directions [10]. Since methylene-bis aminofurazans are reluctant to react with a second mole of formaldehyde, the next step is most likely the reaction of the hydroxyl groups with formaldehyde to yield the di-hemiacetal, **11**, which under acid catalysis cyclizes to give the observed product. Experiments to test this hypothesis are currently under way.

EXPERIMENTAL

Heteronuclear single-quantum correlation (HSCQ) spectra were acquired on a Varian ^{UNITY}INOVA spectrometer operating at a frequency of 499.8 MHz for proton and using a standard 5 mm two channel probe. Samples were dissolved in DMSO-d_6. The acquisition parameters were as follows: The recycle delay was 1.5 s, the 90° pulse width was 15.1 μs, the ^1H sweepwidth was 5.97 ppm, the ^{13}C sweepwidth was 145 ppm, and the acquisition time was 150 ms. The number of *t1* increments was 512 with 8 scans per increment. States-Haberkorn phase cycling was used to obtain phase sensitive data. An additional 1536 points were added to the *F1* dimension via linear prediction. Both *t1* and *t2* were zero-filled to 4096 and 1024 data points and apodized using a Gaussian function prior to Fourier transformation.

4-Aminofurazan-3-carboxylic acid, 6. This compound was made using the procedure of Meyer [5]. The melting (decomposition) point by DSC was 220°C [4].

***n*-Propyl 4-aminofurazan-3-carboxylate, 7.** A dry 250-mL one-neck round bottom flask was equipped with a magnetic stirring bar. 4-Aminofurazan-3-carboxylic acid (12.9 g, 0.10 mol) [5] and 150 mL of anhydrous *n*-propanol were added to the flask, and the contents were stirred. Sulfuric acid (2 mL)

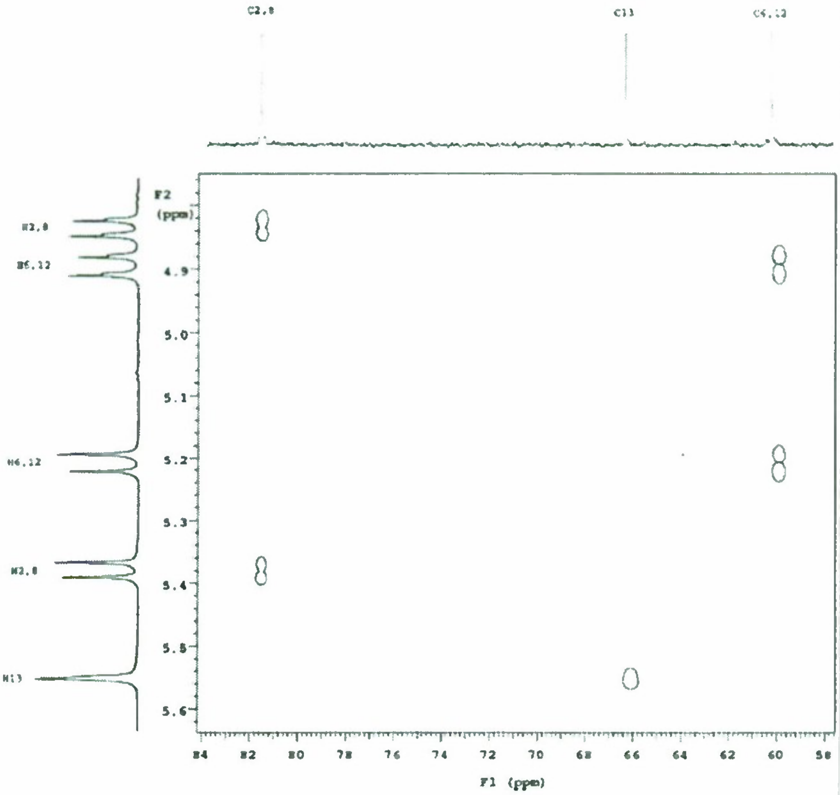


Figure 1. 2D HSQC spectra of octahydro-5H,12H-4,11-methano-1H,7H-bis [1,2,5]oxadiazolo [3,4-d:3′,4′-*j*] [1,7,3,9]dioxadiazacyclododecine @ 500 MHz.

