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1,2,5-Selenadiazoles. Synthesis and Properties (1)

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4-Amino-1,2,5-selenadiazole-3-carboxylic acid and 4-amino-1,2,5-selenadiazole-3-carboxamides have been prepared by ring-cleavage of [1,2,5]selenadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one by basic reagents. The primary amide (III), as well as an *N*-alkyl amide, may be produced by the action of a primary amine. Hydrazine reductively cleaves the selenadiazole ring. The preparation of similar 4-ureido derivatives by ring-cleavage of [1,2,5]selenadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione has been demonstrated with two examples.

N-Butyl-4-ureido-1,2,5-selenadiazole-3-carboxamide is easily hydrolyzed in aqueous base to the corresponding acid, and it has been shown that this reaction proceeds by way of [1,2,5]selenadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione.

The 4-amino-1,2,5-selenadiazole-3-carboxylic acid derivatives have marked cytotoxic, antibacterial, and antifungal activity.

The 1,2,5-selenadiazole ring has been incorporated into fused-ring systems such as the 2,1,3-benzoselenadiazoles (2) and the [1,2,5]selenadiazolo[3,4-*d*]-pyrimidines (3), but monocyclic 1,2,5-selenadiazoles apparently have not been reported except in the Dissertation of Shew (4). Certain 1,2,5-thiadiazoles have been synthesized by cleavage of the pyrimidine ring of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines (5). This type of reaction appeared to be applicable to the synthesis of 4-amino-1,2,5-selenadiazole-3-carboxylic acid derivatives, and this synthesis, together with the properties of the selenadiazole derivatives, is the subject of this report.

Aqueous potassium hydroxide readily cleaved the pyrimidinone ring of [1,2,5]selenadiazolo[3,4-*d*]-pyrimidin-7(6*H*)-one (I) to 4-amino-1,2,5-selenadiazole-3-carboxylic acid (II), which was obtained as the free acid in 85% yield. Reaction of I with ethanolic ammonia at 80° furnished the corresponding amide (III) in 88% yield. The formation of these selenadiazole derivatives is consistent with the results of basic cleavage of [1,2,5]thiadiazolo-[3,4-*d*]pyrimidin-7(6*H*)-one (5a) and of related bicyclic heterocycles (6). The structures were confirmed by an acid-catalyzed recyclization of the amino-carboxamide (III) with ethyl orthoformate to the selenadiazolopyrimidinone (I) and by the preparation of the amino acid (II) from III.

Reactions of I with two primary amines were entirely analogous to the corresponding reactions in the thiadiazolopyrimidine series (5a). Both 4-amino-*N*-butyl-1,2,5-selenadiazole-3-carboxamide (IV) and the primary amide (III) were isolated in approximately equal yields (45% and 47%, respectively) after reaction of I with refluxing butylamine. Similarly, ethanolic methylamine at 80° produced both III and 4-amino-*N*-methyl-1,2,5-selenadiazole-3-carboxamide (V). The formation of two products from I may result (Chart III) either from simultaneous attack of the amine at positions 5 and 7 of the selenadiazolopyrimidinone ring or from amine-exchange reactions of an intermediate, such as A,

