Selenium Heterocycles XXVII (1). Synthesis of Thieno[2,3-*d*]thiazole and Selenolo[3,4-*d*]thiazole. Two Novel Heterocycles.

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Starting from the readily available aryl 2-substituted-4-methyl-5-thiazolyl ketones, a series of 2,6-disubstituted-thieno[3,4-*d*]thiazoles and 2,6-disubstituted-selenolo[3,4-*d*]thiazoles were prepared. The structures of these compounds were confirmed by analytical, spectroscopic methods and through the reaction with dimethyl acetylenedicarboxylate.

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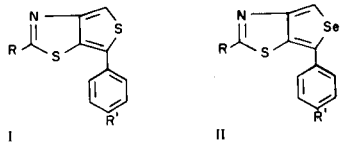
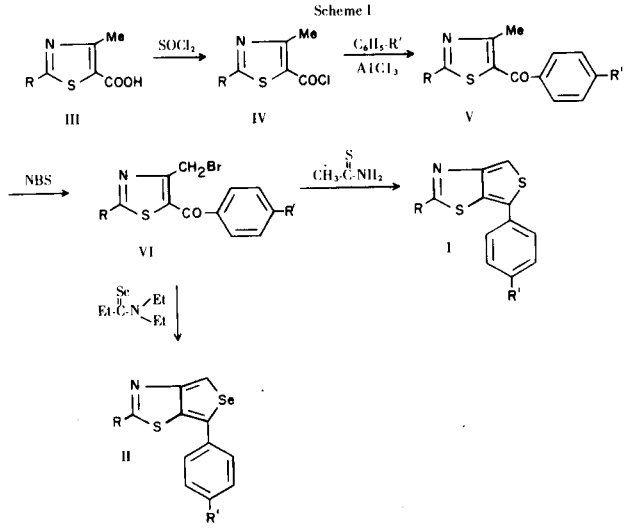
As a continuation of the study on the chemistry of selenium heterocyclic compounds (2-6), and as a part of a program designed to expand the chemistry of fused thiophene and selenophene heterocycles (7,8), it became necessary to synthesize substituted-thieno[3,4-*d*]thiazoles (I) and substituted-selenolo[3,4-*d*]thiazoles (II) for biological evaluation.



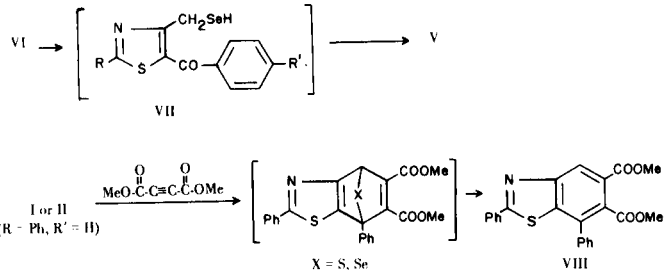
I II

The starting material, aryl 2-substituted-4-methyl-5-thiazolyl ketones (V) could be prepared from the Friedel-Crafts' reaction of 2-substituted-4-methyl-thiazole-5-carboxyl chloride (IV) (9,10) with aromatic hydrocarbons (9). Reaction of *N*-bromosuccinimide with compound V afforded aryl 2-substituted-4-bromomethy-5-thiazolyl ketones (VI) in high yield. Reaction of thioacetamide with the latter, according to our procedure reported previously (7), gave the desired compound I. The reaction of *N,N*-diethylselenopropionamide (11) with compound VI afforded compound V in addition to the desired compound II. It is worthwhile to note that only debromination without reduction of the keto group was observed in all cases. Probably, debromination occured through the intermediate VII. In fact, in all cases we observed the precipitation of selenium in the reaction mixture (Scheme I).

Scheme I



a) R = R' = H; b) R = H, R' = CH_3O-; c) R = Ph, R' = H; d) R = Ph, R' = CH_3O-; e) R = Ph, R' = CH_3S-



The reaction of compound I (R = C_6H_5, R' = H) or II (R = C_6H_5, R' = H) with dimethyl acetylenedicarboxylate afforded dimethyl 2,7-diphenylbenzothiazol-5,6-dicarboxylate (VIII) in support of the structures I and II (Scheme I).