was added drop-wise. A reflux condenser equipped with a nitrogen bubbler was attached to the flask, and the mixture was refluxed for 16 h. A distillation head was then attached, and 25 mL of the *n*-propanol/water azeotrope slowly distilled. The reflux condenser was reattached, and the reaction was refluxed for 6 h more. An additional 50 mL of *n*-propanol was removed by distillation. The reaction was cooled to <0°C using a salt/ice bath, causing the product to precipitate. The latter was collected and washed with a small amount of cold *n*-propanol to yield 15.9 g of the crude *n*-propyl 4-aminofurazan-3-carboxylate (0.093 mol, 93%). The crude product was initally recrystallized from *n*-propanol to give an 80% recovery of a very pure product with a melting point of 90–91°C; however, we found that the crude product was sufficiently pure for further reaction. ^{1}H-NMR (DMSO-d_6): $\delta = 6.38$ (bs, 2H), 4.29 (t, $J = 6.9$ Hz, 2H), 1.70 (hex, $J = 6.9$ Hz, 2H), 0.92(t, $J = 6.9$ Hz, 3H) ppm. ^{13}C-NMR (DMSO-d_6): $\delta = 159.10$ (COO), 156.68 (C_4), 139.78 (C_3), 67.87 (CH_2O), 21.71 (CH_2), and 10.54 (CH_3) ppm. FTIR (film, melt) = 3442(s), 3338(s), 2972(m),1732(s), 1643(s), 525(m), 1465(m), 1402(m),1337(m), 1164(s), 1052(m), 1007(m), 906(m), 826(m), 793(m) cm^{-1}. Anal. Calcd. for $C_6H_9N_3O_3$ (%): C, 42.10; H, 5.30; N, 24.55. Found: C, 41.92; H, 5.05; N, 24.29.

4-Amino-3-hydroxymethylfurazan, 8. N-Propyl 4-aminofurazan-3-carboxylate (1.71 g, 0.01 mol) was dissolved in 10 mL of anhydrous THF. This solution was slowly added to a well-stirred slurry of 0.50 g (0.013 mol) of $LiAlH_4$ in 10 mL of anhydrous THF over a period of 1 h with the temperature

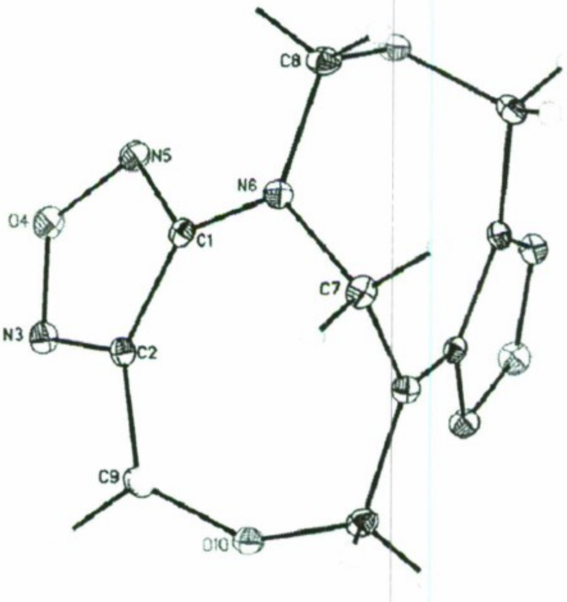


Figure 2. Structure of octahydro-5H,12H-4,11-methano-1H,7H-bis [1,2,5]oxadiazolo [3,4-d:3′,4′-*j*] [1,7,3,9] dioxadiazacyclododecine, **9** as determined by x-ray diffraction, displacement ellipsoids are at the 50% level.

Table 1

Crystal data and structure refinement for 9.

Empirical formula	$C_9H_{10}N_6O_4$
Formula weight	265.22
Temperature	144(2) K
Wavelength	0.71073 Å
Crystal system	Tetragonal
Space group	$P4_32_12$
Unit cell dimensions	a = 6.4141(4) Å (α = 90°) b = 6.4141(4) Å (β = 90°) c = 26.525(3) Å (γ = 90°)
Volume	1091.27 (16) $Å^3$
Z	4
Density (calculated)	1.614 Mg/m^3
Absorption coefficient	0.131 mm^{-1}
F (000)	548
Crystal size	1.00 × 0.70 × 0.70 mm^3
Theta range for data collection	3.07–30.69°.
Index ranges	$-8 \leq h \leq 8$, $-9 \leq k \leq 9$, $-37 \leq l \leq 37$
Reflections collected	12222
Independent reflections	1625 [R_{int} = 0.0235]
Completeness to theta = 30.69°	97.1%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.849
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1625/0/87
Goodness-of-fit on F^2	1.158
Final R indices [$I > 2$sigma (I)]	R_1 = 0.0371, wR_2 = 0.0992
R indices (all data)	R_1 = 0.0380, wR_2 = 0.1000
Absolute structure parameter	0.2 (14)
Largest diff. peak and hole	0.290 and −0.266 e.$Å^{-3}$

maintained below 35°C using a water bath. After stirring for 2 h, the excess hydride was destroyed by the careful addition of 0.50 g of water in THF, 0.50 g 15% NaOH and finally 1.0 g of water. The slurry was heated and filtered. The solid material was re-slurried with 20 mL of hot THF and filtered. The combined filtrates were stripped *in vacuo* to give the crude product as a colorless liquid. The yield was 0.99g (0.005 mol, 86%).^{1}H-NMR (DMSO-d_6): δ = 4.52 (s, 2H), 4.87 (bs, 1H), and 5.95 (bs, 2H) ppm. ^{13}C-NMR (DMSO-d_6): δ = 52.6, 148.23, and 156.19 ppm. FTIR (film) = 3349(vs), 2947(m), 2885(m), 1633(s), 1526(s), 1447(m), 1277(w), 1226(w), 1057(m), 1002(m) and 887(w)cm^{-1}. HR MS (EI); $C_3H_5N_3O_2$ [M]+: calcd. 115.0382; found; 115.0383 amu.

