Synthesis of [1,2,5]Selena(or thia)diazolo[3,4-*e*][1,4]diazepines, [1,2,5]Selena(or thia)diazolo[3,4-*e*][1,4]oxazepines and [1,2,5]Selena(or thia)diazolo[3,4-*c*][1,2,6]thiadiazines

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Novel heterocycles [1,2,5]selenadiazolo[3,4-*e*][1,4]diazepines **3a-c**, [1,2,5]thiadiazolo[3,4-*e*]-[1,4]diazepines **7a-c**, [1,2,5]selenadiazolo[3,4-*e*][1,4]oxaepines **4a,b**, [1,2,5]thiadiazolo[3,4-*e*]-[1,4]oxazepines **9a-c** and [1,2,5]selena(or thia)diazolo[3,4-*c*][1,2,6]thiadiazines **10a,b** were synthesized starting form 4,6-dimethyl[1,2,5]selenadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **1** or 4,6-dimethyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **5**.

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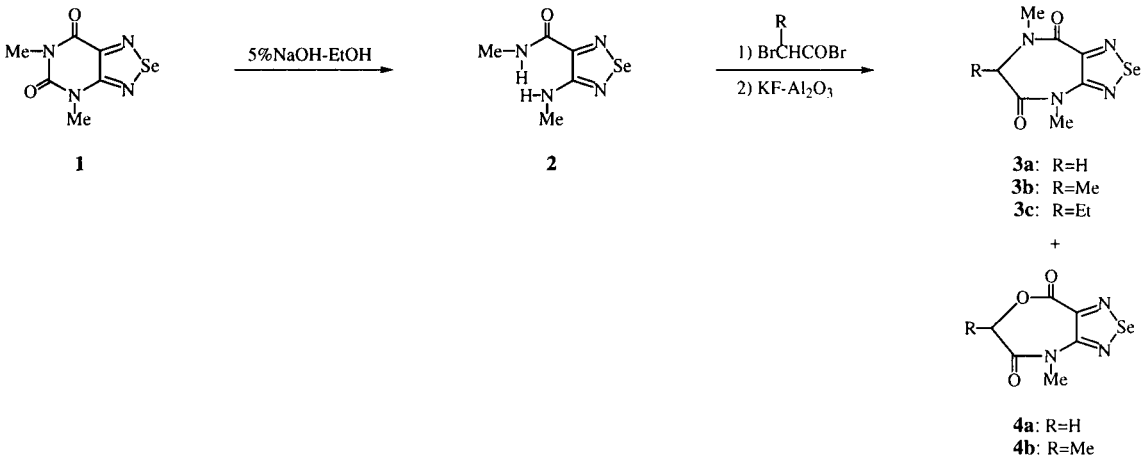
The [1,4]diazepine moiety has been known as useful function for physiological activities and many benzo[1,4]-diazepines having psychotropic or antitumor activities have been reported [1]. Previously we synthesized imidazolo-[4,5-*e*][1,4]diazepines [2] and isoselenazolo(or isothia-zolo)[4,3-*e*][1,4]diazepines [3]. In connection with that work we were interested to synthesize the novel heterocycle, [1,2,5]selena(or thia)diazolo[3,4-*e*][1,4]diazepines. Furthermore we investigated the synthesis of [1,2,5]selena(or thia)diazolo[3,4-*e*][1,4]oxazepines and [1,2,5]selena(or thia)diazolo[3,4-*c*][1,2,6]thiadiazines, which are also previously undescribed classes of heterocycles [4]. We report here syntheses of these ring systems.

