that of good commercial fungicides[12] and some dithiosemicarbazones.[14] Nevertheless, the thiosemicarbazones of none of the 3 types of heterocyclic aldehydes reported here are as effective as a class against *C. globosum* as are thiocarbohydrazones,[16] for example. Since moderate effectiveness against both organisms is important, however, some useful generalizations about chemical structure and activity can be made. The order of decreasing effectiveness (by aldehyde class) of the thiosemicarbazones is pyrrole carboxaldehyde ≅ furfural > *N*-methylpyrrolecarboxaldehyde ≅ thiophenecarboxaldehyde. Substitution at the 4 position does not seem to be important for the first and last types but is for the second and third (*cf.* ref 3). The order of decreasing effectiveness of substituents is aromatic > aliphatic in the case of the pyrrole carboxaldehyde thiosemicarbazones but is reversed for the *N*-methyl analogs. There is no obvious reason why the 5-methylthiophene derivatives (**30-38**) should be completely ineffective (*cf.* ref 4).

Experimental Section

Thiosemicarbazide, the substituted isothiocyanates, and the heterocyclic aldehydes were the purest grades obtainable from commerical sources, and were used as received. The preparation of the 4-substituted thiosemicarbazides has been described.[17]

General Preparation for Thiosemicarbazones (Table I).—To a warm soln of [substituted] thiosemicarbazide (0.01 mole) in H_2O[EtOH] (50 ml) containing HAc (1 ml) was added dropwise a soln of heterocyclic aldehyde (0.01 mole) in EtOH (50 ml). The mixt was heated gently on a steam bath for 1 hr; H_2O was added until the onset of pptn. The ppt which formed on subsequent cooling was sepd by filtration, washed with cold 50% EtOH–H_2O, dried, and recrystd to constant mp. Characteristic ir absorptions: all compds, 3360–3140 (NH); 1630–1595 (CN); 1560–1535 (CNH); 1160–1110 (NCN); 835–800 (CS); **2, 12, 21, 31, 40,** 1640 (C=C).

Ir spectra were measured with a Model 621 Perkin-Elmer spectrophotometer. Elemental analyses were carried out at the microanalytical lab of Drs. Weiler and Strauss in Oxford, England. Melting points were determined using a Fisher-Johns apparatus and have been corrected. The antimicrobial activity of the compds listed in Table I has been evaluated[11] by the tube-dilution method,[12] using pure cultures of *C. globosum* (Strain USDA 1042.4) and *Aspergillus niger* (Strain USDA 215-5373.16).

Acknowledgments.—The authors thank Miss G. Colin for the microbiological screening data, and R. Ironside and V. Boyko for recording the ir spectra.

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Potential Antitumor Agents. Selenoguanosine and Related Compounds[1]

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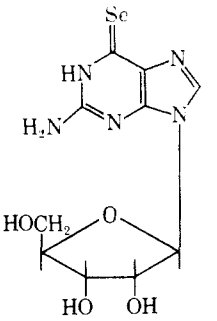
It has been shown previously that 6-selenoguanine[2] exhibits antitumor activity on ascites cells of Sarcoma 180 and against lymphomas L1210 and L-5178Y. These findings have led us to prepare the additional unreported methylseleno 9-β-D-ribosyl derivatives of 6-selenoguanine. We hope these more soluble analogs will offer further improvement in antitumor activity.

This communication describes the synthesis of 6-selenoguanosine[3] (**1**), 6-methylselenoguanine, 6-methylselenoguanosine, and 6-methylselenoinosine and preliminary studies of their biological properties.



Experimental Section[4]

2-Amino-6-seleno-9-β-D-ribofuranosylpurine (6-Selenoguanosine) (1).—Condensed H_2Se (1.5 ml) was bubbled through a soln of 0.3 g (0.013 mole) of Na in 30 ml of abs MeOH. 2-Amino-6-chloro-9-β-D-ribofuranosylpurine[5] (3.0 g, 0.00906 mole) in 70 ml of abs MeOH was introduced into the well-stirred orange soln. The mixture was stirred under N_2 at room temp for 1 hr. The greenish solid was collected by filtration and taken up in 35 ml of 3% Na_2CO_3, and the colloidal Se was filtered off. The filtrate was acidified with glacial AcOH to pH 4 and cooled. The bright yellow solid was collected, washed with cold H_2O, and dried. The yield was 1.75 g (54.4%) mp 197.5° dec. On tlc[6] the R_f value in H_2O is 0.40. *Anal.* ($C_{10}H_{13}N_5O_4Se \cdot 0.5H_2O$) C, H, N.

2-Amino-6-methylseleno-β-D-ribofuranosylpurine (6-Methylselenoguanosine).—A soln of 1.2 g (0.00338 mole) of **1** in 8.45 ml of 0.4 *N* NaOH (0.00338 mole) was stirred at room temp and 0.22 ml (0.00348 mole) of MeI was added. The soln was stirred at room temp for 1 hr. The resulting mixture was filtered and the filtrate extd continuously with Et_2O. After 24 hr, the solid was collected and dried *in vacuo*. The yield was 0.65 g (52.3%). The product was recrystd from EtOH–pet ether (30°–60°), mp 144–147°. On tlc,[6] the R_f value in H_2O is 0.49. *Anal.* ($C_{11}H_{14}N_5O_4Se \cdot 0.5H_2O$) C, H, N.

2-Amino-6-methylselenopurine (6-Methylselenoguanine).—A soln of 2.23 g (0.01 mole) of selenoguanine in 25 ml (0.01 mole) of 0.4 *N* NaOH was stirred at room temp and 0.65 ml (0.01 mole) of MeI added. The soln was kept at room temp for 1 hr. The light yellow solid was collected, washed with H_2O, and dried. The yield was 1.85 g (81.1%). It was recrystd from MeOH, mp 218°. On tlc[6] the R_f value in H_2O is 0.30. *Anal.* ($C_6H_7N_5Se$) C, H, N.

