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Synthesis of Isoselenazolo- or Isothiazolo[4,3-*e*][1,4]diazepines

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Two novel classes of heterocycles, isoselenazolo[4,3-*e*][1,4]diazepines (**3a—c, g, h, k, l, m**) and isothiazolo[4,3-*e*][1,4]diazepines (**3d—f, i, j, n, o**) were synthesized from 7-oxo-6-phenyl-6*H*-isoselenazolo (or -isothiazolo)[4,3-*d*]pyrimidines (**1a, b**) and 4,6-dimethyl 5,7-dioxo-4,5,6,7-tetrahydro-isoselenazolo (or isothiazolo)[4,3-*d*]pyrimidines (**2a, b**).

Keywords—pyrimidine; isoselenazole; isothiazole; isoselenazolo[4,3-*d*]pyrimidine; isothiazolo[4,3-*d*]pyrimidine; isoselenazolo[4,3-*e*][1,4]diazepine; isothiazolo[4,3-*e*][1,4]diazepine

Previously we reported on the synthesis²⁾ and antitumor activity³⁾ of 7-oxo-6-phenyl-6*H*-isoselenazolo[4,3-*d*]pyrimidine (**1a**). We successively studied the synthesis of 4,6-dimethyl-5,7-dioxo-4,5,6,7-tetrahydro-isoselenazolo (or -isothiazolo)[4,3-*d*]pyrimidine⁴⁾ (**2**). In connection with that work we were interested to synthesize some isoselenazolo (or isothiazolo)[4,3-*e*][1,4]diazepines (**3**), which are previously undescribed classes of heterocycles.⁵⁾ We report here a facile synthesis of **3** from **1** or **2**.

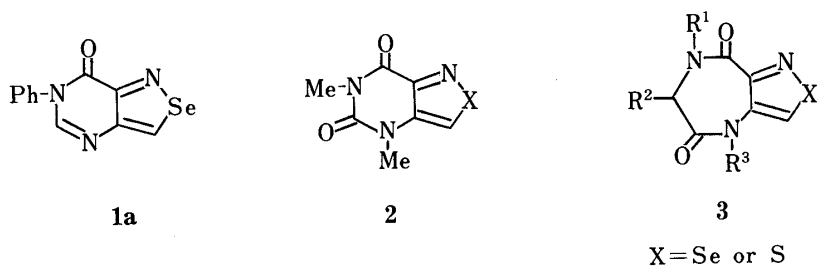


Chart 1

The synthesis of **3a—f** was carried out as illustrated in Chart 2. Synthesis of 7-oxo-6-phenyl-6*H*-isothiazolo[4,3-*d*]pyrimidine (**1b**) and its reaction with malononitrile to give 4-(2,2-dicyanovinyl)amino-3-phenylcarbamoylisothiazole (**4b**) were investigated by us previously.⁶⁾ A similar reaction of **1a** with malononitrile in ethanol in the presence of triethylamine gave 4-(2,2-dicyanovinyl)amino-3-phenylcarbamoylisoselenazole (**4a**) and 6-amino-7-cyano-3-phenyl-3*H*-pyrido[3,2-*d*]pyrimidine-4-one.⁷⁾ Hydrolysis of **4a** or **4b** with hydrochloric acid gave 4-amino-3-phenylcarbamoylisoselenazole (**5a**) or 4-amino-3-phenylcarbamoylisothiazole⁶⁾ (**5b**) quantitatively. Acylation of **5** with bromoacetyl bromide, α -bromopropionyl bromide or α -bromobutyryl bromide in methylene chloride gave 4-(alkylbromoacetyl)amino-3-phenylcarbamoyl-isoselenazoles (or -isothiazoles) (**6a—f**) in 80—90% yields. Successive cyclization of **6a—f** in the presence of sodium ethoxide in ethanol gave the target compounds, 6-alkyl-5,8-dioxo-7-phenyl-4,5,7,8-tetrahydro-6*H*-isoselenazolo (or -isothiazolo)[4,3-*e*][1,4]diazepines (**3a—f**) in 56—83% yields along with a small amount of 4-