Chart I

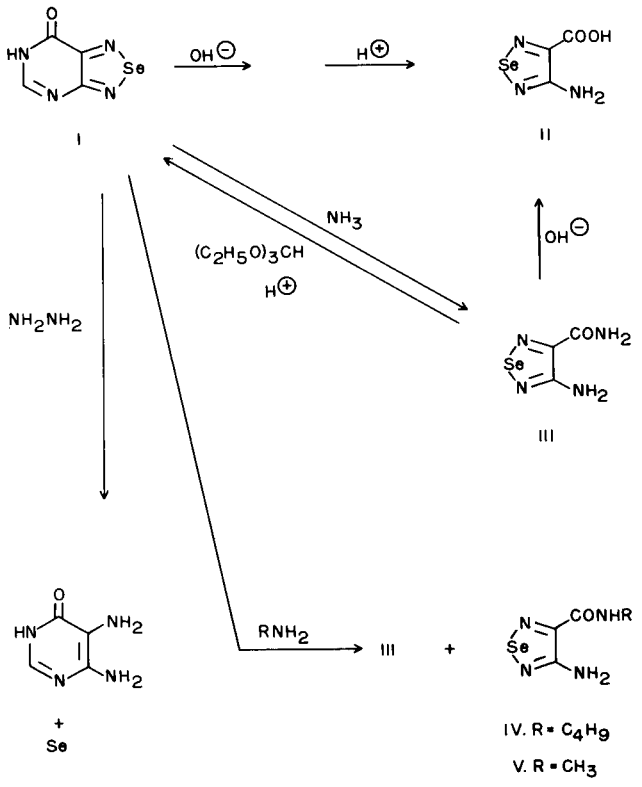


Chart II

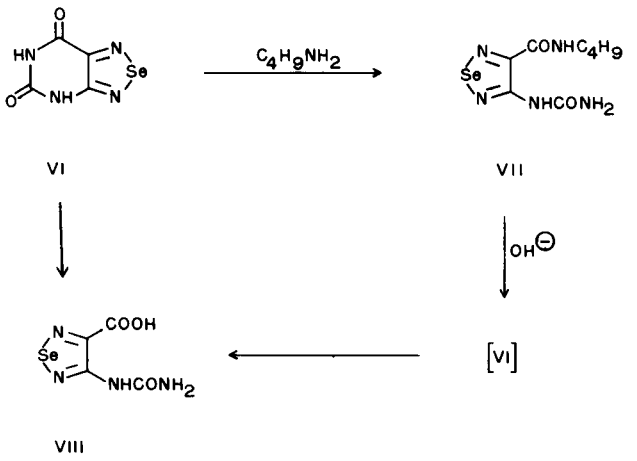
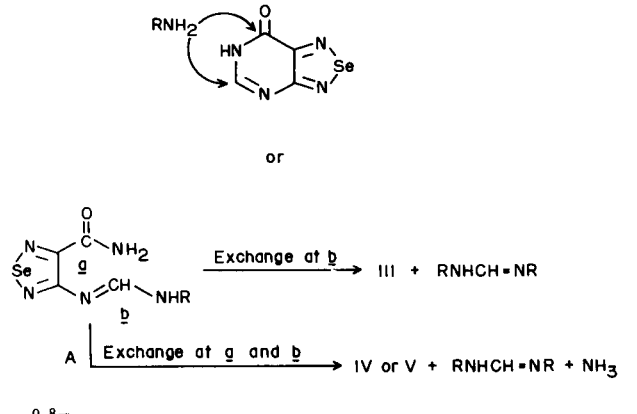


Chart III



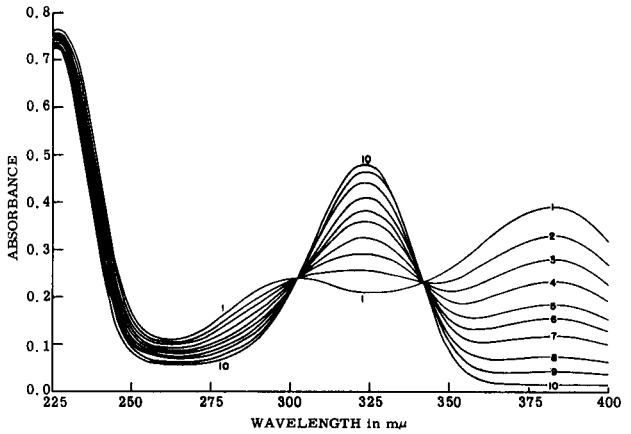


Fig. 1. VI ⟶ VIII. 6×10^{-5} M in 0.1 *N* NaOH at 25°. Time intervals between the addition of the sample to 0.1 *N* NaOH and the time at which the tracing of a curve was begun (at 400 mμ) were as follows: 2.5, 7, 11.5, 16, 22.25, 27.25, 34.5, 48.5, 68.25, 129.5 min. for curves 1-10, respectively.

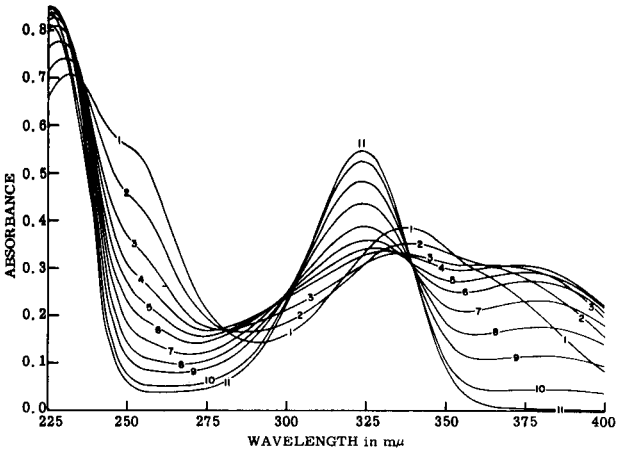


Fig. 2. Alkaline hydrolysis of VII to VIII showing intermediacy of VI. 6.9×10^{-5} M in 4:96 ethanol-0.1 *N* NaOH at 25°. Time intervals between the addition of ethanol solution of VII to 0.1 *N* NaOH and the time at which the tracing of a curve was begun (at 400 mμ) were as follows: 2, 5.5, 10.5, 15.5, 20, 24.75, 32.25, 45, 59, 90, 145.5 min. for curves 1-11, respectively.

after ring opening has occurred at position 5 (5a).

Facile cleavage of [1,2,5]selenadiazolo[3,4-*d*]-pyrimidine-5,7(4*H*,6*H*)-dione (VI) to *N*-butyl-4-ureido-1,2,5-selenadiazole-3-carboxamide (VII) and to 4-ureido-1,2,5-selenadiazole-3-carboxylic acid (VIII) was effected by butylamine and 2 *N* potassium hydroxide, respectively (Chart II). The structure of VII is assigned by analogy to the structures of the thiadiazoles obtained by reaction of amines with the sulfur analog of VI; the thiadiazoles were shown to be *N*-alkyl-4-ureido-1,2,5-thiadiazole-3-carboxamides rather than 4-(3-alkylureido)-1,2,5-thiadiazole-3-carboxamides (5b).

