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Two previously unknown thienopyridopyridazine ring systems, thieno[2',3':5,6]pyrido[2,3-*d*]pyridazine-5,8,9(4*H*,6*H*,7*H*)-trione (**4**) and thieno[3',2':5,6]pyrido[2,3-*d*]pyridazine-4,5,8(6*H*,7*H*,9*H*)-trione (**10**) were synthesized and their chlorination reactions with phosphorus oxychloride were investigated.

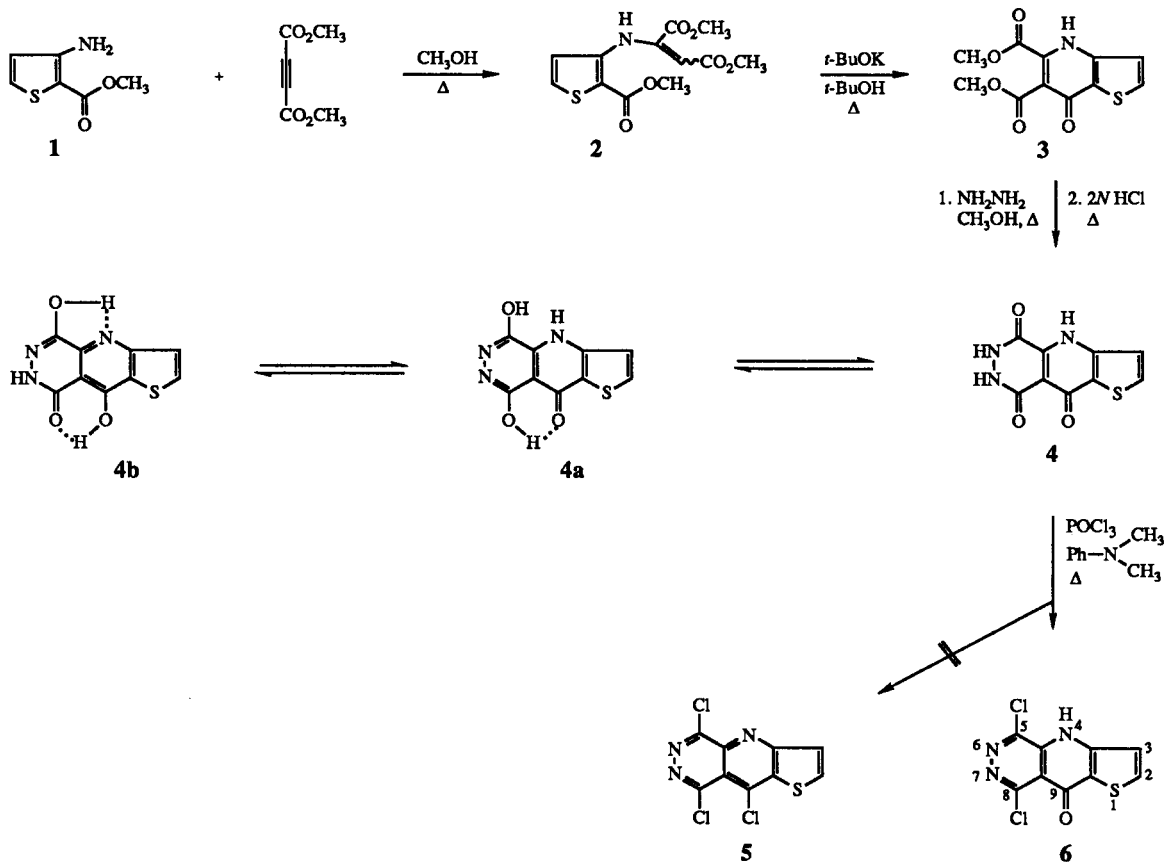
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We have been interested in the synthesis of novel heterocycles containing pyridazine rings [3] and thiophene rings in order to search for new pharmacologically or biologically active compounds [4] and to study their nmr properties [5,6]. The aminothiophenes can be converted to other thiophene-fused heterocycles such as thianaphthenes, thienopyrroles, thienothiazoles, thienoisothiazoles, thienopyrimidines, thienopyridines, thienodiazepines [7], thienofurans, and thienothiophenes [8]. In a search of the literature it is surprising that thienopyridopyridazines have been ignored. In this communication we describe the synthesis of two novel thienopyridopyridazines.