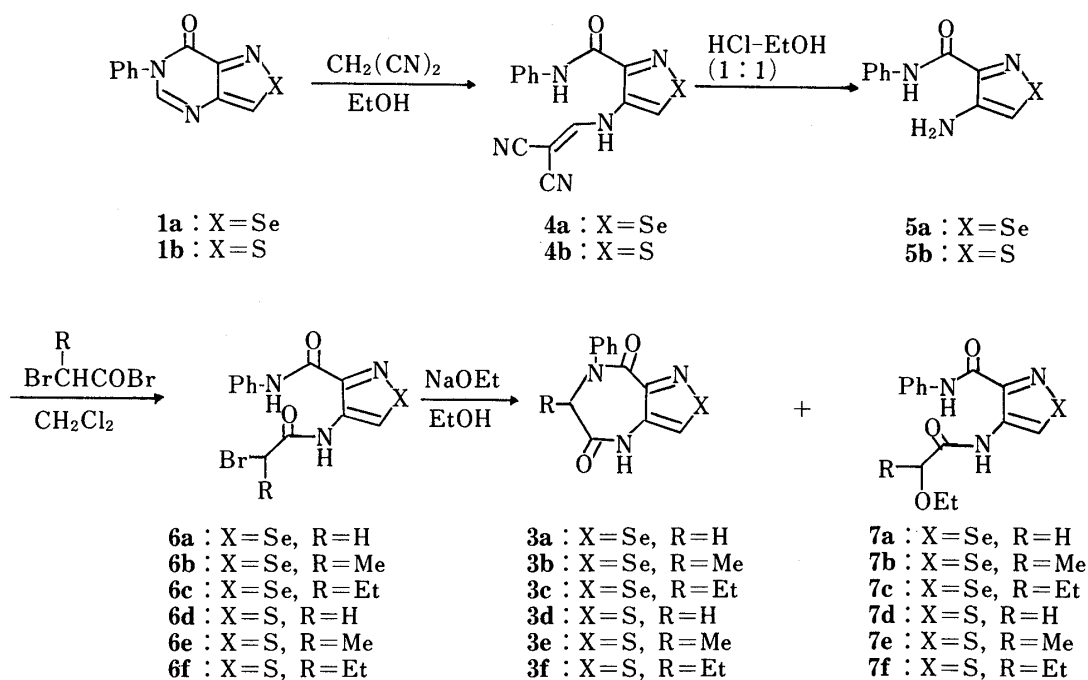


Chart 2

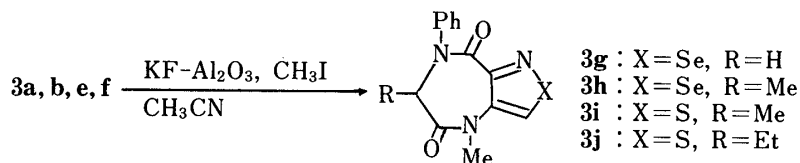


Chart 3

(alkylethoxyacetyl)-amino-3-phenylcarbamoyl-isoselenazoles (or -isothiazoles) (**7a—f**). The yields of **3a—f** decreased as the alkyl groups become bulkier and the yields of the by-products (**7a—f**) increased. The structures of the cyclized compounds were established by their infrared (IR) spectra, proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra, and mass spectra (MS) as well as analytical data.

Methylation of **3a—f** with methyl iodide was carried out in the presence of potassium fluoride-aluminum oxide⁸⁾ as a catalyst in acetonitrile to give **3g—j** in good yields.

For the synthesis of **3k—o**, compounds **2a, b** were used as starting materials as illustrated in Chart 4. We previously observed that the reaction of **2b** with 40% aqueous methylamine gave the pyrimidine ring-opened 4-methylamino-3-methylcarbamoylisothiazole⁶⁾ (**8b**) in 58% yield. Thus we carried out reaction of **2a** with 40% aqueous methylamine in a sealed tube at 120 °C for 4 h to give 4-methylamino-3-methylcarbamoylisoselenazole (**8a**) in 54% yield. Acylation of **8a, b** with α -bromopropionyl bromide or α -bromobutyryl bromide in the presence of potassium carbonate in chloroform gave 4-[*N*-(α -alkyl- α -bromo)acetyl]-*N*-methylamino]-3-methylcarbamoyl-isoselenazoles (or -isothiazoles) (**9a—e**) in 85—90% yields. Our initial attempt to cyclize **9a** in the presence of sodium ethoxide in ethanol gave 4,7-dimethyl-5,8-dioxo-4,5,7,8-tetrahydro-6*H*-isoselenazolo[4,3-*e*][1,4]diazepine (**3k**) in a poor yield. It was found that although this method was successful in the cyclization of **6a—f** to **3a—f**, its application to **9** was ineffective. Therefore we examined bases such as potassium *tert*-butoxide, sodium hydride and potassium fluoride-aluminum oxide. All these bases were better than sodium ethoxide, and potassium fluoride-aluminum oxide was the best reagent

