Selenium-Sulfur Analogs. 6. Selenoisosteres of Levamisole

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A series of three new isosteres of levamisole was prepared by the substitution of the phenyl ring by the thienyl and selenienyl moieties and of the thiazole group by selenazole. The physicochemical properties and infrared spectra of the sulfur- and selenium-containing analogs were very similar. Differentiation was most apparent in the nuclear magnetic resonance spectra where the α- and β-protons of the selenienyl compounds were shifted downfield relative to those of the corresponding thienyl compounds. With deuterated trifluoroacetic acid as the solvent, a more rapid exchange was observed for the α-proton of the selenienyl ring of compounds **17** and **18** compared to that observed for compound **16**.

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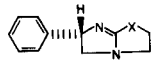
Levamisole {(−)-6-phenyl-2,3,5,6-tetrahydroimidazo-[2,1-*b*]thiazole} (X = S), originally evaluated as an anthelmintic, has generated recent interest as an immunopotentiating agent. As part of our research program to prepare and evaluate selenium-containing analogs of compounds of medicinal interest, we synthesized the selenazole isostere of levamisole, {(−)-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]selenazole} (X = Se). In several assay systems this compound was essentially equivalent to the parent (1). The unique biologic properties of these compounds have stimulated interest in the preparation of their ^{75}Se-labeled analogs. However, the instability of the thiazole ring *in vivo* (2,3) requires the placement of the radionuclide at another site. The 6-thienyl analog of levamisole also has potent pharmacologic effects (4,5). The substitution of a selenienyl moiety at the 6-position would satisfy the requirement for an alternative site, especially because radiolabeled selenophene can be prepared using a variant of the diyne method (6,7). We now report the synthesis of a novel series of selenium isosteres of levamisole encompassing this structural modification (Figure 1).



X = S Levamisole
X = Se Seleno-Levamisole

The selenium isosteres were prepared by modifying the synthetic procedure described by Raeymaekers (4) (Scheme I). Thus, 2-acetylthiophene **1** and 2-acetylselenophene **2** (8) were brominated to give after chromatography the corresponding α-bromoketones **3** and **4**, respectively. Compound **3** previously characterized as an oil (9) was a crystalline solid in our hands. The bromoketones were reacted with commercially available 2-amino-2-thiazoline **5** or 2-amino-2-selenazoline **6** (10) to form the *N*-alkylated products **7-9** which were isolated as their hydrogen bromide salts in yields >90%. Subsequent acetylation of the imino function afforded the corresponding imides **10-12**. Highest yields (60-70%) were realized when dichloroethane was used as solvent. Reduction of the ketone with sodium borohydride gave the enantiomeric alcohols **13-15** in 70-90% yields. Finally, cyclization to the desired levamisole isosteres **16-18** was effected with thionyl chloride followed by treatment with aqueous base.

