

Selenium Heterocycles VIII: Synthesis and Antibacterial Activity of Selenosemicarbazide and 1,3,4-Selenadiazolylcarbamic Acid Esters

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Abstract □ The antibacterial activity of selenosemicarbazide and its acyl derivatives was compared with the activity of their sulfur and oxygen analogs. A series of 1,3,4-selenadiazolylcarbamic acid esters was also prepared and tested. Some of these compounds showed significant antibacterial activity.

Keyphrases □ Selenosemicarbazide and acyl derivatives—synthesis, antibacterial activity compared with sulfur and oxygen analogs □ 1,3,4-Selenadiazolylcarbamic acid esters—synthesis, antibacterial activity □ Antibacterial activity—synthesis of selenosemicarbazide derivatives and 1,3,4-selenadiazolylcarbamic acid esters

Recently, we reported (1, 2) that 1,3,4-thiodiazolylcarbamic acid esters have potent antibacterial and antiviral activity. Bhamaria *et al.* (3) reported that 1-acyl

EXPERIMENTAL¹

The desired compounds were prepared according to Scheme I. The physical data of these compounds are summarized in Tables I and II.

All compounds listed in Table III were tested against *B. subtilis* (NCTC 3610), *S. aureus* (ATCC 6538), *Klebsiella pneumoniae* (ATCC 10031), and *Sarcina lutea* (ATCC 9341).

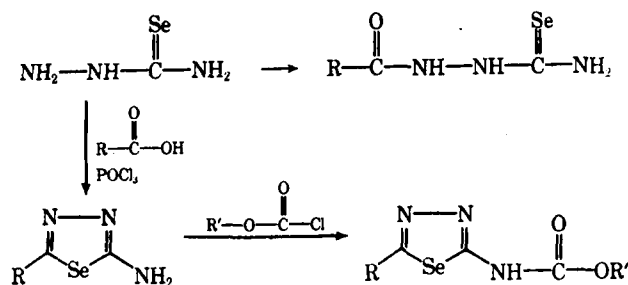
The compounds were dissolved in sterile distilled water and diluted to a 0.5% concentration. Standard paper disks of 6 mm. diameter were immersed in solution and were placed on inoculated assay medium surface². None of the 1-acyl semicarbazides or 1-acyl thiosemicarbazides and their derivatives showed significant activity (Table III).

All compounds listed in Table II were tested against *S. aureus* (ATCC 6538p) and *K. pneumoniae* (ATCC 10031) at different concentrations in liquid medium³. Compounds 6, 7, and 12 at the con-

Table I—1-Acyl Selenosemicarbazides

Compound	R	Melting Point	Yield, %	Crystallization Solvent	Formula	—Analysis, %—	
						Calc.	Found
1	H	172°	50	Water	C ₂ H ₅ N ₂ OSe	C 14.45	14.33
2	C ₂ H ₅	182°	40	Ethanol	C ₄ H ₉ N ₂ OSe	H 3.01	2.96
3	C ₆ H ₅	210–214°	76	Ethanol–water	C ₈ H ₉ N ₂ OSe	C 24.72	24.89
4	<i>p</i> -FC ₆ H ₄	198–200°	72	Water	C ₈ H ₅ FN ₂ OSe	H 4.63	4.55
						C 39.66	39.39
						H 3.70	3.80
						C 36.92	37.02
						H 3.07	2.99

4-alkyl (or aryl) thiosemicarbazides have no significant antibacterial activity against *Escherichia coli* and *Salmonella typhosa* and very limited activity against *Staphylococcus aureus*, but the majority of the compounds tested were active against *Mycobacterium tuberculosis*. Bednarz (4) reported that selenosemicarbazides of aldehydes were active against *M. tuberculosis*, *S. aureus*, *Bacillus subtilis*, and *E. coli*. Therefore, the comparative study of antibacterial activity of a series of selenium compounds and their analogs was of special interest.



Scheme I

centration of 0.6 mg./ml. inhibited the growth of these organisms. No significant inhibition was observed with the other compounds up to the concentration of 2.5 mg./ml.

Selenosemicarbazide was prepared according to the literature (5).

1-Formylselenosemicarbazide (Compound 1)—Selenosemicarbazide (2.76 g., 0.02 mole) and 10 ml. of 99–100% formic acid were refluxed for 20 min. The reaction mixture was filtered hot, allowed to crystallize at room temperature, and recrystallized from water.

