soln, H_2O, $NaHCO_3$, and H_2O, then dried (Na_2SO_4), and concd *in vacuo* to give the product as an oil. The product was chromatographed on a column of SilicAR CC7 using $CHCl_3$ as eluant. The fully blocked tripeptide failed to crystallize from EtOAc–hexane and was used as the oil; yield 17.3 g (74.4%). A suspension of 0.85 g of 10% Pd/C in 5 ml of AcOH and 40 ml of MeOH containing 0.68 g (18.6 mmoles) of dry HCl was hydrogenated for 10 min. A soln of 8.65 g (18.6 mmoles) of Z-γ-*tert*-Bu-Glu-Gly-Gly Me was added in 100 ml of MeOH and hydrogenation was continued until there was no further evolution of CO_2. The reaction mixt was filtered and the filtrate was evapd under reduced pressure. The resulting oil was crystd from MeOH–Et_2O to yield 5.8 g (84.8%): mp 76° dec; $[\alpha]^{26}D$ + 38.8° (*c* 1.16, DMF). *Anal.* ($C_{14}H_{26}ClN_3O_6$) C, H, N.

Z-*O*-*tert*-Bu-Tyr-γ-*tert*-Bu-Glu-Gly-Gly Me (3).—To a mixture of 11.6 g (31.6 mmoles) of γ-*tert*-butyl-Glu-Gly-Gly Me ester·HCl in 200 ml of CH_2Cl_2 was added 3.2 g (31.6 mmoles) of Et_3N and 18.5 g (29.9 mmoles) of Z-*O*-*tert*-butyltyrosine pentachlorophenyl ester. The soln was stirred at room temp for 48 hr, then concd *in vacuo*. The residue was dissolved in EtOAc and washed with 10% citric acid soln, H_2O, $NaHCO_3$, and H_2O, then dried (Na_2SO_4) and concd *in vacuo*. The oily product was chromatographed on a column of Silicar CC7, eluted with 50% $CHCl_3$–EtOAc, and crystd from EtOAc–hexane to yield 13.5 g (66%): mp 117–118°; $[\alpha]^{26}D$ − 4.7° (*c* 1.44, DMF). *Anal.* ($C_{35}H_{48}N_4O_{10}$) C, H, N.

Z-*O*-*tert*-Bu-Tyr-γ-*tert*-Bu-Glu-Gly-Gly (4).—To a soln of 9.4 g (13.7 mmoles) of fully blocked tetrapeptide **3** in 150 ml of MeOH was added 13.7 ml of 1 *N* NaOH and the soln was stirred for 90 min, then concd *in vacuo*. The residue was flooded with H_2O, acidified with 10% citric acid soln, and extd with EtOAc. The EtOAc soln was dried (Na_2SO_4) and concd under reduced pressure. The product was chromatographed on a short column of Silicar CC7, eluted with EtOAc, and crystd from EtOAc in the cold to yield 5.6 g (61%): mp 132–3°; $[\alpha]^{27}D$ − 6.3° (*c* 1.035, DMF). *Anal.* ($C_{34}H_{46}N_4O_{10}$) C, H, N.

Z-*O*-*tert*-Bu-Tyr-γ-*tert*-Bu-Glu-Gly-Gly Pentachlorophenyl Ester (5).—To a suspension of 9.1 g (13.55 mmoles) of the tetrapeptide free acid (**4**) in 200 ml of CH_2Cl_2 was added 6.35 g (15 mmoles) of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide methyl *p*-toluenesulfonate. To the resulting soln was added 4.0 g (15 mmoles) of pentachlorophenol and the soln was shaken for 48 hr at room temp. The solvent was removed *in vacuo* and the residue was washed (H_2O) and crystd from MeOH to yield 10 g (80.3%): mp 185–6°; $[\alpha]^{27}D$ − 3.85° (*c* 1.56, DMF). *Anal.* ($C_{40}H_{45}Cl_5N_4O_{10}$) C, H, N.