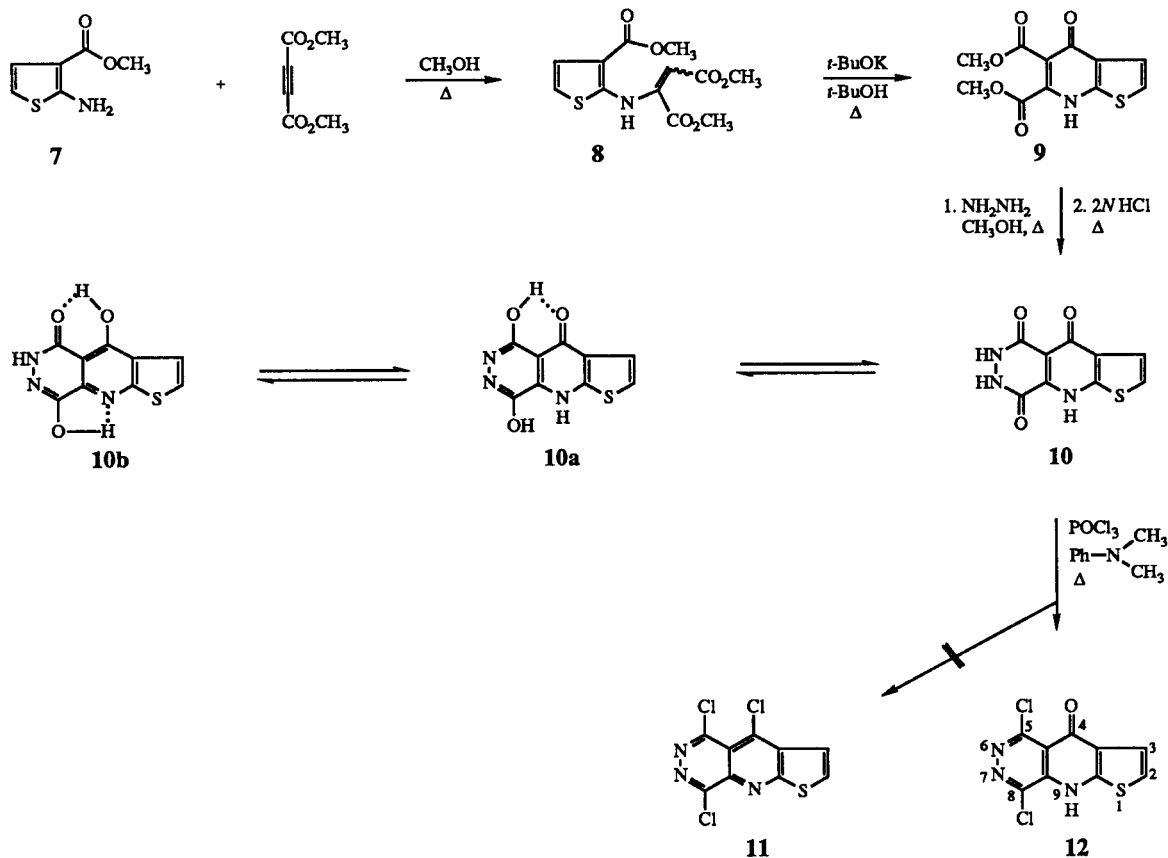
A previous report [9] has shown that a thienopyridine

containing appropriate functionalities can be synthesized in modest yield. Thus, methyl 3-aminothiophene-2-carboxylate (**1**) was heated in methanol with dimethyl acetylenedicarboxylate to afford triester **2** in 62% yield. Cyclization of **2** by heating at reflux (83°) in *t*-butyl alcohol with potassium *t*-butoxide as the catalyst provided dimethyl 7-oxo-4,7-dihydrothieno[3,2-*b*]pyridine-5,6-dicarboxylate (**3**) in 45% yield. When diester **3** was heated with hydrazine in methanol followed by heating with 2*N* hydrochloric acid, a new ring system, thieno[2',3':5,6]pyrido[2,3-*d*]pyridazine-5,8,9(4*H*,6*H*,7*H*)-trione (**4**), was obtained in 87% yield (Scheme I). The trione **4** in the solid state may exist in its tautomeric forms **4a** and **4b** shown in Scheme I as indicat-

Scheme I



Scheme II



ed by its ir spectrum which showed one carbonyl stretching vibration at  $1627 \text{ cm}^{-1}$  and a broad absorption between  $3300$  and  $2800 \text{ cm}^{-1}$ . The carbonyl stretching band was shifted to a significantly lower frequency in the solid state as a result of intramolecular hydrogen bonding.