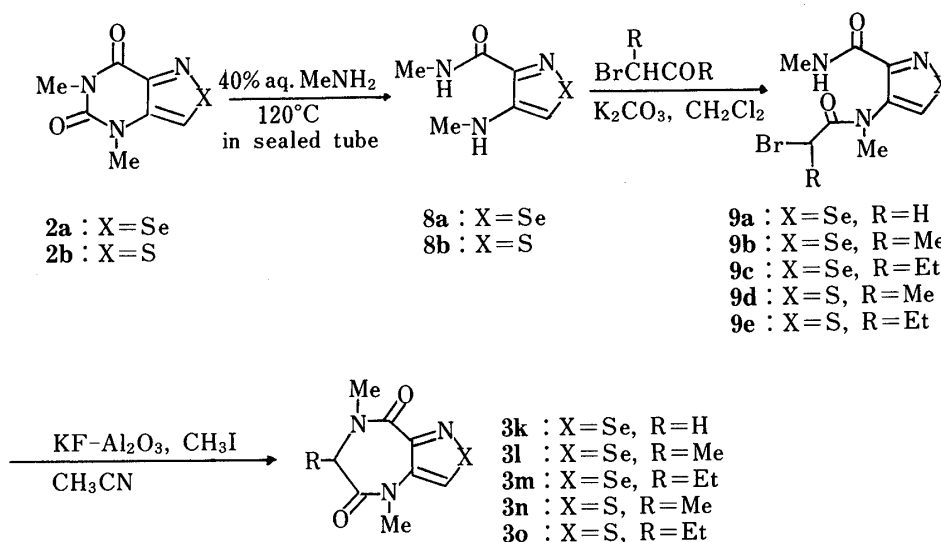


Chart 4

TABLE I. Conditions for Synthesis of **3k**

Solvent	Base	Temp (°C)	Time (h)	Yield (%)
EtOH	EtONa	Reflux	0.5	20
<i>tert</i> -BuOH	<i>tert</i> -BuOK	Reflux	0.5	36
CH ₃ CN	NaH	Reflux	0.5	40
CH ₃ CN	KF-Al ₂ O ₃	Room temp.	1.5	91

(Table I). Thus, the cyclization of **9a—e** in the presence of potassium fluoride–aluminum oxide in acetonitrile proceeded smoothly to give the target compounds, 6-alkyl-4,7-dimethyl-5,8-dioxo-4,5,7,8-tetrahydro-6*H*-isoselenazolo (or -isothiazolo)[4,3-*e*][1,4]-diazepines (**3k—o**) in 82–91% yields.

Consequently, construction of two novel classes of heterocycles, isoselenazolo[4,3-*e*]-[1,4]diazepine and isothiazolo[4,3-*e*][1,4]diazepine has been accomplished from isoselenazolo (or isothiazolo)[4,3-*d*]pyrimidines: Antitumor activity testing of some of the compounds (**3b**, **e**, **5a**, **b**, **6a**, **b**, **d**, **e**) on P 388 lymphocytic leukemia was carried out, but none showed significant activity.

Experimental

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured with a JASCO IR-810 spectrophotometer. MS were measured with a JEOL JMS-DX 300 spectrometer. ¹H-NMR spectra were recorded with a JEOL JNM-MH-100 or JNM-FX-100 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in values (ppm) and abbreviations are as follows: s, singlet; d, doublet; q, quartet; br, broad; m, multiplet.

4-(2,2-Dicyanovinyl)amino-3-phenylcarbamoylisoselenazole (4a)—Compound **1a** (2, 8 g, 10 mmol) and a catalytic amount of triethylamine were added to a solution of malononitrile (4 g, 60 mmol) in 80 ml of ethanol. The mixture was refluxed for 8 h and filtered to remove the resulting solid, 6-amino-7-cyano-3-phenyl-3*H*-pyrido[3,2-*d*]pyrimidine-4-one⁷⁾ (2.1 g, 50%). The filtrate was evaporated to dryness and the residue was chromatographed on silica gel with a mixture of chloroform–methanol (25:1) to give **4a**. Yield 867 mg (25%), mp 250–252 °C (from acetone). ¹H-NMR (DMSO-*d*₆): 7.10–7.90 (5H, m, Ar), 8.80 (1H, d, *J* = 15 Hz, C = CHNH), 9.50 (1H, s, =CH–Se), 10.70 (1H, br, –NHCO–), 11.30 (1H, d, *J* = 15 Hz, C = CHNH). IR (KBr): 1600 (C=O), 2200 (CN) cm^{–1}. MS *m/z*: 343 (M⁺). Anal. Calcd for C₁₄H₉N₃OSe: C, 49.13; H, 2.65; N, 20.46. Found: C, 49.31; H, 2.45; N, 20.53.

4-Amino-3-(*N*-phenyl)carbamoylisoselenazole (5a)—A mixture of **4a** (343 mg, 1 mmol), concentrated aqueous

TABLE II. 4-(α -Alkyl- α -bromo)acetylamino-3-phenylcarbamoyl-isoselenazoles (or isothiazoles)

Compd. No.	X	R	mp (°C)	Yield (%)	Formula	Analysis (%)			MS (<i>m/z</i>) M ⁺
						Calcd (Found)			
						C	H	N	
6a	Se	H	159—160 ^{a)}	88	C ₁₂ H ₁₀ BrN ₃ O ₂ Se	37.23 (37.43)	2.60 (2.51)	10.86 (10.91)	387
6b	Se	CH ₃	115—116 ^{a)}	85	C ₁₃ H ₁₂ BrN ₃ O ₂ Se	38.93 (38.94)	3.01 (2.85)	10.48 (10.55)	401
6c	Se	C ₂ H ₅	89—90 ^{b)}	80	C ₁₄ H ₁₄ BrN ₃ O ₂ Se	40.50 (40.78)	3.40 (3.37)	10.12 (10.16)	415
6d	S	H	134—135 ^{a)}	90	C ₁₂ H ₁₀ BrN ₃ O ₂ S	42.36 (42.45)	2.96 (2.84)	12.35 (12.27)	339
6e	S	CH ₃	107—108 ^{a)}	85	C ₁₃ H ₁₂ BrN ₃ O ₂ S	44.08 (44.02)	3.41 (3.24)	11.86 (11.92)	353
6f	S	C ₂ H ₅	60—61 ^{c)}	81	C ₁₄ H ₁₄ BrN ₃ O ₂ S	45.66 (45.78)	3.83 (3.82)	11.41 (11.32)	367

a) Recrystallized from ethanol. b) Recrystallized from petroleum ether-isopropanol (2:1). c) Recrystallized from isopropanol.