Octahydro-5H,12H-4,11-methano-1H,7H-bis[1,2,5]oxadiazolo[3,4-d:3′,4′-j][1,7,3,9] dioxadiazacyclododecine, 9.. 4-Amino-3-hydroxymethylfurazan (115 mg, 1.0 mmol) and 37% formaldehyde (130 mg, 1.60 mmol) were combined in a small test tube with a magnetic stirring bar. One drop of 37% HCL was added. A precipitate started to form almost immediately. Approximately 0.5 mL of distilled water was added to reduce the viscosity. The mixture was heated to 80°C with a water bath for 10 min, and cooled to room temperature. The white product was collected by filtration. The yield after drying was 52 mg (0.2 mmol, 40%). The compound did not melt but turned dark above 240°C. ^{1}H-NMR (DMSO-d_6): δ = 4.82(d, J = 12Hz, 2H), 4.87(d, J = 14.4 Hz, 2H), 5.20(d, J = 14.4 Hz, 2H), 5.27(d, J = 12 Hz, 2H), 5.55(s, 2H, N-C$\underline{H_2}$-N), ppm. ^{13}C-NMR (DMSO-d_6): δ = 60.56, 66.71, 82.17, 145.11, 153.53 ppm.

FTIR (KBr) = 3002(w), 2946(w), 2888(w), 1584(m), 1517(m), 1458(w), 1397(w), 1327(m), 1281(w), 1206(m), 1143(m), 1080(m), 1034(m), 1011(w), 979(w), 958(w), 944(m), 922(m), 902(m), 878(w), 779(m), 697, 668(m), 632(m), 591(w), 562(w), 476(w), 425(w) cm^{-1}. HR MS (EI); $C_9H_{10}N_6O_4$ [M]+: calcd. 266.0764; found; 266.0766 amu.

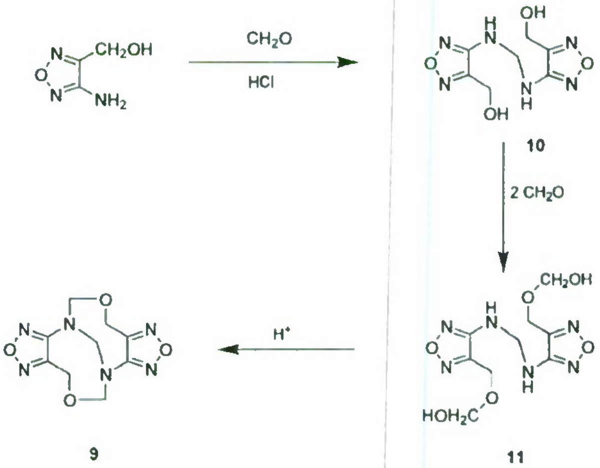
Single-crystal X-ray diffraction analysis of 9. A clear colorless crystal of dimensions 1.00 × 0.70 × 0.70 mm^2 was mounted on a MiteGen MicroMesh using a small amount of Cargille Immersion Oil. Data were collected on a Bruker three-circle platform diffractometer equipped with a SMART APEX II CCD detector. The crystal was irradiated using graphite monochromated MoK$_\alpha$ radiation (λ = 0.71073). An MSC X-Stream low temperature device was used to keep the crystal at a constant −130°C during data collection.

Data collection was performed and the unit cell was initially refined using SMART [v5.625] [11]. Data reduction was performed using SAINT [v6.36A] [12] and XPREP [v6.12] [13]. Corrections were applied for Lorentz, polarization, and absorption effects using SADABS [v2.03] [14]. The structure was solved and refined with the aid of the programs in the SHELXTL-plus [v6.10] system of programs [15]. The full-matrix least-squares refinement on F^2 included atomic coordinates and anisotropic thermal parameters for all non-H atoms. The H atoms were included using a riding model.