***O*-*tert*-Bu-Tyr-γ-*tert*-Bu-Glu-Gly-Gly Pentachlorophenyl Ester·HCl (6),**—A fine suspension of 4.5 g (4.9 mmoles) of tetrapeptide active ester **5** and 0.45 g of 10% Pd/C (prewetted with AcOH) in 150 ml of MeOH was treated with 0.179 g (4.9 mmoles) of dry HCl in MeOH and the suspension was hydrogenated for 2 hr. The reaction mixt was filtered and the filtrate was evapd under reduced pressure. The residue was crystd from MeOH–Et_2O to give 2.85 g (71%): mp 135° dec; $[\alpha]^{27}D$ + 4.9 (*c* 2.54, DMF). *Anal.* ($C_{32}H_{40}Cl_6N_4O_8$) C, H, Cl.

Poly(Tyr-Glu-Gly-Gly)Gly Me (1).—To a soln of 1.1 mg (8.77 μmoles) of glycine Me·HCl and 0.86 g (8.5 mmoles) of Et_3N in 2.4 ml of DMSO was slowly added a soln of 2.79 g (3.4 mmoles) of polymerizing unit **6** in 25.0 ml of DMSO. The transfer vessels were washed with 5.5 ml of DMSO which was added to the reaction mixture giving a final concn of 100 mmoles/l. The reaction mixture was stirred for 6 days, then centrifuged to yield the product which was washed with 35 ml of H_2O 3 times, then placed in 100 ml of H_2O and stirred overnight to remove any remaining DMSO. The fully blocked product was collected by centrifuging, washed with 35 ml of H_2O, 3 times with 35 ml of MeOH, and twice with 35 ml of Et_2O, and dried under vacuum to yield the blocked polymer (0.75 g, 42.5%). This was dissolved in 50 ml of 90% F_3CCO_2H, allowed to stand for 50 min, then concd under reduced pressure. The residue was washed 3 times with Et_2O, suspended in 20 ml of H_2O, and dissolved with addition of 1 *N* NaOH at pH 8.0. The soln was dialyzed against distd H_2O for 4 days, then lyophilized to yield the Na salt of the polypeptide. This material was dissolved in 0.1 *N* NaOH, acidified with 1 *N* HCl to pH 2.5, and dialyzed extensively for 4 days against frequently changed vols of distd H_2O. The polypeptide was lyophilized to yield 0.33 g (57.8%): $[\alpha]^{25}D$ − 9.8° (*c*, 9.51, 0.05 *M* Tris buffer). *Anal.* ($C_{18}H_{22}N_4O_7 \cdot 1.5H_2O$) C, H, N.

Molecular Weight Determination.—Calibrated columns of Sephadex G-100[9] (2.5 × 38.5 cm) and of Corning CPG 10-240 glass granules (2.0 × 28 cm) were employed for the mol wt determination. Using 0.1 *M* NaCl–0.05 *M* KH_2PO_4 corrected to pH 8.0 as eluent, 4 mg of poly(Tyr-Glu-Gly-Gly)Gly Me was filtered through each of these columns. The polypeptide was eluted from each column in a vol equiv to that corresponding to a mol wt of at least 1 × 10^5.

Immunochemical Results.—Two rabbits were treated at weekly intervals with 500 μg of poly(Tyr-Glu-Gly-Gly)Gly Me (**1**). The first 2 weeks they were injected interdermally using complete Freunds adjuvant as suspension medium, and the 3rd week they were injected sc. The injection on the 4th week was done iv using buffered saline. Bleedings were conducted on the following week and the serum from each animal was not found to give a precipitin reaction with up to 10,000 μg of the polymer 1.

To 1-ml aliquots of rabbit antisera to poly(Try-Glu-Ala-Gly)-Gly-*1*-^{14}C Et[3] were added incremental amts of up to 500 μg of polypeptide 1. To each tube was added the equiv point amt of the antigen (30 μg) and the mixt was then incubated at 37°. Each tube gave a precipitin reaction. The precipitates were kept at 4° for 48 hr, washed twice with buffered saline, and collected by centrifugation. The total amt of protein pptd was estimated by the Kjeldahl method. No inhibition of the precipitin reaction was observed using the polypeptide 1.

