Selenium Heterocycles. XXVIII (1). Synthesis of Pyrrolo[3,2-*d*]selenazole and Pyrrolo[3,2-*d*]thiazole. Two Novel Heterocycles

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Starting from the readily available 2-substituted-4-formylselenazoles and 2-substituted-4-formylthiazoles, a series of substituted-pyrrolo[3,2-*d*]selenazoles and substituted-pyrrolo[3,2-*d*]-thiazoles were prepared respectively.

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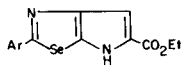
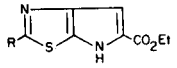
In continuation of our study on the chemistry of selenium heterocyclic compounds (4-9), and as a part of a program designed to expand the chemistry of fused thiazole and selenazole heterocycles (10), it became necessary to synthesize substituted-pyrrolo[3,2-*d*]selenazoles (I) and substituted-pyrrolo[3,2*d*]thiazoles (II) for biological evaluation.



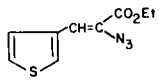
I



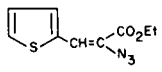
II

The starting material, 2-aryl-4-chloromethylselenazole (IV), could be prepared from the reaction of arylselenobenzamide (III) (11) with 1,3-dichloroacetone, under the conditions reported for the preparation of 2-aryl-4-chloromethylthiazole (12). Heating compound IV with aqueous sulfuric acid gave 2-aryl-4-hydroxymethylselenazole (V). Manganese dioxide oxidation of V in chloroform yielded 2-aryl-4-formylselenazole (VI) in good yield. Condensation of compound VI with ethyl azidoacetate, under the conditions reported previously (13), afforded ethyl α-azido-β-(2-arylselenazol-4-yl)acrylate (VII) (Scheme I).

The nmr spectrum of compound VII was in agreement with the suggested structure. In the nmr spectrum of compound VII, the β-vinylic proton appears at 7.28-7.33 ppm (Table I). This value is similar to the one reported for the thiophene analogs of compound VII, namely, compounds VIII and IX (13).



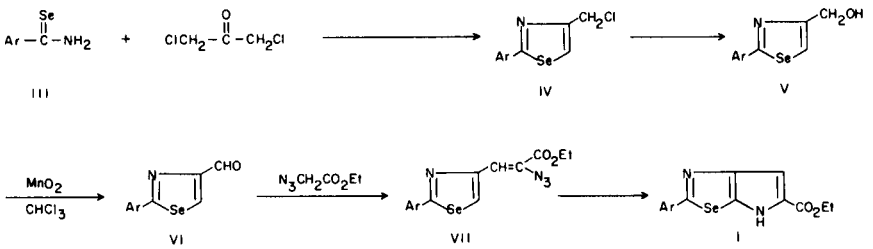
VIII



IX

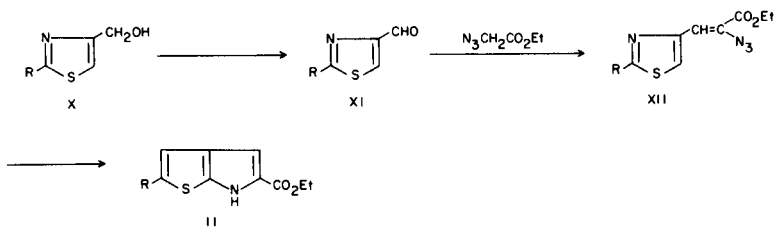
Cyclization of compound VII to the desired compound I was accomplished through heating the former in xylene. The structure of compound I was confirmed by spectro-

Scheme I



a) Ar = C_6H_5, b) Ar = p-BrC_6H_4-, c) Ar = p-ClC_6H_4-,

d) Ar = m-$CH_3C_6H_4$-, e) Ar = p-$CH_3OC_6H_4$-, f) Ar = C_4H_3S-



a) R = H, b) R = CH_3, c) R = C_6H_5

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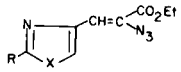
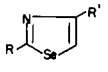
Table I

