Selenium-Sulfur Analogs. 4. Synthesis and Characterization of (±)-β-(2-Amino-1,3-selenazol-4-yl)alanine

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The novel amino acid (±)-β-(2-amino-1,3-selenazol-4-yl)alanine **4a** was prepared from selenourea and 1,3-dichloropropan-2-one via a four-step synthetic sequence. Nuclear magnetic resonance analysis indicated a downfield chemical shift of δ 0.29 to 0.30 and δ 0.57 for the C_5-proton of the protonated 2-amino-and 2-acetamido-1,3-selenazoles respectively compared with the analogous thiazoles. The infrared spectra of the selenazole and corresponding thiazole compounds were virtually identical.

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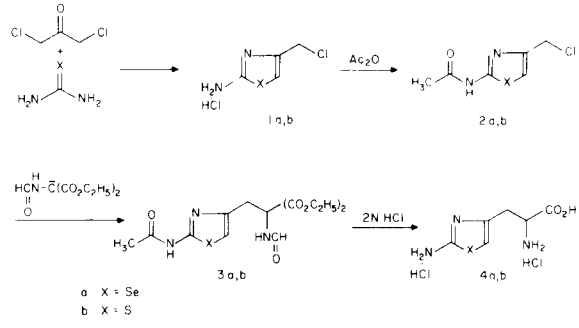
As part of our program to develop new selenium-75 labeled radiopharmaceuticals, we are evaluating novel selenium-containing analogs of the amino acids. Our syntheses of the seleno-analogs of lysine (1) and phenylalanine (2) have been previously described. Because of the similarity of selenium and sulfur, we were interested in the reported synthesis by Silberg, and coworkers (3,4) of an analog of histidine in which one of the imidazole nitrogens was replaced by sulfur. In this paper we present the preparation of the corresponding selenazole compound (±)-β-(2-amino-1,3-selenazol-4-yl)alanine and compare its infrared and nuclear magnetic resonance spectra with those of the sulfur-containing analog.

The synthesis of β-(2-amino-1,3-selenazol-4-yl)alanine **4a** was achieved in a four-step sequence similar to that employed by Silberg, *et al.* (3), for the sulfur analog **4b** (Scheme 1). The condensation of selenourea with 1,3-dichloropropan-2-one yielded the 2-amino-4-chloromethyl-selenazole hydrochloride **1a** which was converted without purification to the 2-acetamido derivative **2a** in a 55% overall yield. Sodium diethyl formamidomalonate was alkylated by **2a** to give the protected amino acid **3a** which was isolated in 16% yield. Hydrolysis gave, after recrystallization, the dihydrochloride **4a** in 83% yield. Except for **1a** which was used without subsequent purification, all the selenium-containing compounds were characterized by ir, nmr and elemental analyses (Table 1) and compared with the corresponding sulfur-containing compounds which were made according to the literature procedure (3).

In the nmr spectra distinctive differences are observed in the chemical shifts of the C_5-proton and the C_4-methylene protons (Table 2). The consistent downfield chemical shift of the C_5-proton of the selenazoles relative to that of the thiazoles can be ascribed to the stronger deshielding effect of selenium compared to sulfur. The magnitude of the downfield shift is less than the δ 0.85 to 0.95 seen for the C_2-H protons of 1,3,4-selenadiazole (5) and 1,3-benzoselenazole (6) or the δ 0.60 to 0.70 reported for the 2-



Scheme I

amino-1,3,4-selenadiazoles (7). There were smaller shift differences of δ 0.29 to 0.30 for the protonated 2-amino compounds **1a,b** and **4a,b** compared to δ 0.57 for the acetamido derivatives **2a,b** and **3a,b**. This may result from a smaller contribution of the selenonium mesomer (X = Se) than of the thionium mesomer (X = S) (Figure 1). The contribution of the thionium mesomer balances the deshielding effect of selenium, an influence which is not as