The nmr spectrum of compound II was also in agreement with the suggested structure. In the nmr spectrum of this compound the proton which is geminal to the selenium atom appears as a strong singlet and a weak doublet centered around the singlet. This doublet is assigned to the splitting caused by the presence of the selenium siotope ^{77}Se with a natural abundance of 7.5%. The selenium splitting constant was found to be 46 cps. This splitting constant was similar to the one reported for the fused selenophene (7,8).

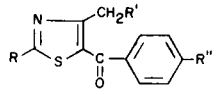
The structure of all compounds was confirmed by analytical and spectroscopic methods.

The physical constants of all compounds prepared are summarized in Tables I and II.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage 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.

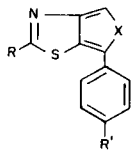
Table I



Compound	R	R′	R″	Yield (%)	M.p. °c (a)	Formula	Calcd C%	Found C%	Calcd. H%	Found H%	Calcd. N%	Found N%
Va	H	H	H	50	78-79 (b)							
Vb	H	H	OCH_3	40	138-140	$C_{12}H_{11}NO_2S$	61.80	61.92	4.72	4.54	6.01	6.19
Vc	Ph	H	H	55	58-59	$C_{17}H_{13}NOS$	73.12	73.01	4.66	4.84	5.02	5.21
Vd	Ph	H	OCH_3	45	124-126 (c)	$C_{18}H_{15}NO_2S$	69.90	69.75	4.85	4.67	4.53	4.71
Ve	Ph	H	SCH_3	35	103-104 (c)	$C_{18}H_{15}NOS_2$	66.46	66.29	4.62	4.45	4.31	4.50
VIa	H	Br	H	70	72-73	$C_{11}H_8BrNOS$	46.81	46.69	2.84	2.65	4.96	4.78
VIb	H	Br	OCH_3	55	101-103	$C_{12}H_{10}BrNO_2S$	46.15	46.34	3.21	3.35	4.49	4.67
VIc	Ph	Br	H	80	92-93	$C_{17}H_{12}BrNOS$	56.98	56.82	3.35	3.52	3.92	4.12
VId	Ph	Br	OCH_3	70	120-121 (c)	$C_{18}H_{14}BrNO_2S$	55.67	55.48	3.61	3.79	3.61	3.52
VIe	Ph	Br	SCH_3	65	153-155 (c)	$C_{18}H_{14}BrNOS_2$	53.46	53.62	3.47	3.58	3.47	3.63

(a) Unless otherwise mentioned the compound was crystallized from ether-petroleum ether. (b) M.p. 79.5-80.5° [lit. (9)]. (c) This compound was crystallized from ether.

Table II



Compound	R	R′	X	Yield (%)	M.p. °c (a)	Formula	Calcd. C%	Found C%	Calcd. H%	Found H%	Calcd. N%	Found N%
Ia	H	H	S	80	126-128 (b)	$C_{11}H_7NS_2$	60.83	60.66	3.23	3.11	6.45	6.63
Ib	H	OCH_3	S	65	56-58 (b)	$C_{12}H_9NOS_2$	58.30	58.56	3.64	3.82	5.67	5.84
Ic	Ph	H	S	85	127-128	$C_{17}H_{11}NS_2$	69.62	69.79	3.75	3.92	4.78	4.86
Id	Ph	OCH_3	S	80	132-133	$C_{18}H_{13}NOS_2$	66.87	66.68	4.02	4.16	4.33	4.51
Ie	Ph	SCH_3	S	65	128-129	$C_{18}H_{13}NS_3$	63.72	63.91	3.83	3.99	4.13	4.01
IIa	H	H	Se	60	99-100 (b)	$C_{11}H_7NSSe$	50.00	50.19	2.65	2.47	3.50	5.15
IIb	H	OCH_3	Se	40	82-84 (b)	$C_{12}H_9NOSSe$	48.98	49.12	3.06	2.91	4.76	4.84
IIc	Ph	H	Se	70	142-143	$C_{17}H_{11}NSSe$	60.00	60.17	3.24	3.42	4.12	4.28
IId	Ph	OCH_3	Se	75	134-135	$C_{18}H_{13}NOSSe$	58.38	58.56	3.51	3.48	3.78	3.87
IIe	Ph	SCH_3	Se	65	141-144	$C_{18}H_{13}NS_2Se$	55.96	56.15	3.37	3.23	3.63	3.77

(a) Unless otherwise mentioned the compound was crystallized from ethanol. (b) This compound was crystallized from ether.

p-Methoxyphenyl 4-Methyl-5-thiazolyl Ketone (Vb).