Hydrolysis of 4,6-dimethyl[1,2,5]selenadiazolo[3,4-*d*]-pyrimidine-5,7(4*H*,6*H*)-dione **1** [5] with 5% aqueous sodium hydroxide in ethanol gave 4-methylamino-3-(*N*-methylcarbamoyl)[1,2,5]selenadiazole **2** in a moderate yield. Acylation of **2** with bromoacetyl bromide, 2-bro-mopropionyl bromide or 2-bromobutyryl bromide fol-lowed by cyclization in the presence of potassium fluo-ride-aluminum oxide [6] gave 6-alkyl-4,7-dimethyl-5,8-dioxo-4,5,7,8-tetrahydro-6*H*-[1,2,5]selenadiazolo[3,4-*e*]-[1,4]diazepines **3a-c** accompanied by a small amount of 6-alkyl-4,5,7,8-tetrahydro-4-methyl-6*H*,8*H*-[1,2,5]selena-diazolo[3,4-*e*][1,4]oxazepines **4a-b**. When the acylated intermediates were allowed to stand in a moist atmos-phere, tar like substances which contain compounds **4** were obtained. The structural confirmation of **4** was car-ried out by mass, ^{1}H nmr and ir spectra. Moreover, we previously observed similar transformation of 4-[*N*-(α-halogenoacyl)-*N*-methylamino]-1-methyl-5-methylcar-bamoylimidazoles to 7-alkyl-1,4-dimethyl-5,8-dioxo-1,4,5,8-tetrahydro-6*H*-imidazolo[4,5-*e*][1,4]oxazepines by refluxing in water [2].

As for the synthesis of 6-alkyl-4,7-dimethyl-5,8-dioxo-4,5,7,8-tetrahydro-6*H*-[1,2,5]thiadiazolo[3,4-*e*][1,4]diaze-pines **7a-c**, 4-methylamino-3-(*N*-methylcarbamoyl)-[1,2,5]thiadiazole **6** [7] which derived from 4,6-dimethyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **5** [8] was treated by a similar method as for the preparation

Scheme 1



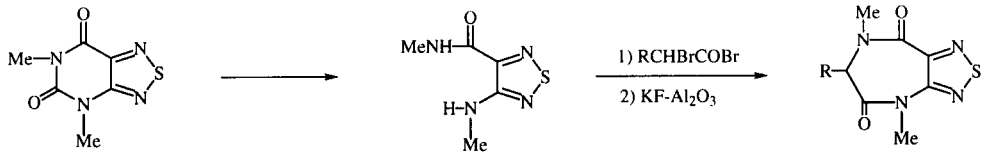
1 **2**

3a: R=H
3b: R=Me
3c: R=Et

+

4a: R=H
4b: R=Me

Scheme 2



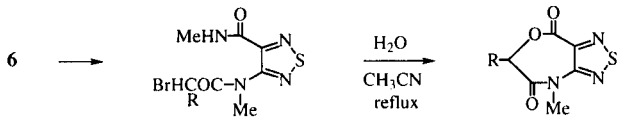
5 **6**

7a: R=H
7b: R=Me
7c: R=Et

of **3**. The yields of **7a-c** decreased when the 6-substituted alkyl group becomes bulky. [1,2,5]Thiadiazolo[3,4-*e*]-[1,4]oxazepines were not observed as by-products. However, when 4-[*N*-α-bromo-α-alkylacetyl-*N*-methylamino-3-methylcarbamoyl[1,2,5]thiadiazoles **8a-c** were refluxed for 3 hours in acetonitrile in the presence of water, [1,2,5]thiadiazolo[3,4-*e*][1,4]oxazepines **9a-c** were obtained in good yields.

Previously we synthesized imidazolo[4,5-*c*][1,2,6]thiadiazines in the hope of having more potent vasodilating activity and some of them showed excellent activity as vasodilators. Thus, we attempted the synthesis of 6,7-dihydro-4,6-dimethyl-5,7-dioxo-4-methyl-4*H*-[1,2,5]selena(or thia)diazolo[3,4-*c*][1,2,6]thiadiazine 5-oxides **10a,b** by the reaction of **2** with thionyl chloride. Although the yield of **10a** was very poor (12%), compound **10b** was obtained in excellent yield (87%). [1,2,5]Selena(or thia)diazolo[3,4-*c*]-[1,2,6]thiadiazines are also novel heterocycles.

