[Chem. Pharm. Bull. 36(8)2902—2908(1988)]

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

TAISEI UEDA,[a] YUZO KATO,[a,1)] JINSAKU SAKAKIBARA*,[a] and MITSUO MURATA[b]

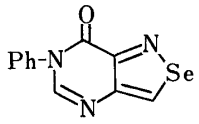
Faculty of Pharmaceutical Sciences, Nagoya City University,[a] Tanabedori, Mizuhoku, Nagoya 467, Japan and Taisho Pharmaceutical Co., Ltd.,[b] 1–403, Yoshino-cho, Ohmiya, Saitama 330, Japan

(Received January 27, 1988)

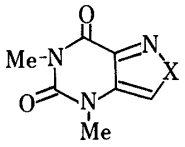
Two novel classes of heterocycles, isoselenazolo[4,3-*e*][1,4]diazepines (**3a**—**c**, **g**, **h**, **k**, **l**, **m**) and isothiazolo[4,3-*e*][1,4]diazepines (**3d**—**f**, **i**, **j**, **n**, **o**) were synthesized from 7-oxo-6-phenyl-6*H*-isoselenazolo (or -isothiazolo)[4,3-*d*]pyrimidines (**1a**,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

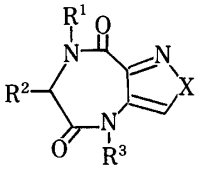
Previously we reported on the synthesis[2)] and antitumor activity[3)] of 7-oxo-6-phenyl-6*H*-isoselenazolo[4,3-*d*]pyrimidine (**1a**). We successively studied the synthesis of 4,6-dimethyl-5,7-dioxo-4,5,6,7-tetrahydro-isoselenazolo (or -isothiazolo)[4,3-*d*]pyrimidine[4)] (**2**). In connection with 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**.



1a



2

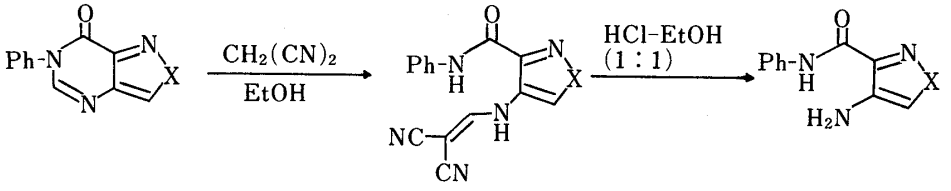


3

X=Se or S

Chart 1

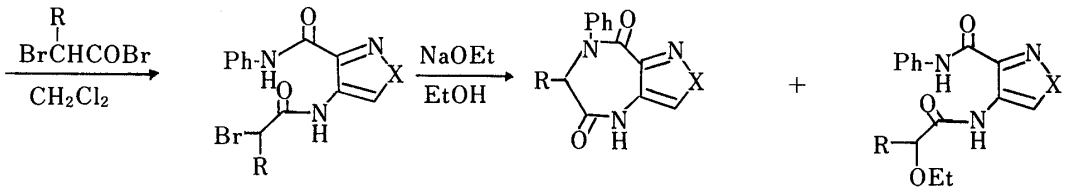
The synthesis of **3a**—**f** was carried out as illustrated in Chart 2. Synthesis of 7-oxo-6-phenyl-6*H*-isothiazolo[4,3-*d*]pyrimidine (**1b**) and its reaction with malononitrile to give 4-(2,2-dicyanovinyl)amino-3-phenylcarbamoylisothiazole (**4b**) were investigated by us previously.[6)] A similar 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-phenylcarbamoylisothiazole[6)] (**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-



1a : X=Se
1b : X=S

4a : X=Se
4b : X=S

5a : X=Se
5b : X=S

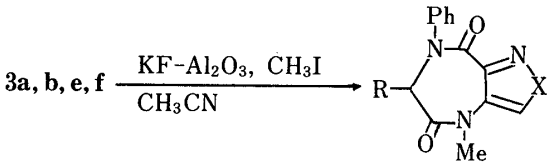


6a : X=Se, R=H
6b : X=Se, R=Me
6c : X=Se, R=Et
6d : X=S, R=H
6e : X=S, R=Me
6f : X=S, R=Et