6-Methylseleno-9-β-D-ribofuranosylpurine (6-Methylselenoinosine).—A soln of 0.192 g (0.00058 mole) of selenoinosine[7] in 1.45 ml (0.00058 mole) of 0.4 *N* NaOH was stirred at room temp, and 0.073 ml (0.00058 mole) of MeI was added. The soln was stirred at room temp for 1 hr. The resulting mixture was extd continuously with Et_2O. After 24 hr the solid was collected by filtration and dried *in vacuo*. The Et_2O soln was evapd to dryness. The yield was 0.175 g (85.0%). The product was recrystd from EtOH–pet ether (30–60°), mp 154–155°. On tlc[6] the R_f value in H_2O is 0.70. *Anal.* ($C_{11}H_{14}N_4O_4Se \cdot H_2O$) C, H, N.

Dissociation Constants.—pK_a values were determined by potentiometric titration using a Radiometer pH meter 26. The selenoguanine, which is very insol in H_2O, was dissolved in boiling

(1) This work has been supported by Grant T-536 from the American Cancer Society and Grant 16538-01 from the United States Public Health Service.
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TABLE I

ULTRAVIOLET SPECTRA AND ACID DISSOCIATION CONSTANTS

Compds	pH 1 λmax, mμ	pH 1 ε	Distd H_2O λmax, mμ	Distd H_2O ε	pH 11 λmax, mμ	pH 11 ε	Methanol λmax, mμ	Methanol ε	pK_a
6-Thioguanine[a]	258	8100			242	8700			8.2
	347	20900			270	7200			
					322	16000			
6-Methylthioguanine[b]	241	7000			228	20200			
	273	10000			313	10600			
	317	13000							
6-Selenoguanine[c]	263	5600	360	10800	318	6900			7.81, 7.62[d]
	372	16500							
6-Methylselenoguanine	329	12700	246	8900	317	12300			
			315	12400					
	pH 4–6								
6-Thioguanosine[e]	257	8800			252	14700			8.33
	342	24800			319	21000			
6-Selenoguanosine	267	4600	264	5600	256	10800			
	365	18200	357	22300	330	17200			
6-Methylthioguanosine[f]							221	15300	
							245	14400	
							310	11000	
6-Methylselenoguanosine			252	9700			221	12900	
			316	13100			252	10000	
							314	10100	
6-Selenoinosine[g]			235	7700					
			345	11200	(Phosphate–citrate buffer, pH 7)				
6-Methylselenoinosine			229	8400			230	8000	
			302	13500			300	17600	

[a] G. B. Elion and G. Hitchings, *J. Amer. Chem. Soc.*, **77**, 1676 (1957). [b] J. A. Montgomery and L. B. Holum, *ibid.*, **79**, 2185 (1957). [c] See ref 2. [d] A. F. Ross, private communication (it was determined by a spectrophotometric method). [e] J. J. Fox, I. Wempen, A. Hampton, and I. L. Doerr, *J. Amer. Chem. Soc.*, **80**, 1669 (1958). [f] C. W. Noell and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 1074 (1962). [g] See ref 7.

TABLE II

EFFECT OF 6-THIOGUANINE, SELENOGUANINE, SELENOGUANOSINE, METHYLSELENOGUANINE, AND METHYLSELENOGUANOSINE ON THE GROWTH OF L-5178Y

Control 100%	% survival 1.0×10^{-4} M	% survival 1.0×10^{-5} M	% survival 1.0×10^{-6} M
Thioguanine	4	9	33
Selenoguanosine	4	8	31
Selenoguanine	12	20	45
Methylselenoguanosine	21	46	80
Methylselenoguanine	24	45	82

H_2O and then cooled to room temp. All determinations were made in duplicate.

Stability Studies.—The half-life from the height of the 360-mμ peak of 1 in H_2O (pH 6.01) at room temp was about 24 hr, in phosphate buffer at pH 7.0 2.5 hr (as compared with 7 hr for selenoguanine). Methylselenoguanine and methylselenoguanosine were stable in both conditions. Because of the demonstrated instability of 6-selenoguanine and 6-selenoguanosine, fresh solns of these two compds were prepared for biological studies.

Biological Testing. (1) **Tissue Culture Study.**—The results of the cell culture using the L-5178Y cell are shown in Table II. The cell viability was determined by the dil agar colony method.[8] Thioguanine, Se-guanine, Se-guanosine, and their derivatives inhibited cell division and caused cell death over a concn range from 1.0×10^{-4} mole to 1.0×10^{-6} mole after 2 hr incubation. 6-Selenoguanosine was found to have activity approx equal to thioguanine. Methylseleno derivatives were less active than thioguanine at lower dosage. It is of interest that selenoguanosine is more soluble than selenoguanine or thioguanine. This may increase its application.

(2) **Enzyme Study.**—Ross and Parks[9] found that selenoguanine was converted to selenoguanosine by a highly purified enzyme (PNP) isolated from human red blood cells. However, the guanase isolated from S-180 cells does not react with selenoguanine. Details will be published elsewhere.

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Amebicides. *l*-Emetine Derivatives

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Some *N*-hydroxyalkyl derivatives of *l*-emetine have a greater amebicidal activity and a lower toxicity than the parent compound.[1,2] We have now synthetized some N-derivatives by the reaction of *l*-emetine with 1-alkyloxy-, 1-alkylthio-, 1-dialkylamino-2,3-epoxypropane (see Table I). The compounds have been evaluated for their acute toxicity (LD_{50}), for their activity against *E. histolytica*,[3] and Ehrlich carcinoma.[4] Com-

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