1-Propionylselenosemicarbazide (Compound 2)—This compound was prepared from propionic acid and selenosemicarbazide similar to 1-formylselenosemicarbazide.

Other 1-acyl selenosemicarbazides were prepared by the method reported previously (6).

1-Benzoylselenosemicarbazide (Compound 3)—Selenosemicarbazide (2.76 g., 0.02 mole) was dissolved in 40 ml. of 4% sodium hydroxide and, while stirring at ice bath temperature, benzoyl chloride (2.8 g., 0.02 mole) was added dropwise. After standing at room temperature for 1 hr., charcoal was added to the reaction mixture, which was then filtered and acidified with 10% hydrochloric acid and the precipitate was recrystallized from ethanol–water.

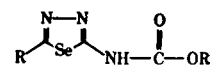
N-(5-Trifluoromethyl-1,3,4-selenadiazol-2-yl)carbamic Acid Ester (Compound 12)—2-Amino-5-trifluoromethyl-1,3,4-selenadiazole (6)

¹ Melting points were taken on a Kofler hot stage microscope and are uncorrected. Their spectra were recorded using a Leitz spectrograph. NMR spectra were recorded on a Varian A60A instrument.

² Antibiotic assay medium, British Pharmacopoeia, 1968.

³ Antibiotic assay medium without agar, British Pharmacopoeia, 1968.

Table II—5-Substituted-1,3,4-selenadiazol-2-yl-carbamic Acid Esters



Compound	R	R'	Melting Point	Yield, %	Crystallization Solvent	Formula	Analysis, %	
							Calc.	Found
5	CH ₃	CH ₃	170°	63	Water	C ₅ H ₇ N ₃ O ₂ Se	C 27.14 H 3.16	27.21 3.09
6	CH ₃	n-C ₄ H ₉	165°	69	Water	C ₈ H ₁₃ N ₃ O ₂ Se	C 36.50 H 4.92	36.29 5.01
7	CH ₃	iso-C ₄ H ₉	155°	77	Water	C ₈ H ₁₃ N ₃ O ₂ Se	C 36.50 H 4.92	36.66 4.99
8	C ₆ H ₅	CH ₃	147°	82	Water	C ₆ H ₉ N ₃ O ₂ Se	C 30.63 H 3.82	30.77 3.78
9	C ₆ H ₅	C ₆ H ₅	119°	80	Water	C ₇ H ₁₁ N ₃ O ₂ Se	C 33.73 H 4.41	33.71 4.49
10	C ₆ H ₅	CH ₃	148°	53	Water	C ₁₀ H ₉ N ₃ O ₂ Se	C 42.40 H 3.18	42.43 3.17
11	C ₆ H ₅	C ₆ H ₅	132°	66	Water	C ₁₁ H ₁₁ N ₃ O ₂ Se	C 44.44 H 3.70	44.26 3.66
12	CF ₃	C ₆ H ₅	204°	77	Water	C ₆ H ₄ F ₃ N ₃ O ₂ Se	C 24.91 H 2.07	25.06 2.11

Table III—Average Zone Size, mm.

R	X	R-NH-NH-C(=X)-NH ₂			
		<i>B. subtilis</i>	<i>K. pneumoniae</i>	<i>S. aureus</i>	<i>Sar. lutea</i>
H	Se	23	48	30	40
HCO	S	—	—	—	—
HCO	Se	20	24	19	45
CH ₃ CO	S	—	—	—	—
CH ₃ CO	Se	21	35	29	32
C ₂ H ₅ CO	S	—	—	—	—
C ₂ H ₅ CO	Se	14	34	23	36
C ₆ H ₅ CO	O	—	—	—	—
C ₆ H ₅ CO	S	—	—	—	—
C ₆ H ₅ CO	Se	19	39	26	41
p-FC ₆ H ₄ CO	Se	19	38	27	42

(0.55 g., 0.025 mole) and chloroformic acid ethyl ester (0.28 g., 0.026 mole) in 18 ml. chloroform were refluxed for 2 hr. After removing the solvent, the residue was crystallized from water to give 0.55 g. (77%) of Compound 12.

All other compounds were prepared similarly (Table II).

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