Acknowledgment.—This work was supported by a grant from the National Science Foundation.

Antifungal Activity of the Thiosemicarbazones of Some Heterocyclic Aldehydes[1]

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Received August 18, 1970

Thiosemicarbazones,[2,3] including those made from heterocyclic aldehydes[4–8] show tuberculostatic, antibacterial,[9] and carcinostatic[10] activity. The question has been raised as to the relative activity of 4-alkyl substituted thiosemicarbazones.[3]

Thiosemicarbazones[11–13] and dithiosemicarbazones[14] made from aliphatic and aromatic aldehydes and ketones have already been shown to be fungistatic. It is reported here that some thiosemicarbazones (I) and 4-substituted thiosemicarbazones (II) made from heterocyclic aldehydes are also effective against cellulolytic fungi.

The compounds prepared in this work are listed in Table I; ir and elemental analysis[15] data confirm the assigned structures. Satisfactory agreement of melting

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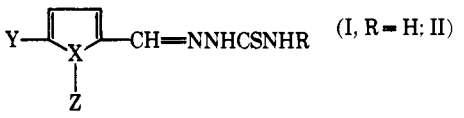
TABLE I

HETEROCYCLIC ALDEHYDE THIOSEMICARBAZONES



No.	X[a]	R	Yield, %	Mp, °C	Formula[b]
1	N	Ph	81[c]	180	$C_{12}H_{12}N_4S$[i]
2	N	Allyl	71[d]	170	$C_9H_{12}N_4S$[i]
3	N	Me	75[c]	186	$C_7H_{10}N_4S$[i]
4	N	Et	61[d]	199	$C_8H_{12}N_4S$[i]
5	N	2-Naphthyl	55[e]	227	$C_{16}H_{14}N_4S$
6	N	3-FC_6H_4	45[c]	192	$C_{12}H_{11}FN_4S$
7	N	m-$O_2NC_6H_4$	95[c]	219	$C_{12}H_{11}N_5O_2S$
8	N	p-$O_2NC_6H_4$	90[e]	218	$C_{12}H_{11}N_5O_2S$
9	N	$Ph(CH_2)_2$	70[f]	121	$C_{14}H_{16}N_4S$
10	N	H	73[g]	203	$C_6H_8N_4S$[j,k]
11	O	Ph	74[d]	187	$C_{12}H_{11}N_3OS$
12	O	Allyl	59[f]	139	$C_9H_{11}N_3OS$
13	O	Me	73[f]	163	$C_7H_9N_3OS$
14	O	Et	49[f]	143	$C_8H_{11}N_3OS$
15	O	1-Naphthyl	73[d]	199	$C_{16}H_{13}N_3OS$
16	O	2-Naphthyl	70[h]	186	$C_{16}H_{13}N_3OS$
17	O	p-$O_2NC_6H_4$	89[h]	192	$C_{12}H_{10}N_4O_3S$
18	O	$Ph(CH_2)_2$	71[f]	122	$C_{14}H_{15}N_3OS$
19	O	H	71[g]	160	$C_6H_7N_3OS$[j-l]
20	S	Ph	79[e]	200	$C_{12}H_{11}N_3S_2$[m]
21	S	Allyl	64[f]	160	$C_9H_{11}N_3S_2$[m]
22	S	Me	88[f]	159	$C_7H_9N_3S_2$[m]
23	S	Et	61[f]	188	$C_8H_{11}N_3S_2$[m]
24	S	1-Naphthyl	80[e]	222	$C_{16}H_{13}N_3S_2$
25	S	2-Naphthyl	49[e]	200	$C_{16}H_{13}N_3S_2$
26	S	m-$O_2NC_6H_4$	94[e]	208	$C_{12}H_{10}N_4O_2S_2$
27	S	p-$O_2NC_6H_4$	84[e]	192	$C_{12}H_{10}N_4O_2S_2$
28	S	$Ph(CH_2)_2$	71[f]	169	$C_{14}H_{15}N_3S_2$
29	S	H	74[h]	193	$C_6H_7N_3S_2$[j-l,n]
30	N	Ph	78[d]	140	$C_{13}H_{14}N_4S$
31	N	Allyl	45[f]	95	$C_{10}H_{14}N_4S$
32	N	Me	80[g]	172	$C_8H_{12}N_4S$
33	N	Et	61[d]	144	$C_9H_{14}N_4S$
34	N	2-Naphthyl	45[d]	183	$C_{17}H_{16}N_4S$
35	N	3-FC_6H_4	41[f]	154	$C_{13}H_{13}FN_4S$
36	N	p-$O_2NC_6H_4$	91[e]	181	$C_{13}H_{13}N_5O_2S$
37	N	$Ph(CH_2)_2$	65[f]	116	$C_{15}H_{18}N_4S$
38	N	**H**	77[d]	166	$C_7H_{10}N_4S$[i]
39	S	Ph	79[f]	157	$C_{13}H_{13}N_3S_2$
40	S	Allyl	94[f]	163	$C_{10}H_{13}N_3S_2$
41	S	Me	97[f]	202	$C_8H_{11}N_3S_2$
42	S	Et	52[f]	178	$C_9H_{13}N_3S_2$
43	S	1-Naphthyl	88[f]	192	$C_{17}H_{15}N_3S_2$
44	S	2-Naphthyl	81[f]	195	$C_{17}H_{15}N_3S_2$
45	S	m-$O_2NC_6H_4$	97[f]	186	$C_{13}H_{12}N_4O_2S_2$
46	S	p-$O_2NC_6H_4$	91[f]	205	$C_{13}H_{12}N_4O_2S_2$
47	S	$Ph(CH_2)_2$	79[f]	175	$C_{15}H_{17}N_3S_2$