Proton Magnetic Resonance of Ethyl β-Substituted-α-azidoacrylate



Compound No.	X	R	2	5	β
VIIa	Se	Ph-	8.1-7.3 (m, 5H, aromatic)	8.81 (s, 1H)	7.28 (s, 1H)
VIIb	Se	*p*-Br-C_6H_4-	8.0-7.5 (q, 4H, aromatic)	8.91 (s, 1H)	7.33 (s, 1H)
VIIc	Se	*p*-Cl-C_6H_4-	8.0-7.33 (q, 4H, aromatic)	8.87 (s, 1H)	7.3 (s, 1H)
VIId	Se	*m*-CH_3-C_6H_4-	7.78-7.2 (m, 4H, aromatic)	8.90 (s, 1H)	7.28 (s, 1H)
VIIe	Se	*p*-$CH_3OC_6H_4$-	7.86 (d, 2H, aromatic, J = 8.5 Hz) 6.93 (d, 2H, aromatic, J = 8.5 Hz)	8.77 (s, 1H)	7.3 (s, 1H)
VIIf	Se	C_4H_3S-	7.60-7.36 (m, 2H, aromatic) 7.20-7.0 (m, 1H, aromatic)	8.83 (s, 1H)	7.23 (s, 1H)
XIIa	S	H-	8.78 (d, 1H, $J_{2,5}$ = 2 Hz)	8.23 (d, 1H, $J_{2,5}$ = 2 Hz)	7.26 (s, 1H)
XIIb	S	CH_3-	2.66 (s, 3H, CH_3)	8.0 (s, 1H)	7.08 (s, 1H)
XIIc	S	Ph-	8.0-7.33 (m, 5H, aromatic)	8.1 (s, 1H)	7.21 (s, 1H)

Table II



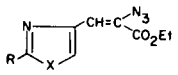
Compound No.	R	R′	M.p., C (a)	Yield	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
IVa	Ph-	CH_2Cl	43-44	90	$C_{10}H_8ClNSe$	46.78	46.99	3.12	3.03	5.46	5.24
IVb	*p*-BrC_6H_4-	CH_2Cl	71-73	95	$C_{10}H_7BrClNSe$	35.77	35.58	2.09	2.27	4.17	4.36
IVc	*p*-ClC_6H_4-	CH_2Cl	84-86	93	$C_{10}H_7Cl_2NSe$	41.24	41.43	2.40	2.59	4.81	4.62
IVd	*m*-$CH_3C_6H_4$-	CH_2Cl	48-50	85	$C_{11}H_{10}ClNSe$	48.80	48.98	3.70	3.88	5.18	5.35
IVe	*p*-$CH_3OC_6H_4$-	CH_2Cl	53-54	88	$C_{11}H_{10}ClNOSe$	46.07	46.26	3.49	3.68	4.89	4.98
IVf	C_4H_3S-	CH_2Cl	62-63	95	$C_8H_6ClNSSe$	36.57	36.38	2.29	2.05	5.33	5.14
Va	C_6H_5	CH_2OH	91-92	85	$C_{10}H_9NOSe$	50.42	50.61	3.78	3.95	5.88	5.69
Vb	*p*-BrC_6H_4-	CH_2OH	143-145	80	$C_{10}H_8BrNOSe$	37.85	37.99	2.52	2.39	4.42	4.31
Vc	*p*-ClC_6H_4-	CH_2OH	121-122	82	$C_{10}H_8ClNOSe$	44.04	44.23	2.94	2.73	5.14	5.36
Vd	*m*-$CH_3C_6H_4$-	CH_2OH	79-80	88	$C_{11}H_{11}NOSe$	52.38	52.19	4.37	4.18	5.56	5.74
Ve	*p*-$CH_3OC_6H_4$-	CH_2OH	67-68	80	$C_{11}H_{11}NO_2Se$	49.25	49.43	4.10	4.18	5.22	5.45
Vf	C_4H_3S-	CH_2OH	93-95	90	C_8H_7NOSSe	39.34	39.17	2.87	2.98	5.74	5.53
VIa	C_6H_5-	CHO	138-140 (b)	90	$C_{10}H_7NOSe$	50.85	50.64	2.97	3.14	5.93	6.15
VIb	*p*-BrC_6H_4-	CHO	104-106	85	$C_{10}H_6BrNOSe$	38.10	38.26	1.90	2.08	4.44	4.26
VIc	*p*-ClC_6H_4-	CHO	111-113	87	$C_{10}H_6ClNOSe$	44.36	44.15	2.22	2.04	5.18	5.36
VId	*m*-$CH_3C_6H_4$-	CHO	40-42	82	$C_{11}H_9NOSe$	52.80	52.97	3.60	3.45	5.60	5.77
VIe	*p*-$CH_3OC_6H_4$-	CHO	82-83	92	$C_{11}H_9NO_2Se$	49.62	49.81	3.38	3.45	5.26	5.38
VIf	C_4H_3S-	CHO	74-76	95	C_8H_5NOSSe	39.67	39.49	2.07	1.96	5.79	5.94

(a) Unless otherwise mentioned the compound was crystallized from ether. (b) B.p. 138-140° (4 mm).

scopic methods (ir, nmr and ms) and chemical analysis.