$C_9H_{10}N_6O_4$, FW = 266.23, Tetragonal, $P4_32_12$, a = 6.4141(4) Å, b = 6.4141(4) Å, c = 26.525(3) Å, α = 90°, β = 90°, γ = 90°, V = 1091.27(16) Å^3, Z = 4, $d$calc = 1.614 Mg/m^3, F(000) = 548, R_1 = 0.0371 for 1580 observed ($I > 2\delta I$) reflections and 0.380 for all 1625 reflections. Goodness-of-fit = 1.158, 87 parameters.

"CCDC 699769 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge

Scheme 2. Proposed reaction pathway for the formation of **9**.



from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif."

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Crystal Structures of the "Two" 4-Aminofurazan-3-carboxylic Acids

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Additional Supporting Information may be found in the online version of this article.

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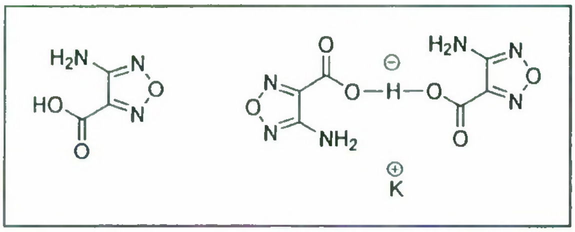

The crystal structures of the two compounds reported to be 4-aminofurazan-3-carboxylic acid have been determined. The compound reported by Sheremetev et al. (J Heterocycl Chem 2005, 42, 519) is the actual 4-aminofurazan-3-carboxylic acid. The compound reported by Meyer (Org Prep Proced Int 2004, 36, 361) is the interesting complex formed from a molecule of the acid and a molecule of the potassium salt of the acid.

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INTRODUCTION

In connection with several projects, we had need for a sizable quantity of 4-aminofurazan-3-carboxylic acid, **1**. There are two recent publications describing syntheses of this compound, one by Meyer [1] and one by Sheremetev et al. [2] The two syntheses are quite similar, involving the same starting compound, similar reagents, and intermediate, as outlined in Figure 1. The final neutralization step is conducted at ambient temperature in the Sheremetev procedure [2] and at 0°C in the Meyer procedure [1]. This turns out to be a critical difference between the two procedures.

When we made our first batch using Meyer's procedure, we obtained a product that seemed to match his reported properties except that the ^{13}C-NMR chemical shifts were different. Meyer reported shifts of 161.3, 157.1, and 143.3 ppm, whereas the compound we isolated had shifts of 160.7, 156.8, and 140.4 ppm. All NMR spectra were recorded in DMSO-d_6, except as noted, as were the spectra in refs. 1 and 2. This concerned us until we noted that the ^{13}C-NMR shifts reported by Sheremetev et al. [2] (160.5, 156.8, and 140.4 ppm) were nearly identical to ours. The fact that Sheremetev et al. had transformed their product into other compounds and had obtained X-ray crystal structures on them, gave us great confidence that the compound we had isolated was indeed **1**. We made several additional batches of the material over a period of about a year and always obtained the same product until, on the fifth batch, we isolated a compound, **2**, with a different crystal habit (plate for **2** vs. prism for **1**). In addition, the ^{13}C-NMR chemical shifts for **2** (161.3, 156.9, and 143.1 ppm) were nearly identical to those reported by Meyer.

Except for the differences in ^{13}C-NMR shifts, the rest of the spectral properties were quite similar. Significant differences were found in the elemental analyses and thermal properties of the two compounds. The compound with the shifts reported by Sheremetev et al. gave an almost perfect C, H, N analysis for $C_3H_3N_3O_3$ (calculated: C, 27.92; H, 2.34; N, 32.55; found C, 27.80; H, 2.42; N, 32.63), whereas the compound with Meyer's shifts gave results that differed significantly (found C, 24.15; H, 1.62; N, 28.25). Obvious differences were observed in the DSC thermograms of the two compounds, as shown in Figures 2 and 3.

At this point, we turned to X-ray crystallography to establish the exact structure of the two compounds. A preliminary analysis of Meyer's compound showed the presence of a heavy atom. There were two possibilities, chlorine and potassium. We then reconsidered the results of the elemental analysis and found that the

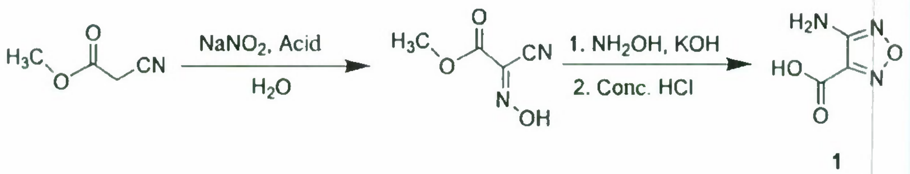

Figure 1. Generalized synthesis of 1.

analytical results fit quite well for a molecular formula of $C_6H_5N_6O_6K$ (calculated: C, 24.33; H, 1.70; N, 28.37: found: C, 24.15; H, 1.62; N, 28.25). An analysis of the compound for potassium gave results consistent with that molecular formula (calculated: K, 13.20: found: 13.2%). With this information in hand, the structure easily refined to the interesting complex formed between the acid and the potassium salt of the acid (Fig. 4). Similar structures have been observed previously [3,4].