It was anticipated that **4** would react with phosphorus oxychloride and *N,N*-dimethylaniline to afford the trichloro compound **5**. However, heating **4** with phosphorus oxychloride and *N,N*-dimethylaniline at  $100\text{--}110^\circ$  for three hours provided 5,8-dichlorothieno[2',3':5,6]pyrido[2,3-*d*]pyridazin-9(4*H*)-one (**6**) in 35% yield. The structure of **6** was confirmed by its infrared spectrum as well as by elemental analysis. That the carbonyl stretching band shifted to a higher frequency at  $1653 \text{ cm}^{-1}$  in comparison to **4** is attributed to the lack of intramolecular hydrogen bonding. The high resolution mass spectrum illustrated the fragmentation sequence  $(\text{M-N}_2)^+$  then  $(\text{M-CO})^+$  which further confirms the structure of **6**.

Likewise, methyl 2-aminothiophene-3-carboxylate (**7**) [10-12], prepared by reacting 1,4-dithiane-2,5-diol and methyl cyanoacetate catalyzed by triethylamine, was allowed to undergo a Michael addition with dimethyl acetylenedicarboxylate to afford triester **8** in 26% yield. Cyclization of triester **8** [9] was effected by refluxing in *t*-butyl

alcohol with potassium *t*-butoxide as the condensing agent to give dimethyl 4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5,6-dicarboxylate (**9**) in 29% yield. The reaction of **9** with methanolic hydrazine followed by heating with 2*N* hydrochloric acid provided a new ring system, thieno[3',2':5,6]pyrido[2,3-*d*]pyridazine-4,5,8(6*H*,7*H*,9*H*)-trione (**10**), in 90% yield. Similar to **4**, **10** may exist in its tautomeric forms **10a** and **10b** shown in Scheme II as supported by its infrared spectrum which showed one carbonyl stretching band at  $1648 \text{ cm}^{-1}$  and a broad absorption band between  $3300$  and  $2800 \text{ cm}^{-1}$ . Phosphorus oxychloride chlorination of **10** gave 5,8-dichlorothieno[3',2':5,6]pyrido[2,3-*d*]pyridazin-4(9*H*)-one in 27% yield. The trichloro derivative was not obtained. The structure of **12** was based on its elemental analyses and spectroscopic properties.

#### EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded on a Beckman FT 1100 spectrometer as potassium bromide pellets and frequencies are expressed in  $\text{cm}^{-1}$ . The  $^1\text{H-nmr}$  spectra were obtained on a JEOL FX-90Q spectrometer in the solvent indicated with TMS as the internal standard and chemical shifts are reported in ppm ( $\delta$ ) and J values are in Hz. Silica gel (70-230

mesh) for column chromatography was obtained from Aldrich Chemical Co. Inc. Elemental analyses were performed by M-H-W laboratories, Phoenix, Arizona. The electron impact mass spectra were acquired by the Midwest Center for Mass Spectrometry at the University of Nebraska-Lincoln, using a Kratos MS-50 mass spectrometer which has Nier-Johnson geometry.

Dimethyl 2-(2'-Methoxycarbonyl-3'-thienylamino)-2-butenedioate (2).

