affects the dissolution rate relationship as a function of diffusion layer thickness. Figure 5 shows the dissolution rates plotted as a function of the polyethylene glycol 4000 percentage composition. An interesting observation that can be made from this plot is that as the percentage of polyethylene glycol 4000 increased from 2 to 5%, the increase in the dissolution rates of form I was higher compared to form II for all stirring speeds except the highest speed of 216 rpm. However, as the percentage increased from 5 to 10%, the relationship was inversed, showing a greater increase in the dissolution rate of form II compared to form I at all stirring speeds.

This analysis further strengthens the postulate that at low percentage composition of polyethylene glycol 4000, the surface property changes affect the dissolution rates of form I more than of form II, but the dissolution rates of form II are affected more than those of form I at high percentage compositions.

These observations clearly show that the dissolution rates of the two sulfathiazole polymorphs can differ significantly even if small amounts of additive such as polyethylene glycol 4000 are added. Furthermore, the comparisons of dissolution rates should be made in conjunction with reference to the diffusion layer thickness since the mechanism of dissolution appears to be highly dependent on this factor.

The study presented here also shows that there is no significant conversion of form II to form I in water in the presence of polyethylene glycol 4000. The bioavailability aspects of these findings will be reported later.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 31, 1975, from the *Department of Pharmacy, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60612*

Accepted for publication May 7, 1975.

The author thanks W. Kolling for technical assistance.

Selenium Heterocycles XVIII: Synthesis and Antibacterial Activity of 4-Substituted (1,2,3-Selenadiazol-5-yl)carbamic Acid Esters and Their Sulfur Analogs

A. SHAFIEE ˣ, I. LALEZARI, S. YAZDANI, F. M. SHAHBAZIAN, and T. PARTOVI

Abstract □ 4-Substituted (1,2,3-selenadiazol-5-yl)carbamic acid esters and their sulfur analogs were prepared from the Curtius rearrangement of the corresponding carboxazides. None of the compounds showed significant antibacterial activity.

Keyphrases □ Selenium heterocycles—synthesis and antibacterial activity of 4-substituted (1,2,3-selenadiazol-5-yl)carbamic acid esters and sulfur analogs □ Sulfur heterocycles—synthesis and antibacterial activity of 4-substituted (1,2,3-thiadiazol-5-yl)carbamic acid esters and selenium analogs □ Antibacterial agents, potential—4-substituted (1,2,3-selenadiazol-5-yl)carbamic acid esters and sulfur analogs

It has been reported that 1,3,4-thiadiazolylcarbamic acid esters have significant antiviral activity (1). These compounds and 1,3,4-selenadiazolylcarbamic acid esters showed antibacterial efficacy (2, 3). 1,2,3-Thiadiazole derivatives of benzimidazole, benzoxazole, and benzothiazole were reported as anthelmintics (4). Some phosphorus compounds having the 1,2,3-thiadiazole ring system showed insecticide activity (5), and 4-amino-1,2,3-thiadiazolesulfonamides exhibited antibacterial properties (6). In a continuing effort to find antiviral and antimicrobial agents, 4-substituted (1,2,3-selenadiazol-5-yl)carbamic acid esters and their sulfur analogs were prepared and their efficacy was determined.

DISCUSSION

Chemistry—4-Substituted 1,2,3-thiadiazole-5-carboxylic acid ethyl esters were prepared by an oxidative cyclization of methyl or methylene ketone semicarbazones with thionyl chloride (7).

4-Substituted 1,2,3-selenadiazole-5-carboxylic acid ethyl esters were prepared following the general method reported previously (8) (Scheme I).

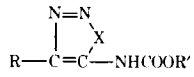
1,2,3-Thiadiazole-5-carboxazides and their selenium analogs were prepared by two independent methods. In Method A, the appropriate ester was hydrolyzed to the carboxylic acid and the carboxazide was prepared with thionyl chloride and sodium azide (Scheme II). In Method B, the ester was reacted with hydrazine hydrate and the corresponding hydrazide was then transformed to the carboxazide by reaction with sodium nitrite in acetic acid (9) (Scheme III).

Curtius rearrangement of the azides was readily achieved in alcohols (Schemes II and III). Although 1,2,3-selenadiazole is unstable at 170–180° and decomposes to give acetylene (8), it is quite stable under the conditions used in this work for the Curtius rearrangement.

The physical data for the prepared compounds are summarized in Table I.

