(broad s, 2H, $-NH_2$), 5.72 (s, 3H, $N-CH_3$) for a crude sample. *Anal.* ($C_6H_6N_6O_3$) C, H, N.

1-Methyl-2-nitro-α-phenyl-5-imidazoleethanol (7). A mixture of 1.7 g (0.012 mole) of 1,5-dimethyl-2-nitroimidazole (**4**)[7] and 1.51 g (0.014 mole) of benzaldehyde in 6.7 g of ethanolic KOH (0.3 g of KOH/25 ml of EtOH) was stirred at room temperature under N_2 atmosphere for 22.5 hr. The mixture was evaporated to dryness *in vacuo* to afford an oil, which was mixed with *ca.* 15 ml of H_2O and extracted with $CHCl_3$ (5 × 10 ml). The extracts were dried ($MgSO_4$) and evaporated to dryness to give an oil. Water was added to the oil, and benzaldehyde was removed by vacuum steam distillation on a rotary evaporator. Ether was added to the residue and an insoluble, yellow solid was obtained. This was collected and washed with Et_2O to afford 1 g of product. Evaporation of the mother liquor gave 1.7 g of semisolid which contained mostly adduct and some **4**. Both fractions were later dehydrated separately to the benzylidene derivative **6**. From an initial run, crude product, mp 111–115°, was recrystallized from Me_2CO–hexane and then from EtOAc to afford crystals melting at 120–121.5°. *Anal.* ($C_{12}H_{13}N_3O_2$) H, N; C: calcd, 58.29; found, 58.89.

1-Methyl-2-nitro-5-styrylimidazole (6). The adduct (**7**) (1.18 g or 47.8 mmoles) was added to a stirred mixture of 3.3 ml of HOAc and 1.1 ml of concentrated H_2SO_4 at room temperature. The mixture was heated at 110° for 20 min in an oil bath, cooled, and poured on ice to give a yellow solid which was collected to give 0.943 g (86%), mp 167–170°. A sample, which was recrystallized twice from Me_2CO–95% EtOH, melted at 170.5–171.5°. *Anal.* ($C_{12}H_{11}N_3O_2$) C, H, N.

1-Methyl-2-nitro-5-imidazolecarboxaldehyde Thiosemicarbazone (8). Compound **6** (1.04 g or 4.55 mmoles) was stirred heterogeneously in 40 ml of MeOH at 10° and O_3 was introduced *via* a capillary tube from a generator (Welsbach Corp., 0.081 mole/hr in O_2 stream) until a clear solution was obtained (8 min). After 15 min of additional stirring, 0.431 g (2.27 mmoles) of $Na_2S_2O_5$ in 5 ml of H_2O was added at below 15°, and, after 10 min, 10 ml of H_2O was added, and the mixture was evaporated to near dryness on a rotary evaporator at *ca.* 60–75° to give a yellow paste. An additional 20 ml of H_2O was added and the mixture was concentrated *in vacuo* until the odor of benzaldehyde was not noticeable. Subsequently, 0.42 g (4.62 mole) of thiosemicarbazide was added, and the mixture was heated on a steam bath for 40 min. After cooling, the yellow product was collected and washed with H_2O to afford 0.89 g (85.5%), mp 277° dec. A sample, which was recrystallized from a large volume of Me_2CO–EtOH, melted at 276° dec; ir 1590 cm^{-1} (mineral oil mull). *Anal.* ($C_6H_8N_6SO_2$) H, N, S; C: calcd, 31.58; found, 32.03.