A mixture of 12.60 g (80.16 mmoles) of methyl 3-aminothiophene-2-carboxylate (**1**) and 18.30 g (128.7 mmoles) of dimethyl acetylenedicarboxylate in 220 ml of *t*-butyl alcohol was heated under reflux for 16 hours. The solvent was removed under reduced pressure and the residue was recrystallized from cyclohexane to afford 14.87 g (62%) of triester **2** as yellow needles, mp 83-85°; ir (potassium bromide): 3191 (NH stretching), 3032 (aromatic CH stretching), 2990, 2952, 2849 (aliphatic CH stretching), 1736, 1689, 1682 (C=O stretching), 1299, 1160, 1037 (C-O stretching); <sup>1</sup>H-nmr (deuteriochloroform): δ 3.78 (s, 3H, OCH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 5.50 (s, 1H, vinyl H), 6.49 (d, J<sub>4,5</sub> = 5.6 Hz, 1H, H-4), 7.34 (d, J<sub>4,5</sub> = 5.6 Hz, 1H, H-5), 11.23 (br s, 1H, NH).

*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>6</sub>S: C, 48.15; H, 4.38; N, 4.68; S, 10.71. Found: C, 48.01; H, 4.34; N, 4.70; S, 10.66.

Dimethyl 7-Oxo-4,7-dihydrothieno[3,2-*b*]pyridine-5,6-dicarboxylate (3).

A warmed solution of 3.25 g (10.86 mmoles) of triester **2** in 50 ml of *t*-butyl alcohol was added dropwise to 15 ml of *t*-butyl alcohol containing 1.65 g (14.00 mmoles, 95% purity) of potassium *t*-butoxide. The resulting mixture was heated under reflux for 3 hours. After cooling, the mixture was evaporated to dryness *in vacuo*. To the remaining solid residue a mixture of ice-water (ca. 100 ml) was added with stirring. The solution was acidified with 20 ml of 1*N* hydrochloric acid. The solution was extracted with dichloromethane (3 x 100 ml). The combined organic extracts were washed with water (100 ml) and dried over anhydrous magnesium sulfate. After filtration the solution was evaporated to dryness *in vacuo* and the residual solid was recrystallized from benzene to yield 1.31 g (45%) of diester **3** as colorless granules, mp 172-174°; ir (potassium bromide): 3090 (aromatic CH stretching), 2954, 2895, 2857 (aliphatic CH stretching), 1743, 1738 (C=O stretching), 1376 (CH bending of CH<sub>3</sub>), 1288, 1124 (C-O stretching); <sup>1</sup>H-nmr (deuteriochloroform): δ 4.00 (s, 6H, OCH<sub>3</sub>), 7.55 (d, J<sub>2,3</sub> = 5.5 Hz, 1H, H-3), 7.93 (d, J<sub>2,3</sub> = 5.5 Hz, 1H, H-2), 12.07 (s, 1H, NH).

*Anal.* Calcd. for C<sub>11</sub>H<sub>9</sub>NO<sub>5</sub>S: C, 49.43; H, 3.39; N, 5.24; S, 12.00. Found: C, 49.30; H, 3.29; N, 5.13; S, 11.78.

Thieno[2',3':5,6]pyrido[2,3-*d*]pyridazine-5,8,9(4*H*,6*H*,7*H*)-trione (4).

To a solution of 1.38 g (5.16 mmoles) of diester **3** in 50 ml of methanol was added 2.00 g (62.4 mmoles) of 85% hydrazine hydrate and the solution was heated under reflux for 72 hours. After cooling the solid was collected by filtration and washed with water, then with methanol. The solid was suspended in 35 ml of water with heating and acidified to pH 3 with 2*N* hydrochloric acid solution. The acidified mixture was heated under reflux for 4 hours. The solid was collected by filtration after cooling, washed with water, then methanol, and dried to afford 1.06 g (87%) of **4** as an off-white powder, mp > 300°; ir (potassium bro-

mid): 3178 (NH stretching), 3086 (aromatic CH stretching), 1628 (C=O stretching); <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ 7.56 (d, J<sub>2,3</sub> = 5.3 Hz, 1H, H-3), 8.31 (d, J<sub>2,3</sub> = 5.3 Hz, 1H, H-2), 12.06 (br s, 3H, NH); ms: m/z (% relative intensity) 237 (M+2)<sup>+</sup> (7), 236 (M+1)<sup>+</sup> (13), 235 (M)<sup>+</sup> (100), 207 (M-CO)<sup>+</sup> (5), 177 (8); hrms: m/z measured 235.0052 (C<sub>9</sub>H<sub>5</sub>N<sub>3</sub>O<sub>3</sub>S requires 235.0052).