3a : X=Se, R=H
3b : X=Se, R=Me
3c : X=Se, R=Et
3d : X=S, R=H
3e : X=S, R=Me
3f : X=S, R=Et

7a : X=Se, R=H
7b : X=Se, R=Me
7c : X=Se, R=Et
7d : X=S, R=H
7e : X=S, R=Me
7f : X=S, R=Et

Chart 2



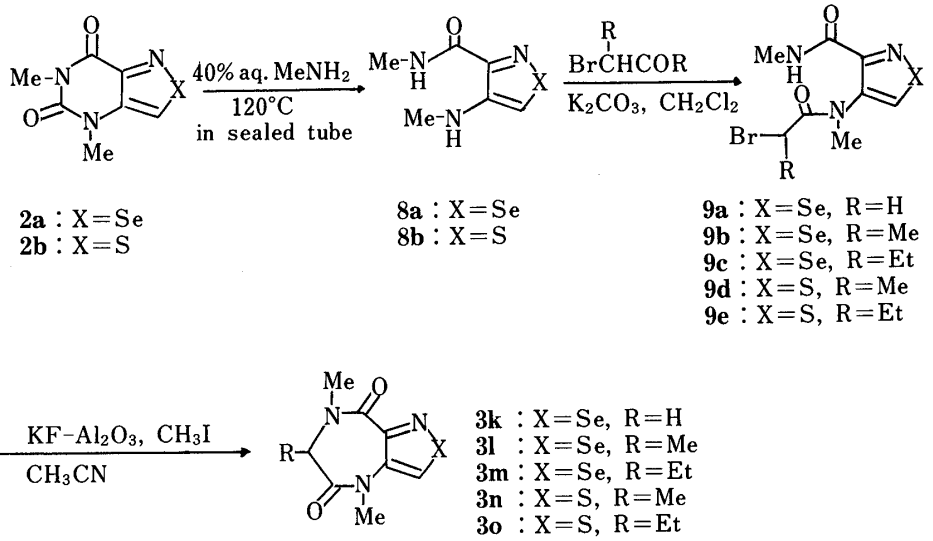
3g : X=Se, R=H
3h : X=Se, R=Me
3i : X=S, R=Me
3j : X=S, R=Et

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) sprectra, proton nuclear magnetic resonance (^{1}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 oxide[8] 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-methylcarbamoylisothiazole[6] (**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



2a : X=Se
2b : X=S

8a : X=Se
8b : X=S

9a : X=Se, R=H
9b : X=Se, R=Me
9c : X=Se, R=Et
9d : X=S, R=Me
9e : X=S, R=Et

3k : X=Se, R=H
3l : X=Se, R=Me
3m : X=Se, R=Et
3n : X=S, R=Me
3o : X=S, R=Et

Chart 4

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

Solvent	Base	Temp (°C)	Time (h)	Yield (%)
EtOH	EtONa	Reflux	0.5	20
tert-BuOH	*tert*-BuOK	Reflux	0.5	36
CH_3CN	NaH	Reflux	0.5	40
CH_3CN	$KF-Al_2O_3$	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. ^{1}H-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-one[7] (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). ^{1}H-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 $C_{14}H_9N_5OSe$: 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 (%) Calcd (Found) C	H	N	MS (m/z) M^+
6a	Se	H	159—160[a]	88	$C_{12}H_{10}BrN_3O_2Se$	37.23 (37.43	2.60 2.51	10.86 10.91)	387
6b	Se	CH_3	115—116[a]	85	$C_{13}H_{12}BrN_3O_2Se$	38.93 (38.94	3.01 2.85	10.48 10.55)	401
6c	Se	C_2H_5	89—90[b]	80	$C_{14}H_{14}BrN_3O_2Se$	40.50 (40.78	3.40 3.37	10.12 10.16)	415
6d	S	H	134—135[a]	90	$C_{12}H_{10}BrN_3O_2S$	42.36 (42.45	2.96 2.84	12.35 12.27)	339
6e	S	CH_3	107—108[a]	85	$C_{13}H_{12}BrN_3O_2S$	44.08 (44.02	3.41 3.24	11.86 11.92)	353
6f	S	C_2H_5	60—61[c]	81	$C_{14}H_{14}BrN_3O_2S$	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 ^{1}H-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_3CH_2–), 2.00—2.40 (2H, m, CH_3CH_2CH), 4.30 (1H, t, J=7.5 Hz, –CH_2CH<), 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_3CH<), 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_3CH_2–), 2.00—2.40 (2H, m, CH_3CH_2CH<), 4.40 (1H, t, J=7.5 Hz, –CH_2CH<), 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 neutalized 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. ^{1}H-NMR ($CDCl_3$): 5.20 (2H, br, NH_2), 7.00—7.80 (5H, m, Ar), 7.90 (1H, s, =CH–Se), 9.20 (1H, br, NH). IR (KBr): 3360, 3270 (NH_2), 1650 (C=O) cm^{-1}. MS *m/z*: 267 (M^+). *Anal.* Calcd for $C_{10}H_9N_3OSe$: 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 CH_2Cl_2 (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-6*H*-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-6*H*-isoselenazolo (or isothiazolo)[4,3-*e*][1,4]diazepines