Starting from the readily available 2-substituted-4-hydroxymethylthiazole (X) (14), the desired compound II was synthesized according to Scheme I. Manganese dioxide oxidation of compound X in chloroform afforded 2-substituted-4-formylthiazole (XI). The condensation of the latter with ethyl azidoacetate (13) gave ethyl α-azido-β-(2-substituted-thiazol-4-yl)acrylate (XII). The structure of

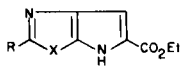
Table III



Compound No.	X	R′	M.p.,°C (a)	Yield	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
XIIa	S	H	69-70	50	$C_8H_6N_4O_2S$	42.86	42.98	3.57	3.39	25.00	24.86
XIIb	S	CH_3	66-68	65	$C_9H_{10}N_4O_2S$	45.38	45.52	4.20	4.36	23.53	23.37
XIIc	S	C_6H_5	101-102	55	$C_{14}H_{12}N_4O_2S$	56.00	56.17	4.00	4.18	18.67	18.49
VIIa	Se	C_6H_5	100-101	50	$C_{14}H_{12}N_4O_2Se$	48.41	48.62	3.46	3.28	16.14	16.32
VIIb	Se	p-BrC_6H_4-	109-110	45	$C_{14}H_{11}BrN_4O_2Se$	39.44	39.67	2.58	2.39	13.15	13.02
VIIc	Se	p-ClC_6H_4-	102-104	50	$C_{14}H_{11}ClN_4O_2Se$	44.04	43.91	2.88	2.65	14.68	14.53
VIId	Se	m-$CH_3C_6H_4$-	72-73	65	$C_{15}H_{14}N_4O_2Se$	49.86	49.67	3.88	3.69	15.51	15.36
VIIe	Se	p-$CH_3OC_6H_4$-	106-108	55	$C_{15}H_{14}N_4O_3Se$	47.75	47.96	3.71	3.90	14.85	14.97
VIIf	Se	C_4H_3S-	71-73	50	$C_{12}H_{10}N_4O_2SSe$	40.79	40.92	2.83	2.65	15.86	15.67

(a) All compounds were crystallized from ether.

Table IV



Compound No.	X	R	M.p.,°C (a)	Yield	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
Ia	Se	Ph-	182-184	80	$C_{14}H_{12}N_2O_2Se$	52.66	52.47	3.76	3.89	8.78	8.95
Ib	Se	p-BrC_6H_4-	235-237	85	$C_{14}H_{11}BrN_2O_2Se$	42.21	42.35	2.76	2.93	7.04	6.92
Ic	Se	p-ClC_6H_4-	220-222	85	$C_{14}H_{11}ClN_2O_2Se$	47.52	47.71	3.11	2.96	7.92	7.76
Id	Se	m-$CH_3C_6H_4$-	184-186	92	$C_{15}H_{14}N_2O_2Se$	54.05	54.23	4.20	4.41	8.41	8.60
Ie	Se	p-$CH_3OC_6H_4$-	181-182	95	$C_{15}H_{14}N_2O_3Se$	51.58	51.39	4.01	4.19	8.02	7.83
If	Se	C_4H_3S-	187-190	92	$C_{12}H_{10}N_2O_2SSe$	44.31	44.15	3.08	2.89	8.62	8.81
IIa	S	H-	136-138	90	$C_8H_8N_2O_2S$	48.98	49.15	4.08	3.89	14.29	14.12
IIb	S	CH_3-	217-219	85	$C_9H_{10}N_2O_2S$	51.43	51.61	4.76	4.59	13.33	13.15
IIc	S	Ph-	175-176	80	$C_{14}H_{12}N_2O_2S$	61.76	61.59	4.41	4.60	10.29	10.12

(a) All compounds were crystallized from carbon tetrachloride.

compound XII was confirmed by ir and nmr (See Table I and Experimental).

Compound XII under heating in xylene lost nitrogen and cyclized to the desired compound II. The physical data of all compounds prepared are summarized in Tables II, III and IV.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer Model 267 spectrograph (potassium bromide discs). The nmr spectra were recorded on a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 ev.

2-Phenyl-4-chloromethylselenazole (IVa).