Microbiological Evaluation—All compounds listed in Table I were tested against *Bacillus subtilis* (NCTC 3610), *Staphylococ-*

Table I—4-Substituted (1,2,3-Selenadiazol-5-yl)carbamic Acid Esters and Their Sulfur Analogs



Compound	R	R′	X	Yield, %	Melting Point[a]	Formula[b]	Analysis, % Calc.	Found
Ia	H	CH_3	S	35	205–206°	$C_4H_5N_3O_2S$	C 30.19	30.28
							H 3.14	3.26
							N 26.42	26.33
Ib	CH_3	CH_3	S	46	193–195°	$C_5H_7N_3O_2S$	C 34.68	34.85
							H 4.05	4.01
							N 24.28	24.17
Ic	C_6H_5	CH_3	S	30	207–208°	$C_{10}H_9N_3O_2S$	C 51.05	51.27
							H 3.83	3.95
							N 17.87	17.99
Id	H	C_2H_5	S	95	210–212°[c]	$C_5H_7N_3O_2S$	C 34.68	34.47
							H 4.05	4.02
							N 24.28	24.35
Ie	CH_3	C_2H_5	S	96	121–124°	$C_6H_9N_3O_2S$	C 38.50	38.35
							H 4.81	4.89
							N 22.46	22.55
If	C_6H_5	C_2H_5	S	88	105–107°	$C_{11}H_{11}N_3O_2S$	C 53.01	53.18
							H 4.42	4.37
							N 16.87	16.93
Ig	H	n-C_3H_7	S	60	194–195°	$C_6H_9N_3O_2S$	C 38.50	38.65
							H 4.81	4.85
							N 22.46	22.34
Ih	CH_3	n-C_3H_7	S	32	105–107°	$C_7H_{11}N_3O_2S$	C 41.79	41.55
							H 5.47	5.62
							N 20.90	20.75
Ii	C_6H_5	n-C_3H_7	S	47	83–85°	$C_{12}H_{13}N_3O_2S$	C 54.75	54.89
							H 4.94	5.12
							N 15.97	15.85
Ij	H	iso-C_3H_7	S	42	205–209°	$C_6H_9N_3O_2S$	C 38.50	38.63
							H 4.81	4.92
							N 22.46	22.62
Ik	CH_3	iso-C_3H_7	S	46	145–148°	$C_7H_{11}N_3O_2S$	C 41.79	41.64
							H 5.47	5.55
							N 20.90	20.83
Il	C_6H_5	iso-C_3H_7	S	42	83–85°	$C_{12}H_{13}N_3O_2S$	C 54.75	54.82
							H 4.94	5.12
							N 15.97	16.15
Im	H	n-C_4H_9	S	60	125–127°	$C_7H_{11}N_3O_2S$	C 41.79	41.83
							H 5.47	5.62
							N 20.90	20.82
In	CH_3	n-C_4H_9	S	28	113–116°	$C_8H_{13}N_3O_2S$	C 44.65	44.71
							H 6.05	6.17
							N 19.53	19.75
Io	C_6H_5	n-C_4H_9	S	43	81–83°	$C_{13}H_{15}N_3O_2S$	C 56.32	56.43
							H 5.42	5.35
							N 15.16	15.19
Ip	H	iso-C_4H_9	S	63	160–163°	$C_7H_{11}N_3O_2S$	C 41.79	41.85
							H 5.47	5.32
							N 20.90	20.98
Iq	CH_3	iso-C_4H_9	S	30	126–129°	$C_8H_{13}N_3O_2S$	C 44.65	44.47
							H 6.05	6.15
							N 19.53	19.62
Ir	C_6H_5	iso-C_4H_9	S	20	129–132°	$C_{13}H_{15}N_3O_2S$	C 56.32	56.28
							H 5.42	5.56
							N 15.16	15.06
Is	H	$CH_2C_6H_5$	S	44	148–151°	$C_{10}H_9N_3O_2S$	C 51.06	51.22
							H 3.83	3.65
							N 17.87	17.63
It	CH_3	$CH_2C_6H_5$	S	60	132–134°	$C_{11}H_{11}N_3O_2S$	C 53.01	53.18
							H 4.42	4.27
							N 16.87	16.69
Iu	C_6H_5	$CH_2C_6H_5$	S	42	146–149°	$C_{16}H_{13}N_3O_2S$	C 61.74	61.85
							H 4.18	4.14
							N 13.50	13.65
IIa	CH_3	CH_3	Se	65	172–173°	$C_5H_7N_3O_2Se$	C 27.27	27.14
							H 3.18	3.21
							N 19.09	19.17
IIb	C_6H_5	CH_3	Se	35	198–200°	$C_{10}H_9N_3O_2Se$	C 42.55	42.63
							H 3.19	3.25
							N 14.89	14.95
IIc	CH_3	C_2H_5	Se	75	160–162°	$C_6H_9N_3O_2Se$	C 30.77	30.82
							H 3.85	3.76
							N 17.95	17.63
IId	C_6H_5	C_2H_5	Se	80	178–181°	$C_{11}H_{11}N_3O_2Se$	C 44.59	44.71
							H 3.72	3.85
							N 14.19	14.25