TABLE III. IR and ¹H-NMR Data for 6a—f

Compd. No.	IR cm ⁻¹	¹ H-NMR (CDCl ₃) ppm
6a	1600, 1660 (C=O), 3350 (NH)	4.00 (2H, s, CH ₂), 7.00—7.80 (5H, m, Ar), 9.20 (1H, br, PhNH), 9.80 (1H, s, =CH-Se-), 11.60 (1H, br, CONH)
6b	1660, 1670 (C=O), 3350 (NH)	2.00 (3H, d, $J=7.5$ Hz, CH ₃ -CH<), 4.50 (1H, q, $J=7.5$ Hz, CH ₃ -CH<), 7.10—7.80 (5H, m, Ar), 9.30 (1H, br, PhNH), 9.80 (1H, s, =CH-Se-), 11.60 (1H, br, CONH)
6c	1660, 1680 (C=O), 3350 (NH)	1.10 (3H, t, $J=7.5$ Hz, CH ₃ CH ₂ -), 2.00—2.40 (2H, m, CH ₃ CH ₂ CH<), 4.30 (1H, t, $J=7.5$ Hz, -CH ₂ CH<), 7.10—7.80 (5H, m, Ar), 9.25 (1H, br, PhNH), 10.00 (1H, s, =CH-Se-), 11.50 (1H, br, CONH)
6d	1600, 1660 (C=O), 3350 (NH)	4.00 (2H, s, CH ₂), 7.00—7.80 (5H, m, Ar), 9.15 (1H, br, PhNH), 9.40 (1H, s, =CH-S-), 11.40 (1H, br, CONH)
6e	1660, 1690 (C=O), 3350 (NH)	2.00 (3H, d, $J=7.5$ Hz, CH ₃ CH<), 4.50 (1H, q, $J=7.5$ Hz, CH ₃ -CH<), 7.10—7.80 (5H, m, Ar), 9.15 (1H, br, PhNH), 9.40 (1H, s, =CH-S-), 11.30 (1H, br, CONH)
6f	1660, 1670 (C=O), 3350 (NH)	1.10 (3H, t, $J=7.5$ Hz, CH ₃ CH ₂ -), 2.00—2.40 (2H, m, CH ₃ CH ₂ CH<), 4.40 (1H, t, $J=7.5$ Hz, -CH ₂ CH<), 7.10—7.80 (5H, m, Ar), 9.15 (1H, br, PhNH), 9.40 (1H, s, =CH-S-), 11.30 (1H, br, CONH)

HCl (50 ml), and ethanol (50 ml) was refluxed for 1.5 h. After cooling, the reaction mixture was neutralized with 20% aqueous NaOH. The resulting crystals were collected by filtration and recrystallized from hexane-benzene (7:3). Yield 187 mg (70%), mp 114—115°C. ¹H-NMR (CDCl₃): 5.20 (2H, br, NH₂), 7.00—7.80 (5H, m, Ar), 7.90 (1H, s, =CH-Se), 9.20 (1H, br, NH). IR (KBr): 3360, 3270 (NH₂), 1650 (C=O) cm⁻¹. MS m/z : 267 (M^+). Anal. Calcd for C₁₀H₉N₃OSe: C, 45.13; H, 3.41; N, 15.79. Found: C, 45.39; H, 3.24; N, 15.71.

4-(α -Alkyl- α -bromo)acetylamino-3-phenylcarbamoyl-isoselenazoles (or -isothiazoles) (6a—f)— α -Bromoalkyl bromide (1 mmol) was added to a solution of **5** (0.5 mmol) in CH₂Cl₂ (20 ml). The mixture was stirred for 1 h. The solvent was distilled off *in vacuo*. The residue was recrystallized from ethanol, isopropanol, or a mixture of petroleum ether-isopropanol (2:1).

6-Alkyl-5,8-dioxo-7-phenyl-4,5,7,8-tetrahydro-6H-isoselenazolo (or -isothiazolo)[4,3-*e*][1,4]diazepines (3a—f)—A mixture of compound **6** (0.25 mmol) in absolute ethanol (30 ml) and sodium ethoxide (0.5 mmol) in absolute ethanol (20 ml) was refluxed for 1 h. The solvent was distilled off, and the residue was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was column-

TABLE IV. 6-Alkyl-5,8-dioxo-7-phenyl-4,5,7,8-tetrahydro-6H-isoselenazolo (or isothiazolo)[4,3-e][1,4]diazepines