2-Amino-5-(1-methyl-2-nitro-5-imidazolyl)-1,3,4-thiadiazole (2). The thiosemicarbazone (**8**) (1.02 g or 4.47 mmoles) was added to a solution of 3.72 g (17.9 mmoles) of $FeCl_3$[8] in 21 ml of H_2O and *ca.* 2–3 ml of EtOH was added to facilitate wetting of the crystals. After 1.5 hr at 80–85°, the mixture was cooled to room temperature and the yellow-orange crystals were collected and washed with H_2O. The yield was 0.684 g (67.5%), mp 260–261°. A sample was recrystallized from EtOH to give mp 263.5° dec; ir 3450, 3350, 3125, 1660 cm^{-1} (mineral oil mull)–comparable high frequency bands were also present in the spectrum of **1**. *Anal.* ($C_6H_6N_6O_2S$) C, H, N, S.

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Potential Antitumor Agents. 2. α- and β-2′-Deoxy-6-selenoguanosine and Related Compounds†

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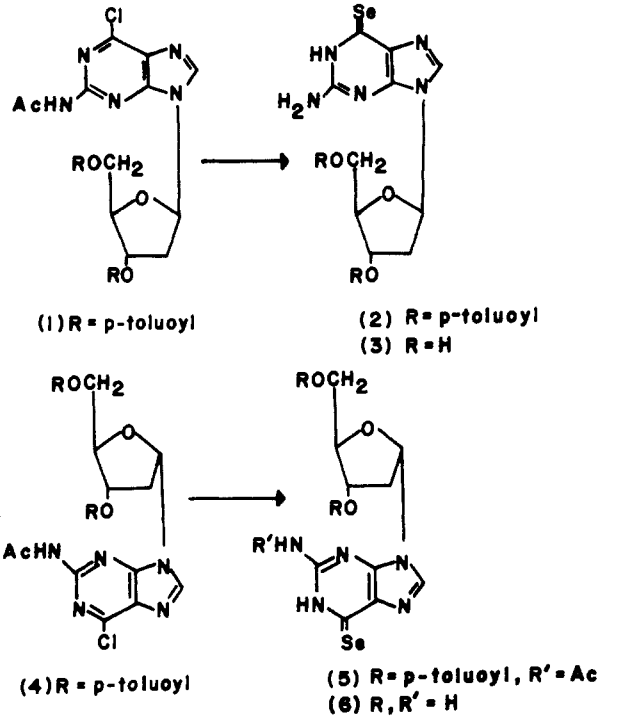
6-Selenoguanine and 6-selenoguanosine were found to have a greater inhibitory effect than either thioguanine or its riboside in Sarcoma 180 ascites cells.[1-3] 6-Selenoguanosine 5′-monophosphate behaves like 6-thioguanosine 5′-monophosphate as a potent competitive inhibitor of guanylate kinase, with inhibition constants of (5.0–7.0) × $10^{-5}M$ and 6.0 × $10^{-5}M$, respectively.[4] These results prompted the synthesis of α- and β-2′-deoxy-6-selenoguanosine (**3** and **6**) for similar biological studies. We now wish to report a convenient two-step synthesis of α- and β-2′-deoxy-6-selenoguanosine (Scheme I) by a modification of the procedure of

Scheme I



Iwamoto, *et al.*[5] The reaction of 2-acetamido-6-chloro-9-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-9*H*-purine (**1**) with alcoholic NaOMe and hydrogen selenide required a long period of 3 days at room temperature because of the low solubility of this compound in MeOH. During this period the *N*-acetyl group was removed, and the partially protected precursor **2** of β-2′-deoxy-6-selenoguanosine (**3**) was obtained in 75% yield. However, the reaction of the α-D anomer **4** required only a short period of time (80 min) to give the protected precursor **5** of α-2′-deoxy-6-selenoguanosine (**6**) in 67% yield.

Treatment of compounds **2** or **5** with methanolic NaOMe gave β-2′-deoxy-6-selenoguanosine (**3**) and α-2′-deoxy-6-selenoguanosine (**6**) in 54 and 70% yields, respectively.

β- and α-2′-deoxy-6-selenoguanisine (**3** and **6**) are unstable in aqueous solution, with the half-life of the 360-nm peak in H_2O at room temperature about 24 hr.