A stirring mixture of 4-methylthiazole-5-carboxyl chloride (IV, R = H; 16.15 g., 0.1 mole) (9) and aluminium chloride (26.7 g., 0.2 mole) in anisole (160 ml.) was heated in a water bath for 10 hours. After cooling, the complex was decomposed with ice-water. The organic layer was separated and the mother liquid was extracted with chloroform. The combined organic solvents were washed with a saturated sodium bicarbonate solution in water. The organic layer was dried, filtered and distilled under reduced pressure. The residue was crystallized from ether to give 9.32 g. (40%) of Vb; m.p. 138-140°, ir: 1640 cm^{-1} (C=O); nmr (deuteriochloroform): 8.90 (s, 1H, H_2), 7.83 (d, 2H, aromatic), 6.93 (d, 2H, aromatic), 3.90 (s, 3H, CH_3O), and 2.63 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 61.80; H, 4.72; N, 6.01. Found: C, 61.92; H, 4.54; N, 6.19.

Compounds Va and Vc were prepared similarly (Table I).

p-Methoxyphenyl 4-Methyl-2-phenyl-5-thiazolyl Ketone (Vd).

A stirring mixture of 4-methyl-2-phenylthiazole-5-carboxyl chloride (IV, R = C_6H_5; 2.375 g., 0.01 mole), anisole (1.08 g., 0.01 mole) and aluminium chloride (1.335 g., 0.01 mole) in carbon disulfide (15 ml.) was refluxed in a water bath for 6 hours

and worked up as above to give 1.39 g. (45%) of Vd, m.p. 124-126°; ir: 1638 cm^{-1} (C=O); nmr (deuteriochloroform): 8.26-8.0 (m, 2H, aromatic), 7.91 (d, 2H, aromatic), 7.63-7.36 (m, 3H, aromatic), 7.03 (d, 2H, aromatic), 3.88 (s, 3H, CH_3O), and 2.66 ppm (s, 3H, CH_3); ms: m/e (relative intensity) 309 (M^+, 100), 308 (98), 278 (97), 219 (23), 135 (64), 104 (28), and 77 (32).

Anal. Calcd. for $C_{18}H_{15}NO_2S$: C, 69.90; H, 4.85; N, 4.53. Found: C, 69.75; H, 4.67; N, 4.71.

Compound Ve was prepared similarly (Table 1).

Phenyl 4-Bromomethyl-5-thiazolyl Ketone (VIa).

A mixture of Va (2.03 g., 0.01 mole) (9) and *N*-bromosuccinimide (1.96 g., 0.011 mole) in 30 ml. of carbon tetrachloride was irradiated with a 500 W (G. E. Photospot) lamp while heating and stirring at reflux temperature for 4 hours. The reaction mixture was cooled and filtered. The solvent was evaporated and the residue was crystallized from ether-petroleum ether to give 1.97 g. (70%) of VIa, m.p. 72-73°; ir: 1645 cm^{-1} (C=O); nmr (deuteriochloroform): 8.60 (s, 1H, H_2), 7.86-7.16 (m, 5H, C_6H_5), and 4.62 ppm (s, 2H, CH_2).

Anal. Calcd. for $C_{11}H_8BrNOS$: C, 46.81; H, 2.84; N, 4.96. Found: C, 46.69; H, 2.65; N, 4.78.

Other aryl 2-substituted-4-bromomethyl-5-thiazolyl ketones were prepared similarly (Table I).

6-Phenylthieno[3,4-*d*]thiazole (Ia).

A solution of Va (282 mg., 1 mmole) and thioacetamide (82.5 mg., 1.1 mmoles) in 10 ml. of ethanol was refluxed for 4 hours. The solvent was evaporated and the residue was purified by tlc (Silica gel, chloroform). The desired compound was crystallized from ether to give 174 mg. (80%) of Ia, m.p. 126-128°; nmr (deuteriochloroform): 8.90 (s, 1H, H_2), 7.63 (s, 1H, H_4), and 7.76-7.20 ppm (m, 5H, Ph); ms: m/e (relative intensity) 217 (M^+, 100), 216 (23), 190 (10), 145 (14), 121 (19), 95 (16), 77 (20), 69 (15), and 45 (12).