(continued)

Table I—*(Continued)*

Compound	R	R'	X	Yield, %	Melting Point[a]	Formula[b]	Analysis, % Calc.	Found
IIe	CH_3	n-C_3H_7	Se	50	115–118°	$C_7H_{11}N_3O_2Se$	C 33.87 H 4.44 N 16.94	33.92 4.14 16.72
IIf	C_6H_5	n-C_3H_7	Se	46	140–142°	$C_{12}H_{13}N_3O_2Se$	C 46.45 H 4.19 N 13.55	46.53 4.21 13.67
IIg	CH_3	iso-C_3H_7	Se	40	120–122°	$C_7H_{11}N_3O_2Se$	C 33.87 H 4.44 N 16.94	33.92 4.25 16.99
IIh	C_6H_5	iso-C_3H_7	Se	48	138–140°	$C_{12}H_{13}N_3O_2Se$	C 46.45 H 4.19 N 13.55	46.32 4.25 13.75
IIi	CH_3	n-C_4H_9	Se	40	115–118°	$C_8H_{13}N_3O_2Se$	C 36.64 H 4.96 N 16.03	36.71 4.83 16.22
IIj	C_6H_5	n-C_4H_9	Se	45	95–97°	$C_{13}H_{15}N_3O_2Se$	C 48.15 H 4.63 N 12.96	48.22 4.52 12.79
IIk	CH_3	$tert$-C_4H_9	Se	50	198–200°	$C_8H_{13}N_3O_2Se$	C 36.64 H 4.96 N 16.03	36.73 4.79 16.17
IIl	C_6H_5	$tert$-C_4H_9	Se	45	180–181°	$C_{13}H_{15}N_3O_2Se$	C 48.15 H 4.63 N 12.96	48.24 4.72 12.99

[a] Unless otherwise indicated, the recrystallization solvent was ethyl acetate. [b] IR, NMR, and mass spectra of all compounds were as expected. [c] Reference 10, mp 217°.

cus 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% (w/v) concentration. Standard paper disks, 6 mm diameter, were immersed in the solution and placed on an inoculated assay medium surface[1]. None of the compounds of Table I showed significant antibacterial activity.

EXPERIMENTAL[2]

Ethyl 4-Phenyl-1,2,3-thiadiazole-5-carboxylate (III)—Thionyl chloride (50 ml) was gradually added to ethyl benzoylacetate semicarbazone (24 g, 0.1 mole) at ice bath temperature, and the mixture was kept 30 min at this temperature. Chloroform (200 ml) was then added, and the mixture was decomposed with an ice-cold saturated sodium bicarbonate solution, separated, and filtered. The organic layer was washed with water and dried. After evaporation of the solvent, the residue was distilled to give 13.5 g (58%) of the desired compound, bp 185–190° (25 mm); *m/e* 234.

Anal.—Calc. for $C_{11}H_{10}N_2O_2S$: C, 56.41; H, 4.27; N, 11.97. Found: C, 56.52; H, 4.38; N, 11.73.

4-Phenyl-1,2,3-thiadiazole-5-carboxyhydrazide (IV) (Method A)—A solution of 23.4 g (0.1 mole) of the ester III in 50 ml of ethanol was added dropwise to a stirred solution of 25 g (0.5 mole) of hydrazine hydrate in 150 ml of ethanol. After 30 min, the solvent was evaporated and the residue was crystallized from ethanol to give 15 g (68%) of the desired compound, mp 130°; *m/e* 220.

Anal.—Calc. for $C_9H_8N_4OS$: C, 49.09; H, 3.64; N, 25.45. Found: C, 49.25; H, 3.55; N, 25.27.