The *N*-butyl amide (VII) was easily hydrolyzed to the acid (VIII) by aqueous base. By analogy to the corresponding thiadiazole (5b), it was anticipated that the selenadiazolopyrimidinedione (VI) would be an intermediate in this process. The ultraviolet spectra depicted in Figure 2 demonstrate the sequence VII ⟶ VI ⟶ VIII. The increase in absorption at 382 mμ and the subsequent decrease correspond to the formation and disappearance of VI (*cf.* Fig. 1). The decrease in absorption at 337 mμ and the increase at 324 mμ correspond to the disappearance of VII and the formation of VIII, respectively. The spectra after curve 6 are similar to the later curves of Figure 1, which shows the course of the ring-opening of VIII in dilute base at 25°. In a separate experiment the reaction was quenched by acidification, and all three of the components (VII, VI, VIII) were separated by chromatography and identified.

TABLE I

1,2,5-Selenadiazoles. Electronic Spectra and Tumor Data

Compound	Ultraviolet Absorption Data (a) λ max in mμ (ε x 10^{-3}) 0.09 *N* HCl	*p*H 7	0.09 *N* NaOH	Tumor Data (b) S180 Toxic Dose	S180 Inactive Dose	L1210 Toxic Dose	L1210 Inactive Dose
II	345 (7.1) 223 (6.3)	337 (6.3) 215 (7.6)	337 (6.3) (c)	4	2	4	2 (d)
III (e, f)	345 (7.5) 222 (7.2)	348 (6.3) 223 (7.7)	348 (6.3) 223 (7.6)	4	2	(g)	2
V	343 (7.9) 260 (sh.) 222 (7.6)	346 (6.7) 260 (sl. sh.) 221 (7.4)	346 (6.7) 260 (sl. sh.) 222 (7.7)	8	3 (h)	6	3
IV (e, i)	345 (7.8) 260 (sh.) 222 (7.4)	348 (6.8) 260 (sl. sh.) 222 (7.9)	348 (6.9) 260 (sl. sh.) (j)	12	6	(k)	6
VII (e)	330 (8.8) 230 (13.8)	330 (8.7) 230 (13.0)	unstable	60	30		50
VIII	329 (8.2) 230 (11.7)	324 (8.5) 225 (12.4)	324 (8.5) 226 (12.2)	(l)	30	50	25
I (m)	338 (11.5) 265 (2.4) 233 (6.7)	339 (11.1) 270 (2.4) 233 (6.9)	365 (8.1) 297 (6.2) 232 (7.1)			(n)	20
VI	340 (10.2) 255 (sh.) 221 (9.2)	339 (9.2) 255 (sh.) 221 (10.1)	unstable			45	22

(a) Sh. = shoulder; sl. = slight; *p*H 7 = phosphate buffer at *p*H 7. (b) See ref. 10; doses in mg./kg./day. (c) Not determined below 220 mμ. (d) Life-span ratio (Treated/Control) = 119%. Single-dose treatment on Day 2: 15 mg./kg., toxic; 7.5 mg./kg., inactive. (e) Solutions used for ultraviolet determinations contained 10% ethanol. (f) λ max (Ethanol) in mμ (ε x 10^{-3}): 355(6.5), 223(8.4). (g) Toxic at 3 mg./kg./day in Adenocarcinoma 755 test. (h) Inhibition ratio (Treated/Control) = 53% at 4 mg./kg./day, but mortality of 2 out of 6 and difference of avg. host-weight change (Treated minus Control) of -3.9 g. indicate some toxicity at this dose. (i) λ max (cyclohexane) in mμ (ε x 10^{-3}): 353(7.1), 245(sh.), 219(7.3). (j) Not determined below 225 mμ. (k) Toxic at 8 mg./kg./day in Adenocarcinoma 755 test. (l) Toxic at 38 mg./kg./day in Adenocarcinoma 755 test. (n) Toxic at 31 mg./kg./day in Adenocarcinoma 755 test. (m) Maxima at 236, 276, 337 mμ are given in ref. 3b for the U.V. spectrum of I in water.

Red or black films and precipitates, indicative of degradation to inorganic selenium, were frequently observed during the preparation, isolation, or subsequent reactions of the selenadiazoles; some of the more obvious examples are the following. Although 4-amino-1,2,5-thiadiazole-3-carboxylic acid hydrazide was obtained in high yield by treating the thiadiazolopyrimidinone analog of I with hydrazine (5a), I was reductively cleaved at room temperature by hydrazine. From this reaction elemental selenium and 5,6-diaminopyrimidin-4(3*H*)-one (as the hemisulfate) were isolated (Chart I). Treatment of the aminocarboxamide (III) or the selenadiazolopyrimidinedione (VI) with hydrazine also produced black precipitates; these reaction products were not investigated. In addition to the two amides (III and V) obtained from the reaction of I with methylamine, a small amount of elemental selenium was also isolated. The reducing agent in this reaction might have been ethanol, used as the solvent, or metallic impurities from the bomb in which the reaction was carried out. The ultraviolet spectrum of a solution

of the aminocarboxamide (III) in 0.1 *N* hydrochloric acid was unchanged after 50 hours at room temperature, but a refluxing solution of III in 0.1 *N* hydrochloric acid under nitrogen first became red and then black.