A solution of selenobenzamide (184 mg., 1 mmole) and 1,3-dichloroacetone (127 mg., 1 mmole) in acetone (10 ml.) was stirred for 2 hours and allowed to stand at 0° overnight. The precipitate, m.p. 146-148°, was gradually added to a stirring solution of concentrated sulfuric acid (3 ml.). The solution was stirred for 15 minutes, and was added to water (20 ml.). The solution was made alkaline with a solution of sodium hydroxide and extracted with chloroform. The organic layer was dried, filtered, and evaporated. The residue was crystallized from ether to give 231 mg. (90%) of IVa, m.p. 43-44°; nmr (deuteriochloroform): 7.96-7.58 (m, 3H, aromatic), 7.50-7.18 (m, 3H, aromatic), and 4.70 ppm (s, 2H, CH_2Cl); ms

m/e (%): 257 (M^+, 100), 222 (47), 154 (26), 119 (3), and 104 (33).

Anal. Calcd. for $C_{10}H_8ClNSe$: C, 46.78; H, 3.12; N, 5.46. Found: C, 46.99; H, 3.03; N, 5.24.

Other 2-aryl-4-chloromethylselenazoles (IVb-IVf) were prepared similarly. (See Table II).

2-Phenyl-4-hydroxymethylselenazole (Va).

A mixture of IVa (2.565 g., 0.01 mole) and dilute sulfuric acid (15 ml. of concentrated sulfuric acid and 60 ml. of water) was refluxed in an oil bath at 108° for 8 hours. The solution was made alkaline with dilute sodium hydroxide and extracted with chloroform. The organic layer was dried, filtered and evaporated, and the residue was crystallized from ether to give Va (2.02 g., 85%), m.p. 91-92°; ir: 3290, 1030 cm^{-1} (OH); nmr (deuteriochloroform): 8.0-7.66 (m, 3H, aromatic), 7.5-7.20 (m, 3H, aromatic), 4.78 (s, 2H, CH_2) and 3.33 (broad s, 1H, OH); ms: m/e 239 (M^+, 100), 210 (19), 141 (22), 104 (43), 83 (30).

Anal. Calcd. for $C_{10}H_9NOSe$: C, 50.42; H, 3.78; N, 5.88. Found: C, 50.61; H, 3.95; N, 5.69.

Other 2-aryl-4-hydroxymethylselenazoles (Vb-Vf) were prepared similarly (See Table I).

2-Phenyl-4-formylselenazole (VIa).

A mixture of Va (2.38 g., 0.01 mole) and manganese dioxide (24 g.) in 150 ml. of chloroform was stirred for 4 hours. The reaction mixture was filtered and evaporated. The residue was distilled under the reduced presure to give 2.12 g. (90%) of VIa, b.p. 138-140°/4 mm; ir: 2810, 1680 cm^{-1} (aldehyde), nmr (deuteriochloroform): 10.07 (s, 1H, HCO), 8.81 (s, 1H, H_5), 8.06-7.80 (m, 2H, aromatic), and 7.56-7.33 ppm (m, 3H, aromatic), ms: m/e (relative intensity) 237 (90), 235 (50), 134 (34), 128 (77) and 104 (36).

Anal. Calcd. for $C_{10}H_7NOSe$: C, 50.85; H, 2.97; N, 5.93. Found: C, 50.64; H, 3.14; N, 6.15.

Other 2-aryl-4-formylselenazoles (VIb-VIf) were prepared similarly.

Ethyl α-Azido-β-(2-phenylselenazol-4-yl)acrylate (VIIa).

To a stirring solution of sodium (276 mg., 12 mmoles) in absolute ethanol (9 ml.) at 0° was added dropwise a solution of VIa (708 mg., 3 mmoles) and ethyl azidoacetate (1548 mg., 12 mmoles) in 10 ml. of absolute ethanol. After two hours at 0°, the mixture was added to a saturated solution of ammonium chloride. The mixture was extrcted with ether. The organic layer was washed once with water and dried (anhydrous sodium sulfate). The ether was evaporated and the residue was purified by tlc (silica gel, chloroform) to give 520 mg. (50%) of VIIa, m.p. 100-101° (ether); ir: 2155 (azide), 1710 cm^{-1} (ester); nmr (deuteriochloroform): 8.81 (s, 1H, H_5), 8.1-7.3 (m, 5H, aromatic), 7.28 (s, 1H, H_β), 4.35 (q, 2H, OCH_2), and 1.35 ppm (t, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{12}N_4O_2Se$: C, 48.41; H, 3.46; N, 16.14. Found: C, 48.62; H, 3.28; N, 16.32.