Compd. No.	X	R ¹	R ²	R ³	mp (°C)	Yield (%)	Formula	Analysis (%)			MS (m/z) M ⁺
								Calcd	Found		
								C	H	N	
3a	Se	Ph	H	H	246—247 ^{a)}	78	C ₁₂ H ₉ N ₃ O ₂ Se	47.07 (47.07)	2.96 2.90	13.72 13.83)	307
3b	Se	Ph	Me	H	252—253 ^{b)}	70	C ₁₃ H ₁₁ N ₃ O ₂ Se	48.76 (48.79)	3.46 3.25	13.12 13.20)	321
3c	Se	Ph	Et	H	235—236 ^{a)}	56	C ₁₄ H ₁₃ N ₃ O ₂ Se	50.31 (50.22)	3.92 3.88	12.57 12.68)	335
3d	S	Ph	H	H	155—156 ^{c)}	83	C ₁₂ H ₉ N ₃ O ₂ S	55.59 (55.85)	3.50 3.46	16.21 16.11)	259
3e	S	Ph	Me	H	245—247 ^{b)}	72	C ₁₃ H ₁₁ N ₃ O ₂ S	57.13 (56.90)	4.06 3.94	15.37 15.24)	273
3f	S	Ph	Et	H	143—145 ^{d)}	62	C ₁₄ H ₁₃ N ₃ O ₂ S	58.52 (58.60)	4.56 4.52	14.62 14.59)	287

a) Recrystallized from methanol. b) Recrystallized from ethanol. c) Recrystallized from isopropanol. d) Recrystallized from isopropanol-benzene (3:1).

TABLE V. IR and ¹H-NMR Data for 3a—f

Compd. No.	IR cm ⁻¹	¹ H-NMR (CDCl ₃) ppm
3a	1650, 1680 (C=O), 3420 (NH)	4.25 (2H, s, CH ₂), 7.40 (5H, s, Ar), 9.00 (1H, s, =CH-Se-), 10.60 (1H, br, NH)
3b	1650, 1690 (C=O), 3450 (NH)	1.00 (3H, d, J=7.5 Hz, CH-CH ₃), 4.60 (1H, q, J=7.5 Hz, -CH-CH ₃), 7.00—7.60 (5H, m, Ar), 8.90 (1H, s, =CH-Se-), 10.70 (1H, br, NH)
3c	1650, 1700 (C=O), 3400 (NH)	0.78 (3H, t, J=7.5 Hz, CH ₃ CH ₂ -), 1.30—1.70 (2H, m, CH ₃ CH ₂ CH ₂ -), 4.30 (1H, t, J=7.5 Hz, CH ₃ CH ₂ CH ₂ -), 7.20—7.60 (5H, m, Ar), 9.20 (1H, s, =CH-Se-), 10.70 (1H, br, NH)
3d	1670, 1690 (C=O), 3400 (NH)	4.30 (2H, s, CH ₂), 7.40 (5H, m, Ar), 8.60 (1H, s, =CH-S-), 10.80 (1H, br, NH)
3e	1640, 1700 (C=O), 3400 (NH)	1.00 (3H, d, J=7.5 Hz, CH-CH ₃), 4.60 (1H, q, J=7.5 Hz, -CH-CH ₃), 7.10—7.60 (5H, m, Ar), 9.60 (1H, s, =CH-S-), 10.70 (1H, br, NH)
3f	1640, 1700 (C=O), 3400 (NH)	0.90 (3H, t, J=7.5 Hz, CH ₃ CH ₂ -), 1.40—1.80 (2H, m, CH ₃ CH ₂ CH ₂ -), 4.20 (1H, t, J=7.5 Hz, CH ₃ CH ₂ CH ₂ -), 7.20—7.50 (5H, m, Ar), 8.60 (1H, s, =CH-S-), 10.80 (1H, br, NH)

chromatographed on silica gel with CHCl₃-MeOH (25:1). From the first eluate, 3 was obtained (Tables IV and V).