*Anal.* Calcd. for C<sub>9</sub>H<sub>5</sub>N<sub>3</sub>O<sub>3</sub>S: C, 45.95; H, 2.14; N, 17.86; S, 13.63. Found: C, 45.88; H, 2.35; N, 17.83; S, 13.84.

5,8-Dichlorothieno[2',3':5,6]pyrido[2,3-*d*]pyridazin-9(4*H*)-one (6).

A mixture of 0.86 g (3.66 mmoles) of **4**, 20 ml of phosphorus oxychloride, and 1.60 g (13.20 mmoles) of *N,N*-dimethylaniline was heated at 100° for 3 hours. After cooling, the mixture was evaporated to dryness *in vacuo*. The purple solid was poured into ca. 120 ml of ice-water. The solid was collected by filtration, washed with water and air dried. The solid was recrystallized from an ethanol-benzene mixture (5:4) to afford 0.35 g (35%) of **6** as short pale yellow needles, mp > 300°; ir (potassium bromide): 3168 (NH stretching), 3086 (aromatic CH stretching), 1664 (C=O stretching); <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ 7.91 (d, J<sub>2,3</sub> = 5.5 Hz, 1H, H-3), 8.69 (d, J<sub>2,3</sub> = 5.5 Hz, 1H, H-2), 12.94 (br s, 1H, NH); ms: m/z (% relative intensity) 275 (M+4)<sup>+</sup> (14), 273 (M+2)<sup>+</sup> (67), 272 (M+1)<sup>+</sup> (11), 271 (M)<sup>+</sup> (100), 243 (M-N<sub>2</sub>)<sup>+</sup> (27), 215 (14), 182 (18), 180 (42); hrms: m/z measured 270.9374 (C<sub>9</sub>H<sub>3</sub>Cl<sub>2</sub>N<sub>3</sub>OS requires 270.9374).

*Anal.* Calcd. for C<sub>9</sub>H<sub>3</sub>Cl<sub>2</sub>N<sub>3</sub>OS: C, 39.72; H, 1.11; N, 15.44; S, 11.78. Found: C, 39.93; H, 1.02; N, 15.58; S, 11.60.

Dimethyl 2-(3'-Methoxycarbonyl-2'-thienylamino)-2-butenedioate (8).

A mixture of 0.62 g (3.94 mmoles) of methyl 2-aminothiophene-3-carboxylate (**7**) and 0.70 g (4.93 mmoles) of dimethyl acetylenedicarboxylate in 15 ml of *t*-butyl alcohol was heated under reflux for 60 hours. The solution was evaporated to dryness *in vacuo*. The residue was dissolved in 2 ml of dichloromethane and column chromatographed eluting with cyclohexane-ethyl acetate (8:1) to recover 0.11 g of starting material. Further elution provided 0.25 g (26%) of the triester **8** as yellow plates upon recrystallization from petroleum ether (bp, 50-110°), mp 92-94°; ir (potassium bromide): 3191 (NH stretching), 2998, 2949, 2846 (aliphatic CH stretching), 1738, 1725, 1687 (C=O stretching), 1304, 1137, 1026 (C-O stretching); <sup>1</sup>H-nmr (deuteriochloroform): δ 3.79 (s, 3H, OCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 3.90 (s, 3H, OCH<sub>3</sub>), 5.52 (s, 1H, vinyl H), 6.55 (d, J<sub>4,5</sub> = 5.6 Hz, 1H, H-4), 7.16 (d, J<sub>4,5</sub> = 5.6 Hz, 1H, H-5), 11.65 (br s, 1H, NH).

*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>6</sub>S: C, 48.15; H, 4.38; N, 4.68; S, 10.71. Found: C, 48.35; H, 4.52; N, 4.73; S, 10.66.

Dimethyl 4-Oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5,6-dicarboxylate (9).