Other ethyl α-azido-β-(2-arylselenazol-4-yl)acrylates (VIIb-VIIf) were prepared similarly.

Ethyl 2-Phenylpyrrolo[3,2-*d*]selenazole-5-carboxylate (Ia).

A solution of VIIa (347 mg., 1 mmole) in xylene (10 ml.) was refluxed for two hours. The solvent was evaporated. The tlc of the residue (silica gel, chloroform) gave 255 mg. (80%) of Ia, m.p. 182-184°; nmr (deuteriochloroform): 10.43 (broad s, 1H, NH), 8.06-7.21 (m, 6H, aromatic), 4.40 (q, 2H, OCH_2), and 1.40 ppm (t, 3H, CH_3); ms: m/e (relative intensity) 320 (M^+, 100), 274 (92), 143 (35), 117 (15), and 104 (26).

Anal. Calcd. for $C_{14}H_{12}N_2O_2Se$: C, 52.66; H, 3.76; N, 8.78. Found: C, 52.47; H, 3.89; N, 8.95.

Other ethyl 2-aryl-pyrrolo[3,2-*d*]selenazole-5-carboxylates were prepared similarly (Table IV).

3-Formylthiazole (XIa).

A mixture of 3-hydroxymethylthiazole (Xa, 1.15 g., 0.01 mole) (15) and manganese dioxide (11.5 g.) in 40 ml. of chloroform was stirred for 4 hours. The reaction mixture was filtered and evaporated to dryness. The residue was crystallized from ether to give 1.02 g. (90%) of XIa, m.p. 61-62° [lit. (16) m.p. 65-66°]; ir: 2830 and 1740 cm^{-1} (aldehyde); nmr (deuteriochloroform): 10.23 (s, 1H, HCO), 9.08 (d, 1H, H_2, $J_{2,5}$ = 2 Hz), and 8.35 ppm (d, 1H, H_5, $J_{2,5}$ = 2 Hz).

Anal. Calcd. for C_4H_3NOS: C, 42.48; H, 2.65; N, 12.39. Found: C, 42.65; H, 2.86; N, 12.18.

Ethyl α-Azido-β-(thiazol-4-yl)acrylate (XIIa).

To a stirring solution of sodium (522 mg., 24 mmoles) in 18 ml. of absolute ethanol at 0° was added dropwsie a solution of XIa (678 mg., 6 mmoles) and ethyl azidoacetate (3096 mg., 24 mmoles) in 30 ml. of absolute ethanol. After 2 hours at 0°, the mixture was added to a saturated solution of ammonium chloride. The mixture was extracted with ether. The organic layer was washed once with water and dried (sodium sulfate). The ether was evaporated and the residue was purified by tlc (silica gel, chloroform) to give 672 mg. (50%) of XIIa, m.p. 69-70° (ether); ir (potassium bromide): 1710 cm^{-1} (ester); nmr (deuteriochloroform): 8.78 (d, 1H, H_2, $J_{2,5}$ = 2 Hz), 8.23 (d, 1H, H_5, $J_{2,5}$ = 2 Hz), 7.26 (s, 1H, H_β), 4.37 (q, 2H, OCH_2), and 1.37 ppm (t, 3H, CH_3).

Anal. Calcd. for $C_8H_8N_4O_2S$: C, 42.86; H, 3.57; N, 25.00. Found: C, 42.98; H, 3.39; N, 24.86.

Other ethyl α-azido-β-(2-substituted-4-thiazolyl)acrylates (XIIb, XIIc) were prepared similarly (Table III).

Ethyl Pyrrolo[3,2-*d*]thiazole-5-carboxylate (IIa).

A solution of XIIa (224 mg., 1 mmole) in xylene (5 ml.) was refluxed for 2 hours. The solvent was evaporated and the residue was crystallized from carbon tetrachloride to give 176 mg. (90%) of IIa, m.p. 136-138°; nmr (deuteriochloroform): 8.71 (s, 1H, H_2), 7.63 (s, 1H, H_4), 4.65 (q, 2H, OCH_2), and 1.53 ppm (t, 3H, CH_3); ms: m/e (relative intensity): 196 (M^+, 66), 151 (24), 150 (100), 122 (14), 95 (20) and 69 (8).

Acknowledgment.

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REFERENCES AND NOTES

(1) A preliminary account of this work was presented in the VIth Symposium on Chemistry of Heterocyclic Compounds, Brno, Czechoslovakia, July 1978. For part XXVII see reference 8.

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