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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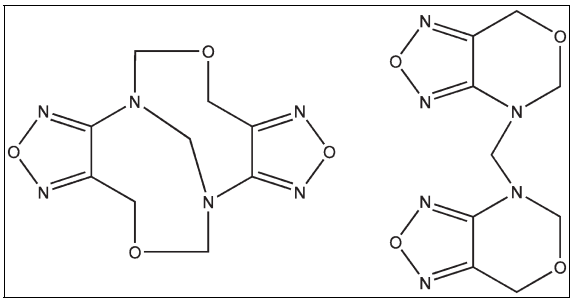

The unusual 12-membered ring compound, octahydro-5H,12H-4,11-methano-1H,7H-bis[1,2,5]oxadiazolo[3,4-d:3′,4′-j][1,7,3,9]dioxadiazacyclododecine is obtained from the acid catalyzed reaction of 3-amino-4-hydroxymethylfurazan with formaldehyde instead of the expected methylene-bridged compound, 4,4′-methylenebis[4,5-dihydro-7H-[1,2,5]oxadiazolo[3,4-d][1,3]oxazine].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

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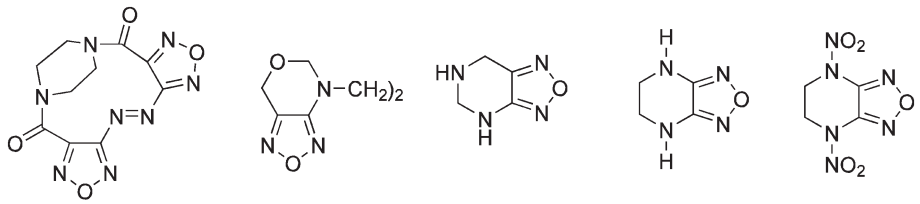
INTRODUCTION

Compounds with [1,2,5]oxadiazole (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 [1,2,5]oxadiazoles 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.



1 **2** **3** **4** **5**

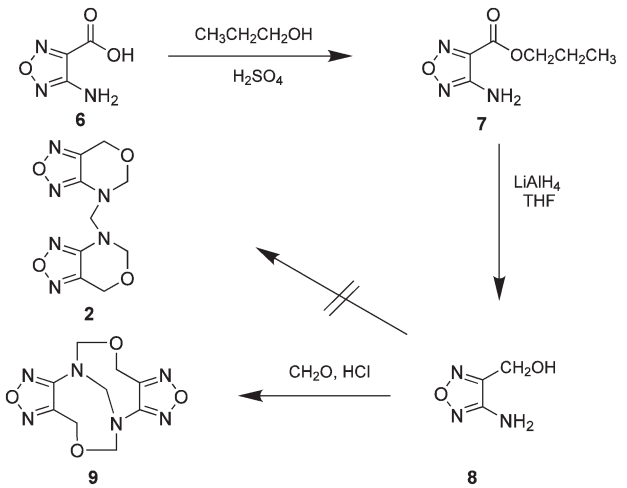
RESULTS AND DISCUSSION

We initially targeted compound **2** via the synthetic route shown in Scheme 1. The known 4-amino[1,2,5]-oxadiazole-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 [1,2,5]oxadiazolopyrazines can be reduced to [1,2,5]oxadiazolopiperazines 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 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 are 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 X-ray data are summarized in Table 1.

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-hydroxymethyl[1,2,5]oxadiazole), **10**, should form first (see Scheme 2). Crystal structures 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.

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**.



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 *t*1 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 *F*1 dimension via linear prediction. Both *t*1 and *t*2 were zero-filled to 4096 and 1024 data points and apodized using a Gaussian function prior to Fourier transformation.

4-Amino[1,2,5]oxadiazole-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-amino[1,2,5]oxadiazole-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) 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