Anal. Calcd. for $C_{11}H_7NS_2$: C, 60.83; H, 3.23; N, 6.45. Found: C, 60.66; H, 3.11; N, 6.63.

Other 2,6-disubstituted-thieno[3,4-*d*]thiazoles were prepared similarly (Table II).

6-Phenylselenolo[3,4-*d*]thiazole (IIa).

A solution of Va (282 mg., 1 mmole) and *N*,*N*-deithylselenopropionamide (211 mg., 1.1 mmoles) (11) in 10 ml. of ethanol was refluxed for 4 hours. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform). The fast moving fraction was crystallized from ether to give 158 mg. (60%) of IIa, m.p. 99-100°; nmr (deuteriochloroform): 9.03 (s, 1H, H_2), 8.33 [s, 1H, H_4; this hydrogen was splitted into a doublet with J = 46 Hz (^{77}Se coupling)], and 7.65-7.23 ppm (m, 5H, Ph); ms: m/e (relative intensity) 265 (M^+, 100), 185 (21), 158 (34), 126 (45), 114 (11), 93 (11), 89 (22), 77 (11), 74 (12), 69 (23), 51 (16), and 39 (14).

Anal. Calcd. for $C_{11}H_7NSSe$: C, 50.00, H, 2.65; N, 5.30. Found: C, 50.19; H, 2.47; N, 5.15.

The slow moving fration was crystallized from ether-petroleum ether to give 40 mg. (20%) of Va, m.p. 78-79°; mixed melting point with an authentic sample 78-79° (9).

Dimethyl 2,7-Diphenylbenzothiazol-5,6-dicarboxylate (VIII).

A solution of Ic (293 mg., 1 mmole) and dimethyl acetylenedicarboxylate (142 mg., 1 mmole) in 10 ml. of xylene was refluxed for 4 days. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform-methanol, 98:2) to give 121 mg. (30%) of VIII, m.p. 148-150° (ether-petroleum ether); ir: 1730 cm^{-1} (ester); nmr (deuteriochloroform): 8.55 (s, 1H, H_4), 8.08-7.85 (m, 2H, aromatic), 7.50-7.38 (m, 8H, aromatic), 3.91 (s, 3H, CH_3O), and 3.50 ppm (s, 3H, CH_3O); ms: m/e (relative intensity) 403 (M^+, 59), 373 (25), 372 (100), 285 (35) 182 (13), 178 (14), 142 (14), 105 (12), 57 (15), and 43 (14).

Anal. Calcd. for $C_{23}H_{17}NO_4S$: C, 68.49; H, 4.22; N, 3.47. Found: C, 68.28; H, 4.41; N, 3.28.

Compound VIII was also obtained in 35% yield from the reaction of IIc with dimethyl acetylenedicarboxylate.

Acknowledgement.

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REFERENCES AND NOTES

(1) A preliminary account of this work was presented in the 6th International Congress of Heterocyclic Chemistry, Tehran, Iran, July 1977. For part XXVI see reference 8.

(2) I. Lalezari, A. Shafiee and M. Yalpani, *Tetrhedron Letters*, 5105 (1969).

(3) I. Lalezari, A. Shafiee and M. Yalpani, *J. Org. Chem.*, **38**, 338 (1973).

(4) A. Shafiee and I. Lalezari, *J. Heterocyclic Chem.*, **12**, 675 (1975).

(5) A. Shafiee, I. Lalezari and F. Savabi, *Synthesis*, 764 (1977).

(6) A. Shafiee, I. Lalezari and F. Savabi, *ibid.*, 765 (1977).

(7) A. Shafiee, *J. Heterocyclic Chem.*, **15**, 473 (1978).

(8) A. Shafiee and E. Behnam, *ibid.*, **15**, 589 (1978).

(9) P. N. Craig and M. P. Olmstead, *J. Org. Chem.*, **22**, 559 (1957).

(10) G. Csavassy and Z. A. Gyorfi, *Ann. Chem.*, 1195 (1974).

(11) F. Malek-Yazdi and M. Yalpani, *Synthesis*, 328 (1977).