From the second eluate, 4-(α-alkyl-α-ethoxyacetyl)amino-3-phenylcarbamoyl-isoselenazoles (or -isothiazoles) (7a—f) were obtained. 7a: Yield 9 mg (11%), mp 136—138 °C. ¹H-NMR (CDCl₃): 1.40 (3H, t, CH₃CH₂-O-), 3.70 (2H, q, CH₃CH₂-O-), 4.10 (2H, s, EtO-CH₂-), 7.10—7.80 (5H, m, Ar), 9.30 (1H, br, PhNH), 10.00 (1H, s, =CH-Se-), 11.70 (1H, br, CONH). IR (KBr): 3400 (NH), 1650, 1680 (C=O) cm⁻¹. MS m/z: 353 (M⁺). 7b: Yield 14 mg (15%), mp 110—112 °C. ¹H-NMR (CDCl₃): 1.30 (3H, d, CH₃-CH-), 1.50 (3H, t, CH₃-CH₂-O-), 3.70 (2H, q, CH₃-CH₂-O-), 4.00 (1H, q, CH₃-CH-), 7.00—7.80 (5H, m, Ar), 9.30 (1H, br, PhNH), 10.00 (1H, s, =CH-Se-), 11.70 (1H, br, CONH). IR (KBr): 3380 (NH), 1660, 1690 (C=O) cm⁻¹. MS m/z: 367 (M⁺). 7c: Yield 15 mg (16%), mp 131—134 °C. ¹H-NMR (CDCl₃): 1.00 (3H, t, CH₃CH₂-CH-), 1.30 (3H, t, CH₃-CH₂-O-), 1.70—2.00 (2H, m, CH₃CH₂CH₂-), 3.50—3.90 (3H, m, CH₃CH₂-O-CH-CO), 7.10—7.80 (5H, m, Ar), 9.30 (1H, br, PhNH), 10.00 (1H, s, =CH-Se-), 11.70 (1H, br, CONH). IR (KBr): 3420 (NH), 1660, 1690 (C=O) cm⁻¹. MS m/z: 381 (M⁺). 7d: Yield 8 mg (3%), mp 270—273 °C. ¹H-NMR (CDCl₃): 1.40 (3H, t, CH₃CH₂-O-), 3.70 (2H, q, CH₃CH₂-O-), 4.15 (2H, s, -O-CH₂-CO), 7.00—7.80 (5H, m, Ar), 9.15 (1H, br, PhNH), 9.40 (1H, s, =CH-S-), 11.40 (1H, br, CONH). IR (KBr): 3400 (NH), 1650, 1680 (C=O) cm⁻¹. MS m/z: 305 (M⁺). 7e: Yield 13 mg (16%), mp 139—141 °C. ¹H-NMR (CDCl₃): 1.25 (3H, d, CH₃-CH-), 1.50 (3H, t, CH₃CH₂-O-), 3.65 (2H, q, CH₃CH₂-O-), 4.00 (1H, q, CH₃-CH-),

7.00–7.80 (5H, m, Ar), 9.10 (1H, br, PhNH), 9.40 (1H, s, =CH–S–), 11.60 (1H, br, CONH). IR (KBr): 3380 (NH), 1650, 1690 (C=O) cm^{-1} . MS m/z : 319 (M^+). **7f**: Yield 22 mg (27%), mp 105–107 °C. $^1\text{H-NMR}$ (CDCl_3): 1.00 (3H, t, $\text{CH}_3\text{CH}_2\text{--CH--}$), 1.40 (3H, t, $\text{CH}_3\text{CH}_2\text{--O--}$), 1.70–2.00 (2H, m, $\text{CH}_3\text{CH}_2\text{--CH--}$), 3.50–3.90 (3H, m, $\text{CH}_3\text{CH}_2\text{--O--CH--}$), 7.10–7.80 (5H, m, Ar), 9.10 (1H, br, PhNH), 9.40 (1H, s, =CH–S–), 11.40 (1H, br, CONH). IR (KBr): 3380 (NH), 1640, 1680 (C=O) cm^{-1} . MS m/z : 333 (M^+).

6-Alkyl-5,8-dioxo-4-methyl-7-phenyl-4,5,7,8-tetrahydro-6H-isoselenazolo (or -isothiazolo)[4,3-*e*][1,4]diazepines (3g–j)—A mixture of **3a** (77 mg, 0.25 mmol), $\text{KF}\cdot\text{Al}_2\text{O}_3$ (120 mg, 0.75 mmol), and acetonitrile (20 ml) was stirred for 10 min. Methyl iodide (178 mg, 1.25 mmol) was added and stirring was continued for 2 h at room temperature. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The resulting solid was purified by column chromatography on silica gel with a mixture of chloroform–methanol (20 : 1) to give **3g**. Similarly, **3h–j** were obtained from **3b**, **3e** and **3f**. **3g**: mp 185–186 °C (from EtOH), yield 80%. $^1\text{H-NMR}$ (CDCl_3): 3.41 (3H, s, N– CH_3), 4.30 (2H, s, CH_2), 7.20–7.60 (5H, m, Ar), 9.00 (1H, s, =CH–Se–). IR (KBr): 1640, 1690 (C=O) cm^{-1} . Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2\text{Se}$: C, 48.76; H, 3.46; N, 13.12. Found: C, 49.01; H, 3.26; N, 12.41. MS m/z (M^+): Calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2\text{Se}$ 321.0015. Found: 320.9974. **3h**: mp 127–129 °C (from benzene), yield 8%. $^1\text{H-NMR}$ (CDCl_3): 1.15 (3H, d, $J=7.5$ Hz, $\text{CH}_3\text{--CH--}$), 3.50 (3H, s, N– CH_3), 4.60 (1H, q, $J=7.5$ Hz, $\text{CH}_3\text{--CH--}$), 7.10–7.60 (5H, m, Ar), 8.98 (1H, s, =CH–Se–). IR (KBr): 1650, 1680 (C=O) cm^{-1} . Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2\text{Se}\cdot\text{C}_6\text{H}_6$: C, 58.27; H, 4.64; N, 10.19. Found: C, 58.23; H, 4.59; N, 9.60. MS m/z : Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2\text{Se}$ 335.0174. Found: 335.0189. **3i**: mp 192–194 °C (from EtOH), yield 75%. $^1\text{H-NMR}$ (CDCl_3): 1.20 (3H, d, $J=7.5$ Hz, $\text{CH}_3\text{--CH--}$), 3.50 (3H, s, N– CH_3), 4.60 (1H, q, $J=7.5$ Hz, $\text{CH}_3\text{--CH--}$), 7.00–7.60 (5H, m, Ar), 8.35 (1H, s, =CH–S–). IR (KBr): 1660, 1670 (C=O) cm^{-1} . MS m/z : 287 (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$: C, 58.52; H, 4.56; N, 14.62. Found: C, 58.78; H, 4.49; N, 14.45. **3j**: mp 148–149 °C (from hexane–benzene (5 : 4)), yield 78%. $^1\text{H-NMR}$ (CDCl_3): 0.80 (3H, t, $J=7.5$ Hz, $\text{CH}_3\text{--CH}_2\text{--CH--}$), 1.40–1.80 (2H, m, $\text{CH}_3\text{--CH}_2\text{--CH--}$), 3.48 (3H, s, N– CH_3), 4.20 (1H, t, $J=7.5$ Hz, $\text{CH}_3\text{--CH}_2\text{--CH--}$), 7.20–7.60 (5H, m, Ar), 8.32 (1H, s, =CH–S–). IR (KBr): 1650, 1690 (C=O) cm^{-1} . MS m/z : 301 (M^+). Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$: C, 59.78; H, 5.02; N, 13.94. Found: C, 59.86; H, 4.80; N, 13.40.