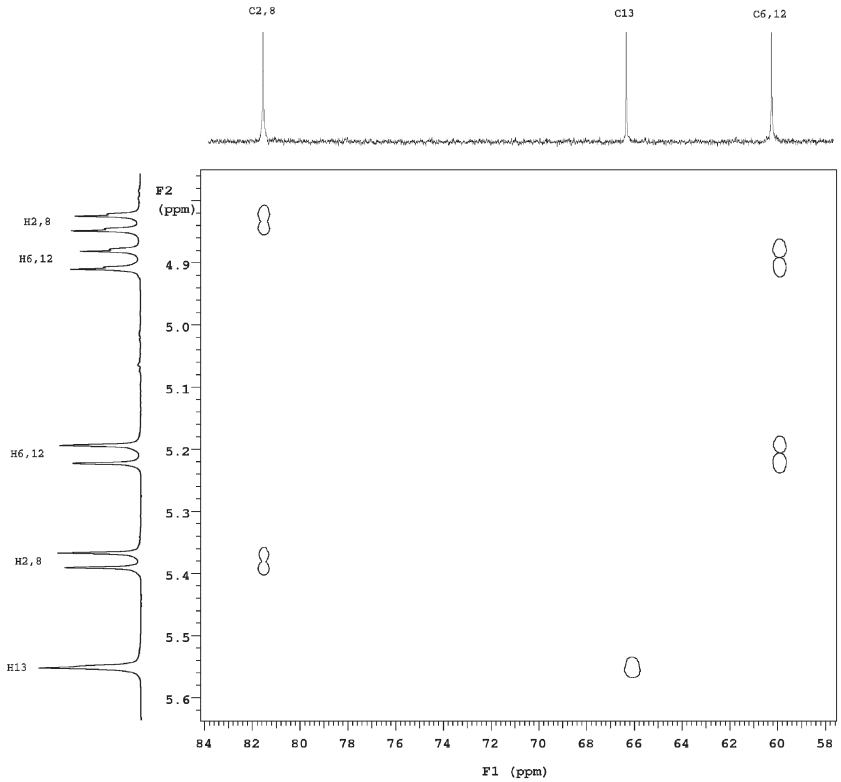


Figure 1. 2D HSQC spectrum of octahydro-5H,12H-4,11-methano-1H,7H-bis[1,2,5]oxadiazolo[3,4-d:3′,4′-*j*][1,7,3,9]dioxadiazacyclododecine at 500 MHz.

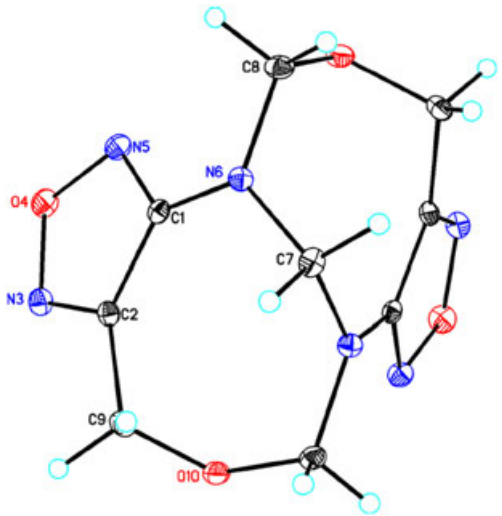


Figure 2. Structure of octahydro-5H,12H-4,11-methano-1H,7H-bis [1,2,5]oxadiazolo [3,4-d:3',4'-j] [1,7,3,9] dioxadiazacyclododecine, **9**, as determined by X-ray diffraction, displacement ellipsoids are at the 50% level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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): δ = 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): δ = 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-hydroxymethyl[1,2,5]oxadiazole, 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 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.

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	$-8 \le h \le 8$, $-9 \le k \le 9$, $-37 \le l \le 37$
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.$Å^{-3}$

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.

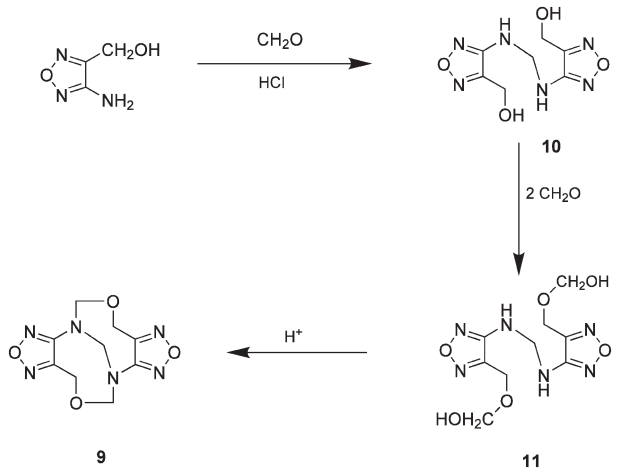
Single-crystal X-ray diffraction analysis of 9. A clear colorless crystal of dimensions 1.00 × 0.70 × 0.70 mm^2 was mounted on a MiteGen MicroMesh using a small amount of Cargille Immersion Oil. Data were collected on a Bruker three-circle platform diffractometer equipped with a SMART APEX II CCD detector. The crystal was irradiated using graphite monochromated MoK_α 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 from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif."

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



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