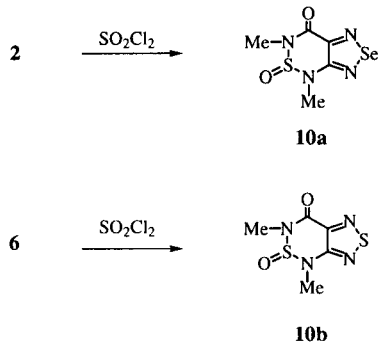
Scheme 3



8

9a: R=H
9b: R=Me
9c: R=Et

Scheme 4



EXPERIMENTAL

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The infrared spectra were measured with a JASCO IR-180 spectrophotometer. Mass spectra were measured with a JEOL JMS-DX 300 mass spectrometer. Proton nuclear magnetic resonance spectra were recorded with a JEOL GSX-400 spectrometer using tetramethylsilane as internal standard. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet.

4-Methylamino-3-(*N*-methylcarbamoyl)[1,2,5]selenadiazole (**2**).

To a solution of **1** (1.4 g) in refluxing ethanol (100 ml) was added 5% aqueous sodium hydroxide (20 ml). The mixture was heated under reflux for 3 hours. The solvent was distilled and water was added to the residue, which was neutralized with 10% hydrochoric acid and was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the chloroform was distilled. The residue was purified by silica gel column chromatography eluting with a mixture of hexane-ethyl acetate (3:1). The title compound **2** was obtained in 79% yield, mp 153-154°; ^{1}H nmr (deuteriochloroform): δ 2.96 (3H, d, J = 4 Hz, C*H*$_3$NH), 3.08 (3H, d, J = 4 Hz, C*H*$_3$NHCO-), 3.70 (1H, bs, CH$_3$N*H*), 7.70 (1H, bs, CH$_3$N*H*CO-); ir (potassium bromide): ν max 3340 cm^{-1} (NH); ms: m/z 220 (M$^+$).

Anal. Calcd. for $C_5H_8N_4OSe$: C, 27.41; H, 3.68; N, 25.57. Found: C, 27.42; H, 3.41; N, 25.55.

General Procedure for the Synthesis of 6-Alkyl-4,7-dimethyl-5,8-dioxo-4,5,7,8-tetrahydro-6*H*-[1,2,5]selenadiazolo[3,4-*e*]-[1,4]diazepines **3a-c** and 6-Alkyl-4,5-dihydro-5,8-dioxo-4-methyl-6*H*,8*H*-[1,2,5]selenadiazolo[3,4-*e*][1,4]oxazepines **4a,b**.

To a solution of **2** (220 mg, 1.0 mmole) in dry dichloromethane (25 ml) was added potassium carbonate (552 mg, 4.0 mmoles) and bromoacetyl bromide, 2-bromopropionyl bromide or 2-bromobutyryl bromide (1.5 mmoles). The mixture was stirred for one hour at room temperature. Water was added to the reaction

mixture and the mixture was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled to give resinous oil, which was dissolved in dry acetonitrile (25 ml). Potassium fluoride-aluminium oxide (672 mg) was added and the mixture was stirred for eight hours at room temperature. Potassium fluoride-aluminium oxide was filtered and the filtrate was evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with a mixture of hexane-ethyl acetate (1:5) to give **3a-c** and **4a,b**.

4,7-Dimethyl-5,8-dioxo-4,5,7,8-tetahydro-6*H*-[1,2,5]selenadiazolo[3,4-*e*][1,4]diazepine (**3a**).

This compound was obtained in 76% yield a colorless prisms, mp 242-243° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 3.28 (3H, s, N-CH_3), 3.50 (3H, s, N-CH_3), 4.00 (2H, s, -CH_2-); ir (potassium bromide): ν max 1640-1690 cm^{-1} (amide C=O); ms: m/z 260 (M^+).