Chemical confirmation of this structure comes from the fact that recrystallization of **2** from acidic water produces **1** and the fact that the treatment of **1** with 0.5 equiv of potassium hydroxide followed by recrystallization of the mixture produces **2** (Fig. 5). We also measured the ^{13}C-NMR chemical shifts for the sodium salt of **1** in a mixture of H_2O/D_2O and obtained shifts of 163.8, 156.12, and 144.1 ppm. Thus, Meyer's compound has chemical shifts that are a rough average of **1** and its sodium salt.

For completeness, we determined the X-ray crystal structure for **1** (Fig. 6). The crystal data for the two compounds are summarized in Table 1.

There are several points that should be noted in the results of the X-ray diffraction of **1** (Fig. 6). At first glance, there would appear to be a center of symmetry among the four molecules in the asymmetric unit. Careful examination of the positions of the protons on O6, O6A, O6B, and O6C reveals that this is not a center of symmetry. Testing with PLATON [5] indicates that there is no missed symmetry. Further evidence on the uniqueness of the four molecules can be seen in the hydrogen bonding (Supporting Information Table S6). In three of the molecules, N1 forms one normal H-bond and one bifurcated H-bond, whereas in the fourth molecule N1 forms only a bifurcated H-bond. O6 forms a bifurcated H-bond in one molecule while in the remaining molecules O6 forms a single H-bond with a donor-H-acceptor angle of 152° ± 9°. The disparity of the sizes and shapes of the displacement ellipsoids indicates possible twinning in the crystal which we were not able to resolve in the diffraction experiment. Data collection was attempted on multiple crystals of this compound and all were similarly flawed with some showing signs of severe twinning as evidenced by streaking in the diffraction pattern and broad spots.

It is somewhat puzzling that **2** would form in such acidic conditions. The best explanation would be that if the acidification process is done slowly and at a low enough temperature, **2** starts to crystallize out and once it has crystallized it is stable under the conditions. It should be noted that **2** is also completely stable to recrystallization from neutral water. It is very easy to avoid the isolation of **2** by simply heating the reaction after the acidification step to dissolve the product, insuring that the pH is still less than 1, then cooling the mixture to crystallize the product.

EXPERIMENTAL

4-Aminofurazan-3-carboxylic acid, 1. A 1000-mL three-neck round-bottomed flask is equipped with a mechanical

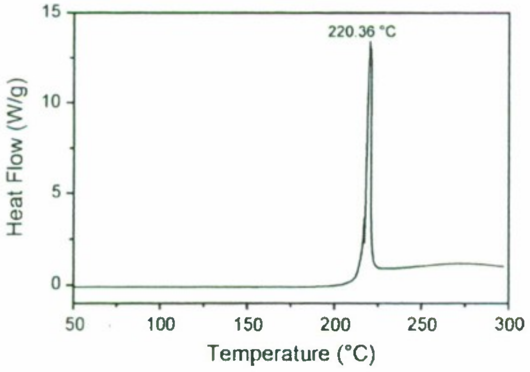

Figure 2. DSC thermogram of 4-aminofurazan-3-carboxylic acid, 1.

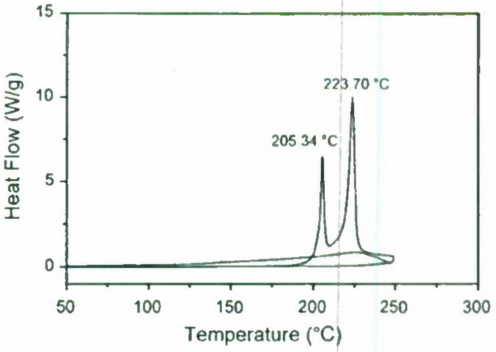

Figure 3. DSC thermogram of Meyer's compound, 2.