Scheme I

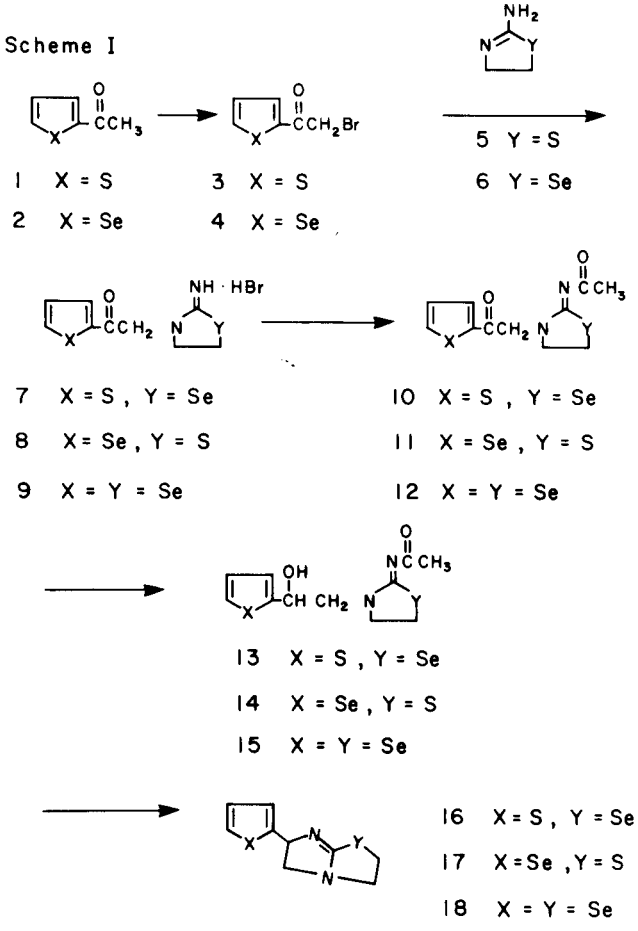


Table 1

Compound No.	% Yield	Mp °C	Spectral Data NMR (δ downfield from TMS)	IR (potassium bromide) (cm^{-1})
7	92	211.5-213 dec	3.48 (m, 2H), 4.03 (m, 2H), 5.27 (s, 2H), 7.25 (t, 1H), 8.00 (m, 2H), 9.37 (broad, 1H), 9.80 (broad, 1H) (a)	2990 (s), 1635 (s), 1590 (s), 1408 (s), 1240 (s)
8	96	206-209 dec	3.57 (m, 2H), 4.03 (m, 2H), 5.35 (s, 2H), 7.55 (dd, 1H), 8.26 (d, 1H), 8.81 (d, 1H), 9.45 (broad, 1H), 9.95 (broad, 1H) (a)	2950 (s), 1650 (s), 1595 (s), 1420 (s), 1240 (s)
9	92	216-218 dec	3.47 (t, 2H), 4.03 (t, 2H), 5.23 (s, 2H), 7.47 (m, 1H), 8.13 (d, 1H), 8.70 (d, 1H), 9.50 (broad, 2H) (a)	3000 (s), 1638 (s), 1590 (s), 1418 (s), 1240-1230 (s)
10	67	131-132	2.13 (s, 3H), 3.02 (t, 2H), 3.75 (t, 2H), 5.02 (s, 2H), 7.12 (m, 1H), 7.65 (d, 1H), 7.80 (d, 1H) (b)	1660 (s), 1618 (s), 1522 (s), 1390 (s), 1270-1235 (s)
11	62	134-137	2.13 (s, 3H), 3.15 (t, 2H), 3.73 (t, 2H), 5.00 (s, 2H), 7.40 (dd, 1H), 8.05 (d, 1H), 8.43 (d, 1H) (b)	1655 (s), 1615 (s), 1520 (s), 1385 (s), 1270-1240 (s)
12	71	125-128	2.15 (s, 3H), 3.02 (t, 2H), 3.73 (t, 2H), 5.02 (s, 2H), 7.37 (m, 1H), 8.03 (d, 1H), 8.40 (d, 1H) (b)	1655 (s), 1618 (s), 1520 (s), 1392 (s), 1265-1230 (s)
13	68	87-89	2.18 (s, 3H), 3.03 (m, 2H), 3.47-4.20 (m, 4H), 5.28 (dd, 1H), 6.12 (broad, 1H), 6.93 (d, 2H), 7.23 (d, 1H) (b)	3360 (s), 1590 (s), 1520 (s), 1390 (s)
14	89	110-112	2.17 (s, 3H), 2.90 (m, 2H), 3.50-4.23 (m, 4H), 5.27 (dd, 1H), 6.37 (broad, 1H), 7.16 (m, 2H), 7.88 (d, 1H) (b)	3375 (s), 1600 (s), 1530 (s), 1410 (s)
15	78	105-108	2.20 (s, 3H), 2.90 (m, 2H), 3.47-4.17 (m, 4H), 5.27 (dd, 1H), 6.27 (broad, 1H), 7.13 (m, 2H), 7.90 (d, 1H) (b)	3370 (s), 1590 (s), 1520 (s), 1390 (s)
16	45	239-242 dec	4.00 (broad, 6H), 6.05 (t, 1H), 7.13 (m, 2H), 7.41 (d, 1H) (c)	3025 (m), 2920 (m), 1565 (s), 1505 1205 (w)
17	73	218-220 dec	4.00 (broad, 6H), 6.08 (t, 1H), 7.27 (q, 2H), 8.10 (d, 1H) (c)	2930 (m), 2750 (m), 1565 (s), 1520 (s),1230 (w), 1210 (w)
18	48	241-243 dec	4.00 (broad, 6H), 6.05 (t, 1H), 7.28 (q, 2H), 8.10 (d, 1H) (c)	3020 (m), 2920 (m), 1570 (s), 1510 (s), 1220 (w), 1195 (w)

(a) Deuteriomethylsulfoxide. (b) Deuteriochloroform. (c) Deuteriotrifluoroacetic acid.