Anal. Calcd. for $C_7H_8N_4O_2Se$: C, 32.45; H, 3.11; N, 21.62. Found: C, 32.40; H, 3.11; N, 21.34.

5,8-Dioxo-4,6,7-trimethyl-4,5,7,8-tetrahydro-6*H*-[1,2,5]selenadiazolo[3,4-*e*][1,4]diazepine (**3b**).

This compound was obtained in 64% yield as colorless prisms, mp 129-131° (from ethanol); ms: m/z 274 (M^+).

Anal. Calcd. for $C_8H_{10}N_4O_2Se$: C, 35.18; H, 3.69; N, 20.51. Found: C, 34.97; H, 3.81; N, 20.33.

4,7-Dimethyl-5,8-dioxo-6-ethyl-4,5,7,8-tetrahydro-6*H*-[1,2,5]selenadiazolo[3,4-*e*][1,4]diazepine (**3c**).

This compound was obtained in 22% yield as colorless prisms, mp 66-68° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 0.99 (3H, t, J = 7 Hz, *C*H_3CH$_2$-), 2.17 (2H, m, CH$_3$*C*H_2-), 3.11 (3H, s, N-CH_3), 3.52 (3H, s, N-CH_3), 3.91 (1H, t, J = 7 Hz, CH$_3$CH$_2$*CH*-); ms: m/z 288 (M^+).

Anal. Calcd. for $C_9H_{12}N_4O_2Se$: C, 37.64; H, 4.21; N, 19.51. Found: C, 37.48; H, 4.50; N, 19.34.

4,5-Dihydro-5,8-dioxo-4-methyl-6*H*,8*H*-[1,2,5]selenadiazolo[3,4-*e*][1,4]oxazepine (**4a**).

This compound was obtained in 12% yield as colorless prisms, mp 174-176° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 3.57 (3H, s, N-CH_3), 4.84 (2H, s, -CH_2-); ir (potassium bromide): ν max 1760 cm^{-1} (-O-CO-), 1650-1710 cm^{-1} (-CON-); ms: m/z 247 (M^+).

Anal. Calcd. for $C_6H_5N_3O_3Se$: C, 29.29; H, 2.05; N, 17.08. Found: C, 29.23; H, 2.06; 16.80.

4,5-Dihydro-4,6-dimethyl-5,8-dioxo-6*H*,8*H*-[1,2,5]selenadiazolo[3,4-*e*][1,4]oxazepine (**4b**).

This compound was obtained in 8% yield as colorless prisms, mp 156-158° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.68 (3H, d, J = 7 Hz, *C*H_3CH-), 3.56 (3H, s, N-CH_3), 4.96 (1H, q, J = 7 Hz, CH$_3$*CH*-); ir (potassium bromide): ν max 1740 cm^{-1} (-O-CO-); ms: m/z 261 (M^+).

Anal. Calcd. for $C_7H_7N_3O_3Se$: C, 32.32; H, 2.71; N, 16.15. Found: C, 32.40; H, 2.84; N, 15.98.

General Procedure for the Synthesis of 6-Alkyl-4,7-dimethyl-5,8-dioxo-4,5,7,8-tetrahydro-6*H*-[1,2,5]thiadiazolo[3,4-*e*]-[1,4]diazepines **7a-c**.

To a solution of **6** (200 mg, 1.0 mmole) in dry dichloromethane (20 ml) was added potassium carbonate (640 mg, 5.0 mmoles) and bromoacetyl bromide, 2-bromopropionyl bromide or 2-bromobutyryl bromide (1.5 mmoles). The mixture was stirred for 30 minutes at room temperature. Water was added to the reaction mixture and the mixture was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled to give resinous oil, which was dissolved in dry acetonitrile (25 ml). Potassium fluoride-aluminium oxide (672 mg) was added and the mixture was stirred for two hours at room temperature. Potassium fluoride-aluminum oxide was removed by filtration and the filtrate was evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with a mixture of chloroform-ethyl acetate (3:1).