Compd. No.	X	R^1	R^2	R^3	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	MS (*m/z*) M^+
3a	Se	Ph	H	H	246—247[a]	78	$C_{12}H_9N_3O_2Se$	47.07 (47.07	2.96 2.90	13.72 13.83)	307
3b	Se	Ph	Me	H	252—253[b]	70	$C_{13}H_{11}N_3O_2Se$	48.76 (48.79	3.46 3.25	13.12 13.20)	321
3c	Se	Ph	Et	H	235—236[a]	56	$C_{14}H_{13}N_3O_2Se$	50.31 (50.22	3.92 3.88	12.57 12.68)	335
3d	S	Ph	H	H	155—156[c]	83	$C_{12}H_9N_3O_2S$	55.59 (55.85	3.50 3.46	16.21 16.11)	259
3e	S	Ph	Me	H	245—247[b]	72	$C_{13}H_{11}N_3O_2S$	57.13 (56.90	4.06 3.94	15.37 15.24)	273
3f	S	Ph	Et	H	143—145[d]	62	$C_{14}H_{13}N_3O_2S$	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 ^{1}H-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–C<u>H</u>$_3$), 4.60 (1H, q, J=7.5 Hz, –C<u>H</u>–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, <u>CH_3</u>CH_2–), 1.30—1.70 (2H, m, CH_3<u>CH_2</u>CH<), 4.30 (1H, t, J=7.5 Hz, CH_3CH_2<u>CH</u><), 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<u>CH_3</u>), 4.60 (1H, q, J=7.5 Hz, –<u>CH</u>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, <u>CH_3</u>CH_2–), 1.40—1.80 (2H, m, CH_3<u>CH_2</u>CH<), 4.20 (1H, t, J=7.5 Hz, CH_3<u>CH_2</u>CH<), 7.20—7.50 (5H, m, Ar), 8.60 (1H, s, =CH–S–), 10.80 (1H, br, NH)

chromatographed on silica gel with $CHCl_3$–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. ^{1}H-NMR ($CDCl_3$): 1.40 (3H, t, <u>CH_3</u>CH_2–O–), 3.70 (2H, q, CH_3<u>CH_2</u>–O–), 4.10 (2H, s, EtO–<u>CH_2</u>–), 7.10—7.80 (5H, m, Ar), 9.30 (1H, br, Ph<u>NH</u>), 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. ^{1}H-NMR ($CDCl_3$): 1.30 (3H, d, <u>CH_3</u>–CH–), 1.50 (3H, t, <u>CH_3</u>–CH_2–O–), 3.70 (2H, q, CH_3–<u>CH_2</u>–O–), 4.00 (1H, q, CH_3–<u>CH</u>–), 7.00—7.80 (5H, m, Ar), 9.30 (1H, br, Ph<u>NH</u>), 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. ^{1}H-NMR ($CDCl_3$): 1.00 (3H, t, <u>CH_3</u>CH_2–CH–), 1.30 (3H, t, <u>CH_3</u>–CH_2–O–), 1.70—2.00 (2H, m, CH_3<u>CH_2</u>CH), 3.50—3.90 (3H, m, CH_3<u>CH_2</u>–O–<u>CH</u>–CO), 7.10—7.80 (5H, m, Ar), 9.30 (1H, br, Ph<u>NH</u>), 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. ^{1}H-NMR ($CDCl_3$): 1.40 (3H, t, <u>CH_3</u>CH_2–O–), 3.70 (2H, q, CH_3<u>CH_2</u>–O–), 4.15 (2H, s, –O–<u>CH_2</u>–CO), 7.00—7.80 (5H, m, Ar), 9.15 (1H, br, Ph<u>NH</u>), 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. ^{1}H-NMR ($CDCl_3$): 1.25 (3H, d, <u>CH_3</u>–CH–), 1.50 (3H, t, <u>CH_3</u>CH_2–O–), 3.65 (2H, q, CH_3<u>CH_2</u>–O–), 4.00 (1H, q, CH_3–<u>CH</u>–),