4-Methylamino-3-methylcarbamoylisoselenazole (8a)—A mixture of **2a** (245 mg, 1 mmol) and 40% aqueous methylamine (20 ml) was heated in a sealed stainless steel tube at 120 °C for 4 h. After cooling, the excess aqueous methylamine was distilled off. The residue was chromatographed on silica gel with a mixture of chloroform–methanol (25 : 1) to give a colorless oil. Yield 128 mg (54%). $^1\text{H-NMR}$ (CDCl_3): 2.90 (3H, d, CH_3NH); 2.96 (3H, d, $\text{CH}_3\text{NHCO--}$), 7.30 (1H, br, NHCH_3), 7.50 (1H, s, =CH–Se–), 8.20 (1H, br, NHCO--). IR (KBr): 3370 (NH), 1660 (C=O) cm^{-1} . MS m/z : 219 (M^+).

4-[N-(α -Alkyl- α -bromo)acetyl-N-methylamino]-3-methylcarbamoyl-isoselenazole (or -isothiazole) (9a–e)— α -Bromoalkyl bromide (1 mmol) in dichloromethane (20 ml) was added to a solution of **8** (0.5 mmol) in dichloromethane (20 ml). Potassium carbonate (276 mg, 2 mmol) was added and the mixture was stirred for 2 min. The reaction mixture was extracted with chloroform. The extract was dried, the solvent was distilled *in vacuo*, and the residue was recrystallized from ethanol. **9a**: Yield 153 mg (90%), mp 154–156 °C. $^1\text{H-NMR}$ (CDCl_3): 2.88 (3H, d, $J=6$ Hz, CH_3NH), 3.16 (3H, s, CONCH_3), 3.36 (2H, s, CH_2), 7.08 (1H, br, CH_3NH), 9.34 (1H, s, =CH–Se–). IR (KBr): 3400 (NH), 1640, 1660 (C=O) cm^{-1} . MS m/z : 339 (M^+). Anal. Calcd for $\text{C}_8\text{H}_{10}\text{BrN}_3\text{O}_2\text{Se}$: C, 28.34; H, 2.97; N, 12.39. Found: C, 28.15; H, 2.87; N, 12.62. **9b**: Yield 155 mg (88%), mp 192–194 °C. $^1\text{H-NMR}$ (CDCl_3): 1.78 (3H, d, $J=7.5$ Hz, $\text{CH}_3\text{CH--}$), 2.96 (3H, d, $J=6$ Hz, CH_3NH), 3.22 (3H, s, CONCH_3), 4.08 (1H, q, $J=7.5$ Hz, $\text{CH}_3\text{CH--}$), 7.12 (1H, br, CH_3NH), 9.50 (1H, s, =CH–Se–). IR (KBr): 3380 (NH), 1635, 1650 (C=O) cm^{-1} . MS m/z (M^+) Calcd for $\text{C}_9\text{H}_{12}\text{BrN}_3\text{O}_2\text{Se}$: 352.9278. Found: 352.9250. **9c**: Yield 158 mg (86%), mp 172–174 °C. $^1\text{H-NMR}$ (CDCl_3): 0.90 (3H, t, $J=7.5$ Hz, $\text{CH}_3\text{CH}_2\text{CH--}$), 2.40–2.80 (2H, m, $\text{CH}_3\text{CH}_2\text{CH--}$), 2.96 (3H, d, $J=6$ Hz, CH_3NH), 3.24 (3H, s, CONCH_3), 3.78 (1H, t, $J=7.5$ Hz, $\text{--CH}_2\text{--CH--}$), 7.14 (1H, br, CH_3NH), 9.52 (1H, s, =CH–Se–). IR (KBr): 3400 (NH), 1640, 1660 (C=O) cm^{-1} . MS m/z : 367 (M^+). **9d**: Yield 132 mg (86%), mp 187–189 °C. $^1\text{H-NMR}$ (CDCl_3): 1.78 (3H, d, $J=7.5$ Hz, $\text{CH}_3\text{CH--}$), 2.98 (3H, d, $J=6$ Hz, CH_3NH), 3.24 (3H, s, CONCH_3), 4.10 (1H, q, $J=7.5$ Hz, $\text{CH}_3\text{CH--}$), 8.78 (1H, s, =CH–S–). IR (KBr): 3380 (NH), 1640, 1670 (C=O) cm^{-1} . MS m/z : 305 (M^+). **9e**: Yield 141 mg (88%), mp 129–130 °C. $^1\text{H-NMR}$ (CDCl_3): 0.89 (3H, t, $J=7.5$ Hz, $\text{CH}_3\text{CH}_2\text{CH--}$), 1.80–2.20 (2H, m, $\text{CH}_3\text{CH}_2\text{CH--}$), 2.96 (3H, d, $J=6$ Hz, CH_3NH), 3.24 (3H, s, CONHCH_3), 3.76 (1H, t, $J=7.5$ Hz, $\text{CH}_3\text{CH}_2\text{CH--}$), 7.16 (1H, br, CH_3NH), 8.82 (1H, s, =CH–S–). IR (KBr): 3400 (NH), 1650, 1675 (C=O) cm^{-1} . MS m/z : 319 (M^+).