The ultraviolet spectra of the 4-amino-1,2,5-selenadiazole-3-carboxamides in aqueous media (Table I) have absorption maxima at 221-223 and 343-348 mμ; the amino acid (II) displays similar maxima in acidic solution, and these maxima are shifted hypsochromically by 8 mμ in neutral and basic solutions. The long-wavelength maxima of the ureido derivatives (VII, VIII) and of the selenadiazolopyrimidines occur near 330 and 340 mμ, respectively, in the non-ionized forms. The anion of VIII shows maximum absorption at 324 mμ. The long-wavelength maxima of the selenadiazoles and the two selenadiazolopyrimidines occur at longer wavelengths than do those of their corresponding sulfur analogs. These bathochromic shifts are approximately 17-22 mμ in the spectra of the 4-amino-1,2,5-selenadiazole derivatives and about 25-28 mμ in the spectra of the ureido derivatives and the selenadiazolopyrimidines (7).

The N.M.R. spectra of 4-amino-1,2,5-selenadiazole-3-carboxamide (III) and of the *N*-methyl amide (V) in dimethylsulfoxide-d_6 show singlet peaks (2 protons), assignable to the amino group, at 7.05 and 7.07 p.p.m., respectively. The amide protons of III produce a broad doublet centered at 7.82 p.p.m., and the amide proton (NH) of V gives a broad peak at 8.53 p.p.m.

The infrared spectrum of the selenadiazolopyrimidinone (I) has a strong band at 1680 cm^{-1} and that of the selenadiazolopyrimidinedione (VI) has strong bands at 1720 and 1675 cm^{-1}. These carbonyl absorptions are consistent with the well-known (8) predominance of oxo forms of heterocycles having oxygen functions adjacent to ring-nitrogen atoms. Interpretation of the spectra of the selenadiazoles in terms of ring-skeletal vibrations is complicated by bending (NH_2, NH, CH) and stretching (C-N, C-O, C=O) modes of the functional groups. Provided that this fact is kept in mind, a few band positions may be noted. A weak band is present in the spectra of I-VIII at 800-790 cm^{-1}. This band is distinct and sharp in all spectra except those of VI and VII in which several bands appear near 800 cm^{-1}. The spectrum of deuterated III still included the sharp band near 800 cm^{-1} (shifted from 796 cm^{-1} to 793 cm^{-1}). The spectra of compounds I-VII have a strong band, sometimes comparable in intensity to the carbonyl bands, at 1605-1575 cm^{-1}. The spectrum of VIII shows only a shoulder in this region (plus a strong band at 1545 cm^{-1} and a strong doublet at 1675 and 1645 cm^{-1}), but its potassium salt produces strong bands at 1625 and 1605 cm^{-1} (one of which should be due to the carboxylate ion). Two weak-or medium-intensity bands near 760 and 740 cm^{-1} (ranges, approximately 780-735 cm^{-1} and 760-715 cm^{-1}) appear in the spectra of compounds I-VIII except for the spectrum of II, which has a single strong band at 750 cm^{-1}. In place of the doublet at 737 and 717 cm^{-1} in III, bands at 760, 728, and 697 cm^{-1} appeared in the spectrum of deuterated III. (An inflection near 760 cm^{-1} in the spectrum of III suggests that a band near this position may be covered by the doublet in III.) The strong band at 1575 cm^{-1} disappeared (except for a shoulder assumed to be due to residual-NH_2) after deuteration of III, and a new medium-strong band appeared at 1532 cm^{-1}. The band at 1575 cm^{-1}, therefore, may be a composite band due to both -NH_2 and ring vibrations. Additional details are given in the Experimental Section.

The four amino selenadiazole derivatives (II-V) were highly cytotoxic to KB cells in culture, the average ED_{50} values falling within the range 0.25-0.45 mcg./ml. (9). The ureido derivatives (VII, VIII) and the two selenadiazolopyrimidines (I, VI) were less cytotoxic by 1-2 orders of magnitude (9). The pattern of toxicity *in vivo* was similar: the amino derivatives were quite toxic to mice in Sarcoma 180 and Lymphoid Leukemia L1210 tests; the remaining derivatives (I, VI-VIII) were considerably less toxic (Table I). At nontoxic doses the selenadiazoles did not display significant activity in these two neoplastic test systems (10). The aminoselenadiazoles (II-V) have marked, broad-spectrum antifungal and antibacterial activity (9).