4-Phenyl-1,2,3-thiadiazole-5-carboxazide (V) (Method A)—To a stirred solution of the carboxyhydrazide IV (22 g, 0.1 mole) in 200 ml of 50% acetic acid at 50° was added dropwise a solution of sodium nitrite (6.9 g, 0.1 mole) in 100 ml of water. The reaction mixture was stirred for 30 min, and the precipitate was filtered, washed with water, and dried under reduced pressure at room temperature, mp 102–103° dec.; *m/e* 231; IR (potassium bromide): 2190 and 2155 cm^{-1} (azide).

4-Phenyl-(1,2,3-thiadiazol-5-yl)carbamic Acid Methyl Ester (Ic) (Method A)—A solution of the azide V (2.31 g, 0.01 mole) in 50 ml of absolute methanol was refluxed for 5 hr. The solvent was evaporated, and the residue was crystallized from ethyl acetate to give 0.84 g (40%) of Ic, mp 207–208°; *m/e* 235; NMR (deuterochloroform): δ 7.1 (broad s, 1H, NH), 7.17 (s, 5H, aromatic), and 3.52 (s, 3H, OCH_3) ppm.

Anal.—Calc. for $C_{10}H_9N_3O_2S$: C, 51.05; H, 3.83; N, 17.87. Found: C, 51.23; H, 3.95; N, 17.79.

Other 4-phenyl-(1,2,3-thiadiazol-5-yl)carbamic acid esters were prepared similarly from 4-phenyl-1,2,3-thiadiazole-5-carboxazide and appropriate alcohols (Table I).

4-Methyl-1,2,3-selenadiazole-5-carboxyhydrazide (VI) (Method A)—A solution of 21.9 g (0.1 mole) of ethyl 4-methyl-1,2,3-selenadiazole-5-carboxylate (8) in 50 ml of methanol was added dropwise to a stirred solution of 25 g (0.5 mole) of hydrazine hydrate in 100 ml of ethanol. The mixture was allowed to stand at room temperature to complete the precipitation. The crystals were filtered and recrystallized from ethanol to give 12.3 g (60%) of the desired compound, mp 151–153°.

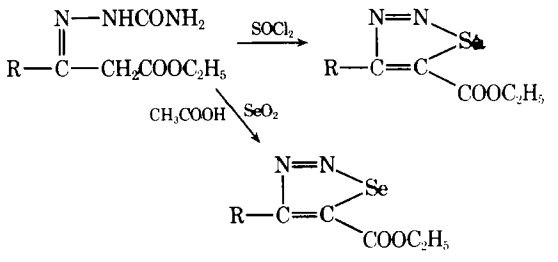
Anal.—Calc. for $C_4H_6N_4OSe$: C, 23.41; H, 2.93; N, 27.32. Found: C, 23.57; H, 2.85; N, 27.14.

4-Phenyl-1,2,3-selenadiazole-5-carboxyhydrazide was prepared similarly, mp 115–117°.

Anal.—Calc. for $C_9H_8N_4O_2Se$: C, 38.16; H, 2.83; N, 19.79. Found: C, 38.28; H, 2.73; N, 19.63.

4-Methyl-1,2,3-selenadiazole-5-carboxazide (VII) (Method A)—A solution of sodium nitrite (6.9 g, 0.1 mole) in 100 ml of water was added dropwise to a stirred solution of the carboxyhydrazide VI (20.5 g, 0.1 mole) in 200 ml of 50% acetic acid at 0–5°. After the addition was complete, the reaction mixture was stirred for 30 min. The precipitate was filtered, washed with water, and dried under reduced pressure at room temperature, mp 30–32°.

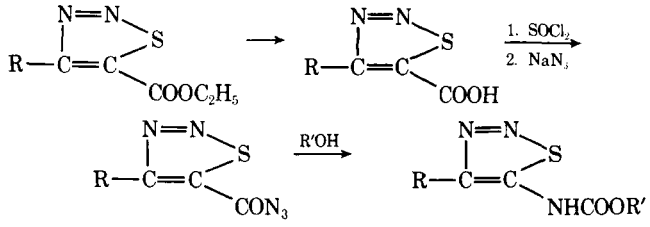
4-Phenyl-1,2,3-selenadiazole-5-carboxazide was prepared simi-



Scheme I

[1] AAM, antibiotic assay medium, The British Pharmacopoeia, 1968.

[2] Melting points were taken on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded using a Leitz model III spectrophotometer. Mass spectra were recorded on a Varian Mat 111 instrument. NMR spectra were determined with a Varian A-60A instrument.



Scheme II

larly, mp 86–88°; IR (potassium bromide): 2165 and 2137 cm^{-1} (azide).