6-Alkyl-4,7-dimethyl-5,8-dioxo-4,5,7,8-tetrahydro-6H-isoselenazolo (or -isothiazolo)[4,3-*e*][1,4]diazepines (3k–o)— $\text{KF}\cdot\text{Al}_2\text{O}_3$ (400 mg, 2.5 mmol) was added to a solution of **9** (0.5 mmol) in acetonitrile (20 ml) and the mixture was stirred for 1.5 h. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of chloroform–methanol (10 : 1). **3k**: mp 154–156 °C (from hexane–AcOEt (5 : 4)), yield 91%. $^1\text{H-NMR}$ (CDCl_3): 3.26 (3H, s, N– CH_3), 3.88 (3H, s, N– CH_3), 3.94 (2H, s, CH_2), 8.98 (1H, s, =CH–Se–). IR (KBr): 1650, 1670 (C=O) cm^{-1} . MS m/z : 259 (M^+). Anal. Calcd for $\text{C}_8\text{H}_9\text{N}_3\text{O}_2\text{Se}$: C, 37.22; H, 3.51; N, 16.28. Found: C, 37.44; H, 3.31; N, 16.55. **3l**: Viscous oil, yield 82%. $^1\text{H-NMR}$ (CDCl_3): 1.50 (3H, d, $J=7.5$ Hz, $\text{CH}_3\text{CH--}$), 3.10 (3H, s, N– CH_3), 3.42 (3H, s, N– CH_3), 3.42 (3H, s, N– CH_3), 4.32 (1H, q, $J=7.5$ Hz, $\text{CH}_3\text{CH--}$). IR (film): 1650, 1680 cm^{-1} . MS m/z (M^+): Calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2\text{Se}$: 273.0017. Found: 273.0019. **3m**: Viscous oil, yield 86%. $^1\text{H-NMR}$ (CDCl_3): 0.92 (3H, t, $J=7.5$ Hz, $\text{CH}_3\text{CH}_2\text{--}$), 1.80–2.20 (2H, m, $\text{CH}_3\text{CH}_2\text{CH--}$), 3.07 (3H, s, N– CH_3), 3.39 (3H, s, N– CH_3), 3.92 (1H, t, $J=7.5$ Hz, $\text{CH}_3\text{CH}_2\text{CH--}$), 8.90 (1H, s, =CH–

Se-). IR (film): 1650, 1680 (C=O) cm^{-1} . MS m/z (M^+): Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_2\text{Se}$: 287.0173. Found: 287.0179. **3n**: Viscous oil, yield 90%. $^1\text{H-NMR}$ (CDCl_3): 1.50 (3H, d, $J=7.5$ Hz, $\text{CH}_3\text{CH}-$), 3.14 (3H, s, N- CH_3), 3.44 (3H, s, N- CH_3), 4.30 (1H, q, $J=7.5$ Hz, $\text{CH}_3\text{CH}-$), 8.38 (1H, s, =CH-S-). IR (film): 1650, 1740 (C=O) cm^{-1} . MS m/z (M^+): Calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2\text{S}$: 225.0572. Found: 225.0570. **3o**: Viscous oil, yield 91%. $^1\text{H-NMR}$ (CDCl_3): 0.96 (3H, t, $J=7.5$ Hz, CH_3CH_2-), 1.80–2.20 (2H, m, $\text{CH}_3\text{CH}_2\text{CH}-$), 3.12 (3H, s, N- CH_3), 3.44 (3H, s, N- CH_3), 3.98 (1H, t, $J=7.5$ Hz, $\text{CH}_3\text{CH}_2\text{CH}-$), 8.28 (1H, s, =CH-S-). IR (film): 1650, 1740 (C=O) cm^{-1} . MS m/z (M^+): Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$: 239.0729. Found: 239.0711.

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References and Notes

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