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}H-NMR ($CDCl_3$): 1.00 (3H, t, CH_3CH_2–CH–), 1.40 (3H, t, CH_3CH_2–O–), 1.70—2.00 (2H, m, CH_3CH_2–CH–), 3.50—3.90 (3H, m, CH_3CH_2–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-6*H*-isoselenazolo (or -isothiazolo)[4,3-*e*][1,4]diazepines (3g—j)——A mixture of **3a** (77 mg, 0.25 mmol), KF–Al_2O_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}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 $C_{13}H_{11}N_3O_2Se$: 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 $C_{13}H_{11}N_3O_2Se$ 321.0015. Found: 320.9974. **3h**: mp 127—129 °C (from benzene), yield 8%. ^{1}H-NMR ($CDCl_3$): 1.15 (3H, d, J=7.5 Hz, CH_3–CH–), 3.50 (3H, s, N–CH_3), 4.60 (1H, q, J=7.5 Hz, CH_3–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 $C_{14}H_{13}N_3O_2Se \cdot C_6H_6$: C, 58.27; H, 4.64; N, 10.19. Found: C, 58.23; H, 4.59; N, 9.60. MS *m/z*: Calcd for $C_{14}H_{13}N_3O_2Se$ 335.0174. Found: 335.0189. **3i**: mp 192—194 °C (from EtOH), yield 75%. ^{1}H-NMR ($CDCl_3$): 1.20 (3H, d, J=7.5 Hz, CH_3–CH–), 3.50 (3H, s, N–CH_3), 4.60 (1H, q, J=7.5 Hz, CH_3–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 $C_{14}H_{13}N_3O_2S$: 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}H-NMR ($CDCl_3$): 0.80 (3H, t, J=7.5 Hz, CH_3–CH_2–CH–), 1.40—1.80 (2H, m, CH_3–CH_2–CH–), 3.48 (3H, s, N–CH_3), 4.20 (1H, t, J=7.5 Hz, CH_3–CH_2–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 $C_{15}H_{15}N_3O_2S$: 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}H-NMR ($CDCl_3$): 2.90 (3H, d, CH_3NH); 2.96 (3H, d, CH_3NHCO–), 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}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$_3$NH), 9.34 (1H, s, =CH–Se–). IR (KBr): 3400 (NH), 1640, 1660 (C=O) cm^{-1}. MS *m/z*: 339 (M^+). *Anal.* Calcd for $C_8H_{10}BrN_3O_2Se$: 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}H-NMR ($CDCl_3$): 1.78 (3H, d, J=7.5 Hz, CH_3CH–), 2.96 (3H, d, J=6 Hz, CH_3NH), 3.22 (3H, s, CONCH$_3$), 4.08 (1H, q, J=7.5 Hz, CH$_3$CH–), 7.12 (1H, br, CH$_3$NH), 9.50 (1H, s, =CH–Se–). IR (KBr): 3380 (NH), 1635, 1650 (C=O) cm^{-1}. MS *m/z* (M^+) Calcd for $C_9H_{12}BrN_3O_2Se$: 352.9278. Found: 352.9250. **9c**: Yield 158 mg (86%), mp 172—174 °C. ^{1}H-NMR ($CDCl_3$): 0.90 (3H, t, J=7.5 Hz, CH_3CH_2CH), 2.40—2.80 (2H, m, CH_3CH_2CH–), 2.96 (3H, d, J=6 Hz, CH_3NH), 3.24 (3H, s, CONCH$_3$), 3.78 (1H, t, J=7.5 Hz, –CH_2–CH–), 7.14 (1H, br, CH$_3$NH), 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}H-NMR ($CDCl_3$): 1.78 (3H, d, J=7.5 Hz, CH_3CH), 2.98 (3H, d, J=6 Hz, CH_3NH), 3.24 (3H, s, CONCH$_3$), 4.10 (1H, q, J=7.5 Hz, CH_3CH), 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}H-NMR ($CDCl_3$): 0.89 (3H, t, J=7.5 Hz, CH_3CH_2CH), 1.80—2.20 (2H, m, CH_3CH_2CH), 2.96 (3H, d, J=6 Hz, CH_3NH), 3.24 (3H, s, CONHCH$_3$), 3.76 (1H, t, J=7.5 Hz, CH_3CH_2CH–), 7.16 (1H, br, CH$_3$NH), 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-6*H*-isoselenazolo (or -isothiazolo)[4,3-*e*][1,4]diazepines (3k—o)——KF–Al_2O_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}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 $C_8H_9N_3O_2Se$: 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}H-NMR ($CDCl_3$): 1.50 (3H, d, J=7.5 Hz, CH_3CH–), 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, CH_3CH). IR (film): 1650, 1680 cm^{-1}. MS *m/z* (M^+): Calcd for $C_9H_{11}N_3O_2Se$: 273.0017. Found: 273.0019. **3m**: Viscous oil, yield 86%. ^{1}H-NMR ($CDCl_3$): 0.92 (3H, t, J=7.5 Hz, CH_3CH_2–), 1.80—2.20 (2H, m, CH_3CH_2CH–), 3.07 (3H, s, N–CH_3), 3.39 (3H, s, N–CH_3), 3.92 (1H, t, J=7.5 Hz, CH_3CH_2CH–), 8.90 (1H, s, =CH–