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Table I. Effect of 6-Selenoguanosine, α-2′-Deoxy-6-thioguanosine, β-2′-Deoxy-6-thioguanosine, α-2′-Deoxy-6-selenoguanosine, and β-2′-Deoxy-6-selenoguanosine on the Growth of L-5178Y

	% survival		
Control 100%	1.0×10^{-4} M	1.0×10^{-5} M	1.0×10^{-6} M
6-Selenoguanosine	4	8	35
α-2′-Deoxy-6-thioguanosine	18	65	73
β-2′-Deoxy-6-thioguanosine	10	13	34
α-2′-Deoxy-6-selenoguanosine	66	78	88
β-2′-Deoxy-6-selenoguanosine	12	16	50

Experimental Section‡

2-Amino-6-seleno-9-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-9*H*-purine (2). Condensed H_2Se§ (1.62 ml) was bubbled through a soln of 0.80 g (0.0035 g-atom) of Na in 300 ml of abs MeOH. 2-Acetamido-6-chloro-9-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-9*H*-purine (1) (2.26 g, 0.004 mole) was introduced into the well-stirred soln. The mixture was stirred under N_2 at room temp for 3 days. The greenish solid was collected by filtration and washed with MeOH (10 ml). The residue (2.49 g) was recrystd from MeOH to give 1.53 g (75%) of the product: mp 133–137°; uv λ_{max}^{MeOH} 357.5 (ϵ_{max} 11,940), 239 nm (40,660); $[\alpha]^{25}D$ −88.4° (*c* 0.206, MeOH). The analytical sample was recrystd from MeOH. *Anal.* ($C_{26}H_{25}N_5SeO_5 \cdot H_2O$) C, H, N. The elemental analysis suggested that compound 2 is a hygroscopic hydrate.

2-Amino-9-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine-6-selenol (β-2′-Deoxy-6-selenoguanosine) (3). Partially protected β-2′-deoxy-6-selenoguanosine (2) (1.65 g, 0.003 mole) was introduced into a soln of 0.207 g of Na (0.009 g-atom) in 50 ml of abs MeOH, and the mixture was stirred and kept overnight under N_2. The reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in 50 ml of ice-cold H_2O and the soln was extracted with $CHCl_3$ (5 × 40 ml). The aqueous layer was clarified by filtration. The clear yellow filtrate was acidified (pH 4–5) with AcOH and kept 30 min in an ice bath. The yellow solid was filtered off, washed with 5 ml of cold H_2O and 10 ml of Et_2O, and dried to give 0.57 g (54%) of 3: mp 166–167° (bubbling). Reprecipitation of 3 from Na_2CO_3 soln did not purify further the product because of its instability in aqueous soln. On tlc# the R_f value in H_2O is 0.42: uv $\lambda_{max}^{pH\ 1.0}$ 370.5 (ϵ_{max} 21,100), 270 nm (6100); $\lambda_{max}^{H_2O}$ 358 (ϵ_{max} 25,800), 263.5 nm (6200); $\lambda_{max}^{pH\ 11.0}$ 330 (ϵ_{max} 18,100), 225 nm (11,950). *Anal.* ($C_{10}H_{13}O_3N_5Se \cdot H_2O$) C, H, N.

2-Acetamido-6-seleno-9-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl)-9*H*-purine (5). Condensed H_2Se (1.0 ml) was bubbled through a soln of 0.3 g (0.013 g-atom) of Na in 60 ml of abs EtOH. 2-Acetamido-6-chloro-9-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl)-9*H*-purine (4) (2.2 g, 0.0039 mole) in 40 ml of abs EtOH was introduced into the well-stirred soln. The mixture was stirred under N_2 at room temp for 80 min. The greenish solid was collected by filtration and washed with EtOH (10 ml). The residue was recrystd from 100 ml of EtOH to give 1.6 g (67.4%) of 5: mp 139°; uv λ_{max}^{MeOH} 361.5 (ϵ_{max} 16,340), 239 nm (45,320); $[\alpha]^{25}D$ −17.16° (*c* 0.204, MeOH). *Anal.* ($C_{28}H_{27}N_5SeO_6$) C, H, N.

