Selenium Heterocycles. XXXIX [1]. Synthesis of Thieno[3,4-*d*]thiazole, Thieno[3,4-*d*]selenazole, Selenolo[3,4-*d*]thiazole and Selenolo[3,4-*d*]selenazole

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Starting from readily available methyl 2-substituted-4-methyl-5-thiazolyl ketone and methyl 4-methyl-2-phenyl-5-selenazolyl ketone, thieno[3,4-*d*]thiazole, thieno[3,4-*d*]selenazole, selenolo[3,4-*d*]thiazole and selenolo[3,4-*d*]selenazole were prepared. The structures of all compounds were confirmed by analytical and spectroscopic methods.

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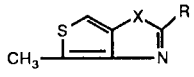
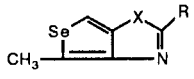
In continuation of the study on the chemistry of selenium heterocyclic compounds [2-8] and as a part of a program designed to expand the chemistry of fused thiophene and selenophene heterocycles [9,10], it became necessary to synthesize 2-substituted-6-methylthieno[3,4-*d*]-thiazole (**1**, X = S), its selenium analog (**1**, X = Se), 2-substituted-6-methylselenolo[3,4-*d*]thiazole (**2**, X = S), and its selenium analog (**2**, X = Se) for biological evaluation.



1



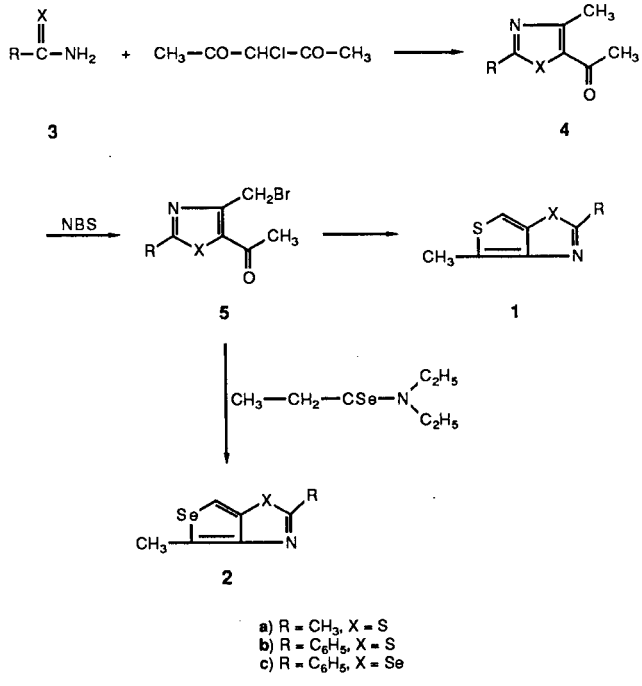
2

The starting material methyl 4-methyl-2-phenyl-5-selenazolyl ketone (**4c**) could be prepared from the reaction of selonobenzamide (**3c**) [11] with 3-chloroacetylacetone [12]. Reaction of *N*-bromosuccinimide with compound **4c** afforded methyl 4-bromomethyl-2-phenyl-5-selenazolyl ketone (**5c**) in moderate yield. Reaction of thioacetamide with the latter, according to our procedure reported previously [9], gave the desired compound **1c**. The reaction of *N,N*-diethylselenopropionamide [13] with compound **5c** afforded compound **2c**.

Reaction of *N*-bromosuccinimide with methyl 2-substituted-4-methyl-5-thiazolyl ketones **4a** or **4b** [14,15] gave methyl 2-substituted-4-bromomethyl-5-thiazolyl ketone **5a** or **5b**. Reaction of thioacetamide with **5a** or **5b** afforded 2-substituted-6-methylthieno[3,4-*d*]thiazoles **1a** or **1b** in high yield. The reaction of *N,N*-diethylselenopropionamide with compounds **5a** or **5b** yielded 2-substituted-6-methylselenolo[3,4-*d*]selenazoles **2a** or **2b**.

The nmr spectrum of compound **2** was 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 isotope ^{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 [9,10].

Scheme 1



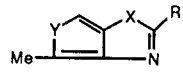
a) R = CH_3, X = S
b) R = C_6H_5, X = S
c) R = C_6H_5, X = Se

The structure of all compounds was confirmed by analytical and spectoscopic methods. The physical constants of compounds **1** and **2** prepared are summarized in Table 1.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer Model 781 spectrograph (potassium bromide disks). The nmr spectra were recorded on a Varian T-60A 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 1



Compound	R	X	Y	Yield (%)	MP °C [a]	Formula	Calcd. C%	Found C%	Calcd. H%	Found H%	Calcd. N%	Found N%
1a	CH_3	S	S	70	79-80	$C_7H_7NS_2$	49.70	49.62	4.14	4.02	8.28	8.17
1b	C_6H_5	S	S	75	81-82	$C_{12}H_9NS_2$	62.34	62.19	3.90	4.01	6.06	5.98
1c	C_6H_5	Se	S	70	89-90	$C_{12}H_9NSSe$	51.80	51.75	3.24	3.12	5.04	4.90
2a	CH_3	S	Se	80	83-84	C_7H_7NSSe	38.89	38.74	3.24	3.09	6.48	6.51
2b	C_6H_5	S	Se	80	86-87	$C_{12}H_9NSSe$	51.80	51.91	3.24	3.36	5.04	4.96
2c	C_6H_5	Se	Se	65	79-80	$C_{12}H_9NSe_2$	44.31	44.46	2.77	2.69	4.31	4.43

[a] All Compounds crystallized from ether-petroleum ether.