EXPERIMENTAL

Except for III, infrared absorption bands are listed to the nearest 5 cm^{-1} in the region 1750-650 cm^{-1} (or 450 cm^{-1}); s = strong, m = medium, w = weak, b = broad, sh. = shoulder, v = very. Infrared spectra were determined in potassium bromide discs with either a Perkin-Elmer 521 or a Perkin-Elmer Model 221G spectrophotometer. Ultraviolet spectra were recorded with a Cary Model 14 recording spectrophotometer. Melting points were determined either on a Kofler Heizbank apparatus or in a capillary tube in a Mel-Temp apparatus. The latter are designated "cap." N.M.R. spectra were recorded with a Varian Associates A60 spectrophotometer with tetramethylsilane as internal standard.

[1,2,5]Selenadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (I).

The method of preparation was similar to that of Carr, Sawicki, and Ray (3b). From a mixture of 2.52 g. of 5,6-diaminopyrimidin-4(3*H*)-one, 2.22 g. of selenium dioxide, and 110 ml. of water stirred at room temperature for 64 hours was obtained a precipitate amounting to 3.15 g. (after it had been washed with water and dried) and a second crop of 360 mg. Recrystallization of the first crop from 5:2 water-dimethylformamide yielded 2.28 g. (57%) of a pure specimen (Found: C, 24.05; H, 1.23; N, 27.87) that decomposed, without melting, above 328°. ν in cm^{-1}: 1680vs, 1585s, 1500m, 1460mw, 1390m, 1350mw, 1315mw, 1275s, 1190sh., 1115w, 1090w, 905m, 870wb, 830sh., 800mw, 780w, 750sh., 735w, 715w, 675w.

[1,2,5]Selenadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (VI).

The published procedure (3d) was employed, except for the use of the hydrochloride of 4,5-diaminouracil, and gave a 63% yield of analytically pure VI; m.p. 350-355° dec. ν in cm^{-1}: 1720vs, 1675s, 1575s, 1455m, 1445m, 1360ms, 1355ms, 1275ms, 1135w, 1005w, 850wb, 810mb, 785w, 755m, 740m, 690w, 600m, 525m, 495sh., 480m, 450wm, 435m.

4-Amino-1,2,5-selenadiazole-3-carboxylic Acid. A. From [1,2,5]-Selenadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one (I).

A suspension of 6.02 g. of I in 100 ml. of 2 *N* aqueous potassium hydroxide solution was heated at the reflux temperature for 0.5 hour. The starting material dissolved and the solution deposited a white crystalline solid. After the mixture had been chilled in an ice bath, the solid was collected by filtration, washed with cold 90% ethanol, and dried *in vacuo* at 78° for 1.5 hours; wt., 3.3 g. A second crop, obtained in similar fashion after the combined filtrate and washings had been concentrated, raised the yield of the potassium salt of 4-amino-1,2,5-selenadiazole-3-carboxylic acid to 6.3 g. (91%). (Calcd. for $C_3H_2N_3O_2SeK$: C, 15.66; H, 0.88; N, 18.26. Found: C, 15.75; H, 1.00; N, 18.29.) The potassium salt was dissolved in 125 ml. of hot water, and the hot solution acidified to *p*H 1 with 15 ml. of 2 *N* hydrochloric acid. The yellow solid that precipitated was collected by filtration, washed with water (20 ml.) and ethanol (20 ml.), and dried *in vacuo* at 100° over phosphorus pentoxide: yield, 4.9 g. (85%), decomposes above 185° (cap.). Ultraviolet data indicated that this material was comparable in quality to a specimen that had been recrystallized twice from water. ν in cm^{-1}: 1685ms, 1595s, 1525m, 1465m, 1425w, 1385w, 1310s, 1115ms, 1000w, 800w, 755s, 700w, 690w, 535m, 465m.

Anal. Calcd. for $C_3H_3N_3O_2Se$: C, 18.77; H, 1.58; N, 21.89; Se, 41.12. Found: C, 19.18; H, 1.80; N, 21.95; Se, 41.18.

B. From 4-Amino-1,2,5-selenadiazole-3-carboxamide.

A mixture of 382 mg. of the aminoamide (III), 10 ml. of ethanol, and 20 ml. of 1 *N* sodium hydroxide was heated under reflux for 1 hour, allowed to stand at room temperature for 18 hours and acidified to *p*H 2 with 6 *N* hydrochloric acid. The yellow solid that precipitated upon acidification amounted to 306 mg. (80%); its infrared and ultraviolet spectra were identical with those of a pure specimen of II obtained from I.

4-Amino-1,2,5-selenadiazole-3-carboxamide (III).