2-Amino-9-(2′-deoxy-α-D-*erythro*-pentofuranosyl)-9*H*-purine-6-selenol (α-2′-Deoxy-6-selenoguanosine) (6). 2-Acetamido-6-seleno-9-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl)-9*H*-purine (5) (1.5 g, 0.0025 mole) was introduced into a soln of Na (0.13 g, 0.0057 g-atom) in 70 ml of abs MeOH, and the mixture was stirred and kept overnight under N_2. The reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in 15 ml of ice-cold H_2O, and the soln was extracted with $CHCl_3$ (5 × 20 ml). The aqueous layer was clarified by filtration. After the clear, yellow soln was acidified (pH 5–6) with AcOH and kept 1 hr at 0°, the yellow solid was filtered off, washed with 2–3 ml of cold H_2O and 10 ml of Et_2O, and dried to give 0.6 g (70%) of 6: mp 176° (bubbling). Because of the high solubility of the compound in H_2O, it is important to use a minimum amount of ice-cold H_2O for the acid precipitation. On tlc# the R_f value in H_2O was 0.42: uv $\lambda_{max}^{pH\ 1.0}$ 371 (ϵ_{max} 21,900), 270 nm (5700); $\lambda_{max}^{H_2O}$ 357 (ϵ_{max} 25,210), 262.5 nm (5810); $\lambda_{max}^{pH\ 11.0}$ 330 (ϵ_{max} 18,170) 254 nm (11,460). *Anal.* ($C_{10}H_{13}O_3N_5Se \cdot H_2O$) C, H, N.

Effects on Cultured Mouse Leukemia Cells. The preliminary results of the tissue culture studies using L-5178Y cells are shown in Table I. The cell viability was determined by the dilute agar colony method.[6] 6-Selenoguanosine, α-2′-deoxy-6-thioguanosine, β-2′-deoxy-6-thioguanosine, α-2′-deoxy-6-selenoguanosine (6), and β-2′-deoxy-6-selenoguanosine (3) inhibited cell division and caused cell death over a range from 1.0×10^{-4} to 1.0×10^{-6} mole after 2-hr incubation. β-2′-Deoxy-6-selenoguanosine (3) was found to have activity approximately equal to β-2′-deoxy-6-thioguanosine, but the α-seleno derivative 6 was much less active than α-2′-deoxy-6-thioguanosine. Further study of these compounds is in progress. Because of the instability of 2′-deoxy-6-selenoguanosine, fresh solutions of these compounds were prepared for each use in biological studies.

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‡All melting points are uncorrected. Analyses were carried out at Micro-Analysis, Inc., Marshallton, Wilmington, Del., and MidWest Microlab, Inc., Indianapolis, Ind.

§98.0% minimum purity H_2Se from the Matheson Co., Inc., East Rutherford, N. J. 07073.

#Polygram CEL 300 PEI from Brinkmann Instruments, Inc., Westbury, N. Y.

New Compounds

Terpene Compounds as Drugs. 13.[1] *o*-Terpenylaminomethylphenols and Their *N*-Methyl Derivatives

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The interesting properties of several phenol derivatives and terpenoid compds used in the therapy of respiratory tract diseases have been recognized for a long time.[2] In a search for novel expectorant and antitussive agents, we synthesized a series of *o*-terpenylaminomethylphenols and their *N*-methyl derivatives (II, X = H) (Table II). Besides, in view of some similarity between these structures and the expectorant bromhexine[3] (*N*-cyclohexyl-*N*-methyl-2-amino-3,5-dibromobenzylamine), we also prepared compds II, where X = Br or Cl. N-Substituted salicylidenimines (I) were obtained by condensing the appropriate salicylaldehyde with the terpenylamine. Compds I were reduced to secondary amines (II), a number of which were N-methylated with HCHO–HCOOH.