4,5-Dimethyl-5,8-dioxo-4,5,7,8-tetrahydro-6*H*-[1,2,5]thiadiazolo[3,4-*e*][1,4]diazepine (**7a**).

This compound was obtained in 68% yield as colorless prisms, mp 137-139° (from isopropyl alcohol); ^{1}H nmr (deuteriochloroform): δ 3.31 (3H, s, N-CH_3), 3.35 (3H, s, N-CH_3), 4.05 (2H, s, -CH_2-); ms: m/z 212 (M^+).

Anal. Calcd. for $C_7H_8N_4O_2S$: C, 39.61; H, 3.80; N, 26.40. Found: C, 39.61; H, 3.66; N, 26.78.

5,8-Dioxo-4,6,7-trimethyl-4,5,7,8-tetrahydro-6*H*-[1,2,5]thiadiazolo[3,4-*e*][1,4]diazepine (**7b**).

This compound was obtained in 58% yield as colorless prisms, mp 138-140° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.56 (3H, d, J = 7 Hz, *C*H_3CH-), 3.15 (3H, s, N-CH_3), 3.54 (3H, s, N-CH_3), 4.27 (1H, q, J = 7 Hz, CH$_3$-*CH*-); ms: m/z 226 (M^+).

Anal. Calcd, for $C_8H_{10}N_4O_2S$: C, 42.47; H, 4.45; N, 24.76. Found: C, 42.50; H, 4.31; N, 24.87.

4,7-Dimethyl-5,8-dioxo-6-ethyl-4,5,7,8-tetrahydro-6*H*-[1,2,5]thiadiazolo[3,4-*e*][1,4]diazepine (**7c**).

This compound was obtained in 47% yield as colorless prisms, mp 123-125° (from isopropyl alcohol); ^{1}H nmr (deuteriochloroform): δ 0.93 (3H, t, J = 7 Hz, -CH$_2$*C*H_3), 2.04 (2H, m, -*C*H_2CH$_3$), 3.16 (3H, s, N-CH_3), 3.50 (3H, s, N-CH_3), 3.96 (1H, m, -CH-); ms: m/z 240 (M^+).

Anal. Calcd. for $C_9H_{12}N_4O_2S$: C, 44.99; H, 5.03; N, 23.32. Found: C, 45.00; H, 4.96; N, 23.52.

General Procedure for the Synthesis of 6-Alkyl-4,5-dihydro-5,8-dioxo-4-methyl-6*H*,8*H*-[1,2,5]thiadiazolo[3,4-*e*][1,4]oxazepines **9a-c**.

To a solution of **6** (200 mg) in dichloromethane (20 ml) was added potassium carbonate (460 mg) and bromoacetyl bromide, bromopropionyl bromide or bromobutylryl bromide (1.1 mmoles). The mixture was stirred for thirty minutes at room temperature. Water was added to the reaction mixture, which was extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled to give **8a-c**, which were dissolved in the mixture of acetonitrile (5 ml) and water (0.5 ml) and the solution was refluxed for three hours. The solvent was distilled and the residue was column chromatographed on silica gel eluting with a mixture of *n*-hexane and ethyl acetate (2:1) to give **9a-c**.

4,5-Dihydro-5,8-dioxo-4-methyl-6*H*,8*H*-[1,2,5]thiadiazolo[3,4-*e*]-[1,4]oxazepine (**9a**).

This compound was obtained in 82% yield as colorless prisms, mp 108-110° (from ethanol); ^{1}H nmr (deuteriochloro-

form): δ 3.56 (3H, s, N-CH_3), 4.84 (2H, s, -CH_2-); ir (potassium bromide): ν max 1730 cm^{-1} (CO-O-), 1690 cm^{-1} (N-C=O); ms: m/z 199 (M^+).