A mixture containing 6.03 g. of the selenadiazolopyrimidinone (I), 200 ml. of absolute ethanol, and 200 ml. of anhydrous ammonia was heated in a stainless steel bomb for 20 hours at 80° and then evaporated *in vacuo* to 100 ml. The yellow crystalline solid that formed during the evaporation was collected by filtration, washed with ethanol (2 x 25 ml.), and dried *in vacuo* at room temperature: yield, 5.03 g. (88%); m.p., 218° with sublimation. An analytical sample, melting at 218°, was obtained by sublimation at 180° and 0.5 mm. ν in cm^{-1}: 3450s, 3330m, 3265m, 3200-3150mb, 1673s, 1575sb, 1510m, 1423ms, 1388m, 1356ms, 1132w, 1080w, 796w (sharp), 737m, 717m, 650mb, 580mb, 488m, 467sh., 453ms.

Anal. Calcd. for $C_3H_4N_4OSe$: C, 18.86; H, 2.11; N, 29.33; Se, 41.34. Found: C, 19.06; H, 2.31; N, 29.47; Se, 41.1.

Deuterated III.

A specimen of III was dissolved in deuterium oxide by warming to 50° and was maintained in solution, with occasional warming, for 6 hours. The residue obtained by lyophilization was used to record an infrared spectrum. ν in cm^{-1}: 3440wb, 2580ms, 2545sh., 2430m, 2370ms, 2340sh., 1650s, 1600-1575sh., 1532ms, 1440s, 1405m, 1340-1325mb, 1200mw, 1132w, 1065w, 912w, 793w (sharp), 760w, 728w, 697w, 677vw, 612m, 515wb, 440m. Prominent bands in the regions 2600-2500 and 2450-2300 cm^{-1}, together with only weak broad NH-absorption centered near 3440 cm^{-1}, indicated that most of the hydrogen had been exchanged for deuterium. Also, the shift or disappearance of other bands (*e.g.* 1356 cm^{-1} and 650 cm^{-1}) supported this conclusion. A new band at 1200 cm^{-1} was in the region expected for ND_2-bending corresponding to the NH_2-mode generally found in the 1600 cm^{-1} region. In connection with the two bands in the 800-700 cm^{-1} region mentioned in the discussion section, it may also be noted that the displacement of the center of a broad band at 515 cm^{-1} from the band at 717 cm^{-1} in the spectrum of III slightly exceeded the factor of 1.37 expected for replacement of NH by ND. Next to the amide I band (1650 cm^{-1}, shifted from 1673 cm^{-1}), the strongest band in the spectrum of deuterated III was at 1440 cm^{-1} followed by a new band, mentioned in the discussion, at 1532 cm^{-1}. The distinct, sharp band in the 800-790 cm^{-1} region was obvious in the spectra of both deuterated and undeuterated III.

Reaction of [1,2,5]Selenadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one with Butylamine.

A solution of 8.04 g. of I in 200 ml. of dry, redistilled *n*-butylamine was heated at the reflux temperature for 2 hours, evaporated *in vacuo* to a brei, diluted with 50 ml. of hot hexane, and filtered. The solid was washed with hot hexane (3 x 15 ml.) and dried *in vacuo* at 56° over phosphorus pentoxide. This fraction was shown by its infrared spectrum and melting point (217° with sublimation) to be 4-amino-1,2,5-selenadiazole-3-carboxamide; wt., 3.58 g. (47%). The filtrate, together with the washings, was evaporated *in vacuo* to a yellow syrup that solidified on standing. Trituration of the solid with 30 ml. of an ethanol-hexane mixture (1:4), filtration, and drying *in vacuo* gave 3.66 g. (37%) of *N*-butyl-4-amino-1,2,5-selenadiazole-3-carboxamide: m.p., 67-68°. An additional 830 mg. (total yield = 45%), m.p. 68-69°, was obtained by evaporating the filtrate to a syrup, diluting with 10 ml. of hexane, and chilling. ν in cm^{-1}: 1660s, 1650s, 1605s, 1535s, 1525sh., 1460m, 1450m, 1425m, 1375m, 1345w, 1335w, 1300mw, 1280m, 1260w, 1225w, 1155m, 1110w, 1060sh.b, 1020w, 945w, 895w, 855w, 820vw, 795w, 765m, 740m, 710w, 685w, 655m, 635m, 530m, 490m, 465m.

Anal. Calcd. for $C_7H_{12}N_4OSe$: C, 34.02; H, 4.90; N, 22.67; Se, 31.95. Found: C, 34.06; H, 4.99; N, 22.81; Se, 31.73.

Reaction of [1,2,5]Selenadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one with Methylamine.

A mixture of 15 ml. of absolute ethanol, 15 ml. of anhydrous methylamine, and 402 mg. of I was heated in a stainless steel bomb at 80° for 18 hours. Evaporation of the yellow reaction solution *in vacuo* left 421 mg. of solid (m.p. 120-125°). A 298-mg. portion of the residue was dissolved in 4 ml. of hot methanol, and several portions of chloroform were added and partially evaporated *in vacuo*. The final solution (*ca.* 4 ml.), which was beginning to deposit solid, was placed on a column (20 x 1.5 cm.) of silica gel H (Merck), and the column was eluted with chloroform-methanol (99:1). Evaporation of the first 50-ml. fraction of eluate yielded 205 mg. of a yellow crystalline solid that melted at 135-137° and proved to be *N*-methyl-4-amino-1,2,5-selenadiazole-3-carboxamide. Recrystallization of the solid from water did not alter its melting point. ν in cm^{-1}: 1660s, 1650s, 1580s, 1525s, 1460sh., 1415ms, 1405m, 1380m, 1280ms, 1160m, 1140m, 990mw, 840w, 790w, 765m, 735m, 695w, 680w, 630m, 490m, 455s. N.M.R. signals (δ in p.p.m.; solvent, DMSO-d_6): 2.80 (CH_3, doublet); 7.07 (NH_2, singlet); 8.53 (amide-NH-, broad).