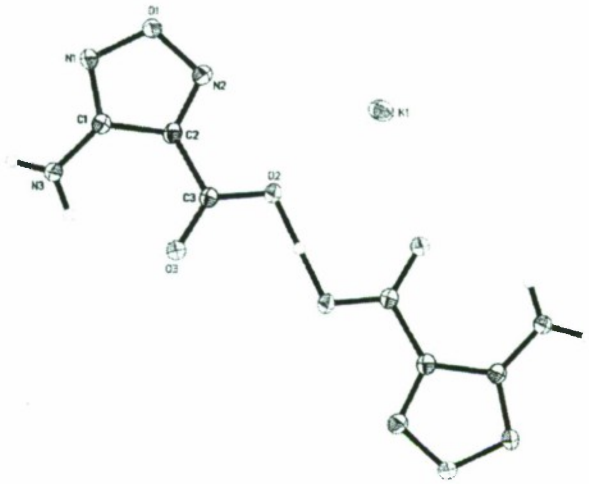

Figure 4. X-ray crystal structure of Meyer's compound, **2**. Displacement ellipsoids are at the 50% level.

stirrer, 125-mL pressure equalizing dropping funnel, and a thermometer. Methyl cyanoacetate [59.4 g (53.4 mL, 0.60 mol)], sodium nitrite (50.0 g, 0.724 mol), and water (240 mL) are added to the flask, and the contents stirred and chilled to 0°C using a salt/ice bath. Acetic acid (46 mL, 0.80 mol) is added dropwise over 15 min. The cooling bath is removed and the mixture stirred for 4 h. The reaction is recooled to 0°C using a salt/ice bath, and the pH is adjusted to 1 using conc. HCl (~60 mL). The solution is transferred to a 1000-mL separatory funnel and extracted with ethyl acetate (3× 150 mL). The combined ethyl acetate extracts are washed with 100 mL of brine, dried over $MgSO_4$, and then concentrated *in vacuo* to yield the product. The yield is 76.8 g (0.60 mol).

A 1000-mL three-neck round-bottomed flask was equipped with a mechanical stirrer and thermometer. Water (150 mL) is added. This solution is stirred and potassium hydroxide (33.6 g, 0.60 mol) is added. The solution is cooled with an ice bath and 50% hydroxylamine (39.6 g, 0.60 mol) is added. Methyl 2-cyano-2-(hydroxyimino)acetate (76.8 g, 0.60 mol) is dissolved in 150 mL water and added in small portions to the stirred mixture. The cooling bath is removed. After the mixture is stirred for 1.5 h, additional KOH (67.2 g, 1.2 mol) is added portion-wise to the orange-red mixture. The mixture is heated to 100°C for 2 h using an oil bath. The mixture is cooled to 10°C using an ice bath and then acidified to pH < 1 using conc. hydrochloric acid (~125 mL). The solution is heated until all the product is in solution, and the pH is rechecked to make sure it is still below 1. Additional concentrated hydrochloric acid is added if necessary. The solution is chilled to 0°C using a salt-ice bath. After about 1 h, the product is collected and dried. The yield is 49.2 g (0.38 mol, 64%). The melting (decomposition) point by DSC (3°/min) is 220°C (ref. 2; 213–214°C).

Synthesis of 2 from 1. Authentic 4-aminofurazan-3-carboxylic acid, **1**, (1.29 g, 10 mmol), 5 mL of H_2O, and 85% KOH (0.33 g, 5 mmol) are combined in a 20-mL scintillation flask equipped with a magnetic stirring bar. The contents are stirred at 100°C until the acid dissolves. The mixture is then cooled to 0°C and the product collected and dried. The yield of **2** is 1.40 g (4.7 mmol, 94%). The compound is identical in all respects to the product isolated from the Meyer's procedure.

X-Ray Crystal Structure of Compounds 1 and 2. Single-crystal X-ray diffraction data on **1** and **2** were collected at 100°K and 173°K, respectively, using MoKα radiation (λ = 0.71073 Å) and a Bruker APEX 2 CCD area detector. The samples were prepared for data collection by coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a MicroMesh mount (MiTeGen) and transferred immediately to the diffractometer. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS, Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were included using a riding model [coordinate shifts of N applied to H atoms] with N—H distance set at 0.86 Å.

The 0.301 × 0.224 × 0.136 mm^3 crystal of **1** was triclinic in space group $P\ -1$ with unit cell dimensions a = 9.755(8) Å, b = 9.775(8) Å, c = 11.463(14) Å, α = 108.362(12)°, β = 105.613(12)°, and γ = 108.118(8)°. Data were 92.0% complete to 24.41°θ. The asymmetric unit contains four molecules. Full information on data collection, refinement, and results of the X-ray studies are given in Supporting Information Tables S1–S6.

The 0.64 × 0.20 × 0.04 mm^3 crystal of **2** was monoclinic in space group $P2/c$ with unit cell dimensions a = 10.060(4) Å, b = 4.5742(18) Å, c = 12.170(5) Å, and β = 107.298(6)°.

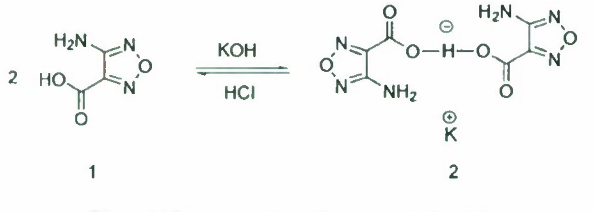

Figure 5. Interconversion of compounds **1** and **2**.