Se–). IR (film): 1650, 1680 (C=O) cm^{-1}. MS *m/z* (M^+): Calcd for $C_{10}H_{13}N_3O_2Se$: 287.0173. Found: 287.0179. **3n**: Viscous oil, yield 90%. ^{1}H-NMR ($CDCl_3$): 1.50 (3H, d, J=7.5 Hz, $\underline{CH_3}CH$–), 3.14 (3H, s, N–CH_3), 3.44 (3H, s, N–CH_3), 4.30 (1H, q, J=7.5 Hz, $CH_3\underline{CH}$–), 8.38 (1H, s, =CH–S–). IR (film): 1650, 1740 (C=O) cm^{-1}. MS *m/z* (M^+): Calcd for $C_9H_{11}N_3O_2S$: 225.0572. Found: 225.0570. **3o**: Viscous oil, yield 91%. ^{1}H-NMR ($CDCl_3$): 0.96 (3H, t, J=7.5 Hz, $\underline{CH_3}CH_2$–), 1.80—2.20 (2H, m, $CH_3\underline{CH_2}CH$–), 3.12 (3H, s, N–CH_3), 3.44 (3H, s, N–CH_3), 3.98 (1H, t, J=7.5 Hz, $CH_3CH_2\underline{CH}$–), 8.28 (1H, s, =CH–S–). IR (film): 1650, 1740 (C=O) cm^{-1}. MS *m/z* (M^+): Calcd for $C_{10}H_{13}N_3O_2S$: 239.0729. Found: 239.0711.

Acknowledgements This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan. The authors thank Misses T. Naito and S. Kato of this Faculty for elemental analyses and NMR measurements.

References and Notes

1) Present address: *Institute of Applied Microbiology, University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113, Japan.*
2) T. Ueda, Y. Shibata, J. Sakakibara, M. Inoue and T. Ishida, *Chem. Pharm. Bull.*, **30**, 3424 (1982).
3) H. Ito, J. Sakakibara and T. Ueda, *Cancer Lett.*, **28**, 61 (1985).
4) T. Ueda, H. Yoshida and J. Sakakibara, *Synthesis*, **1985**, 695.
5) These ring systems have not yet appeared in *Chem. Abstr.*
6) T. Ueda, Y. Shibata, Y. Kato and J. Sakakibara, *Tetrahedron*, **43**, 3917 (1987).
7) T. Ueda, Y. Shibata and J. Sakakibara, *Chem. Pharm. Bull.*, **33**, 3065 (1985).
8) J. Yamawaki and T. Ando, *Chem. Lett.*, **1979**, 755; J. Yamawaki, T. Ando and T. Hanafusa, *ibid.*, **1981**, 1143.