6-(2-Thienyl)-2,3,5,6-tetrahydroimidazo[2,1-*b*]selenazole **16**, 6-(2-selenienyl)-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole **17**, and 6-(2-selenienyl)-2,3,5,6-tetrahydroimidazo-[2,1-*b*]selenazole **18**, isolated as their hydrogen chloride salts, as well as all intermediates, are stable for at least a year under ambient conditions. The three target compounds show nearly identical retention times with silica gel chromatography, and infrared spectra are quite similar except for subtle differences in the 1190-1240 cm^{-1} region. Differentiation of the isomers is most apparent upon consideration of nuclear magnetic resonance spectra. In compound **16**, the chemical shifts of the α- and β- protons of the thiophene ring occur at δ 7.41 and δ 7.13, respectively. In the corresponding selenophene analogs **17** and **18**, the α-absorption is shifted to δ 8.10 (Δ = 0.69 δ), whereas the β-absorption occurs at δ 7.27 (Δ = 0.14 δ). These downfield shifts of the ring protons may be attributed to the greater deshielding effect of the selenium atom relative to that of sulfur, and are observed in all selenophene intermediates. The chemical shifts of the α-protons in both the thiophene and selenophene series correlate well with the values reported for the heterocycles bearing similar substituents at the α′-position (11). The nuclear magnetic resonance spectra of compounds **16-18** were recorded in deuterated trifluoroacetic acid, and in this solvent a very rapid exchange is observed for the α-proton of the selenophene ring in compounds **17** and **18**. No such exchange is seen in compound **16** within the same time period. However, this latter finding is consistent with the documented slower rate of exchange found for the α-proton of thiophene (12).

The biologic evaluations of these compounds and the synthesis of the radiolabeled derivatives are in progress and will be reported elsewhere.

Table 2

Compound No.	Molecular Formula	Elemental Analysis Calculated C	H	N	Se	Found C	H	N	Se
7	$C_9H_{11}BrN_2OSSe$	30.52	3.13	7.91	—	30.61	3.33	7.99	—
8	$C_9H_{11}BrN_2OSSe$	30.52	3.13	7.91	—	30.56	3.10	8.35	—
9	$C_9H_{11}BrN_2OSe_2$	26.95	2.77	6.99	39.38	26.63	2.73	7.28	38.83
10	$C_{11}H_{12}N_2O_2SSe$	41.91	3.84	8.89	—	42.10	4.18	8.75	—
11	$C_{11}H_{12}N_2O_2SSe$	41.91	3.84	8.89	—	42.29	3.98	8.74	—
12	$C_{11}H_{12}N_2O_2Se_2$	36.48	3.34	7.74	43.61	36.65	3.30	7.70	43.81
13	$C_{11}H_{14}N_2O_2SSe$	41.64	4.45	8.83	—	41.81	4.53	8.68	—
14	$C_{11}H_{14}N_2O_2SSe$	41.64	4.45	8.83	—	41.92	4.54	8.86	—
15	$C_{11}H_{14}N_2O_2Se_2$	36.28	3.87	7.69	43.36	36.40	3.90	7.68	43.80
16	$C_9H_{10}N_2SSe$	36.80	3.75	9.54	26.92	37.00	3.81	9.50	26.66
17	$C_9H_{10}N_2SSe$	36.80	3.75	9.54	26.92	36.63	3.61	9.36	26.38
18	$C_9H_{10}N_2Se_2$	31.72	3.23	8.22	46.40	32.00	3.48	8.26	45.76

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary point apparatus and are uncorrected. Analyses were performed by Schwartzkopf Microanalytical Laboratories, Woodside, NY. Spectral data were obtained using a Perkin-Elmer Infrared Spectrophotometer Model 700 and a Varian T-60 NMR Spectrometer and were consistent with the proposed structures.

2-Imino-3-(2-thenoylmethyl)selenazolidine Hydrobromide (**7**).

A mixture of 2-bromoacetylthiophene (**3**) (3.90 g, 19 mmoles) and equimolar 2-aminoselenazoline (**6**) (2.84 g) in 60 ml dry acetonitrile was heated at reflux for 2 hours. After cooling, the white solid was filtered, washed with acetonitrile and air dried, yield, 92%, mp 211.5-213° dec.

2-Imino-3-(2-selenenoylmethyl)thiazolidine Hydrobromide (**8**).