[a] Y = H for 1–**38**; Y = CH_3 for **39**–**47**; Z = H for **1**–**10**; Z = CH_3 for **30**–**38**. [b] *Anal.* C, H, N, S (also F for **6** and **35**). Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values. Solvents used for recrystn: [c] MeOH–H_2O; [d] C_6H_6; [e] Me_2CO–H_2O; [f] C_6H_6–hexane; [g] EtOH–H_2O; [h] EtOH. Previous report of this compd in [i] F. Fujikawa, F. Hirao, T. Shiota, M. Natio, and S. Tsukuma, *Yakugaku Zasshi*, **87**, 1493 (1967); *Chem. Abstr.*, **69**, 43751 (1967). [j] R. E. Hagenbach and H. Gysin, *Experentia*, **8**, 184 (1952). [k] F. E. Anderson, C. J. Duca, and J. V. Scudi, *J. Amer. Chem. Soc.*, **73**, 4967 (1951). [l] J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins, and W. A. Lott, *ibid.*, **73**, 906 (1951). [m] F. Fujikawa, Japanese Patent 14,685, July 25 1964); *Chem. Abstr.*, **62**, 527*b* (1965). [n] L. W. Clemence and H. J. Eichel, U. S. Patent 2,746,-972, May 22, 1956; *Chem. Abstr.*, **51**, 2871*a* (1957).

points has been obtained for the 12 compounds reported previously.

In a standard tube-dilution test,[12] with pure fungal cultures, the effectiveness of the thiosemicarbazones against *Chaetomium globosum* (2-week incubation) was as follows: (a) **14** and **19** were effective at 10 μg/ml, (b) **1**, **6**, **7**, **9**, **17**, and **31** were effective at 100 μg/ml, and (c) **3**, **10**, **13**, **20**, **22**, **24**, **29**, **35**, and **38** were effective at 1000 μg/ml. Against *Aspergillus niger* (48-hr incubation), **1**, **6**, **7**, and **9** were effective at 100 μg/ml; **13**, **14**, **19**, **20**, **22**, **29**, and **31** were effective at 1000 μg/ml.

The antifungal activity of **14** and **19** is equivalent to

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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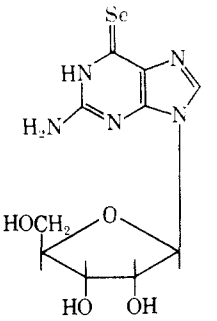
Received June 5, 1970

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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