Anal. Calcd. for $C_4H_6N_4OSe$: C, 23.42; H, 2.95; N, 27.32; Se, 39.50. Found: C, 23.42; H, 3.02; N, 27.36; Se, 39.3.

Evaporation of solvent from the second 50 ml. of eluate left 89 mg. of gummy residue. Recrystallization of this material from water gave 38 mg. of a yellow solid that was identified by its melting point (218° with sublimation) and infrared spectrum as 4-amino-1,2,5-selenadiazole-3-carboxamide.

A reaction mixture obtained in the same manner from 5.0 g. of I contained a suspended solid after the bomb had been chilled and opened. Filtration yielded 175 mg. of grey-black crystals; m p., 221°.

Anal. Found: Se, 100 ± 0.5%.

N-Butyl-4-ureido-1,2,5-selenadiazole-3-carboxamide (VII).

A mixture of 5.5 g. of [1,2,5]selenadiazolo[3,4-*d*]pyrimidine-5,7-(4*H*,6*H*)-dione (VI) and 100 ml. of *n*-butylamine (dried over calcium hydride) was heated at the reflux temperature for 3.5 hours. The reaction solution was filtered from a small amount of red amorphous material, the filtrate evaporated, and the residue recrystallized from 125 ml. of ethanol: yield, 5.88 g. (79%), m.p. 172° (cap.). ν in cm^{-1}: 1705ms, 1685s, 1640s, 1600s, 1540s, 1475ms, 1465sh., 1445w, 1435sh., 1405w, 1380s, 1315w, 1295w, 1255sh., 1230ms, 1210m, 1140mb, 975wb, 950w, 905w, 825w, 815w, 800sh., 790m, 760m, 735w, 705sh., 690w, 650w.

Anal. Calcd. for $C_8H_{13}N_5O_2Se$: C, 33.11; H, 4.52; N, 24.13; Se, 27.22. Found: C, 33.17; H, 4.53; N, 23.92; Se, 27.0.

4-Ureido-1,2,5-selenadiazole-3-carboxylic Acid (VIII).

A mixture of 6.51 g. of VI and 200 ml. of 2 *N* aqueous potassium hydroxide solution was stirred at 21°. The starting material dissolved within one minute, and the resulting solution began depositing a yellow solid after five minutes. The mixture was stirred for 3 hours at 21°; the yellow solid (8.1 g.) was collected by filtration and dissolved in 200 ml. of hot water; and the resulting solution was diluted slowly with 250 ml. of hot ethanol. The product (7.5 g.) that crystallized from the chilled solution was evidently hydrated. A crystalline specimen prepared by a second recrystallization from 55% aqueous ethanol, subsequent recrystallization from water, and drying *in vacuo* at 100° for 5 hours was shown to be a monohydrate.

Anal. Calcd. for $C_4H_3KN_4O_3Se \cdot H_2O$: C, 16.50; H, 1.73; N, 19.25; H_2O, 6.2. Found: C, 16.81; H, 1.89; N, 19.26; H_2O (by vapor phase chromatography), 6.4.

Recrystallization of a crude specimen from 5:1 ethanol-water gave unhydrated white needles; dec. > 240° (cap.). λ max in mμ (ϵ x 10^{-3}):

229 (11.6), 328 (8.4) in 0.1 *N* hydrochloric acid. ν in cm^{-1}: 1705s, 1625s, 1605ms, 1535m, 1480m, 1425m, 1410m, 1350ms, 1240m, 1150w, 1130sh., 985w, 910w, 820w, 800m, 775m, 755m, 690w.

Anal. Calcd. for $C_4H_3KN_4O_3Se$: C, 17.59; H, 1.11; N, 20.51; Se, 28.91. Found: C, 17.64; H, 1.18; N, 20.21; Se, 28.95.

A solution of 273 mg. of the potassium salt in 10 ml. of hot water was acidified with 1.1 ml. of 1 *N* hydrochloric acid, the mixture was chilled, and the precipitated acid was collected on a filter and washed with water: wt., 201 mg. (86%), m.p. (indefinite), approximately 210-220° dec. (cap.). ν in cm^{-1}: 1675s, 1645s, 1590sh., 1570sh., 1545s, 1490m, 1415m, 1395w, 1310m, 1225m, 1130w, 1070w, 965w, 910w, 800w, 770m, 760sh., 750mw, 685w, 630w, 605w, 575m, 510w, 465w.