Anal. Calcd. for $C_6H_5N_3O_3S$: C, 36.18; H, 2.53; N, 21.11. Found: C, 36.33; H, 2.40; N, 20.80.

4,5-Dihydro-4,6-dimethyl-5,8-dioxo-6*H*,8*H*-[1,2,5]thiadiazolo-[3,4-*e*][1,4]oxazepine (**9b**).

This compound was obtained in 68% yield as colorless prisms, mp 123-125° (from ethanol); ^1H nmr (deuteriochloroform): δ 1.71 (3H, d, J = 7 Hz, CH-CH_3), 3.60 (3H, s, N-CH_3), 4.93 (1H, q, J = 7 Hz, -C*H*CH_3); ir (potassium bromide): ν max 1745 cm^{-1} (CO-O-) , 1700 cm^{-1} (N-C=O); ms: m/z 213 (M^+).

Anal. Calcd. for $C_7H_7N_3O_3S$: C, 39.43; H, 3.31; N, 19.71. Found: C, 39.20; H, 3.21; N, 19.50.

4,5-Dihydro-5,8-dioxo-4-methyl-6-ethyl-6*H*,8*H*-[1,2,5]thiadiazolo[3,4-*e*][1,4]oxazepine (**9c**).

This compound was obtained in 45% yield as colorless prisms, mp 86-87° (from ethanol); ^1H nmr (deuteriochloroform): δ 1.08 (3H, t, J = 7Hz, -CH_2C*H*$_3$), 2.12 (2H, m, -C*H*$_2CH_3$), 3.56 (3H, s, N-CH_3), 4.60 (1H, t, J = 7 Hz, -CH-); ir (potassium bromide): ν max 1742 cm^{-1} (CO-O-), 1700 cm^{-1} (N-CO); ms: m/z 227 (M^+).

Anal. Calcd. for $C_8H_9N_3O_3S$: C, 42.29; H, 3.99; N, 18.50. Found: C, 42.34; H, 4.21; N, 18.76.

6,7-Dihydro-4,6-dimethyl-7-oxo-4-methyl-4*H*-[1,2,5]selenadiazolo[3,4-*c*][1,2,6]thiadiazine 5-Oxide (**10a**).

To a solution of **2** (110 mg) in pyridine (2 ml) was added dropwise thionyl chloride (120 mg) at 0°. The mixture was stirred for one hour at room temperature and was extracted chloroform. The extract was washed with 10% hydrochloric acid and then with water. The organic layer was dried over magnesium sulfate. The solvent was distilled and the resulting crystals were recrystallized from ethanol to give prisms, mp 208-210° in 12% yield; ^1H nmr (deuteriochloroform): δ 3.46 (3H, s, N-CH_3), 3.54 (3H, s, N-CH_3); ir (potassium bromide): ν max 1690 cm^{-1} (amide C=O).

Anal. Calcd. for $C_5H_6N_4O_2Se$; C, 22.65; H, 2.28; N, 21.13. Found: C, 22.89; H, 2.57, N, 21.40.

6,7-Dihydro-4,6-dimethyl-7-oxo-4-methyl-4*H*-[1,2,5]thiadiazolo[3,4-*c*][1,2,6]thiadiazine 5-Oxide (**10b**).

The solution of **6** (86 mg) in pyridine (2 ml) was added dropwise thionyl chloride (89 mg) at 0° and the mixture was treated by the same procedure as for the synthesis of **10a** to give colorless prisms, mp 127-128° (from ethanol) in 87% yield; ^1H nmr (deuteriochloroform): δ 3.47 (3H, s, N-CH_3), 3.56 (3H, s, N-CH_3); ir (potassium bromide): ν max 1690 cm^{-1} (amide C=O).

Anal. Calcd. for $C_5H_6N_4O_2S_2$: C, 27.52; H, 2.77; N, 25.67. Found: C, 27.66; H, 2.70; N, 26.01.

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