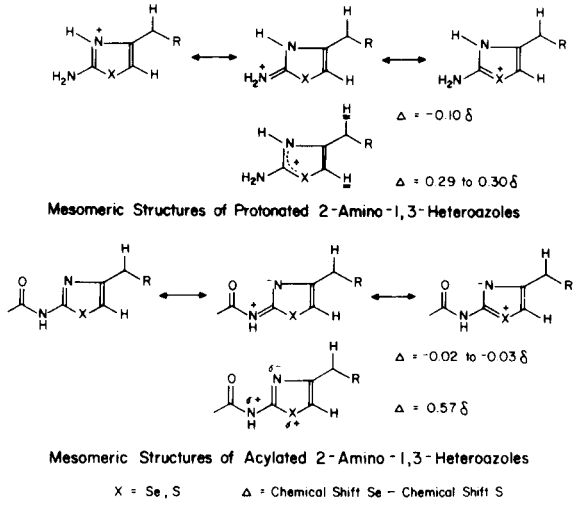


Figure I

0022-152X/81/010205-02$02.25

Table 1

Physical Data

Compound No.	M.p.	Yield	Recrystallization Solvent	Formula	Calculated C	Calculated H	Calculated N	Calculated Se	Observed C	Observed H	Observed N	Observed Se
2a	170.0-171.5	55%	benzene	$C_6H_7ClN_2OSe$	36.33	2.97	11.79	—	36.53	3.12	11.80	—
3a	201.0-202.5	16%	ethanol	$C_{14}H_{19}N_3O_6Se$	41.59	4.74	10.39	19.53	41.46	4.94	10.60	19.91
4a	—	80%	ethanol-ether	$C_6H_{11}Cl_2N_3O_2Se$	23.47	3.61	13.69	25.72	23.23	4.09	13.23	25.87

Table 2

Comparison of the NMR Data for (±)-β-(2-Amino-1,3-selenazol-4-yl)alanine and Its Intermediates and the Corresponding Sulfur Analogs

Compound No.	Solvent	δ C_5-H	Δ (a)	δC_4-CH_2-	Δ (a)
1a	DMSO-d_6	7.30		4.60	
			0.30		−0.10
1b	DMSO-d_6	7.00		4.70	
2a	deuteriochloroform and DMSO-d_6	7.40		4.53	
			0.57		−0.02
2b	deuteriochloroform and DMSO-d_6	6.83		4.55	
3a	deuteriochloroform and DMSO-d_6	7.00		3.58	
			0.57		−0.03
3b	deuteriochloroform and DMSO-d_6	6.43		3.62	
4a	deuterium oxide-TFA	7.07		3.28	
			0.29		−0.10
4b	deuterium oxide-TFA	6.78		3.38	

(a) $\Delta = \delta_{Se} - \delta_S$.

significant when the molecule is acylated. The upfield shift of C_4-methylene protons in the protonated amine derivatives also may be attributed to the smaller contribution of the selenonium resonance structure and the lower electronegativity of selenium. In the 2-acetamido derivatives **2a,b** and **3a,b** where the onium mesomers are not so important the slightly weaker inductive effect of selenium is manifested in a small 0.02 to 0.03 upfield shift of the C_4-methylene protons.

The infrared spectra of the 1,3-selenazole and corresponding 1,3-thiazole analogs are virtually identical, a situation similar to that observed with the 1,2,3-selenadiazoles and 1,2,3-thiadiazoles. The differences that exist apparently are not great enough to manifest characteristic changes in the infrared region.

EXPERIMENTAL

2-Acetamido-4-chloromethyl-1,3-selenazole (**2a**).

To a solution of 1,3-dichloropropan-2-one (8.54 g., 67.2 mmoles) in 35 ml. of acetone was gradually added 450 ml. of acetone containing selenourea (8.20 g., 66.7 mmoles). The resulting mixture was stirred at ambient temperature for 16 hours. The solid that formed was collected by filtration, washed with acetone and digested with ethanol. The slurry was filtered and the filtrate diluted with hexane. The oil that separated crystallized slowly and was collected by filtration. The hygroscopic solid (m.p. 182.5-185.8) was dissolved in 80 ml. of acetic anhydride, heated at reflux for 2 hours, then poured over ice water and the precipitate collected by filtration. The reddish brown solid was recrystallized from benzene to give 8.62 g. (36.3 mmoles) of of the product in an overall yield of 55%.

Diethyl 2-(2-Acetamido-1,3-selenazol-4-yl)methyl-2-formamidomalonate (**3a**).

To 20 ml. of dry ethanol as added 0.46 g. of sodium hydride (50% in oil dispersion). The solution was cooled to 0° and diethyl formamidomalonate (2.03 g., 10.0 mmoles) was added with stirring, followed by the chloromethylselenazole **2a** (2.37 g., 10.0 mmoles). The reaction was stirred at 0-5° for 24 hours. The crude product was collected by filtration, extracted with acetone, and the acetone was evaporated to give a whitish solid that was purified by column chromatography on alumina with hexane-ethylacetate (1:1 v/v) as the eluent. The product-containing fractions were isolated, evaporated to dryness, and the residue recrystallized from ethanol to give 0.66 g. (1.6 mmoles) of **3a** in 16% yield.

β-(2-Amino-1,3-selenazol-4-yl)alanine (**4a**).

A solution of **3a** (0.30 g., 0.75 mmole) in 4 ml. of concentrated hydrochloric acid was heated at reflux for 3 hours. The solvent was removed under reduced pressure and the residue crystallized from ethanol-ether to give **4a** in 80% yield (0.18 g., 0.6 mmole).

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