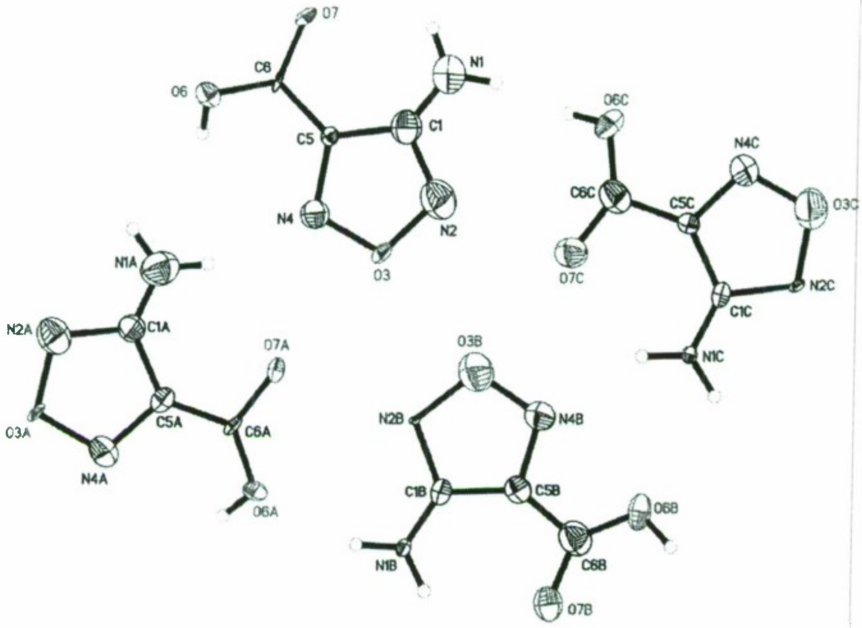

Figure 6. X-ray crystal structure of 4-aminofurazan-3-carboxylic acid, **1**. Displacement ellipsoids are at the 50% level.

Table 1

Crystal data and structure refinement for compounds **1** and **2**.

	1		**2**	
Empirical formula	$C_3H_3N_3O_3$		$C_3H_{2.50}K_{0.50}N_3O_3$	
Formula weight	129.08		148.13	
Temperature	100(2) K		173(2) K	
Wavelength	0.71073 Å		0.71073 Å	
Crystal system	Triclinic		Monoclinic	
Space group	*P* −1		*P*2/*c*	
Unit cell dimensions (Å and °)	$a = 9.755(8)$	$\alpha = 108.362(12)$	$a = 10.060(4)$	$\alpha = 90$
	$b = 9.775(8)$	$\beta = 105.613(12)$	$b = 4.5742(18)$	$\beta = 107.30(1)$
	$c = 11.463(14)$	$\gamma = 108.118(8)$	$c = 12.170(5)$	$\gamma = 90$
Volume	900.6(15) Å^3		534.7(4) Å^3	
Z	8		4	
Density (calculated)	1.859 Mg/m^3		1.840 Mg/m^3	
Absorption coefficient	0.169 mm^{-1}		0.537 mm^{-1}	
F(000)	504		300	
Crystal size	0.301 × 0.224 × 0.136 mm^3		0.64 × 0.20 × 0.04 mm^3	
θ range for data collection	2.05 to 24.41°		2.12 to 28.76°	
Index ranges	$-10 \leq h \leq 11$		$-13 \leq h \leq 13$	
	$-10 \leq k \leq 11$		$-5 \leq k \leq 6$	
	$-11 \leq l \leq 13$		$-16 \leq l \leq 16$	
Reflections collected	5919		5340	
Independent reflections	2738 [*R*(int) = 0.0415]		1385 [*R*(int) = 0.0664]	
Completeness to θ = 25.00°	92.0%		99.9%	
Absorption correction	Semi-empirical from equivalents			
Max. and min. transmission	0.9773 and 0.9508		0.984 and 0.909	
Refinement method	Full-matrix least-squares on F^2			
Data/restraints/paramcters	2738/252/293		1385/3/97	
Goodness-of-fit on F^2	0.946		1.040	
Final *R* indices [$I > 2\sigma(I)$]	$R1 = 0.0549$, $wR2 = 0.0911$		$R1 = 0.0467$, $wR2 = 0.0989$	
R indices (all data)	$R1 = 0.0777$, $wR2 = 0.0963$		$R1 = 0.0825$, $wR2 = 0.1144$	
Extinction coefficient			0.015(5)	
Largest diff. peak and hole	0.696 and −0.233 e Å^{-3}		0.383 and −0.428 e Å^{-3}	

Data were 99.9% complete to 25.00° θ. The asymmetric unit contains two molecules sharing a single proton between their carboxyl groups plus one potassium ion. Full information on data collection, refinement, and results of the X-ray studies are given in Supporting Information Tables S7–S12.