4-Methyl-(1,2,3-selenadiazol-5-yl)carbamic Acid Methyl Ester (IIa) (Method A)—A solution of the azide VII (2.16 g, 0.01 mole) in 50 ml of absolute methanol was refluxed for 4 hr. Then the mixture was filtered and evaporated. The residue was crystallized from ethanol–ethyl acetate to give a 1.1 g (50%) of the desired compound, mp 172–173°; NMR (trifluoroacetic acid): δ 4.06 (s, 3H, OCH_3) and 2.40 (s, 3H, CH_3) ppm.

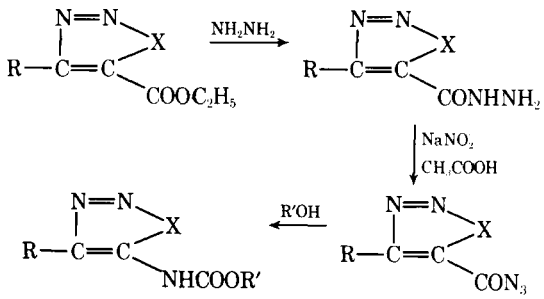
Other 4-substituted (1,2,3-selenadiazol-5-yl)carbamic acid esters were prepared similarly from the azide and appropriate alcohols.

1,2,3-Thiadiazole-5-carboxylic Acid Ethyl Ester (VIII) (Method B)—Ethyl formylacetate semicarbazone (70 g, 0.4 mole), cooled in an ice bath, was treated slowly with 84 ml of thionyl chloride. The mixture was allowed to stand at room temperature for 30 min, and then chloroform (300 ml) was added. The mixture was decomposed with ice-cold saturated sodium bicarbonate solution and filtered. The organic layer was washed with water, separated, and filtered. The solvent was evaporated and the residue was distilled to give 26.6 g (38%) of the product, bp 115° (25 mm) [lit. (6) bp 103–105° (14 mm)].

1,2,3-Thiadiazole-5-carboxylic Acid (IX) (Method B)—To a solution of VIII (15.8 g, 0.1 mole) in 30 ml of ethanol–water (1:1) was added a solution of sodium hydroxide (4 g, 0.1 mole) in 10 ml of water, and the mixture was heated on a steam bath for 30 min. The solution was acidified (hydrochloric acid) and evaporated to dryness. Then the acid was extracted with ether (soxhlet) to give 12.35 g (95%) of the desired compound, mp 105–108° [lit. (6) mp 104–106°].

1,2,3-Thiadiazol-5-carboxyl Chloride (X) (Method B)—A mixture of the acid IX (13 g, 0.1 mole) and thionyl chloride (30 ml) was refluxed for 4 hr. Excess thionyl chloride was removed under reduced pressure, and the residue was fractionated to give 12.6 g (85%) of the desired compound, bp 80–81° (25 mm).

1,2,3-Thiadiazole-5-carboxazide (XI) (Method B)—A stirred solution of sodium azide (7.15 g, 0.11 mole) in 15 ml of water, chilled in an ice bath, was treated with the acid chloride (X) (14.85 g, 0.1 mole) in 30 ml of acetone. After the addition of the chloride, the reaction mixture was stirred for 30 min. Then 50 ml of water was added, and the azide was extracted with chloroform. The organic layer was dried (sodium sulfate) and filtered. The solvent



Scheme III

was evaporated to give an oil, 10.85 g (70%); IR (potassium bromide): 2190 and 2155 cm^{-1} (azide).

(1,2,3-Thiadiazol-5-yl)carbamic Acid Ethyl Ester (Id) (Method B)—A solution of the azide XI (15.5 g, 0.1 mole) in 100 ml of absolute ethanol was refluxed for 6 hr. The solvent was evaporated and the residue was crystallized from ethyl acetate to give 15.6 g (90%) of Id, mp 210–212° [lit. (10) mp 217° dec.]; NMR (deuterochloroform): δ 8.87 (s, 1H, H_4), 4.10 (q, 2H, OCH_2), and 1.17 (t, 3H, CH_3) ppm; *m/e* 173.

Other (1,2,3-thiadiazol-5-yl)carbamic acid esters and 4-methyl-(1,2,3-thiadiazol-5-yl)carbamic acid esters were prepared similarly.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 19, 1975, from the *Department of Chemistry, College of Pharmacy, Tehran University, Tehran, Iran.*

Accepted for publication May 7, 1975.

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