Methyl 4-Methyl-2-phenyl-5-selenazolyl Ketone (**4c**).

To a stirring solution of selenobenzamide (5.55 g, 0.03 mole) in dry acetone (60 ml) at 0° was added dropwise a solution of 3-chloroacetylacetone (4.035 g, 0.03 mole) in 10 ml of dry acetone. After the addition was complete the mixture was stirred at room temperature for 30 minutes and then refluxed for 5 hours. The solvent was removed and the residue was treated with saturated aqueous sodium bicarbonate solution and extracted with chloroform. The chloroform was evaporated and the residue was crystallized from ethanol to give 4.35 g, (55%) of **4c**, mp 65-67°; ir: 1635 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): 8.40 (m, 2H, aromatic), 7.60 (m, 3H, aromatic), 3.60 (s, 3H, CH_3), and 2.60 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{11}NOSe$: C, 54. 55; H, 4.17; N, 5.30. Found: C, 54.67; H, 4.07; N, 5.16.

Methyl 4-Bromomethyl-2-phenyl-5-selenazolyl Ketone (**5c**).

A mixture of **4c** (2.64 g, 0.01 mole) and *N*-bromosuccinimide (1.96 g, 0.01 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 2.74 (80%) of **5c**, mp 124-125°C; ir: 1645 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): 8.07 (m, 2H, aromatic), 7.58 (m, 3H, aromatic), 5.03 (s, 2H, CH_2), and 2.60 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{10}BrNOSe$: C, 41.98; H, 2.92; N, 4.08. Found: C, 42.05; H, 3.04; N, 4.19.

Methyl 4-Bromomethyl-2-methyl-5-thiazolyl Ketone (**5a**).

This compound was prepared similar to **5c** in 60% yield, mp 55-56° (ether-petroleum ether); ^1H nmr (deuteriochloroform): 4.80 (s, 2H, CH_2), 2.60 (s, 3H, CH_3), and 2.40 ppm (s, 3H, CH_3); ms: m/e (relative intensity) 235 (75), 233 (75), 220 (10), 192 (10), 154 (100), 139 (36), 112 (38), 70 (95) and 43 (97).

Anal. Calcd. for C_7H_8BrNOS: C, 35.90; H, 3.42; N, 5.98. Found: C, 35.78; H, 3.58; N, 6.12.

Methyl 4-Bromomethyl-2-phenyl-5-thiazolyl Ketone (**5b**).

This compound was prepared similar to **5c** in 85% yield, mp 109-110°; ^1H nmr (deuteriochloroform): 7.90 (m, 2H, aromatic), 7.42 (m, 3H, aromatic), 4.73 (s, 2H, CH_2, Br), and 2.45 ppm (s, 3H, CH_3); ms: m/e (relative intensity) 297 (74), 295 (74), 216 (100), 70 (19) and 59 (99).

Anal. Calcd. for $C_{12}H_{10}BrNOS$: C, 48.65; H, 3.38; N, 4.73. Found: C, 48.56; H, 3.43; N, 4.85.

6-Methyl-2-phenylthieno[3,4-*d*]selenazole (**1c**).

A solution of **5c** (343 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 (silcia gel, chloroform). The desired compound was crystallized from ether-petroleum ether to give 195 mg (70%) of **1c** mp 89-90°; ^1H nmr (deuteriochloroform): 7.90 (m, 2H, aromatic), 7.50 (s, 1H, H_4), 7.40 (m, 3H, aromatic), and 2.60 ppm (s, 3H, CH_3); ms: m/e (relative intensity): 279 (M^+, 100), 199 (75), 174 (23), 96 (26), 78 (15), 64 (30) and 52 (26).

Anal. Calcd. for $C_{12}H_9NSSe$: C, 51.80; H, 3.24; N, 5.04. Found: C, 51.75; H, 3.12; N, 4.90.

Compounds **1a** and **1b** were prepared similarly (Table 1).

6-Methyl-2-phenylseleno[3,4-*d*]selenazole (**2c**).

A solution of **5c** (343 mg, 1mmole) and *N,N*-diethylselenopropionamide (211 mg 1.1 mmoles) [13] 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-petroleum ether to give 211 mg (65%) of **2c**, mp 79-80°; nmr (deuteriochloroform): 8.13 [s, 1H, H_4; this hydrogen was split into a doublet with J = 46 Hz (^{77}Se coupling)], 8.00 (m, 2H, aromatic), 7.50 (m, 3H, aromatic), and 2.60 ppm (s, 3H, CH_3); ms: m/e (relative intensity) 327 (79), 325 (M^+, 74), 243 (57), 215 (96), 214 (100), 200 (52), 159 (95), 146 (71), 129 (96), 116 (98), 86 (98), 77 (31), 63 (41), 55 (39) and 41 (84).

Anal. Calcd. for $C_{12}H_9NSe_2$: C, 44.31; H, 2.77; N, 4.31. Found: C, 44.46; H, 2.69; N, 4.43.

Compounds **2a** and **2b** were prepared similarly (Table 1).

Acknowledgement.

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