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DRAFT

Reaction of n-Propyl 4-Amino-[1,2,5]oxadiazole-3-Carboxylate with KH: Synthesis of Bis[1,2,5]oxadiazolo[3,4-b:3’,4'-f][1,5]diazocine-5,10(4H,9H)-dione and Poly ((1,2,5-oxadiazole-3,4-diyliminocarbonyl)

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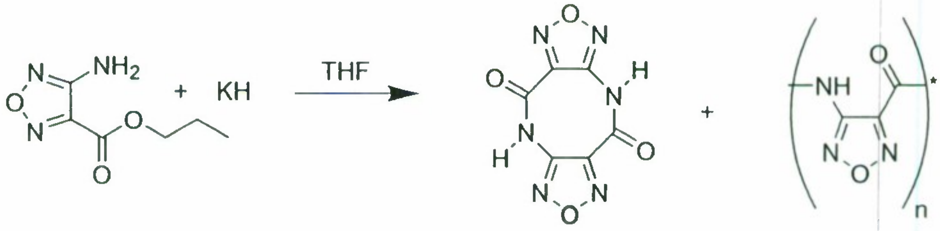
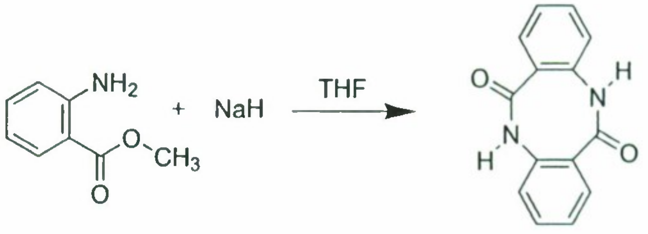
Abstract:

The reaction of n-propyl 4-amino-[1,2,5]oxadiazole-3-carboxylate with KH in THF produces a 65:35 mixture of the interesting bis[1,2,5]oxadiazolo[3,4-b:3',4'-f][1,5]diazocine-5,10(4H,9H)-dione and poly(1,2,5-oxadiazole-3,4-diyliminocarbonyl). The compounds can be separated based on their different solubility characteristics in water.





Reaction of n-Propyl 4-Amino-[1,2,5]oxadiazole-3-Carboxylate with KH

50% Potassium hydride (8.00 g, 60 mmole) is weighted out in a dry 250 ml round bottom flask that is equipped with a magnetic stirring bar. The flask is capped with a septum and flushed with dry nitrogen. 10 ml of dry hexanes is added via canula and the mixture stirred and then allowed to settle. Most of the mineral oil/hexanes mixture is pipeted off using a syringe equipped with a blunt tipped needle. The washing process is repeated one more time then 100 ml of dry THF is added. The n-propyl 4-aminofurazan-3-carboxylate is dissolved in 30 ml of dry THF and added slowly via syringe. The reaction is stirred until the evolution of hydrogen slows (about one hour) The solution is a bright yellow at this time. (Caution: even at this scale some heat is evolved). The solution was then stirred at 50 °C for one hour and the solution turned a deeper yellow. The temperature is slowly raised to 60 °C and the mixture stirred hydrogen evolution stops and then for 30 additional minutes. It was then cooled to < -10 °C and quenched by the careful addition of 3.6 grams of acetic acid via syringe. The solvent is stripped and 60 ml of water is added and the resulting slurry was heated to boiling for 5 minutes then cooled to 0 °C. The slightly off white product was collected, washed with water and ethanol. It is air dried over night and then under high vacuum for 24 hours.

The crude product (3.34g, 30mmole) is added to 300 ml of boiling water in a 1000ml Erlenmeyer flask equipped with a magnetic stirring bar. The crude product slowly dissolves. The solution is filtered hot through a fiberglass filter to remove a small amount of insoluble material. The solution is chilled to 0 °C using an ice-water bath. A gelatinous material forms. This is filtered off using a paper filter. The material is dried in a vacuum oven for 40 hours. The yield is 1.25 g (11.3 mmol, 37.5%).

The aqueous layer is frozen and lyophilized.

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January 17, 2012

VIA FEDEX

Defense Technical Information Center
8725 John J Kingman Road Ste 0944
Fort Belvoir, VA 22060-6218

RE: Award No. N00014-08-1-0060
The University of Southern Mississippi---GR03122

Dear Sir or Madam:

Enclosed for your records, please find one copy of the Final Technical Report for Award No. N00014-08-1-0060, along with an SF298.

Should you have any questions or need any additional information, please contact me.

Sincerely,

Alison Darsey

Alison A. Darsey, J.D.
Associate Grants Administrator
alison.darsey@usm.edu