Anal. Calcd. for $C_4H_4N_4O_3Se$: C, 20.44; H, 1.72; N, 23.83. Found: C, 20.59; H, 1.81; N, 23.89.

Cyclization of 4-Amino-1,2,5-selenadiazole-3-carboxamide (III) to [1,2,5]Selenadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one.

A mixture consisting of 382 mg. of III, a small crystal of *p*-toluenesulfonic acid, and 70 ml. of triethyl orthoformate was heated under a nitrogen atmosphere at 120° for 74 hours. Filtration of the turbid mixture and concentration of the filtrate *in vacuo* at 45° left an oily residue that was converted into a solid by the addition of 10 ml. of ethanol. The solid was collected by filtration, washed with ethanol (2 x 5 ml.), and dried *in vacuo*; wt., 216 mg. Trituration with 1:2 ethanol-hexane of the residue obtained by evaporating the combined filtrate and washings gave an additional 81 mg. of product; total yield, 74%. The infrared and ultraviolet spectra of both portions were the same as those of [1,2,5]selenadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one.

Alkaline Hydrolysis of *N*-Butyl-4-ureido-1,2,5-selenadiazole-3-carboxamide. A. Preparative Procedure.

A solution of 290 mg. of VII in 25 ml. of ethanol and 20 ml. of 1.0 *N* aqueous sodium hydroxide was stirred at room temperature for 24 hours. A crystalline precipitate that began to form within 2.5 hours redissolved when the mixture was concentrated to about 20 ml. The concentrated solution was acidified with 3.9 ml. of 6 *N* hydrochloric acid, and the precipitate of 4-ureido-1,2,5-selenadiazole-3-carboxylic acid was collected on a filter and washed with water; wt., 194 mg. (83%). The infrared and ultraviolet spectra were identical with those of a specimen of the acid (VIII) obtained from VI.

B. Course of the Reaction.

To a solution of 290 mg. of VII in 20 ml. of ethanol at 25° was added 20 ml. of 1 *N* sodium hydroxide previously equilibrated at 25°. The reaction solution was kept at 25° for 1 hour, acidified with 15 ml. of 2 *N* hydrochloric acid to quench the reaction, and then concentrated to dryness *in vacuo* at temperatures below 35°. The residue was leached twice with hot dimethylformamide. The residue obtained by evaporating the dimethylformamide amounted to 335 mg. A concentrated solution of the residue in dimethylformamide was applied to a column of 12 g. of silica gel previously washed with 92:8 chloroform-methanol. Elution of the column with 92:8 chloroform-methanol gave a fraction consisting of the *N*-butylamide (VII) contaminated with VI. Trituration of this fraction with ethanol and evaporation of the ethanol filtrate afforded 64 mg. (22% recovery) of VII, m.p. 171°.

The ethanol-insoluble portion was combined with later fractions eluted by the same solvent mixture. Recrystallization from water gave 45 mg. (21%) of VI, m.p. 355-360° dec. Elution of the column with 1:1 chloroform-methanol gave 63 mg. of impure VI (72% pure by U.V.).

Further elution of the column with 1:1 chloroform-methanol yielded impure VIII that was triturated with ethanol and then combined with small fractions eluted by butanol-water-acetic acid (5:3:2). Reprecipitation of this material from a sodium hydroxide solution by acidification gave 42 mg. (18%) of the ureido acid (VIII). The three isolated components were identified by their ultraviolet and infrared spectra and by thin-layer chromatography.

Reduction of [1,2,5]Selenadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one by Hydrazine.

A 602-mg. portion of I was dissolved in 12 ml. of commercial hydrazine (95+%) at room temperature, and the mixture, which had become black within 20 minutes, was stirred for 20 hours and then diluted with 17 ml. of water. The resulting mixture was quickly chilled (to counteract the rise in temperature caused by dilution with water) and then stirred at room temperature for 4 hours. Filtration removed a black solid that was washed well with ethanol: wt., 218 mg. (92% yield as Se); m.p. 221°. Found: Se, 99.5%.

The filtrate was concentrated *in vacuo* to a red-brown solid that was dissolved in 50 ml. of water and 5 ml. of 2 *N* sulfuric acid. The solution was poured onto a column of CG-120 (H^+) cation exchange resin, the column was washed with water and then with 1 *N* aqueous ammonia, and the aqueous ammonia effluent was concentrated to a solid residue. A solution of the solid in water (25 ml.) was acidified with 2 *N* sulfuric acid (1.4 ml.) and chilled. A precipitate was collected by filtration, washed well with water and ethanol, and dried *in vacuo* over phosphorus pentoxide; wt., 177 mg. (33% yield). Recrystallization of this material, which was about 95% pure according to ultraviolet absorption data, from 50% ethanol gave a pure specimen (100 mg.) that was identified as 5,6-diaminopyrimidin-4(3*H*)-one hemisulfate by comparison of its infrared and ultraviolet spectra with those of an authentic specimen and by thin-layer chromatography (silica gel, 5:3:2 butanol-water-acetic acid).

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