The above procedure was followed, refluxing 2-bromoacetylselenophene (**4**) (5.04 g, 20 mmoles) with equimolar 2-aminothiazoline (**5**) (2.04 g), yield, 96%, mp 206-209° dec.

2-Imino-3-(2-selenenoylmethyl)selenazolidine Hydrobromide (**9**).

The above procedure was followed, allowing 2-bromoacetylselenophene (5.04 g, 20 mmoles) to react with equimolar 2-aminoselenazoline (2.98 g), yield, 92%, mp 216-218° dec.

2-Acetylimino-3-(2-thenoylmethyl)selenazolidine (**10**).

To a mixture of acetic anhydride (6.5 g, 63 mmoles) and equimolar pyridine (5.0 g) in 100 ml dichloroethane stirred at reflux were added 5.66 g (16 mmoles) of **7** in portions over 3 hours. Within the next hour, a clear orange colored solution resulted. After cooling, the reaction mixture was filtered. The filtrate was concentrated to a small volume and toluene was added. After chilling, the gummy residue which separated was washed with 1 *N* ammonium hydroxide solution, extracted with methylene dichloride, dried over magnesium sulfate and concentrated to a solid. The solid was crystallized from toluene (charcoal) to give 67% yield, mp 131-132°.

2-Acetylimino-3-(2-selenenoylmethyl)thiazolidine (**11**).

Compound **8** (6.73 g, 19 mmoles) was acetylated using the procedure described for the acetylation of compound **7**, crystallized yield, 62%, mp 134-137°.

2-(Acetylimino)-3-(2-selenenoylmethyl)selenazolidine (**12**).

Compound **9** (7.20 g, 18 mmoles) was acetylated using the procedure described for the acetylation of compound **7**, crystallized yield, 71%, mp 125-128°.

2-Acetylimino-3-[2-hydroxy-2-(thienyl)ethyl]selenazolidine (**13**).

To a suspension of 3.47 g (11 mmoles) of **10** in 35 ml absolute methanol stirred at 0-5° was added sodium borohydride (300 mg, 8 mmoles) in portions over 10 minutes. After stirring for 4 hours at room temperature, the reaction mixture was concentrated to a semi-solid residue which was partitioned between methylene dichloride and water. The organic layer was separated, dried over magnesium sulfate, and concentrated to a heavy syrup which was dissolved in chloroform and chromatographed on silica gel using 2% methanol in chloroform as eluent. The product was crystallized from toluene-ether to give 68% yield, mp 86.5-89°.

2-(Acetylimino)-3-[2-hydroxy-2-(selenienyl)ethyl]thiazolidine (**14**).

Compound **11** (3.25 g, 10.3 mmoles) was reduced following the procedure described for the reduction of compound **10**, crystallized yield, 89%, mp 110-112°.

2-(Acetylimino)-3-[2-hydroxy-2-(selenienyl)ethyl]selenazolidine (**15**).

Compound **12** (4.00 g, 11 mmoles) was reduced following the procedure described for the reduction of compound **10**, crystallized yield, 78%, mp 105-108°.

6-(2-Thienyl)-2,3,5,6-tetrahydroimidazo[2,1-*b*]selenazole (**16**).

To a solution of **13** (314 mg, 1 mmole) in 10 ml chloroform stirred at ambient temperature, thionyl chloride (360 mg, 3 mmoles) was added dropwise. After stirring for three hours, 10 ml 10% sodium carbonate solution was added and the mixture was heated to reflux for 1 hour. The mixture was cooled, the organic phase was separated, dried over magnesium sulfate, and concentrated to a heavy yellow liquid. The addition of isopropyl alcohol saturated with hydrochloric acid, followed by ether, produced a yellow solid, mp 238-241° dec. Crystallization from ethanol (charcoal) gave 45% yield, mp 240-242° dec.

6-(2-Selenienyl)-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole (**17**).

Cyclization of compound **14** (318 mg, 1 mmole) to the desired product was achieved by following the procedure described for the cyclization of compound **13**, crystallized yield, 73%, mp 218-220° dec.

6-(2-Selenienyl)-2,3,5,6-tetrahydroimidazo[2,1-*b*]selenazole (**18**).

Cyclization of compound **15** (364 mg, 1 mmole) to the desired product was achieved by following the procedure described for the cyclization of compound **13**, crystallized yield, 48%, mp 241-243° dec.

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