A warmed solution of 2.67 g (8.92 mmoles) of triester **8** in 50 ml of *t*-butyl alcohol was added dropwise to 15 ml of *t*-butyl alcohol containing 1.25 g (10.58 mmoles, 95% purity) of potassium *t*-butoxide and was treated as described [9]. The diester **9** was obtained in 29% yield (0.70 g) as colorless prisms after recrystallization from cyclohexane, mp 101-103°, lit [9] 120-121°; ir (potassium bromide): 3078 (aromatic CH stretching), 2957, 2854 (aliphatic CH stretching), 1736, 1689 (C=O stretching), 1386 (CH bending of CH<sub>3</sub>), 1299, 1152 (C-O stretching); <sup>1</sup>H-nmr (deuteriochloroform): δ 3.99 (s, 6H, OCH<sub>3</sub>), 7.51 (s, 2H, H-2 and H-3), 12.02 (s, 1H, NH).

*Anal.* Calcd. for C<sub>11</sub>H<sub>9</sub>NO<sub>5</sub>S: C, 49.43; H, 3.39; N, 5.24; S, 12.00. Found: C, 49.67; H, 3.55; N, 5.24; S, 11.89.

Thieno[3',2':5,6]pyrido[2,3-*d*]pyridazine-4,5,8(6*H*,7*H*,9*H*)-trione (10).

A solution of 0.65 g (2.43 mmoles) of diester **9** in 25 ml of methanol containing 2.0 g (62.4 mmoles) of 85% hydrazine hydrate was heated under reflux for 60 hours. After cooling the solution was evaporated to dryness *in vacuo*. The residual solid was washed with methanol and dried. To the solid 15 ml of water was added and the mixture was adjusted to pH 3 with 2*N* hydrochloric acid. The resulting mixture was heated under reflux for 3 hours. After cooling the solid was collected by filtration and washed with water until the washings were neutral, then washed with methanol, and dried to give 0.51 g (89%) of **10** as an off-white solid, mp >300°; ir (potassium bromide): 3150 (NH stretching), 3068 (aromatic CH stretching), 1648 (C=O stretching); <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): 9.0° δ 7.62 (d, J<sub>2,3</sub> = 5.9 Hz, 1H, H-3), 7.71 (d, J<sub>2,3</sub> = 5.9 Hz, 1H, H-2).

*Anal.* Calcd. for C<sub>9</sub>H<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S: C, 45.95; H, 2.14; N, 17.86; S, 13.63. Found: C, 46.09; H, 2.04; N, 17.78; S, 13.47.

5,8-Dichlorothieno[3',2':5,6]pyrido[2,3-*d*]pyridazin-4(9*H*)-one (12).

A mixture of 0.48 g (2.04 mmoles) of **10**, 12 ml of phosphorus oxychloride, and 0.9 g (7.43 mmoles) of *N,N*-dimethylaniline was heated at 100° for 3 hours. After cooling the mixture was evaporated to dryness *in vacuo*. The purple residual solid was added to 100 ml of ice-water with stirring. The solid was collected by filtration, washed with water, and air dried. The solid was dissolved in boiling *N,N*-dimethylformamide (ca. 10 ml) and 0.5 g of silica gel was added, then the mixture was evaporated to dryness *in vacuo*. The mixture then was chromatographed on a silica gel column eluting with a dichloromethane-ethyl acetate mixture (20:1) to give 0.15 g (27%) of **12** as yellow needles upon recrystallization

from a benzene-ethanol mixture (1:1), mp >300°; ir (potassium bromide): 3165 (NH stretching), 3083 (aromatic CH stretching), 1661 (C=O stretching); <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ 7.74 (d, J<sub>2,3</sub> = 6.2 Hz, 1H, H-3), 8.33 (d, J<sub>2,3</sub> = 6.2 Hz, 1H, H-2), 12.69 (br s, 1H, NH), ms: m/z (% relative intensity) 273 (M+2)<sup>+</sup> (2), 271 (M)<sup>+</sup> (3), 180 (2), 149 (7), 137 (16), 95 (15), 81 (52), 69 (100), 55 (26); hrms: m/z measured 270.9366 (C<sub>9</sub>H<sub>3</sub>Cl<sub>2</sub>N<sub>3</sub>OS requires 270.9374).

*Anal.* Calcd. for C<sub>9</sub>H<sub>3</sub>Cl<sub>2</sub>N<sub>3</sub>OS: C, 39.72; H, 1.11; N, 15.44. Found: C, 39.91; H, 1.00; N, 15.39.

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